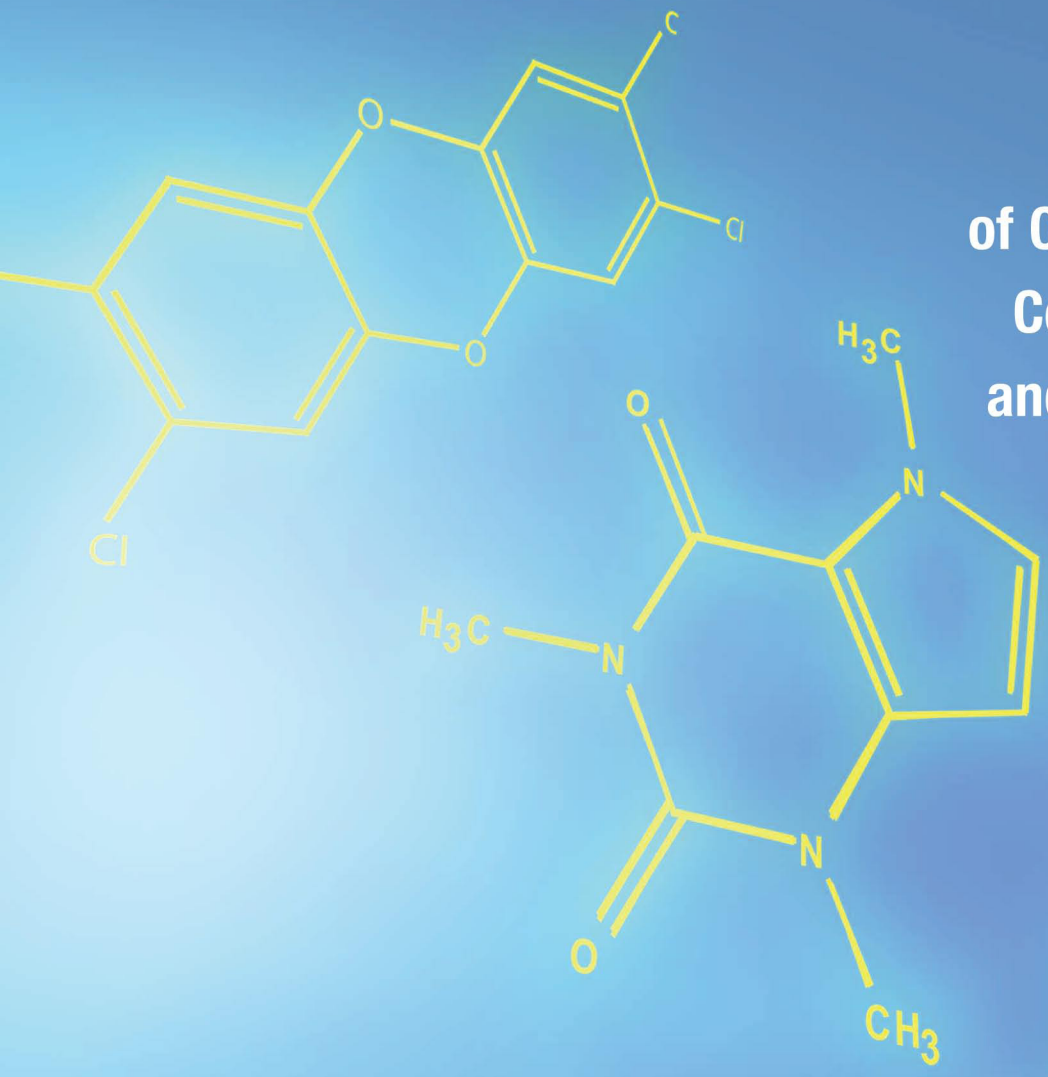
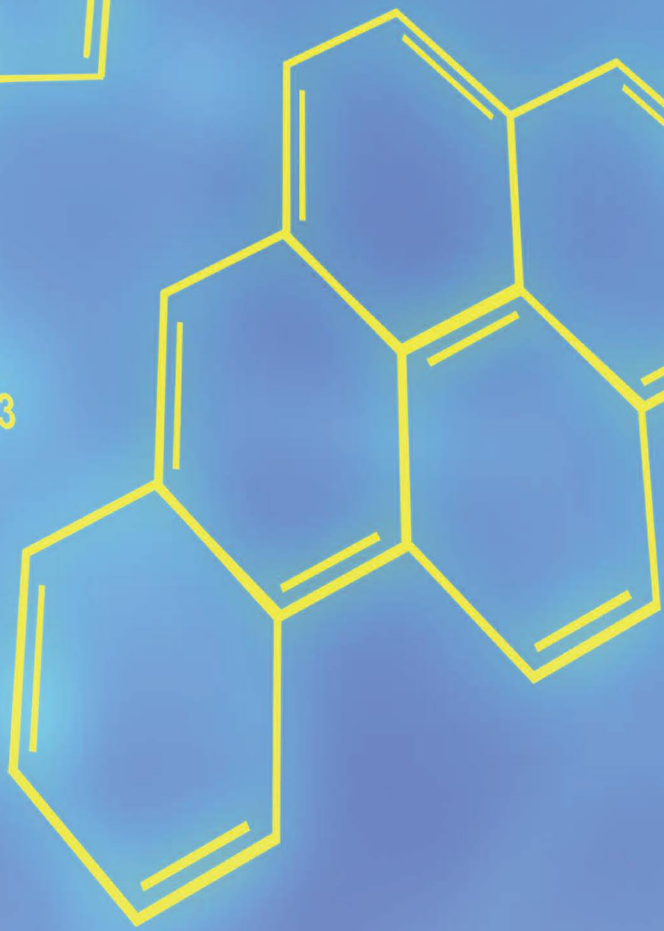
Committees on Toxicity Mutagenicity Carcinogenicity of Chemicals in Food, Consumer Products and the Environment





Committee on TOXICITY

Committee on CARCINOGENICITY

Committee on MUTAGENICITY

Annual Report 2012

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

Annual Report 2012

Contents

About the Committees

This is the twenty-third 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 is normally excluded from the discussion. In exceptional circumstances, and at the Chairman's discretion, the member may be allowed to contribute to the discussion (e.g to answer specific questions), but not to 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, Advisory Committee on Pesticides and Scientific Advisory Committee on Nutrition.

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

I am pleased to present this report, which summarises the work of the Committee on Toxicity (COT) during 2012. 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 2012, the Committee published four statements covering: possible toxic interactions of caffeine and alcohol; an evaluation of FSA's research programme on phytoestrogens; developments in toxicogenomics and their potential relevance to toxicological risk assessment; and risks of chemical toxicity and allergic disease in relation to infant diet. The last of these presented initial conclusions from an ongoing programme of work that is being undertaken in collaboration with the Scientific Advisory Committee on Nutrition (SACN), which will determine whether any changes are warranted to the Government's current dietary advice for infants and young children.

Work was also completed on two major reports compiled by working groups of the Committee. The first, which was produced jointly with the Advisory Committee on Pesticides (ACP), addressed methods of regulatory risk assessment for exposures to pesticides in bystanders and residents living near to treated crops. The second concerned possible long-term toxicity following an incident in 1988, in which water supplies in Camelford, North Cornwall, were contaminated by aluminium sulphate. This was a detailed and thorough investigation, and I am extremely grateful to Professor Frank Woods, a former Chairman of COT, who chaired the working group.

Other activities included consideration of proposed default values for parameters such as body weight, to be used in chemical risk assessment when empirical data are not available, and review of the toxicological reference dose for dioxins.

The Committee's work has wide-ranging impacts. An example in 2012 was guidance that the Food Standards Agency issued, in particular to people in the bodybuilding community, not to use "fat-burner" products containing the chemical 2,4-dinitrophenol (DNP). This action, which followed two deaths in people believed to have taken such substances, was underpinned by advice that had been given by COT in 2003.

Sadly, in 2012, the Committee lost the services of two long-standing members, Professor Alan Boobis and Dr John Foster, whose valuable expertise is much missed. I thank them for all of the work that they did on behalf of the Committee, and also the secretariat, who as ever, have given us tremendous support.

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

COT evaluations

Caffeine and alcohol: combined effects on health and behaviour

1.1 The Committee on Toxicity (COT) was asked by the Food Standards Agency to comment on concerns that caffeine in energy drinks may interact with alcoholic beverages in causing adverse behavioural or toxic effects.

1.2 Since 2004, energy drinks have been the fastest growing sector of the drinks market in the UK. The popularity of consuming energy drinks mixed with alcoholic beverages has also increased. Moreover, individuals who consume high quantities of both energy drinks and alcohol are perceived to engage in a greater degree of risk-taking. This has raised concerns about the health effects of caffeine and alcohol in combination. In particular, a phenomenon described as “wide awake drunk” has been suggested, in which the stimulatory effect of caffeine prevents consumers of alcohol from realising how intoxicated they are, thereby increasing the potential for toxic damage to the body and adverse behavioural effects. Most energy drinks contain levels of caffeine approximately equivalent to those found in a cup of coffee (approximately 80mg caffeine per 250ml can).

1.3 Currently beverages containing more than 150 mg/l caffeine (other than those based on coffee or tea) must carry the statement ‘High caffeine content’. Under new Regulations, which come into effect on the 13 December 2014, these beverages must carry the statement ‘High caffeine content. Not recommended for children or pregnant or breast feeding women’ in the same field of vision as the name of the beverage, followed by a reference in brackets to the caffeine content expressed in mg per 100ml. There are currently no legal restrictions on the amount of caffeine that may be present in a food or drink product.

1.4 Caffeine acts primarily as a stimulant, increasing arousal and vigilance, reducing fatigue, and decreasing reaction times in some tasks. At higher doses, it can induce insomnia, anxiety, tremors, and seizures. Susceptibility to the effects of caffeine varies between individuals as people develop tolerance with repeated exposure.

1.5 Alcohol is widely consumed in the UK with at least one alcoholic drink being reported as consumed in the week before interview by 68% of men and 54% of women in the 2009 General Lifestyle Survey carried out by the Office for National Statistics. It depresses brain function, and outward signs of intoxication include impaired sensory perception and control of movements, slowed cognition, and stupor. How exactly it causes these effects has not been fully elucidated.

1.6 Accurate estimates of the extent to which alcohol and caffeine are consumed together are not available. One of the reasons for this is that drinks containing alcohol and caffeine are often sold separately and mixed by the consumer rather than being formulated in a single product – for example rum with cola or energy drinks with vodka.

1.7 Various studies were identified which provided relevant information. These included studies of the association between consumption of energy drinks and alcohol, and whether this is influenced by genetic constitution; of risk-taking behaviour, adverse alcohol-related incidents and use of illicit drugs in people who consume alcohol with energy drinks; and of brain function following experimental dosing with caffeine and alcohol in combination. In addition a number of published reports described cases of illness or death following consumption of caffeine with alcohol.

1.8 The balance of evidence suggests that higher intake of caffeine is associated not only with higher alcohol intakes but also with use of other psychoactive substances. There is limited evidence that the relationship may be determined, at least in part, by an individual's genetic make-up. It appears that, at least in some population groups, there is a correlation between high consumption of alcohol and of energy drinks specifically. However, it is unclear whether this is because consumption of energy drinks causes people to drink more alcohol, or because people who are inclined to more risky behaviour tend generally to consume larger quantities of psychoactive substances, including caffeine and alcohol.

1.9 A number of studies have suggested that caffeine can reduce the outward effects of alcohol, especially on reaction times, but other investigations have failed to support this. The evidence that perceptions of alcohol intoxication are modified by caffeine is conflicting. Overall, the range of methods used in reported studies prevents firm conclusions on whether caffeine counteracts the short-term effects of alcohol on brain function.

1.10 Published case reports of illness or death following consumption of caffeine and alcohol in combination do not allow firm conclusions about the contribution of either substance, or on whether caffeine increases the toxicity of alcohol.

1.11 Overall, the COT concludes that the current balance of evidence does not support a harmful toxicological or behavioural interaction between caffeine and alcohol. However, because of limitations in the available data, there is substantial uncertainty, and if important new evidence emerges in the future, then this conclusion should be reviewed.

1.12 The full COT statement can be found at: http://cot.food.gov.uk/pdfs/cotstatementcaffalco201204.pdf

Default values to be used in risk assessment in the absence of actual measured data

1.13 The COT considered guidance published by the European Food Safety Authority (EFSA) Scientific Committee on default values to be used in the absence of empirical data. These values were for bodyweights of different age groups, chronic daily total liquid intake for adults, factors for converting concentrations of substances in the feed or drinking water of laboratory rats and mice to intakes, and uncertainty factors. In addition the guidance advised on the rounding of figures when deriving health-based guidance values. The EFSA guidance is available at: http://www.efsa.europa.eu/en/efsajournal/doc/2579.pdf. The proposed default

values do not need to be used in all cases; alternative values can be used, provided that justification is given.

1.14 Dietary exposure assessments used by the COT generally use empirical data on people's bodyweight within the relevant dietary surveys. Therefore the COT would not usually need to use default bodyweights. However, the COT considered the suggested EFSA defaults of 70 kg for adults, 12 kg for children aged 1-3 years, and 5 kg for infants to be reasonable.

1.15 Similarly, the COT would usually use empirical data on liquid consumption. However, the proposed default of 2 L/day was considered reasonable.

1.16 Some of the factors for converting concentrations of chemicals in the feed of rats and mice to intakes were the same as previously published by the World Health Organization. However, these had been checked and extended. The COT agreed with the proposed factors, which are replicated below. However, the factors should not be used inappropriately; for example, palatability problems can reduce food or water consumption and therefore chemical intake.

1.17 Factors for converting concentrations in feed to daily dose (ppm in diet x factor = mg/kg bw intake)

Study duration	Rat	Mouse
Subacute	0.12	0.2
Subchronic	0.09	0.2
Chronic	0.05	0.15

1.18 Factors for converting concentrations in drinking water to daily dose (ppm in water x factor = mg/kg bw intake)

Study duration	Rat	Mouse
Subacute	0.12	0.18
Subchronic	0.09	0.15
Chronic	0.05	0.09

1.19 The proposed subdivision of the default 100-fold uncertainty factor into sub-factors of 4.0 and 2.5 for inter- species variation in toxicokinetics and toxicodynamics, respectively, and 3.16 each for inter-individual variation in toxicokinetics and toxicodynamics, was consistent with the existing view of the COT as expressed in the 2007 report on Variation and Uncertainty in Toxicology (available at: http://cot.food.gov.uk/pdfs/vutreportmarch2007.pdf). However, the COT cautioned that removing individual sub-factors or replacing them with data-derived values might reduce the reassurance of safety provided by the total composite uncertainty factor. This is because when the default composite uncertainty factor of 100 is used, if one of the individual sub-factors is not adequate for a particular chemical, there will be compensation if one or more of the other sub-factors is larger than necessary for that particular chemical. This potential to compensate for inadequacy

of an individual sub-factor might be reduced if some sub-factors were removed or replaced by data-derived values, and the latter needs to be justified on a case-by-case basis.

1.20 The COT agreed with the proposed approach to rounding of expressing health-based guidance values to one significant figure unless the rounded figure varies by more than 10% from the unrounded figure, in which case the value should be expressed to two significant figures. Rounding should only be at the very end of the process.

Dioxins - reanalysis by EPA

1.21 The COT considered a risk assessment of non-cancer end points for dioxins; Volume 1 of the United States of America Environmental Protection Agency's (US EPA) Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments, accompanied by a second volume of appendices[1] . A subsequent US EPA assessment (Volume 2) yet to be published would cover the cancer end points.

1.22 The EPA reanalysis established a reference dose (RfD) of 0.7 pg/kg bw/day, which is about 3 times lower than the tolerable daily intake (TDI) established by the COT (2 pg/kg bw/day). A number of topics were discussed, such as: the inclusion and exclusion criteria for studies; the use of human data relating to the accident in Seveso in 1976 to establish the RfD; end points addressed in the studies; and the physiologically based pharmacokinetic (PBPK) model and uncertainty factors applied in deriving the RfD. The Committee commented on the US EPA approach in deriving the RfD in comparison with that used by the COT to establish the TDI.

1.23 The US EPA had identified four epidemiological studies and 78 animal bioassays as presenting potentially useful results. After further evaluation, one epidemiology study and 30 animal bioassays had been excluded. The RfD had been derived on the basis of two epidemiological studies related to the Seveso accident, which were considered to provide robust data (Mocarelli et al., 2008[2]; Baccarelli et al., 2008[3]). The modified Emond PBPK model together with the epidemiology studies had been used to derive the point of departure (POD). The EPA comments on the animal data with regard to the National Toxicology Programme (NTP) and FSA-funded studies of Bell et al., 2007, previously reviewed by the COT[3] had also been taken into consideration.

1.24 The COT noted that the Seveso cohort had experienced very high peak exposures to 2,3,7,8-tetrachloro-p-dioxin (TCDD) as a consequence of an industrial accident, and that it might not be appropriate to extrapolate from a POD based on such exposures to populations continuously exposed to much lower background levels of dioxins. An increased level of thyroid-stimulating hormone (TSH), presumed to be

[1] available at: http://www.epa.gov/iris/supdocs/1024index.html and http://www.epa.gov/iris/supdocs/dioxinv1sup_apps.pdf

[2] Mocarelli, P. et al (2008). Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality. Environ Health Perspect116: 70-77.

[3] Baccarelli, A. et al (2008). Neonatal thyroid function in Seveso 25 years after maternal exposure to dioxin.PLoS Med 5: e161.

secondary to other effects, suggested increased clearance of the thyroid hormone, thyroxine (T4). There was a question of whether effects on TSH resulting from increased activity of hepatic liver enzymes, such as the UDP-glucuronosyltransferases (UGTs), were a consequence of current body burden or a lasting effect of the peak exposure in 1976. Other factors such as medications and iodine deficiency could also influence thyroid activity.

1.25 The COT concluded that the Seveso data represented an atypical exposure scenario which could not necessarily be equated with body burdens resulting from lower chronic exposures, and that it was uncertain whether reported health outcomes resulted from an acute or continuous exposure.

1.26 The COT agreed that the assumption of a constant half-life value for the clearance of TCDD from long-term or chronic exposure was not well-supported biologically. TCDD measurements shown in Table 3-14 of the EPA report indicated that the elimination of TCDD may depend on age, protein binding, induction of CYP1A2 and fat content, and that individuals displayed different trends. Although there was some evidence of non-linearity at high doses of TCDD, perhaps due to protein binding, whether there were similar changes at low doses was still unknown. Induction of CYP1A2 in animals was not a good reflection of what happened in humans.

1.27 The COT agreed that use of a PBPK model was preferable to emphasis on half-life, and that a one compartment model was not appropriate. The sensitivity analysis indicated that the PBPK model was influenced by the Hill coefficient. However, this did not appear consistent with known data on organ blood flow.

1.28 The COT agreed with the US EPA approach of excluding studies with higher exposure levels than those providing a basis for deriving a RfD. The US EPA RfD had been based on two epidemiological studies that associated TCDD exposures with adverse health effects. Mocarelli et al. (2008) reported decreased sperm concentration and sperm motility in men who were exposed to TCDD during childhood as a consequence of the Seveso accident in 1976. The POD for derivation of a candidate RfD had been calculated by estimating dose as the mean (across persons) of the peak exposure following the accident. The study by Baccarelli et al. (2008) analysed developmental effects and increased TSH levels in neonates. The POD was then calculated from estimates of maternal exposure during pregnancy. The COT considered that the Baccarelli study appeared to be more reliable as the effects reported in the Mocarelli study could be due to acute exposure. Furthermore, the differential effects according to age at the time of the acute exposure could have been influenced by the choice of age cut-points in the analysis.

1.29 The US EPA report had applied the TSH benchmark level of 5 µU/mL, established by the World Health Organization as an indicator of possible iodine deficiency, in evaluating the equivalent effect size (for chemically-induced hypothyroidism) related to TCDD exposure. The COT agreed that this was acceptable. Elevated TSH was described as an indirect indicator of increased clearance of thyroid hormones, which could be due to induction of UGTs. Changes in T4 levels could affect brain development, and Members found it unusual that only levels of TSH were reported,

since circulating T4 levels are biologically more important. It was asked whether T4 levels would have been measured but not reported in the publication if they were not altered. It was also asked whether chronic stimulation of TSH would maintain T4 at normal levels. Deficiency of iodine or exposure to compounds inhibiting T4 synthesis would be more potent causes of hypothyroidism than compounds stimulating the UGTs, and would be expected to show a steeper dose response relationship.

1.30 The COT commented that the changes in sperm parameters observed in the Moccarelli study were not functionally significant, although the power to detect a functional change could have been limited by the small number of participants. The uncertainty in exposure estimation also needed to be considered. It was noted that some changes in sperm quality were within the normal range. It was also possible that there was a time-window of sensitivity which could have resulted in an acute effect leading to long-term compromise of reproductive function. Nevertheless the observed abnormalities were undesirable, even if not strictly adverse, and could be employed as the basis of a conservative approach.

1.31 The COT discussed the logic of using the animal data as support for the RfD derived from the human data and whether the epidemiology data would support the protective nature of a TDI derived from the animal data given the differences in exposure scenarios. The animal studies at the lower end of the candidate RfD distribution were dominated by mouse studies. The US EPA had been less confident in these models due to the lack of key mouse-specific data and the use of large toxicokinetic interspecies extrapolation factors. It was mentioned that human AhR receptors are less responsive than those in certain mouse strains. The COT had higher confidence in the rat data, and these were not contradicted by the human data. The Committee concluded that the animal data would have been a preferable basis for establishing the RfD, with human data supporting the animal data and providing reassurance and a reality check.

1.32 Although the US EPA had used the human data as the basis for its RfD, and COT had used animal data in setting its TDI, the difference in the values obtained was driven by the different uncertainty factors applied in extrapolation from a lowest observed adverse effect level (LOAEL) to a no observed adverse effect level (NOAEL). COT had applied an uncertainty factor of 3 and US EPA had selected a factor of 10. There were two points to consider in selecting an appropriate factor: the steepness of the dose response relationship (and the position of the LOAEL on the curve), and the severity of the effect. Changes in TSH and sperm counts were indicators of toxicity, but not viewed as severe effects. However, information on the shape of the dose-response relationship was lacking.

1.33 On balance, the COT concluded that its TDI of 2 pg/kg bw/day did not need to be reviewed, and that the new epidemiological data described in the US EPA report provided additional support for the value previously set.

Expression of uncertainty

1.34 Following publication of the COT report on Variability and Uncertainty in Toxicology of Chemicals in Food, Consumer Products and the Environment in 2007[4], the FSA had 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[5]. 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). The FSA had subsequently commissioned research to assess the COT's draft uncertainty framework from a social science perspective and in 2011 the COT was presented with the report of the social science research. Following discussion of this report, the SSRC had issued a paper giving a social science perspective on the expression of uncertainty in risk assessment[6].

1.35 The key messages of the paper were:

- *Even the best communication strategies will not work for everyone.*
- *Numerical and verbal quantifiers of risk and uncertainty are subject to highly variable interpretations and qualifications based on varied social contexts.*
- *It is therefore vital to understand how risk and uncertainty are understood by experts and non-experts before a communication strategy is devised.*
- *This understanding should inform not only the communication of risk and uncertainty but the entire assessment and management process. It should form part of a codified Risk Assessment Policy.*

1.36 The COT agreed with the SSRC's advice that standardised terminology was unlikely to be helpful in communication of uncertainty, particularly to the general public. Rather, the wording needed to be tailored to the particular circumstances of each risk assessment. However, it was important to describe the major sources of uncertainty in the assessment, and the direction and potential magnitude of their impact. For estimates of quantitative parameters (e.g. dietary intake of a chemical), it was considered helpful to express uncertainty as a range of plausible numerical values. In contrast, qualitative questions (e.g. on whether or not a chemical was teratogenic), could be answered on the balance of available evidence, with an indication of how robust that evidence was (i.e. how likely it was that the conclusion might be overturned by future research). A checklist of sources of uncertainty, which had been proposed in the earlier report by Dr Andrew Hart[7], had been tried out by the Secretariat. So far it had not proved to be very helpful, but the COT agreed that it could be revisited at a later stage.

1.37 The Interdepartmental Group on Health Risks from Chemicals (IGHRC) held a workshop on uncertainty which had been attended by officials of different Government Departments and Agencies. The Secretariat of the COT provided the COT's conclusions on this subject at the meeting.

[4] http://cot.food.gov.uk/cotreports/cotwgreports/cotwgvut
[5] http://www.food.gov.uk/science/research/foodcomponentsresearch/riskassessment/t01programme/t01projlist/t01056/
[6] TOX 2012/12; available at http://cot.food.gov.uk/pdfs/tox201212.pdf
[7] http://www.foodbase.org.uk/results.php?f_category_id=&f_report_id=676

Phytoestrogens Research Programme

1.38 Phytoestrogens are naturally occurring compounds found in some plant-based foods, notably soya. These compounds, as their name suggests, have structural similarities to the female sex hormone, oestradiol. This has prompted concern that consuming phytoestrogens might have oestrogenic, anti-oestrogenic and/or other effects in humans. These effects could be either adverse or beneficial and might differ in particular subgroups of the population.

1.39 The Phytoestrogen Research Programme (T05/T06) was established to improve assessment of the risks and benefits from dietary phytoestrogens and the scientific evidence base underpinning advice to consumers. In 2011 the COT was asked to review briefly the final projects on-going at the time of an earlier 2007 review, and to consider the overall contribution of the Phytoestrogen Research Programme to risk assessment for phytoestrogens.

1.40 The COT noted that the three on-going studies were based on a recommendation that the programme concentrate on human studies. However, while well designed and conducted, their results were not sufficiently strong to support definitive conclusions. The COT noted that the research programme had earlier made a significant contribution to a COT report on phytoestrogens published in 2003. A significant strength of the programme had been the development of analytical standards for a wide range of phytoestrogens.

1.41 Overall the COT considered that the T05 programme had met its original remit and had delivered work of at least satisfactory scientific quality and in some cases of very high quality. The work had delivered value for money in all cases and in some cases exceptional value for money. The programme had covered areas not addressed elsewhere and helped to reduce uncertainties in the understanding of phytoestrogen effects and exposures. In doing so the programme had assisted in delivering the FSA's policy requirements.

1.42 The COT Statement is available at: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2012/cot201201

Risks of chemical toxicity and allergic disease in relation to infant diet

1.43 The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that bears on the Government's dietary recommendations for infants and young children. The review will identify new evidence that has emerged since the Government's current recommendations were formulated, and will appraise that evidence to determine whether the advice should be revised. SACN is examining the nutritional basis for the advice, and asked the COT to advise on risks of toxicity that might need to be taken into account. In addition to other adverse effects, this includes the influence of the diet on development of allergic and autoimmune disease.

1.44 The first phase of the review focuses on the diet of infants (0-12 months old), and will be followed by consideration of dietary recommendations for young children (1-

5 years old). For the first phase, the COT selected a number of chemicals to be evaluated on the basis of their known or suspected adverse effects and the potential for dietary exposure of infants through breastfeeding, infant formula and weaning foods.

1.45 In 2012, a statement was published, setting out the COT's conclusions regarding a subset of the chemicals selected for evaluation:

- Caffeine: Available information does not provide a basis for refining the current advice that breastfeeding mothers should avoid drinking too much strong tea or coffee (only occasionally rather than every day).

- Alcohol: Evidence supports the current recommendations that breastfeeding mothers should consume no more than 1 or 2 units of alcohol once or twice a week.

- Methylmercury: The exposure of infants to methylmercury from breast milk, infant formula and weaning foods does not exceed the current safety guideline. The toxicity of methylmercury is at present being reviewed by the European Food Safety Agency (EFSA) and there may be a need for further evaluation by COT depending on the EFSA conclusions.

- Dioxins and dioxin-like compounds: Dietary exposures of infants may briefly exceed the safety guideline, but because the exceedence would only be for a short time, it would not be expected to produce a build-up in the body to levels that would be harmful. Furthermore, there is clear evidence from multiple studies that exposures are decreasing over time.

- Phthalates: In the UK, the exposures of infants to phthalates from breast milk, infant formula and weaning foods are unlikely to exceed the safety guidelines.

- Bisphenol A: The exposures of infants to bisphenol A from breast milk, infant formula and weaning foods are well below the safety guideline. Moreover, exposures are likely to be even lower in the future as a result of decreased use of the chemical in plastic bottles used for infant feeding. The COT will review its conclusions following completion of an ongoing EFSA re-evaluation of BPA.

- Legacy pesticides: These are a group of pesticides that were banned during the 1980s and 1990s, but which, because of their persistence in the environment, can still be detected in the food chain. The few studies that are available indicate that levels in breast milk are declining, and do not point to a concern for the health of UK infants

1.46 The COT is currently evaluating the other chemicals that have been selected for consideration (vitamin A, soy phytoestrogens, aluminium, lead, brominated flame retardants and persistent organic pollutants), and will publish statements on these in the near future.

1.47 Scientific evidence concerning the influence of infant diet on risks of allergic and autoimmune disease will also be addressed in a separate review.

1.48 The full COT statement can be found at: http://cot.food.gov.uk/pdfs/cotstatementoverarch201203.pdf

Toxicogenomics data in risk assessment

1.49 The term "toxicogenomics" refers to the production of large quantities of biological information about the regulation of genes, proteins and metabolism in cells, in a way that can be applied in toxicology. It is an area of science that has been developing rapidly. As part of the COT's remit to advise on new scientific advances that bear on the understanding of toxic risks from chemicals, a statement was compiled, reviewing important developments in toxicogenomics since the last COT statement on the topic in 2009, and considering the aspects of risk assessment to which toxicogenomics might contribute.

1.50 In recent years, there has been major expansion in the use of laboratory techniques that produce large quantities of information about the function of cells and organisms. These techniques have been used to investigate a large number of different diseases and the biological consequences of chemical exposures. In parallel with this, there has been improvement in the availability and quality of analytical software that can be used to discern meaningful patterns in such data. The ways in which toxicogenomic findings are interpreted have also changed to take a greater consideration of how different genes and metabolic pathways relate to one another.

1.51 Most progress within the field of toxicogenomics has been made where it has been applied to measuring changes in gene activity. As a result, the conclusions of the COT on the use of toxicogenomics in risk assessment were largely based on such studies. In the future, those conclusions may be applicable to toxicogenomic studies applied to other material such as proteins and metabolites.

1.52 Possible uses of toxicogenomics in risk assessment for chemicals include:

- To help characterise the biochemical processes by which a substance produces toxic effects
- To provide information on differences between species in their response to chemical exposures, enabling better assessment of the implications for human health of toxicological findings in laboratory animals
- To help develop reliable ways of assessing aspects of chemical toxicity that avoid the use of laboratory animals
- To identify and understand the effects of chemicals at doses below those which produce overt toxicity, which may be relevant for assessing the risk of human exposure to low levels of a chemical
- To improve understanding of when toxicological findings for one substance are likely to apply to another with similar chemical structure
- To identify chemicals in body fluids that can be measured as markers of exposure to a chemical or of its effects on the body (known as "biomarkers")

1.53 As yet, there are few examples of toxicogenomics being applied for such purposes, most published data having been generated for other reasons, and not to answer specific questions in risk assessment. However, the potential is there, provided

that findings are sufficiently reproducible within and between laboratories, and can be linked with required confidence to specific biochemical pathways that are relevant to toxic effects.

1.54 The COT will continue to monitor developments in this rapidly evolving field.

1.55 The full COT statement can be found at: http://cot.food.gov.uk/pdfs/cotstatementtgxinra201202.pdf

Committee procedures

Horizon Scanning

1.56 At the February 2012 meeting, the COT were invited to consider emerging or developing topics of importance within the COT remit, which might be included in future agendas for detailed discussion. They also received a presentation from Mr Terry Donohoe (Chemical Safety Division of the FSA) who described the activities of the FSA and the European Food Safety Authority EFSA on emerging risks.

1.57 Possible topics for future discussion included:

Vitamin E

1.58 COT had agreed in 2009 that a full review of vitamin E in pregnancy was not necessary at that time, but that the topic should remain under review. A paper would be presented to the Committee on Carcinogenicity of Chemicals in Food Consumer Products and the Environment (COC) in 2012, discussing evidence for an association of vitamin E supplementation with risk of prostate cancer. The Secretariat would continue to monitor the literature in this area and update the Committee if significant research was published indicating adverse effects of vitamin E within the COT's remit

Obesogens

1.59 Some researchers had suggested a possible role of xenobiotic chemicals that could disrupt the normal developmental and homeostatic controls over adipogenesis and energy balance, in the increasing prevalence of obesity. The environmental obesogen hypothesis proposed that obesogens could predispose individuals to obesity and/or related metabolic disorders under the influence of the typical high-calorie, high-fat Western diet. The COT agreed that it would be useful to examine this area as some of the reported effects were observed at very low doses in some animal studies. It was also agreed that since obesity was a huge and complex area, it was important to define clearly what question would be addressed - namely, the strength of evidence for a direct contribution of chemicals to obesity. It was noted that a mother's diet and lifestyle before and during pregnancy could have long-term effects on the metabolism of her children, and would therefore need to be considered as possible confounders in human studies.

Consideration of whether the 10-fold uncertainty factor for interspecies extrapolation is sufficient for developmental toxicity

1.60 In 2011, the COT had agreed that it would be useful to investigate this topic and that relevant new data should be reviewed. It was noted that human and primate data would be limited, and that comparisons of sensitivity between rodent species could also be considered. It was anticipated that a discussion paper would be brought to the COT in the autumn.

Other possible topics

- *Plant micro RNAs* - these were known to survive in the gut and therefore it would be interesting to know whether they can be taken up into the body.

- *Immunotoxic effects of environmental chemicals* – a question was raised about the validity of methods for detecting effects on the immune system that had been used in some recent epidemiological studies.

1.61 It was agreed that there was a good balance of expertise on the Committee, especially with the addition of the two new Members who would be appointed shortly. It was suggested that some additional expertise in paediatrics (perhaps from a member of SACN) was needed for the discussions related to complementary and young child feeding. Toxicogenomics should be added to the template of requirements in order to ensure that expertise in this area was maintained in the future.

1.62 Members were invited to make suggestions for future topics and were reminded that they may draw particular issues to the attention of the Secretariat at any time.

Working Groups

Bystander Risk Assessment Working Group (BRAWG)

1.63 The BRAWG was 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 were:

- To agree definitions 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 risks arising from these exposures in the light of current knowledge

1.64 The BRAWG considered an opinion on pesticide exposure assessment for regulatory risk assessment that was published in 2010 by the Panel on Plant Protection Products and their Residues (PPR) of the European Food Safety

Authority (EFSA), and research funded by the Department for Environment, Food and Rural Affairs (Defra), which was aimed at better assessment of the factors influencing exposures of bystanders and residents to pesticides. The Group prepared a draft report through a series of meetings, and revised it after consultation and comments at an open public meeting in 2011.

1.65 The draft report was then considered by the full COT and ACP committees in March 2012. Further revisions were made to the report, which was then endorsed by the COT and ACP at meetings in October and November 2012, respectively. The final report is available at http://cot.food.gov.uk/pdfs/brawgreport.pdf.

Working Group on the review of epidemiological literature on organophosphates and health outcomes relating to the nervous system

1.66 In 1999, the COT published a report entitled 'Organophosphates,' which considered whether 'single, prolonged or repeated exposure to low doses of organophosphates cause long-term adverse health effects'. Low doses were defined as 'those which do not produce overt acute toxicity accompanied by recognised clinical symptoms or signs of acute toxicity'. The focus was on five neurological health outcomes: neuropsychological abnormalities; electroencephalographic (EEG) abnormalities; peripheral neuropathy and neuromuscular dysfunction; psychiatric illness; and effects on the autonomic nervous system.

1.67 In addition to drawing conclusions, the report made recommendations for further research to establish whether the risk of more severe neurological and neuropsychiatric disease was increased by low-level exposure to organophosphates. To address these recommendations, research was subsequently funded jointly by a number of Government departments, and findings were reviewed by the COT at its meetings in September 2007, and September and December 2009. On those occasions the COT reached a number of conclusions about the results reported, but noted that the data needed to be considered in the context of a wider review of epidemiological studies published since 1999. Also, in December 2007, the COT was informed of a request from the Advisory Committee on Pesticides (ACP) for an updated review of the published literature on organophosphates, to include neuropsychological and neuropsychiatric effects. The COT agreed that systematic review procedures should be applied and that it was important to continue to liaise with the ACP and the Medical and Scientific Panel of the Veterinary Products Committee.

1.68 The COT considered a draft review of the epidemiological literature on organophosphates and health outcomes related to the nervous system at its September 2012 meeting. This had been undertaken by the HPA COT Secretariat and the HPA Toxicology Unit, Imperial College London. The Committee agreed to establish a Working Group to consider the review in detail. External experts with expertise on epidemiology, psychiatry, epidemiological psychiatry, neurophysiology and neurology were recruited to participate in the Working Group, in addition to COT members with expertise in epidemiology. The first meeting of the Working Group would be held in February 2013.

Lowermoor Subgroup

1.69 The COT Lowermoor Subgroup (LSG) had been established in 2001 to advise Health and Environment ministers on possible long-term health effects arising from a 1988 water pollution incident in North Cornwall, and on the adequacy of existing monitoring and research programmes. The water pollution incident had occurred on 6 July 1988 at the Lowermoor water treatment works near Camelford, North Cornwall. A contractor's relief tanker had put 20 tonnes of aluminium sulphate into the water supply at the works. Water supplies to an estimated 20,000 people had been polluted with aluminium, sulphate and metals dissolved from pipework and plumbing materials (copper, lead and zinc). Flushing of the distribution system to remove the contaminated water had resulted in the disturbance of old sediments in the water mains, mainly deposits of iron and manganese oxides, leading to raised levels of these metals in the water.

1.70 The LSG had produced a comprehensive report on the incident which the COT had discussed previously as a draft in 2005 and 2007. Due to a case of congophilic angiopathy in an individual from the area who had died at an unusually young age, a Coroner's inquest had been opened and, following correspondence with the Coroner and receipt of legal advice, publication of the report was delayed until the Coroner's proceedings were completed. The inquest had concluded in March 2012, and given the time that had elapsed, it was considered appropriate for the report to be updated and for the COT to review the final version before publication.

1.71 The COT considered that the updated report provided an extremely thorough assessment of the relevant science, taking into account some major gaps in the available data. There had been potential for a high spike of aluminium exposure from water over the few days immediately after the incident, in addition to lower level background exposures, but there were no animal studies simulating this pattern of exposure, and the exposures that actually occurred were uncertain. Members endorsed the work that had been carried out in relation to the Coroner's inquest.

1.72 In the light of the report's findings, Members had a number of additional recommendations for the handling of future incidents involving significant environmental contamination. Depending on the scale of exposure and potential adverse impact on health, and also on likely levels of public concern, consideration should be given to:

- Environmental sampling at an early stage to inform and validate models of the contamination
- Replication of environmental sampling and measurements by independent laboratories
- Sensitivity analyses to characterise uncertainties in modelled exposures (and possibly modelling of exposures by more than one independent group)
- Collection of biological samples and/or measurement of biomarkers at an early stage to assess individual exposures and/or their effects
- A population register of those exposed, drawn up at the earliest opportunity, with early planning of follow-up

- Health studies based on exposure (or good proxies for exposure) and not limited only to those reporting symptoms or illness
- Early, targeted literature review to establish which health outcomes might be expected at the estimated exposure levels, and rapid collation of any reports of unexpected effects, so that they can be taken into account in the design of follow-up studies and healthcare responses.
- Prompt investigation of associated reports of ill-health in animals, including examination of tissue or blood samples
- 'In vivo' animal experiments in appropriate model systems, especially if unexpected health outcomes or syndromes are reported

1.73 The final report is published at: (http://cot.food.gov.uk/cotwg/lowermoorsub/)

Ongoing work

Risks arising from the infant diet and the development of atopic and autoimmune disease

1.74 As part of the SACN review of the UK Government recommendations on complementary and young child feeding, the COT were asked to provide advice on risks arising from the infant diet related to the development of atopic and autoimmune disease.

1.75 To assist in the development of this advice, the FSA prepared an external research call to identify an external contractor to undertake a detailed review of the published literature. When completed, this will be presented to the COT so that the evidence can be discussed and any conclusions shared with SACN. The COT discussed in detail the scope and the approach that the literature review should take, allowing the research call to be refined; it was noted that the FSA would work with the appointed contractors to ensure that the review met the COT specifications.

1.76 The literature review is unlikely to be completed before the autumn of 2013.

SACN review of dietary guidelines for vitamin D

1.77 The SACN are undertaking a review of their recommendations on appropriate levels of vitamin D intake. As part of this process, COT were asked to provide SACN with advice on the effects of high levels of vitamin D intake. The SACN review began in 2011, will be completed in 2014, and will include a public consultation.

1.78 The COT are continuing to review the potential toxicity of vitamin D exposure. The Committee have considered introductory papers on the scope of the review, an overview of the adverse effects of vitamin D, including data from epidemiology studies, human supplementation studies and animal studies and a discussion paper on serum calcium measurement.

1.79 Elevated levels of vitamin D are associated with the occurrence of hypercalcaemia and hypercalciuria. This occurs because vitamin D promotes the absorption of calcium and resorption of calcium from bone; the resulting high blood calcium levels result in calcium deposition in soft tissues, diffuse dimineralisation of bones and irreversible renal and cardiovascular toxicity.

1.80 It is anticipated that the COT review will be submitted to SACN by the spring of 2013 with further updates as required.

Toxicity of chemicals in the infant diet

1.81 The COT has been asked to consider aspects of the toxicity of chemicals in the infant diet, in support of the SACN review of Government recommendations on complementary and young child feeding. The COT reviews aim to identify whether current advice is appropriate in relation to potential toxicity, or whether there is a need for new or revised advice. In addition to the overarching statement on risks of chemical toxicity and allergic disease in relation to infant diet (see paragraphs 1.43 to 1.48), more detailed reviews commenced in 2012, and statements will be published in 2013:

Potential risks from high levels of aluminium in the infant diet

1.82 The aim of this statement is to provide an overview of the potential risks from high levels of aluminium in the infant diet. The total aluminium content of food includes naturally present aluminium, aluminium as a contaminant, food additives and aluminium from food contact materials. Additional exposure can come from drinking water used in food preparation, including reconstitution of infant formula, as well as water that is directly consumed. Infant exposures to aluminium in the UK have been calculated and form the basis of the risk characterisation.

Potential risks from high levels of lead in the infant diet

1.83 The aim of this statement is to provide an overview of the potential risks from high levels of lead in the infant diet. There are currently no Government recommendations on complementary and young child feeding that relate to lead. The general population is exposed to lead via food, water, air, soil and dust. Infants may also be exposed to lead from breast milk and for small children and infants ingestion of soil and dust can be an important contributor. Infant exposures to lead in the UK have been calculated and form the basis of the risk characterisation.

Potential risks from high levels of vitamin A in the infant diet

1.84 The aim of this statement is to provide an overview of the potential risks from high levels of vitamin A in the infant diet. Vitamin A is an essential micronutrient , but very large intakes may lead to hypervitaminosis A, resulting in toxicity. The COT awaits the results of the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) to support improved assessment of vitamin A intake in infants.

Potential risks from high levels of soy phytoestrogens in the infant diet

1.85 The aim of this statement is to provide an overview of the potential risks associated with high levels of soy isoflavones, genistein, daidzein and glycitein in infant diet. Infants can be exposed to isoflavones through breast milk and cows' milk, with the highest exposure estimated for infants consuming soy-based weaning diet and exclusively fed soy-based infant formulas.

2012 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

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Declaration of COT members' interests during (2012) the period of this report (a up-to-date version can be found on the COT website) TO BE UPDATED

Professor David Coggon OBE		
Personal Interest		**Non Personal Interest**
Shareholder Halifax/Lloyds Standard Life		**Trustee** Colt Foundation
Mr Derek Bodey		
Personal Interest		**Non Personal Interest**
None		None
Professor Alan Boobis (ceased 31 March 2012**)**		
Personal Interest		**Non Personal Interest**
Consultancy Endura Fine Chemicals Proctor & Gamble Sumitomo Chemical (UK) Plc		**Member** ECETOC Task Force on Guidance for Classification of Carcinogens under GHS EFSA Chemical Contaminants in the Food Chain Panel EFSA Plant Protection Products and their Residues Panel EFSA Scientific Committee Working Group on Risk-Benefit Assessment EFSA Scientific Committee Working Group on the Benchmark Dose ILSI HESI, ILSI Europe and ILSI Research Foundation Working groups on Generic Risk Assessment Issues JECFA (vet drugs) JMPR
Shareholder Banco Santander SA Barclays BG Group BT Group Centrica Plc HBOS Iberdrola SA Lloyds Bank National Grid Scottish Power		**Editor-in-Chief** Elsevier - Food and Chemical Toxicology **Research Contract** Department of Health Commission of the EU (FP6) Food Standards Agency Medical Research Council **Misc** GlaxoSmithKline - Support by Industry ILSI HESI - unpaid Chair of Board of

		Trustees ESRC - PhD Studentship
Dr Roger Brimblecombe		
Personal Interest		**Non Personal Interest**
Shareholder Vertex Pharmaceuticals, Inc **Advisor** MVM Life Sciences Partnership LLP **Member** Home Office Advisory Council on the Misuse of Drugs National Trust – Nominations Committee **Misc** 2gether NHS Foundation Trust - Non-Exec, Director & Mental Health Act Manager Drug Discovery World - Consultant Editor		**Member** British Pharmacological Society British Toxicology Society Society for Medicines Research
Professor Janet Cade		
Personal Interest		**Non Personal Interest**
None		Kellogg - PhD student
Dr Rebecca Dearman		
Personal Interest		**Non Personal Interest**
Consultancy European Chemical Plasticizers Industry (ECPI) Research Institute for Fragrance Materials (RIFM) The European Chemical Industry Council (CEFIC) **Employee** University of Manchester **Shareholder** AstraZeneca Syngenta CTL		**Research Grant** American Chemical Council AstraZeneca BASF ECPI Novartis Proctor & Gamble RIFM Syngenta Syntaxin Unilever

Dr John Foster (ceased 1 September 2012**)**		
Personal Interest		**Non Personal Interest**
Shareholder and Employee AstraZeneca		**Misc** British Toxicology Society – Member of Executive Committee Society of Toxicologic Pathology - Member and Editor in Chief of journal *Toxicologic Pathology*
Dr Mark Graham		
Personal Interest		**Non Personal Interest**
Employee AstraZeneca		None
Dr Anna Hansell		
Personal Interest		**Non Personal Interest**
Employee Department of Epidemiology & Public Health Imperial College, London (includes Small Area Health Statistics Unit)		**Research Grant** AstraZeneca **Misc** ESRC - PhD Studentship
Shareholder Halifax		
Supporter (non-active) Greenpeace		
Professor David Harrison		
Personal Interest		**Non Personal Interest**
Consultant University of Canberra University of Florida Quintiles		**Trustee** Medical Research Scotland Melville Trust
Shareholder Avipero		**Research collaboration** Myriad Genetics Cytosystems Genentech Somalogic Destina Ltd Antoxis Ltd Biopta Ltd

		MDX Health Nucana Ltd
		Misc Office of the Scottish Charity Regulator - Board member Breakthrough Breast Cancer - Research funding Cancer Research UK

Professor Roy Harrison (joined 1 April 2012)

Personal Interest		**Non Personal Interest**
Consultant		**Trustee**
Shareholder		**Research collaboration**
		Misc

Professor Brian Houston

Personal Interest		**Non Personal Interest**
Consultancies and Direct Employment Simcyp Xenotech GSK Pfizer		**Support by Industry** GSK Pfizer Lilly Servier
Membership ISSX BPS BTS		
Specific Interests Drug Metabolism & Pharmacokinetics		

Professor Justin Konje

Personal Interest		**Non Personal Interest**
None		**Misc** PerkinElmer - financial support for research programme Bayer Schering Healthcare

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Employee Leatherhead Food Research(LFR)		**Member** British Toxicology Society Society of Toxicology
		Member of the editorial board Food and Chemical Toxicology Xenobiotica
		Misc Various pharmaceutical and other companies - Contract research at LFR and consultancy
Professor Ian Morris		
Personal Interest		**Non Personal Interest**
Consultancy Takada Pharmaceuticals		**Member** Department of Health, Yorkshire and Humber Research for Patient Benefit Research Committee
Membership British Society for Toxicology Society for Endocrinology Society for Medicines Research Society for study of Fertility		**Misc** Son is a student fellow of the British Heart Foundation
Dr Nicholas Plant		
Personal Interest		**Non Personal Interest**
Employee University of Surrey		**Research Funding** AstraZeneca - GlaxoSmithKline Pfizer
		Member International Society for the Study of Xenobiotics (ISSX) MHRA Pharmacovigilance Expert Advisory Group

		Misc Xenobiotica - Associate Editor Frontiers in Predictive Toxicology – Editorial Board British Toxicology Society – Secretary of Education sub-committee
Professor Robert Smith		
Personal Interest		**Non Personal Interest**
Membership Rodenticide Resistance Action Group		**Misc** Support by Industry - Research costs for a student monitoring rodenticide resistance
Dr John Thompson		
Personal Interest		**Non Personal Interest**
None		None
Professor Faith Williams (joined 1 April 2012**)**		
Personal Interest		**Non Personal Interest**
Shareholding Rio Tinto National Grid Vodaphone BP SSE Aviva		**Member** Commission on Human Medicines (currently invited expert) EMA Ad Hoc Group 3Rs ILSI Expert Working Group **Current and recent research funding** Astra Zeneca Syngenta HPA Department of health BBSRC Pfizer

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 2012, the Committee completed interim guidance on a strategy for genotoxicity testing and mutagenic hazard assessment of impurities in chemical substances and a guidance document on the human health significance of mutagenicity. The finalised strategy and guidance documents were published on the COM website. The COM considered the *in vitro* genotoxicity assessment of nanomaterials, the genotoxicity of chlorophenols and completed a review of the current scientific progress regarding cell transformation assays for the prediction of carcinogens. Statements on these topics were also published on the COM website.

The Committee also considered the evidence for hormesis in mutagenicity dose-response relationships and a Food Standards Agency funded research project on the genotoxic consequences of exposure to mixtures of food-derived chemical carcinogens. Horizon scanning was discussed at the October meeting.

Dr D Lovell Chair
PhD BSc (Hons) FBS CStat CBiol CSci

COM evaluations

Interim Guidance on a Strategy for Genotoxicity Testing and Assessment of Impurities

2.1 The COM has a remit to provide UK Government Departments and Agencies with advice on the most suitable approaches to testing chemical substances for genotoxicity. The COM has been asked to advise on the need for a generic strategy to test and evaluate the genotoxicity of impurities present in chemical substances. The COM has not previously published guidance on impurities. The published strategy represents the most appropriate at the time of publication.

2.2 The COM recommended a staged approach to genotoxicity data assessment which is presented in the guidance statement.

2.3 The COM concluded that the genotoxicity assessment of impurities present in chemical substances is guided by knowledge of the structure, estimated exposure and the application of the Threshold of Toxicological Concern (TTC) concept to select impurities which require evaluation (i.e. 0.15 µg/person (0.0025 µg/kg body weight/day for a 60 kg adult) proposed by Kroes et al 2004).[8] In situations where it is not possible to undertake an estimation of exposure, or the structure of the impurity has not been or cannot be determined, then a pragmatic cut off concentration of 0.1% can be used as a guide for priority setting for genotoxicity assessment. The genotoxicity testing strategy needs to be derived on a case-by-case basis but should, where the structure of the impurity is known, include (quantitative) structure-activity relationship ((Q)SAR) evaluation of impurities selected for genotoxicity assessment, coupled with expert judgement and reference to genotoxicity data on similar substances. Genotoxicity testing of isolated or synthesised impurities should be undertaken where a (Q)SAR evaluation indicates potential for mutagenicity, and where exposure cannot be confirmed to be below the TTC, and should include an Ames test and an *in vitro* micronucleus (MNvit) test. In situations where the structure of the impurity has not been or cannot be determined and is unknown, and where exposure cannot be confirmed to be below the TTC, then the first step in the evaluation for impurities selected for genotoxicity assessment should be to conduct an Ames test and an MNvit test. If the available evidence suggests that an impurity should be considered to be mutagenic then levels should be controlled to as low as reasonably practical.

[8] Kroes et al (2004), list of exceptions to the use of the TTC

- High potency carcinogens (e.g. aflatoxin-like, azoxy- or N-nitroso substances)
- Steroids
- Inorganic substances
- Metals, including essential metals
- Polymers, oligomers
- Proteins
- Substances known/predicted to bioaccumulate
- Insoluble nanomaterials
- Radioactive substances

Substances likely to exert local effects (on GI tract, respiratory tract or skin)

2.4 The full guidance statement can be found at http://www.iacom.org.uk/guidstate/documents/COM2012S2impuritiesfinal2012finalforinternetr.pdf

Human Health Significance of Chemical Induced Mutagenicity

2.5 The purpose of this introductory guidance was to provide information on chemically induced mutagenesis relevant to human health to the informed lay reader. It includes information on the role of mutagenesis in cancer, inherited genetic disease (and teratogenesis) and a glossary.

2.6 The full guidance statement can be found at http://www.iacom.org.uk/guidstate/documents/humanhealthsignificancefinal.pdf

Genotoxicity Assessment of Nanomaterials

2.7 The COM has previously advised on nanomaterials genotoxicity in 2005 as part of a joint review undertaken with the Committees on Toxicity and Carcinogenicity. The COM considered recent literature on the *in vitro* genotoxicity testing of nanomaterials outlining some discrepancies in *in vitro* data and the potential confounding factors when existing standard assays are used for the testing of nanomaterials.

2.8 The COM reached the following conclusions:

i) The standard protocols as used in genotoxicity testing of chemicals could not be directly applied to nanomaterials and that test conditions should be modified/optimised using a case-by-case approach. However each test would require physico-chemical characterisation of the nanomaterials in the test medium and direct evidence for uptake into cells. The most appropriate *in vitro* package was gene mutation in mammalian cells (*hprt* gene mutation assay) and the *in vitro* micronucleus test. Because nanomaterials may not penetrate bacterial cell walls and because of the inability of bacterial cells to phagocytose particles, bacterial gene mutation tests should not be used for nanomaterials.

ii) There was currently no convincing evidence that nanomaterials induce DNA-mediated genotoxic effects. There is evidence for oxidative DNA damage with many of the nanomaterials that have been tested for genotoxicity, and evidence that carbon nanotubes may induce aneuploidy by interaction with the mitotic spindle apparatus. There was a need for more investigations into possible modes of genotoxic action by nanomaterials.

iii) More information on nanomaterials' uptake and persistence in cells should be the priority for further research.

iv) At the present time, the limited available genotoxicity data on nanomaterials did not allow definitive conclusions to be reached. There remained considerable uncertainty regarding the nature of genotoxic hazards identified in the available

studies. These uncertainties do not permit a generic approach to hazard characterisation to be identified.

2.9 The full guidance statement can be found at http://www.iacom.org.uk/statements/documents/nanomaterialsfinal2012.pdf

Chlorophenols

2.10 The Food Standards Agency has asked for advice on the genotoxicity of chlorophenol compounds to assist in developing advice to consumers on the implications of the occurrence of chlorophenol contaminants in wine.

2.11 The COM reached the following conclusions:

i) The amount of data available for assessing the mutagenicity of chlorophenols is generally limited, with a particular paucity of *in vivo* genotoxicity data. The majority of tests, particularly for cytogenetic effects, were conducted to old protocols and the data have limitations. Chlorophenols can contain numerous impurities, including dioxins, which are carcinogenic but not genotoxic, though the occurrence of genotoxic impurities cannot be ruled out.

ii) The chlorophenols that have been tested did not cause mutations in bacterial cells.

iii) Clastogenic effects have been reported *in vitro* for a number of chlorophenols, particularly, the trichlorophenols, may have been due to the generation of free radicals from redox cycling of quinones and semi-quinones or auto-oxidation and may not be relevant *in vivo*, particularly at low levels of exposure.

iv) There was insufficient evidence to conclude on whether or not the clastogenicity was via a direct or indirect mechanism, and whether there was a threshold for any mode of action.

v) Although there is some limited evidence to suggest that trichlorophenols could be considered as a common mechanism group, overall the data on genotoxicity and mode of genotoxic action for chlorophenols did not allow conclusions on a common mechanism group to be drawn.

vi) There was insufficient information to establish whether the chloroanisoles would have the same genotoxic properties as the chlorophenols.

vii) Conclusions on individual compounds are presented in the statement.

2.12 The full statement can be found at http://www.iacom.org.uk/statements/documents/Chlorophenolsstatement2.pdf

Cell Transformation Assays for the Prediction of Carcinogens

2.13 The Committee on Carcinogenicity (COC) has asked the COM for a review of the current scientific progress regarding cell transformation assays for the prediction of

carcinogens. The COM considered cell transformation assays based on: Syrian hamster embryo (SHE) cells (at pH 6.7 or pH ≥ 7.0), and the mouse cell lines BALB/c 3T3, C3H10T1/2 and Bhas 42. The assessment of the SHE *in vitro* test system was previously considered by the COM in 1994 and 1996.

2.14 The COM reached the following conclusions:

i) The SHE CTAs as currently used do not discriminate between genotoxic and non-genotoxic carcinogens.

ii) The SHE cell transformation assay would be inappropriate for regulatory screening of chemicals such as pharmaceuticals and agrochemicals for potential carcinogenicity, and further that it should not be used in place of an *in vivo* rodent carcinogenicity study.

iv) The available evidence from the OECD DRP number 31 and ECVAM pre-validation reports are not sufficient to recommend routine regulatory use of the SHE CTAs (pH 6.7 and pH 7.0) and BALB/c 3T3.

v) Further prospective validation of these assays using a wider range of carcinogens and non-carcinogens is required.

vi) The available evidence from the published literature does not support the routine use of the Bhas42 CTA in a regulatory setting. There is a need for further validation data, the development of an agreed protocol and photo-catalogue for the evaluation of morphologically transformed foci.

vii) There is a need to invoke quality control procedures for assessment of subjective morphology assessments of transformed colonies or foci. The use of peer review procedures should be considered.

viii) There is a need for more research to understand the molecular mechanism(s) of cell transformation. The available information on senescence by-pass is promising but no definite conclusions can be reached regarding the CTAs considered in this statement.

ix) An important aspect of the validation of CTAs is the development of objective biological markers of cell transformation. The available information on gene markers and use of infrared spectroscopy is promising.

2.15 The full statement can be found at http://www.iacom.org.uk/statements/documents/COM12S4-CellTransformationAssayStatementfinalforinternet_000.pdf

Hormesis in Mutagenicity Dose-Response Relationships

2.16 The COM considered evidence for hormesis in mutagenicity dose-response relationships. The COM and COC had previously considered proposals on hormesis in 2003. The COM acknowledged that a hormetic effect may be possible

in genotoxicity, for example, via the induction of DNA repair at low doses. However, overall, the COM concluded that the data did not provide evidence for hormesis.

Genotoxic Consequences of Exposure to Mixtures of Food-Derived Chemical Carcinogens

2.17 The COM has previously expressed an interest in the evaluation of the mutagenicity of chemical mixtures. One important recommendation was to consider the possibility of mutagenic synergy and the implications of such a finding for risk assessment. The COM considered research funded by the Food Standards Agency (FSA) following a call for proposals *'to address the mixture effects of mixtures of genotoxic and non-genotoxic chemicals in food.'* As part of the external review process, the FSA sought the views of COM on the draft final report of the research project. This item was reserved business pending publication of the research

Horizon Scanning

2.18 The horizon scanning exercise provides information which can be used by Government Departments/Regulatory Agencies to identify important areas for future work. The horizon scanning exercise for 2011 was delayed due to full agendas until the March 2012 meeting and the 2012 horizon scanning exercise was undertaken in October 2012. Regarding progress on topics raised in the 2011 horizon scanning exercise, the COM was advised that a summary statement on photogenotoxicity and a review of swimming pool disinfection by-products were being taken forward.

2.19 The COM agreed that the main priorities in 2013 would be a review of the Pig-A assay and consideration of mutation spectra of genotoxic substances. The evaluation of the Comet assay by the Japanese Centre for the Validation of Alternative Methods was still considered to be important but of a lower priority while awaiting the outcome of a future review meeting on this topic in March 2013.

2.20 With regard to additional projects, the COM expressed an interest in topics associated with gene sequencing to understand the relation between mutation and cancer; human variability; environmental factors; and mutational changes in individual tumours. Also, a review of gene expression profiling of genotoxic and non-genotoxic carcinogens and consideration of alternative methods to the SHE assay were suggested. The COM also suggested a review of epigenetics and the role of genetic stability, however, it was noted that this was currently being reviewed by the COC. Another potential topic of interest related to the benchmark dose, *in vivo* genotoxic potency and the Margin of Exposure approach to genotoxicity risk assessment was suggested, however it was noted that this topic was currently being reviewed by the International Life Sciences Institute. The topics of human germ cell mutagenicity and germ cell testing were also suggested as future topics.

DECLARATION OF INTERESTS DURING THE PERIOD OF THIS REPORT

Member	Personal Interest		Non-Personal Interest	
	Company	**Interest**	**Company**	**Interest**
Prof P B Farmer (Chairman) (until 31.10.12)	Santander Foreign & Colonial Torotrak ILSI HESI EFSA	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 (until 31.03.2012)	Covance AstraZeneca Diageo HBOS Marks & Spencer	Consultant Shareholder Shareholder Shareholder Shareholder	NONE	NONE
Dr Stephen Dean (from 01.04.12)	WIL Research, Europe	Salary Employee Equity Holder	NONE	NONE
Dr B M Elliott	Syngenta AstraZeneca Elliott GT Ltd Regulatory Science Associates	Pension 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
Professor G Jenkins	NONE	NONE	Hoffman-LaRoche Unilever CEFIC/ECETOC	Research Grant 2008 – 2010 Consultancy 2008 Research Grant 2008 - 2010 Honorarium 2008
Professor D Kirkland Professor D Kirkland (continued)	Kirkland Consulting GSK 3i Standard Life Corning Covance	Principal Shareholder Shareholder Shareholder Shareholder Shareholder and share option holder	NONE	NONE

	ILSI HESI	Committee member		
Dr D P Lovell (Member until 31.10.12, then Chair from 1.11.12)	National Grid plc EFSA EFSA member ECVAM ESAC	Shareholder Member & Vice Chair Working Group on Threshold of Toxicological Concern Working Group on Genotoxicity Testing Strategies Working Group on Statistical Approaches (Member & Chair)	Member of various working Group Peer Review panels	
Dr A Lynch	GlaxoSmithKline	Salary Shareholder	NONE	NONE
Professor F Martin (from 01.04.2012)	Cable & Wireless	Shareholder	Unilever	Research Grant 2008 - present
Dr E M Parry (until 31.03.2012)	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 Takeda	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultant		

COMMITTEE ON THE 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/).

The COC held four meetings in 2012, because of the cancellation of the November 2011 meeting. During the year we were asked for advice by a number of Government departments or agencies. The Medicines and Healthcare Regulatory Agency (MHRA) asked whether the existing advice on the carcinogenic risks of polyurethane breast implants needed to alter in the light of a new review; the Food Standards Agency (FSA) sought advice on the possible carcinogenic hazard to consumers from insulin-like growth factor in the diet and we contined our consideration of the relative vulnerability of children to asbestos, at the request of the Department for Education. Also, we continued the review of our guidance on carcinogenic risk assessment and published two new guidance statements.

As always, I am grateful to members of the committee for the invaluable advice they have provided during the year and to the secretariat for their support. I look forward to working with them on more challenges in 2013.

Professor David H Phillips
BA PhD DSc FRCPath

COC Evaluations

COM review on cell transformation assays

3.1 At the horizon scanning discussion in January 2012, the COC suggested that there should be a consideration of cell transformation assays as an *in vitro* screen for carcinogenicity given the renewed interest in these assays and a recent report from the European Centre for the Validation of Alternative Methods. It was noted that cell transformation assays are formally within the remit of the COM and so it was referred to that committee. At its November 2012 meeting, the COC discussed the resultant COM statement.

3.2 The COC considered the difficulties in the methodology used in these assays. These included the length of time for the automated process to produce results, the problems with pH, and inconsistencies between protocols and the selectivity and sensitivity of different cell lines. The committee thanked the COM for its thorough review of the topic.

ILSI/HESI workshop on less-than-lifetime exposure to carcinogens.

3.3 In 2009, the COC had expressed an interest in the outcome of a workshop to be held by the International Life Sciences Institute Health and Environment Institute (ILSI/HESI), which aimed to develop a framework for assessing the risk from less-than-lifetime exposures to carcinogens. At its January 2012 meeting, the committee considered a published paper which presented the proposed framework ('A proposed framework for assessing risk from less-than-lifetime exposures to carcinogens' - Felter et al 2011, Critical Reviews in Toxicology volume 41, number 6, pp 507-544). The framework consists of a number of sequential questions laid out as a decision tree and the committee considered that the guidance would encourage case-by case judgements, rather than the application of a prescribed process. It was noted that the approach included a large number of general assumptions, and concerns were raised about the higher doses administered in studies with shorter dosing regimens and the possibility of secondary modes of action. It was considered that extrapolation from less-than-lifetime studies to assess longer-term exposure was likely to be over-precautionary. It was suggested that useful information might be obtained from human studies of patients treated for Hodgkin's disease and secondary cancers.

3.4 Overall, the COC considered that, as general guidance, the ILSI/HESI framework was informative but members expressed concern that the underlying approach was directed towards the US approach to cancer risk assessment, which estimates cancer risk by low-dose extrapolation of animal data, and which the COC does not endorse.

Polyurethane-coated breast implants

3.5 The COC considered the safety of polyurethane-coated breast implants in 1991 and 1994 when studies had shown that a degradation product of the polyurethane foam, 2,4-toluenediamine (2,4-TDA), should be regarded as a probable genotoxic carcinogen. At the time, the Medicines and Healthcare Products Regulatory

Agency (MHRA) had advised that the benefits of using these implants did not outweigh the small, unquantifiable carcinogenic risk. At the November meeting, the MHRA asked the COC to consider an updated review, produced by the Agency, of the relevant literature on the risks and benefits of these implants, and to consider whether the advice should be changed.

3.6 It was noted that old animal carcinogenicity data showed that 2,4-TDA was a potent carcinogen in both rats and mice at low doses and that the review had found few new studies of relevance. Localised, low-grade fibrosis may also be a concern as implants could be in place for 10 years or more. Members also commented on a Derived Minimal Effect Level (DMEL) for 2,4-TDA calculated in the report and expressed concern about uncertainty in the Physiologically Based Pharmacokinetic Modelling (PBPK) carried out.

3.7 In conclusion, it was agreed that the new information did not alter the Committee's position on these breast implants and it was recommended that the MHRA did not alter its advice on their carcinogenicity.

Horizon scanning

3.8 The COC undertakes "horizon scanning" exercises at regular intervals with the aim of identifying new and emerging issues which have the potential to impact on public health.

Due to the cancellation of the last meeting in 2011, the 2011 Horizon scanning exercise was undertaken in January 2012 and is reported here.

3.9 Two new topics were identified by the Secretariat at the 2011 exercise and these were considered by the Committee, together with those outstanding from the 2010 exercise. From these and items suggested by Members, the COC decided that the following items should be taken forward:

- Vitamin E and prostate cancer risk – considered to be high priority
- *In utero*/whole life exposure model of carcinogenesis – to be covered in the forthcoming new Guidance Statements
- Cell transformation assays as an *in vitro* screen for carcinogenesis – this was considered to be within the remit of the COM
- Exposure to environmental tobacco smoke and childhood cancer
- Mononuclear cell leukaemia in the Fischer 344 rat
- The use of Zebrafish in mechanistic studies

In the 2012 exercise a number of new topics were considered together with those outstanding. The following priorities were assigned:

High priority:

- Epigenetics and cancer
- Relevance of PPAR-α agonism to humans
- Alcohol attributable burden of cancer incidence
- Nanomaterials

Medium/high priority:

- In utero/'whole life' exposure models of carcinogenesis and Alternatives to the 2-year bioassay - these two items will be considered as part of the forthcoming new Guidance Statement G7 (Alternatives to the 2-year bioassay)
- Thresholds of genotoxicity – to take forward potentially as a topic of interest in a joint COT/COC/COM scanning meeting

Medium Priority

- Mode of action framework update
- Environmental tobacco smoke exposure in childhood and cancer risk
- Dose response modelling in epidemiology studies - this will be covered as part of the Guidance Statement G2 (Interpretation of Evidence of Carcinogenicity in Humans)

Low Priority

- Mechanistic studies in Zebrafish

Ongoing work

Relative Vulnerability of Children to Asbestos

3.10 Asbestos is a well known carcinogen that can cause both mesothelioma and lung cancer. Asbestos was used in the past in the building of homes, schools and other buildings and hence there is a potential for individuals to be exposed to asbestos from this historical use. An independent advisory group called the "Asbestos in Schools Steering Group" aims to promote effective management of asbestos in schools and to contribute to the development of guidance on such management. The group reports to the Department for Education (DfE). Following discussions in this Group, the DfE had asked the Department of Health for a study of the risk of asbestos to children and the Department had facilitated a DfE request for advice from the COC on the relative vulnerability of children to asbestos. In July 2011, COC members agreed an appropriate strategy to take forward a consideration of this issue.

3.11 During the meetings in 2012, the COC considered a number of papers which reviewed information relevant to this issue. These included a review of the epidemiological literature/case-studies on childhood exposure to asbestos and the risk of developing mesothelioma in later life; recent advice of the Health and Safety Executive's scientific advisory committee, the Working Group on Action to Control Chemicals (WATCH), on the risks from low-level exposure to asbestos in adults; and a review of the available animal data on the comparative differences between the effects of juvenile versus adult exposure to asbestos. A review of the levels of asbestos found in school buildings provided an exposure perspective to the discussions, as did a paper on the levels of asbestos found in residences, including houses and flats, which provided information on background levels of asbestos in

homes. At the July meeting, the Committee considered the differences between adults and children in terms of respiratory physiology, immunology and dosimetry. Members also considered a non-peer reviewed paper entitled "Effect of children's age and life expectation on mesothelioma risk", prepared by Robin Howie Associates, and submitted by Mr Lees of the Asbestos in Schools group.

3.12 During the year, the COC sought the view of two experts to aid its consideration. In July, it heard from a pediatric respiratory consultant, Professor Andrew Bush (Professor of Paediatric Respirology at Imperial College & Consultant Paediatric Chest Physician at the Royal Brompton & Harefield NHS Foundation Trust), working in the field of juvenile respiratory physiology, to aid the discussion of the differences between the respiratory system in adults and children. Professor Jonathan Grigg (Professor of Paediatric Respiratory and Environmental Medicine at Barts and the London School of Medicine, Queen Mary University of London) attended the November meeting to provide an insight on whether it was possible to extrapolate information on the effects of particulates in the juvenile lung to fibres. He presented some modelling data generated specifically for the Committee's assessment by Dr Robert Sturm (Division of Physics and Biophysics, University of Salzburg).

3.13 A first draft of a statement, based on the papers and the Committee's deliberations since July 2011, was considered in November. The final statement is expected to be agreed in 2013.

IGF-1: Possible carcinogenic hazard to consumers

3.14 Interleukin Growth Factor 1 (IGF-1) is a growth factor which has a variety of biological effects including the promotion of cell division and growth. It has been proposed that exposure to dietary IGF-1 could increase the risk of certain cancers. The COC is considering an extensive range of data which covers dietary absorption, levels of IGF-1in food and the association between blood levels of IGF-1 and the risk of certain types of cancer. The review is ongoing and it is hoped that it will be completed by the end of 2013.

Vitamin E and prostate cancer

3.15 In 2011, analysis of results from the selenium and vitamin E cancer prevention trial (SELECT), which investigated the chemoprotective effects of selenium and vitamin E, suggested that vitamin E supplementation in healthy men significantly increased the risk of prostate cancer; the results of this study contrasted with the findings of other authors, who have reported both a protective effect and no effect.

3.16 The Food Standards Agency has asked that the Committee review the information available on vitamin E and prostate cancer, including epidemiological, animal and *in vitro* studies on this topic. The review is ongoing and it is hoped it will be completed in 2013.

Guidance statements

3.17 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, which has several drawbacks. 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. 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.

3.18 During 2012, the COC completed the overarching statement G1: "A strategy for the risk assessment of chemical carcinogens". It also completed a statement on risk characterisation methods for carcinogens, which discusses the approaches that the committee recommends for the risk characterisation of non-threshold and threshold carcinogens. The guideline also discusses other approaches that are not endorsed by the COC, and gives the reasons why.

A guideline on the use of biomarkers in carcinogenic risk assessment was discussed and is expected to be published in 2013.

DECLARATION OF INTERESTS DURING (2012) THE PERIOD OF THIS REPORT

Member	**Personal Interest**		**Non-personal Interest**	
	Company	Interest	Company	Interest
Professor David H Phillips (Chairman)	Aviva Banco Santander BG Group Bradford & Bingley Centrica National Grid Takeda	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultancy		
Dr Carolyn Allen	None	None	None	None
Prof Alan Boobis OBE	Bank Santander Barclays Bank BG Group BT Group Centrica Iberdrola SA National Grid Lloyds Endura Fine Chemicals Astra Zeneca GlaxoSmithKline DuaneMorris Coca-Cola (from Oct 2012)	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultancies	Food Standards Agency Department of Health Health Protection Agency Medical Research Council European Chemical Industry Council – Long range Initiative Medical Research Council GlaxoSmith Kline ILSI, ILSI HESI & ILSI Europe Board of Trustees/	Research Contracts PhD studentship Trustee/Director (non-remunerated) (past Chair of HESI) Vice-

			Directors ILSI HESI Risk 21 project ILSI HESI, ILSI Europe & ILSI Research Foundation Working Groups on generic risk assessment issues. JMPR JECFA (vet drugs) EFSA CONTAM Panel (Panel on chemical contaminants in the food chain) EFSA PPR Panel Working Groups on Cumulative Assessment Groups for Pesticides; Risk Assessment of Pesticide Metabolites EFSA working group on Identification of Emerging Risks EFSA	president of ILSI Europe Co-Chair Member Chair/Member

			Scientific Committee Working Group on Threshold of Toxicogical Concern DG SANCO SCHER Working Group on Mixtures of Chemicals WHO IPCS Working Groups on Chemical Mixtures and on Mode of Action FP7 COSMOS Project Scientific Advisory Board of FP6/7 projects: PREDICT – IV ACROPOLIS and HEROIC Science Advisory Board, Swiss Centre for Applied Human Toxicology, Basel, Switzerland.	
Dr Phil Carthew	Unilever	Salary	None	None

Prof Peter B Farmer (to 31.10.12)	Santander Bradford & Bingley Foreign & Colonial Torotrak EFSA ILSI HESI	Shareholder Shareholder Shareholder Shareholder Member of Scientific Panel Committee Member	Van Geest Foundation	Research support
Mrs Rosie Glazebrook	BT Group Lloyds TSB National Grid	Shareholder Shareholder Shareholder	NONE	NONE
Dr Peter Greaves	Actelion Pharmaceuticals Ltd, Allschwil, Switzerland. Arena Pharmaceuticals, Inc., San Diego, California Astellas Pharma Europe Ltd Daiichi Sankyo, Edison, New Jersey Experimental Pathology Laboratories Inc., Sterling, Virginia GlaxoSmithKline, Ware Hyperion Therapeutics, Inc., San Francisco, California Johnson & Johnson Pharmaceutical Research & Development LLC, Raritan, New Jersey Novo Nordisk,A/S,	Consultant	EFSA ILSI	Member of Scientific Panel Committee Member

	Malov, Denmark Shire Pharmaceutical Development Ltd, Basingstoke, UK Sun Coast Tox Inc., San Diego, California. Biotie Therapies Inc., S. San Francisco			
Dr David Lovell	National Grid plc	Shareholder	AstraZeneca National Grid plc EFSA EFSA member ECVAM ESAC	Spouse shareholder Member & Vice Chair Working Group on Threshold of Toxicological Concern Working Group on Genotoxicity Testing Strategies Working Group on Statistical Approaches (Member & Chair) Member of various working Group Peer Review panels
Dr Brian G Miller	Iberdrola SA	Shareholder	None	None
Prof Julian Peto (from 1 April 2012)	None	None	None	None

Dr Christopher Powell	GlaxoSmithKline	Shareholder and salary	None	None
Dr Lesley Rushton (from 1 April 2012)	Friends Provident Northern Rock Epidemiological Advice relating to dermatitis study to Unilever. Epidemiological advice on study to Transport and General Workers Union Epidemiological review of occupational causes of malignant melanoma.	Share holder Shareholder Consultancy Consultancy Expert witness	CONCAWE (Conservation of Clean Air and Water Europe) CEFIC (European Chemistry Council) Other grants from UK government agencies & departments e.g. Food Standards Agency, Health & Safety Executive. ECETOC Scientific Committee	Research support Research support Research support External Committee member
Dr P Vineis (until 31 March 2012)	None	None	None	None
Dr Heather Wallace (from 1 April 2012)	Bank Santander SA BT Group	Shareholder Shareholder	None	None
Dr N Wallis	Pfizer Bristol Myers Squibb	Shareholder Salary	None	None
Dr Lindsay Wright (until 31 March 2012)	AstraZeneca	Salary and shareholder	None	None

ANNEX 1 - Terms of Reference

To advise at the request of:
Food Standards Agency
Public Health England
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 Conduct for members of the COC/COM/COT

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[5]

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 (see overleaf) set out by the Committee on Standards in Public Life[6];

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

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[7]

· 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.

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.

Currently located at: http://www.bis.gov.uk/assets/biscore/goscience/c/cop-scientific-advisorycommittees.pdf

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 nonspecific 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 [8] 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 nonpersonal*, 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.

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."*[9] 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[10] 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 Committee.
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 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[11] which gives any person legal rights of access to information which is held by a public authority.
3. The Committee has agreed to hold open meetings as standard practice. Interest groups, consumer organisations etc can attend (subject to the appropriate procedures for handling commercially sensitive information and research not in the public domain, paragraphs 9-15 refer).
4. The Committee appoints lay/public interest member(s) to help to increase public scrutiny of Committee business.
5. The Committee has agreed to the publication of agendas, draft and finalised minutes, discussion papers and statements on the internet.
6. Statements will summarise all the relevant data, such as information regarding potential hazards/risks for human health in respect of the use of products and chemicals, and any recommendations for further research.
7. The Committee will be asked for an opinion based on the data available at the time of consideration. It is recognised that, for many chemicals, the toxicological information is incomplete and that recommendations for further research to address these gaps may form part of the Committee's advice
8. The release of documents (papers, minutes and statements) where the Committee has agreed an opinion on the available unpublished data but where further additional information is required in order to finalise the Committee's conclusions, needs to be considered on a case-by case basis. The relevant considerations include 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.

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

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 2011/12 the budget for the COT, excluding Secretariat resources was £26,000.00. 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 £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.
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 in a year. COT members are expected to attend 7 meetings in a year. Members should allow appropriate preparation time. Meetings will usually be in London.
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 reappointed
at the end of their (3 year) term.

ANNEX 4 – Good Practice Agreement for Scientific Advisory Committees

INTRODUCTION

The Government Chief Scientific Adviser's *Guidelines on the Use of Scientific and Engineering Advice in Policy Making*[9] set out the basic principles which government departments should follow in assembling and using scientific advice. The key elements are to:

- **identify early** the issues which need scientific and engineering advice and where **public engagement** is appropriate;
- draw on a **wide range of expert advice** sources, particularly when there is uncertainty;
- adopt an **open and transparent approach** to the scientific advisory process and publish the evidence and analysis as soon as possible;
- **explain publicly the reasons for policy decisions**, particularly when the decision appears to be inconsistent with scientific advice; and
- **work collectively** to ensure a joined-up approach throughout government to integrating scientific and engineering evidence and advice into policy making.

The *Code of Practice for Scientific Advisory Committees*[10] and the *Principles of Scientific Advice to Government*[11] provide more detailed guidance on the operation of scientific advisory committees (SACs) and their relationship with their sponsor Departments.

The Food Standards Agency's Board adopted a **Science Checklist** in 2006 (updated in 2012) that makes explicit the points to be considered in the preparation of policy papers and proposals dealing with science-based issues, including those which draw on advice from the SACs.

These **Good Practice Guidelines** were drawn up in 2006 by the Chairs of the independent SACs that advise the FSA based on, and complementing, the Science Checklist. They were updated in 2012 in consultation with the General Advisory Committee on Science (GACS).

The Guidelines apply to the SACs that advise the FSA and for which the FSA is sole or lead sponsor Department:

- Advisory Committee on Animal Feedingstuffs
- Advisory Committee on Microbiological Safety of Foods
- Advisory Committee on Novel Foods and Processes
- Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment[12]

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9 http://www.bis.gov.uk/assets/bispartners/goscience/docs/g/10-669-gcsa-guidelines-scientific-engineering-advice-policy-making.pdf

10 http://www.bis.gov.uk/assets/BISPartners/GoScience/Docs/C/11-1382-code-of-practice-scientific-advisory-committees.pdf

11 http://www.bis.gov.uk/go-science/principles-of-scientific-advice-to-government

- Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment[4]
- Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment[13]
- Social Science Research Committee
- General Advisory Committee on Science

For the SACs with a shared sponsorship the Guidelines apply formally to their advice to the FSA; they may opt to follow them also in advising other sponsor Departments.

All these committees share important characteristics. They:

- are independent;
- work in an open and transparent way; and
- are concerned with risk assessment and/or science governance, not with decisions about risk management.

The Guidelines relate primarily to the risk assessment process since this is the main purpose of most of the SACs. However, the SACs may, where appropriate, comment on risks associated with different risk management options, highlight any wider issues raised by their assessment that they feel should be considered (distinguishing clearly between issues on which the SAC has an expert capability and remit, and any other issues), or any evidence gaps and/or needs for research or analysis.

In addition, GACS and SSRC may advise the FSA on aspects of the governance of risk management, or on research that relates to risk management.

Twenty nine 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.

The SACs have agreed to review their application of the principles annually and report this in their Annual Reports. Compliance with the Guidelines will also be covered in the annual self assessments by Members and annual feedback meetings between each SAC Chair and the FSA Chief Scientist.

[12] Joint FSA/HPA Secretariat, HPA lead
[13] Joint FSA/HPA, FSA lead

PRINCIPLES

Defining the problem and the approach

1. The FSA will ensure that issues it asks an SAC to address are clearly defined and take account of stakeholder expectations in discussion with the SAC Secretariat and where necessary the SAC Chair. The SAC Chair will refer back to the FSA if discussion suggests that further iteration and discussion of the task is necessary. Where an SAC proposes to initiate a piece of work the SAC Chair and Secretariat will discuss this with FSA to ensure the definition and rationale for the work and its expected use by the FSA are clear.

Seeking input

2. The Secretariat will ensure that stakeholders are consulted at appropriate points in the SAC's considerations. It will consider with the FSA whether and how stakeholder views need to be taken into account in helping to identify the issue and frame the question for the committee.
3. Wherever possible, SAC discussions should be held in public.
4. The scope of literature searches made on behalf of the SAC will be clearly set out.
5. Steps will be taken to ensure that all available and relevant scientific evidence is rigorously considered by the committee, including consulting external/additional scientific experts who may know of relevant unpublished or pre-publication data.
6. Data from stakeholders will be considered and weighted according to quality by the SAC.
7. Consideration by the Secretariat and the Chair (and where appropriate the whole SAC) will be given to whether expertise in other disciplines will be needed.
8. Consideration will be given by the Secretariat or by the SAC, in discussion with the FSA, as to whether other SACs need to be consulted.

Validation

9. Study design, methods of measurement and the way that analysis of data has been carried out will be assessed by the SAC.
10. Data will be assessed by the committee in accordance with the relevant principles of good practice, e.g. qualitative social science data will be assessed with reference to guidance from the Government's Chief Social Researcher[14].
11. Formal statistical analyses will be included wherever appropriate. To support this, each SAC will have access to advice on quantitative analysis and modelling as needed.
12. 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.

[14] Quality in Qualitative Evaluation: A Framework for assessing research evidence http://www.civilservice.gov.uk/wp-content/uploads/2011/09/a_quality_framework_tcm6-7314.pdf; The Magenta book http://www.hm-treasury.gov.uk/d/magenta_book_combined.pdf

13. The list of references will make it clear which references have been subject to external peer review, and which have been peer reviewed through evaluation by the Committee, and if relevant, any that have not been peer reviewed.

Uncertainty

14. When reporting outcomes, SACs 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.
15. Any assumptions made by the SAC will be clearly spelled out, and, in reviews, previous assumptions will be challenged.
16. Data gaps will be identified and their impact on uncertainty assessed by the SAC.
17. An indication will be given by the SAC about whether the evidence base is changing or static, and if appropriate, how developments in the evidence base might affect key assumptions and conclusions.

Drawing conclusions

18. The SAC will be broad-minded, acknowledging where conflicting views exist and considering whether alternative interpretations fit the same evidence.
19. Where both risks and benefits have been considered, the committee will address each with the same rigour, as far as possible; it will make clear the degree of rigour and uncertainty, and any important constraints, in reporting its conclusions.
20. SAC 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. If it is not possible to reach a consensus, a minority report may be appended to the main report, setting out the differences in interpretation and conclusions, and the reasons for these, and the names of those supporting the minority report.
21. The SAC'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.
22. SACs will make recommendations about general issues that may have relevance for other committees.

Communicating SACs' conclusions

23. Conclusions will be expressed by the SAC in clear, simple terms and use the minimum caveats consistent with accuracy.
24. It will be made clear by the SAC where assessments have been based on the work of other bodies and where the SAC has started afresh, and there will be a clear statement of how the current conclusions compare with previous assessments.
25. The conclusions will be supported by a statement about their robustness and the extent to which judgement has had to be used.
26. As standard practice, the SAC secretariat will publish a full set of references (including the data used as the basis for risk assessment and other SAC 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.

27. The amount of material withheld by the SAC 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.
28. Where proposals or papers being considered by the FSA Board rest on scientific evidence produced by a SAC, the Chair of the SAC (or a nominated expert member) will be invited to the table at the Open Board meetings at which the paper is discussed. To maintain appropriate separation of risk assessment and risk management processes, the role of the Chairs will be limited to providing an independent view and assurance on how their committee's advice has been reflected in the relevant policy proposals, and to answer Board Members' questions on the science. 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.
29. The SAC will seek (and FSA will provide) timely feedback on actions taken (or not taken) in response to the SAC's advice, and the rationale for these.

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 doseresponse 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 *nongenotoxic*
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.
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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.
LC50: The theoretical lethal concentration for 50% of a group of organisms
LD50: The dose of a toxic compound that causes death in 50% of a group of experimental animals to which it is administered. It can be used to assess the acute toxicity of a compound, but is being superseded by more refined methods.
Leukaemia: A group of neoplastic disorders (see tumour) affecting blood-forming elements in the bone marrow, characterised by uncontrolled proliferation and disordered differentiation or maturation. Examples include the lymphocytic leukaemia’s which develop from lymphoid cells and the myeloid leukaemia’s which are derived from myeloid cells (producing red blood cells, mainly in bone marrow).

Ligand: A molecule which binds to a receptor.
Lipids: Fats, substances containing a fatty acid and soluble in alcohols or ether, but insoluble in water.
Lipophilic: 'Lipid liking' - a substance which has a tendency to partition into fatty materials.
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 pretreated
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 protooncogene).
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 individualseven
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 subunits 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 selfdestruction 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 → carcinoma sequence in the large bowel in humans, and the papilloma → carcinoma sequence in mouse skin.
Tumour initiation: A term originally used to describe and explain observations made

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

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

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

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

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

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

Xenobiotic: A chemical foreign to the biologic system.

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

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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.++

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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[++]

2010 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Food Standards Agency/Department of Health, June 2011[++]

2011 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 2012

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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Peanut Allergy, Department of Health (1998)**

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Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment: Variability and Uncertainty in Toxicology of Chemicals in Food, Consumer Products and the Environment, FSA/1150/0307 (2007).++

Guidance on a Strategy for the Risk Assessment of Chemical Carcinogens. Department of Health (2004)+

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Available on the COM website at
http://www.iacom.org.uk/index.htm

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