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

Annual Report 2015

Contents

About the Committees

This is the twenty-fifth 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 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, and it is considered to be a conflict of interest, he or she may, at the Chairman's discretion be allowed to take part in the discussion, but is excluded from decision-making. Annex 1 contains the terms of reference under which the Committees were set up. The Code of Conduct is at Annex 2 and Annex 3 describes the Committees' policy on openness. Annex 4 is 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 listed at Annex 7.

These three Committees also provide expert advice to other advisory committees, such as the Scientific Advisory Committee on Nutrition, and there are links with the General Advisory Committee on Science, Veterinary Products Committee and the Expert Committee on Pesticides (formerly the Advisory Committee on Pesticides – ACP).

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: https://www.gov.uk/government/groups/committee-on-carcinogenicity-of-chemicals-in-food-consumer-products-and-the-environment-coc
COM: https://www.gov.uk/government/organisations/committee-on-mutagenicity-of-chemicals-in-food-consumer-products-and-the-environment

This report contains summaries of the discussions and links to the Committees' published statements. Paper copies are available upon request to the Secretariats.

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 2015. The COT assesses chemicals for their potential to harm human health. Evaluations are carried out at the request of the Food Standards Agency, Department of Health, Public Health England, and other Government Departments and Regulatory Authorities, and are published on the Internet as statements or shorter position papers. Details of membership, agendas and minutes are also published on the Internet.

During 2015, the Committee held six meetings. The committee reviewed the risks to infants and young children from a variety of contaminants, based on new information on exposure. These include hexabromocyclododecanes, plybrominated biphenyls, lead and aluminium. Work on HBCDDs and PBBs was completed during the year, and statements were published on these topics. Work on lead and aluminium will be completed in 2016.

The Committee considered a series of systematic reviews on the role of the infant diet and the development of atopic and autoimmune disease. This work is ongoing and will be completed in 2016, with the publication of a number of statements and the full reports, once the reviews have been accepted for publication.

The Committee completed its consideration of the risks from potassium-based for sodium chloride. A combined sub-group has been established with the SACN to underetake a risk-benfit assessment, to ensure the advice provide adequatelyu reflects both the positive and negative consequences of replacement of sodium salt with potassium salt. The Committee completed its consideration of the possible effects of soya on thyroid function in subjects with hypothyroidism and has prepared a statement on its conclusions. The COT provided comments to the EFSA on its draft opinions on the analysis and expression of uncertainty and on the safety of caffeine.

A number of submissions were received from the the Home Office Centre for Applied Science and Technology (CAST) regarding new formulations of novinamide (PAVA) and CS spray. These were dicussed as reserved business due to the confidential nature of some of the information received.

The Committee discussed several scientific areas of potential relevance, including the microbiome, toxicokinetics following weight change and emerging non-animal methods for toxicity testing. A watching brief will be kept on these topics for developments relevant to the work of the committee.

2015 was my first year as chair of the committee. In fact, I took over in April 2015. I would like to thank all members and the secretariat for their support and hard work over this period and for making my task as chair an enjoyable and rewarding experience.

Professor A Boobis (Chairman)
OBE PhD CBiol FRSB FBTS

COT evaluations

EFSA consultation on a draft scientific opinion on the safety of caffeine

1.1 The European Food Safety Authority (EFSA) issued a Draft Scientific Opinion on the safety of caffeine for public consultation on 15 January 2015[1]. The COT response is available as paper TOX/2015/13 at http://cot.food.gov.uk/sites/default/files/2015-13%20Caffeine%20response%20for%20EFSA%20%28for%20information%29.pdf.

Hexabromocyclododecanes in the infant diet

1.2 The Scientific Advisory Committee on Nutrition (SACN) is reviewing the scientific evidence that bears on the Government's dietary recommendations for infants and young children. The Committee on Toxicity (COT) was asked to review the risks of toxicity from chemicals in the infant diet. This statement focuses on possible risks from hexabromocyclododecanes (HBCDDS).

1.3 Technical mixtures of HBCDDs have been widely used as flame retardants incorporated in polymers and textiles, construction materials, furniture, and electrical equipment. By international agreement, the use of HBCDDs for all but construction purposes was banned in 2014. However HBCDDs are environmentally persistent, and exposures will continue to occur following the ban.

1.4 Infants can be exposed to HBCDDs through their presence in breast milk as well as other foods and domestic dust.

1.5 HBCDDs cause toxic effects on the liver, thyroid hormones, and reproductive and nervous systems in experimental animals. Only limited data are available from studies of HBCDDs in human populations, and they do not allow a meaningful assessment of risks at the levels to which we are exposed through food.

1.6 The available toxicological data are insufficient to establish health-based guidance values for HBCDDs, and the COT concluded that it was more appropriate to consider the ratios between the highest doses that had been found not to cause adverse effects in animal studies and the estimated exposures of infants. Such ratios are known as "margins of exposure", and their interpretation should take into account uncertainties in the toxicological database, in the extrapolation from animals to humans, and in the estimation of exposure.

1.7 Overall the analysis indicated that estimated exposures via breast milk and food are not a cause for concern, but that high levels found in some samples of domestic dust are of potential concern. No data are available on potential

[1] http://www.efsa.europa.eu/en/consultations/call/150115.htm

exposures in the UK from infant formula, commercially produced infant foods or drinking water.

1.8 Given that most uses of HBCDDs are being phased out, and that the main source of exposure to residual environmental HBCDDs is ingested domestic dust, the priority is for continued monitoring of levels of HBCDDs in dust to ensure that they are declining as expected. It would also be useful to measure levels in infant formula and commercially produced infant foods, but this is of lower priority.

1.9 The full COT statement can be found at: https://admin.food.gov.uk/sites/default/files/HBCDDsstatementfinal.pdf

Lead ammunition group final report

1.10 The Lead Ammunition Group (LAG) is an independent body which was established in 2010 to advise the FSA and Defra on the risks to wildlife and to human health of spent lead ammunition. The COT has commented on the human health aspects of the final LAG report but as this has report has not yet been published, the COT's comments remain reserved.

1.11 Current FSA advice, issued in 2012, states that regular consumers of lead shot game should reduce their consumption and that this is particularly important for vulnerable groups such as infants and young children, and pregnant women and women trying for a baby as lead exposure can harm the developing brain and nervous system.

Nonivamide (PAVA) and 2-chlorobenzylidene malononitrile (CS) formulation as irritant sprays

1.12 The COT previously reviewed the safety-in-use of irritant sprays containing pelargonyl vanillylamide (nonivamide, or PAVA) or 2-chlorobenzylidene malononitrile (CS) in various solvents (in 1998, 1999, 2005 and 2013), and considered combined exposure to PAVA and sprays in 2006. The Home Office Centre for Applied Science and Technology (CAST) had received submissions for the reformulation of both PAVA and CS using a new non-flammable solvent. The COT was asked for its advice. This item was taken as reserved business as it contained commercially-sensitive information.

2-Chlorobenzylidene malononitrile (CS) formulation as an irritant spray

1.13 The Home Office Centre for Applied Science and Technology (CAST) had received a further submission for the reformulation of CS using a new non-flammable solvent, trioctyl phosphate. The COT was asked for advice. This item

was taken as reserved business as it contained commercially-sensitive information.

Polybrominated biphenyls (PBBs) in the diet of infants

1.14 The Committee on Toxicity (COT) was asked to review the risks of toxicity from chemicals in the infant diet. This statement focuses on potential risks from polybrominated biphenyls (PBBs). None of the Government's current dietary recommendations for infants and young children relates to PBBs.

1.15 PBBs are a class of brominated chemicals that were previously used as flame retardants in the production of synthetic fibres and polymers. The chemical structure of PBBs incorporates two linked phenyl rings, to which bromine atoms are attached in varying numbers and positions making up 209 possible different molecules, known as congeners. The PBB molecules can rotate around the linkage between the rings, resulting in a planar or non-planar conformation. In the planar conformation they have a structure and activity similar to those of dioxins, and hence they are also known as dioxin-like PBBs.

1.16 Production and use of PBBs has been increasingly restricted throughout the world over the past four decades. However exposures still occur due to the material being widely distributed in the environment and foods. Although there are EU regulations limiting or preventing the use of PBBs, there are no regulations specifically limiting the levels in foods arising from contamination.

1.17 The COT concluded that separate approaches should be adopted for the risk assessment of the planar and non-planar PBBs. Exposure to the planar, dioxin-like PBBs should be assessed by comparison with the tolerable daily intake (TDI) for dioxin-like compounds. For the non-planar PBBs, the data on liver carcinogenicity could be used as a basis for risk assessment. However there would be considerable uncertainties in this approach due to the questionable human relevance of the effect and because the technical mixture tested was not representative of the profiles of PBBs to which people are exposed from foodstuffs.

1.18 Even so, a meaningful risk assessment could not be performed for the PBBs, because the exposure of infants could not be estimated due to the lack of adequate data on levels of different PBBs in food and the environment in the UK.

1.19 Further research on the toxicity of PBBs is not a high priority since their use is now restricted. However the Committee considers that it would be useful to obtain more data on levels of PBBs in foods in the UK although exposures are likely to decrease further over time.

1.20 The full COT statement on PBBs in the infant diet can be found at:

http://cot.food.gov.uk/sites/default/files/pbbstatementfinal.pdf

Polybrominated biphenyls (PBBs) in the diet of infants and 1 to 5 year old children

1.21 The COT also considered a review of PBBs in the diet of 1-5 year old children that included up-dated exposures for infants.

1.22 In considering any potential risks to 1-5 year old children, and the up-dated exposures of infants, the COT confirmed that different approaches should be taken when assessing the potential risks from planar or non-planar PBBs as agreed when previously assessing the infant only exposures.

1.23 The COT reviewed the available estimates of exposures to PBBs in infants (0 to 12 months) and young children (1 to 5 years) from the diet and the environment.

1.24 The only relevant occurrence data available for planar PBBs related to their presence in food (excluding breast milk or infant formula). The 97.5th percentile upper bound exposures to planar PBBs were up to 0.21 pg WHO-TEQ/kg bw/day in the diet of 4 to 12 month olds, and up to 0.13 pg WHO-TEQ/kg bw/day in the diet of 1 to 5 year olds. These upper bound exposures represent less than 10.5% of the TDI in 4 to 12 month olds, and less than 6.5% in 1 to 5 year olds. Because of the large number of data below the LOD, the upper bound approach overestimates actual exposure, and because extrapolating the TEFs assigned to PCB congeners to the corresponding PBB is conservative, actual exposures relative to the TDI could be very much lower.

1.25 The COT reviewed estimated exposure to non-planar PBBs from food and breast milk; no relevant occurrence data were available for infant formula. The 97.5th percentile upper bound exposures to non-planar PBBs were up to 1620 pg/kg bw/day in the diet of 4 to 12 month olds, and up to 1544 pg/kg bw/day in the diet of 1 to 5 year olds. Overall, 97.5th percentile upper bound exposures to non-planar PBBs from the diet (excluding breast milk) resulted in margins of exposure (MOEs) greater than 92,600 for 4 to 12 month olds, and MOEs greater than 97,200 for 1 to 5 year olds.

1.26 Exposures via breast milk had been assessed as exposures in exclusively breastfed 0 to 6 month olds, and exposures in ‘non-exclusively’ breastfed 4 to 18 month olds, based on the highest reported concentration of PBBs in breast milk sampled in the UK. In exclusively breastfed 0 to 6 month olds, high level exposures to non-planar PBBs were up to 4391 pg/kg bw/day. In ‘non-exclusively’ breastfed infants, 97.5th percentile exposures were up to 3440 pg/kg bw/day in 4 to 12 month olds, and up to 1620 pg/kg bw/day in 12 to 18 month olds. Overall, the high level exposures to non-planar PBBs in exclusively breastfed 0 to 6 month olds resulted in MOEs greater than 43,600, and the 97.5th percentile exposures in

'non-exclusively' breastfed 4 to 12 month olds and 12 to 18 month olds resulted in MOEs that were greater than 43,600 and 93,000 respectively.

1.27 The occurrence data for non-planar PBBs in dust (obtained from a study in South Africa) resulted in 95th percentile exposure estimates of up to 159 pg/kg bw/day in 9 to 12 month olds, and up to 144 pg/kg bw/day in 1 to 5 year olds. These exposures resulted in an MOE of 943,000 for infants aged 9 to 12 months and of MOEs greater than 1,040,000 for 1 to 5 year olds. Relevant occurrence data were not available for other non-dietary sources of exposure (i.e. air or soil).

1.28 Members confirmed that extrapolating the TEFs assigned to PCB congeners to the corresponding PBB congeners was a conservative approach. In addition, Members noted that the use of the NOAEL derived from the NTP carcinogenicity study to calculate the MOEs for non-planar PBBs was not inappropriate as the critical endpoint for the study was considered to have a threshold as it had occurred by a non-genotoxic mode of action (calculation of a benchmark dose would be the more usual approach to carcinogens with a genotoxic mode of action).

1.29 Regarding the lack of occurrence data for PBBs in water, Members stated that PBBs would not be expected to be present at significant levels, as based on the behaviour of similar compounds it was likely that they would bind to sediment.

1.30 Members agreed that the approach taken in the provisional risk assessment was conservative, due in part to the upper bound approach that was taken with the large number of data that were below the LOD.

1.31 In the Committee's previous review of PBBs, the Committee had concluded that the available carcinogenicity data for non-planar PBBs was of questionable relevance to humans, and that the technical mixture that was tested in the NTP carcinogenicity study was not representative of the profiles of PBBs to which people are exposed in the environment and foodstuffs, and that this introduced further uncertainty.

1.32 Taking into account all of the uncertainties surrounding the exposure estimates, exposures to PBBs relative to to the TDI for dioxin-like compounds were minor, and the large margins of exposure in the assessment of non-planar PBBs did not indicate a cause for concern.

1.33 The Committee confirmed that there were still insufficient occurrence data to be able to complete a meaningful risk assessment, and that, as there were no new data available, it would not be worthwhile preparing a statement or an addendum to the existing statement on infant exposures.

Skin sensitisation from exposure to pesticides - follow-up on the recommendations of the Bystander Risk Assessment Working Group (BRAWG) report

1.34 In 2012, the COT and the Advisory Committee on Pesticides (ACP) published the report of a joint Bystander Risk Assessment Working Group (BRAWG) on methods used in regulatory assessments of potential health risks to residents and bystanders from the application of pesticides. The BRAWG report noted a concern that some individuals might become sensitised to pesticides and recommended that, as risk factors for dermal sensitisation were not well understood, further consideration was needed to justify the default assumptions used when characterising and quantifying the potential of pesticide formulations to induce skin sensitisation in humans. This matter was considered by the COT in 2014.

1.35 The COT had discussed the current methods used to determine whether a chemical was a skin sensitiser, and particularly considered the local lymph node assay (LLNA), which was now the test required by European Union regulations to assess the skin sensitisation potential of pesticide active substances and formulations. An invited expert had been present at the meeting in 2014, who had agreed to subsequently provide the COT with a number of relevant papers. These papers covered the validation of the LLNA, comparison of potency in the LLNA with human data, the collection of a database of human skin sensitisers, and the impact of vehicle on the results of the LLNA. The COT had also asked for information from the Health and Safety Executive's (HSE) Chemicals Regulation Directorate (CRD) on whether there had been any documented cases of skin sensitisation in operators caused by pesticide products that were not labelled as sensitisers, or skin sensitisation in bystanders, residents or non-professional pesticide users. The submitted papers and the information from CRD, including information from two reporting schemes on pesticide exposure monitoring in the UK, were now available.

1.36 The Committee agreed that the key factors to consider were whether there was evidence that following dilution of a skin sensitiser by 1/100 in would no longer cause skin sensitisation and/or whether there was sufficient evidence from surveillance programmes that the risk was low or minimal.

1.37 The Committee noted that Basketter et al. (Contact Dermatitis 53, 260-7; 2005) had observed a linear relationship between results in the LLNA and human skin sensitisation data, albeit with some variability. However, while this was adequate for the chemicals considered, these did not include any pesticides. The COT agreed that there was no specific evidence to demonstrate that a dilution factor of 100 was adequate to ensure that a skin sensitiser would no longer have a sensitising effect.

1.38 The data provided by the CRD on the results of pesticide exposure monitoring schemes provided very little evidence of sensitisation in people exposed to pesticides. The Committee was relatively reassured by this, although mild cases would be expected to be more common than severe cases and these would be less likely to be picked up by the schemes.

1.39 The data from the CRD included reports of effects on skin in workers following exposure to the relatively new active substance pinoxaden, which was a potent sensitiser in the LLNA and a skin irritant, though it was not clear whether these effects were due to sensitisation or irritation. There was also a report from the NPIS programme of wheeze, facial swelling and swelling of the throat, though no skin reactions, in a group of cadets who had crawled through a field that had been treated with pinoxaden. The level of exposure would have been high relative to that in most bystanders and residents. Members considered that the possibility of more intensive, targeted monitoring of pinoxaden should be considered.

1.40 Overall, the Committee agreed that there was no specific evidence demonstrating that following dilution of a skin sensitiser by 1/100 it would no longer cause skin sensitisation, but it was reassured by the absence of reports from available pesticide exposure monitoring schemes.

1.41 The Committee recommended further and expanded monitoring for skin sensitisation, particularly of new pesticide active substances suspected of causing sensitisation.

Soya consumption and thyroid status

1.42 The Committee considered unpublished results from three FSA funded research projects to assess: a) the effect of soya phytoestrogen supplementation on thyroid status and cardiovascular risk markers in patients with subclinical hypothyroidism; b) the effects of soya in men with type 2 diabetes and subclinical hypogonadism (three months treatment)[2]; and c) the effects of soya in women within two years of the onset of the menopause (six months treatment)[3]. This was combined with a review of all the evidence which had become available since 2003 COT report on phytoestrogens and health[4] , concerning potential effects of phytoestrogens on thyroid function.

[2] The effect of soya protein with and without isoflavones in men with type 2 diabetes and subclinical hypogonadism – A randomized double blind parallel study. University of Hull.
[3] Soya protein with isoflavones reduce bone turnover markers in women during their early menopause – A randomised double blind placebo controlled parallel study. University of Hull.
[4] http://cot.food.gov.uk/cotreports/cotwgreports/phytoestrogensandhealthcot

1.43 The Committee noted that whilst not entirely consistent, results from the first two parts of the project in patients with subclinical hypothyroidism both pointed to effects. The results indicate that soya protein alone does not have an effect on thyroid function in patients with sub-clinical hypothyroidism. Thus, any effects observed in the study appear to have depended on the exposure to isoflavones. Although levels remained within the normal range, the consistency of the changes in thyroid hormone levels that followed consumption of soya protein containing phytoestrogens, both in women within 2 years after the onset of menopause, and in men with type II diabetes and subclinical hypogonadism, supported the possibility of adverse effects on thyroid function from soya ingestion in people with subclinical or overt hypothyroidism.

1.44 Since the 2003 COT report, several human studies have provided new data concerning the impact of soya consumption on thyroid function. Some of these investigations suggest that there could be clinically relevant effects in people with treated or sub-clinical hypothyroidism, but the evidence is not entirely consistent.

1.45 There are no indications that high intakes of soya impact materially on thyroid function in people in whom thyroid function is not already impaired. However, the evidence that is now available, although not entirely consistent, suggests that higher intake of soya phytoestrogens, either in food or in dietary supplements, may sometimes precipitate a transition to overt hypothyroidism in people with subclinical, compensated hypothyroidism, and may also affect the dose of thyroxine that is needed in patients who are on treatment for hypothyroidism.

1.46 This should not have major clinical implications. However, endocrinologists should be made aware of the possibility that consumption of soya phytoestrogens (including in dietary supplements) may affect thyroid function and response to treatment with thyroxine.

1.47 In view of the persisting uncertainties, there should be continued monitoring of the scientific literature on this topic. However, since any clinical implications are unlikely to be of major importance, further research in this area need not be a priority for future funding by the Food Standards Agency

The Committee agreed a statement which can be found at https://admin.food.gov.uk/sites/default/files/soyathyroidstatementfinal.pdf

Committee procedures

EFSA Consultation on a draft guidance document on uncertainty in scientific assessment

1.48 EFSA issued a Draft Guidance Document on Uncertainty in Scientific Assessment on 18 June 2015[5]. The COT submitted a response to the consultation and agreed to revisit the topic to consider whether there should be any changes to how the COT expresses uncertainty once the EFSA guidance had been finalised and experience had been obtained from its application by the Panels. The response is available as paper TOX/2015/26 at http://cot.food.gov.uk/sites/default/files/TOX2015-26%20EFSA%20uncertainty%20guidance_0.pdf

Horizon Scanning

1.49 At their February 2015 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. Members noted the list of agenda items that were planned or underway for 2015, and discussed several other topics that might also be considered.

Consultations of the European Food Safety Authority (EFSA)

1.50 Members noted that a number of new EFSA opinions/reports were expected during the next year, and would be brought to the attention of the Committee if they were relevant to the work of the FSA and COT.

Update on Tox21 and ToxCast

1.51 A brief overview of recent developments in these American initiatives was presented. Members were asked for their thoughts on the topics, which they had considered in previous years. The Committee noted the major challenges faced by the Tox21 project. In particular, there had been poor progress in the integration of metabolism with *in vitro* assays.

1.52 The Committee supported the objective of ToxCast to prioritise substances for *in vivo* testing, which otherwise would not be tested. The Committee indicated that it would welcome a presentation on progress in this area in due course, although it was not considered a priority in the short term.

Modelling kinetics

[5] http://www.efsa.europa.eu/en/consultations/call/150618

1.53 New publications had become available stemming from a European-wide cooperative initiative on physiologically-based toxicokinetic modelling. The Committee agreed that it would be useful to keep abreast of developments in this area, particularly as it might be asked in the future to advise on risk assesments using such models.

Human Biomonitoring in the UK and Europe

1.54 Members were informed that PHE would be updating the Committee in May 2015 on the progress of projects in this area. It would be helpful to establish the extent and scope of biomonitoring studies that were currently on-going in the UK, and it was agreed that a useful way forward would be to conduct a literature search looking for publications from such studies, and to contact funders who might be supporting research using biomonitoring. In addition, biomonitoring was carried out as part of routine health surveillance for some occupational hazards (e.g. in workers exposed to lead). Members were invited to send information on ongoing biomonitoring work, potential funders who could be contacted and an appropriate focus for the literature review.

The microbiome

1.55 The Committee agreed that it would be helpful to have a presentation on emerging evidence concerning the effect of an individual's microbiome on susceptibility to chemical toxicity.

Synthetic Biology and the implications of the discipline for the work of COT in its toxicological assessments.

1.56 Members noted that synthetic biology was an importantant emerging area of research and development, but concluded that it did not have special implications for the toxiocological risk assessments carried out by the COT, and therefore was not a high priority for more detailed discussion at this stage.

Other potential future topics

1.57 Members discussed their approach to assessing risks from mixtures of congeners (e.g. in flame retardants) which was carried out on a case-by-case basis. Opportunities for extrapolating from one congener to others that might be present in a mixture were mentioned as a possible way of improving assessments, but this would depend on the availability of data. It was noted that while data on the toxicity of individual congeners that occurred in food and the environment were often sparse, understanding of the differing pharmacological effects of stereochemical isomers in medicines tended to be better because there was more knowledge about anticipated molecular targets.

1.58 The approach taken by the EFSA to the assessment of enantiomeric mixtures in pesticides might provide useful insights. In addition, it would be helpful to review the published literature on the toxicity of congeners alone and in combination. Members agreed to propose terms for inclusion in a literature search for that purpose.

1.59 Exposure to chemicals other than nicotine (e.g. additives and flavourings) from electronic-cigarettes (e-cigarettes) was identified as another possible area for future discussion. Exposure to chemicals from this source would also be relevant to bystanders, and it would probably be necessary to consider the role of nano-particles. PHE agreed to update the Committee on developments in this area in due course.

Balance of expertise on the Committee

1.60 It was agreed that the following types of specialist expertise are required by the Committee for some or all of its evaluations:

Analytical techniques	Biochemistry
Bioinformatics	Biomonitoring
Cell biology	Clinical practice
Dietary exposure assessment	Endocrinology
Environmental exposure assessment	Epidemiology
Human toxicology	Immunology
Mathematical Modelling	Mechanistic toxicology
Molecular biology	Neurotoxicology
Nutrition	Occupational health epidemiology
Paediatrics	Pharmacokinetics
Pharmacology	Probabilistic modelling
Reproductive toxicology	Respiratory toxicology
Risk assessment	Statistical aspects of experimental design
Statistics	Systems biology
Toxicogenomics	Toxicological pathology
Xenobiotic metabolism	

1.61 It would not be necessary to have an individual member for each listed expertise as some people would have a combination of the required skills. Additional key experts are also invited to attend meetings for specific topics to supplement missing expertise.

Presentation on the microbiome

1.62 Prof. Tim Gant of PHE gave a presentation about the microbiome, in response to the COT request during the discussion of horizon scanning at the February 2015

meeting. Prof. Gant had been exploring the emerging toxicity issue of the effect of an individual's microbiome on chemical toxicity on behalf of the Health and Environmental Sciences Institute (ILSI HESI), and the presentation was based on work presented at the International Human Microbiome Consortium meeting that took place in March 2015.

1.63 The presentation provided background information about the microbiome using the gut microbiome as an exemplar and how a variety of genetic and environmental factors (e.g. age, diet, ethnicity and disease state) can alter it. The presentation also gave some examples of how the microbiome might impact toxicological responses, and discussed how the aforementioned genetic and environmental factors could result in altered susceptibility to chemicals via the microbiome. Members were asked to comment on the subject and discuss whether the microbiome was a topic that the Committee should consider further.

1.64 Members recognised that while there was a plethora of observational data available regarding the impact of certain genetic and environmental factors on the microbiome, there was currently a paucity of data on the functional consequences of these effects. Members noted that there were significant differences between human and animal microbiomes, and that these differences could impact on the way *in vivo* toxicology studies were interpreted during future risk assessments.

1.65 Members discussed the overall stability of the microbiome, and considered the potential impact that various changes to an individual's environment (e.g. treatment with antibiotics or cohabitation with a partner) could have on the microbiome and thus their response to future chemical exposures. Members also discussed the rate at which such environmental changes could begin to impact the microbiome (e.g. how soon after cohabitation began would the microbiome adapt), and the length of time for which they might impact it (e.g. how long does it take for the microbiome to recover after dietary-induced change).

1.66 Members also noted that a key point when considering changes to the microbiome, and the impact of these changes on toxicological responses, was not the change in the diversity of the microbiome but rather the change in its overall function. It was possible that while one microbe may replace another, they may have the same biological capabilities and output, and therefore the change may have no impact on toxicological response.

1.67 Overall, Members considered the microbiome to be of potential toxicological relevance and would like to consider further information on the microbiome and the impact of genetic and environmental factors such as ethnicity, diet and disease state in the future, once the functional consequences of these factors were better understood.

Working Groups and workshops

COT/COC Subgroup on synthesising epidemiological evidence

1.68 The COT and COC set up a subgroup to review the approaches to synthesising epidemiological evidence that are used by the Committees in chemical risk assessments and to make recommendations for COT/COC guidance. The terms of reference are to provide guidance that can be used by expert advisory committees for synthesis of epidemiological evidence, to review recent practice by expert advisory committees for synthesis of epidemiological evidence, with a focus on systematic reviews, to identify key points of current best practice methodologies used in systematic review and meta-analysis, and to identify and make recommendations for areas requiring further work. Further information on the subgroup can be found at: http://cot.food.gov.uk/cotwg/cot-coc-epi-sub-group

COT/SACN Subgroup on potassium

1.69 The COT and SACN set up a subgroup to prepare integrated risk benefit advice on potassium replacements for sodium chloride and sodium based additives. Further information on the sub group can be found at:

http://cot.food.gov.uk/cotwg/joint-sacn/cot-potassium-based-sodium-replacers-working-group

Toxicokinetics (TK) workshop

1.70 The COT held a symposium on the 18th March 2015 to discuss the effects of obesity on toxicokinetics (TK). The aim had been to provide a basis for interpreting FSA-funded research on biomonitoring of persistent organic pollutants (POPs) in obese subjects, and to consider more generic implications for the risk assessment process.

1.71 Following the workshop, the COT agreed a summary:

The aim of the first discussion was to consider the tissue distribution data of POPs measured in obese and non-obese patients in a FSA research project. The FSA was seeking discussion on available options and to determine the optimum modelling solution for analysis of this data set. Some of the key points from these discussions were:

- Different modelling options, such as PBPK (physiologically based pharmacokinetics) or simpler models, available for data analyses. Discussion was also had around the modelling that may be used for the analysis of the different subsets of data in this study.

- There are currently follow-up data from five individuals which have shown substantial heterogeneity in the results and there was discussion around how representative these results would be. Samples from four additional individuals were awaiting analysis.

- The need to consider other POPs/chemicals because dioxins are a historical problem whereas levels of other POPs, for example, brominated flame retardants (BFRs) have increased in recent years.

- There is added value of comparing data in this study to other data concerning POPs, obese individuals and POP levels in tissues. There are also reviews on the influence of bariatric surgery on certain pharmaceuticals which may provide useful information for POPs.

- Discussion around whether anything could have been done differently and whether further studies should be considered.

- Current models do not predict the initial results. Possible factors that could explain this were discussed including CYP1A2 binding. There are a number of physiologic changes that take place subsequent to bariatric surgery and/or weight loss which could impact the kinetics of dioxins/POPs. Certain medications (lipid lowering drugs and statins) could play a role in disturbing the kinetics of these chemicals. It was highlighted that the data was likely to be congener specific.

1.72 Insufficient data had been presented at the symposium to consider building TK models. It was considered that compared to pharmaceutical drugs, for environmental chemicals there was usually a lack of good TK data which can be used in modelling. The US had made a substantial investment into the development of non-animal methods and had started to utilise a bottom-up *in vitro* and *in silico* approach, in which TK extrapolation plays a key role. It was noted that the COT should keep a watching brief on this topic.

Ongoing work

Developmental toxicity and the uncertainty factor for interspecies extrapolation

1.75 The Committee had considered papers on this topic in 2013 and 2014. It had concluded that there were strong indications that the 10-fold uncertainty factor for interspecies variation in developmental toxicity was not always adequate, and having considered data on effects other than in utero toxicity, extended this conclusion to non-developmental outcomes also. The Committee had agreed that

a paper should be written for publication in a peer-reviewed journal. A short COT statement could then be produced, based on the paper.

1.76 A manuscript had been drafted focussing on developmental toxicity. An external reviewer had subsequently provided comments on the draft manuscript.

1.77 The original aim of the paper had been to identify the frequency of cases in which the 10-fold uncertainty factor would not be adequate. The Committee concluded that an alternative approach should be taken of starting from the position that the 10-fold uncertainty factor was not adequate for thalidomide and then assessing the strength of evidence that there were other chemicals for which it was also inadequate. Thus the approach taken so far could be presented as a screening exercise to identify candidate chemicals. This would then be followed by more in-depth critical evaluation for those chemicals, including by an epidemiologist and a toxicologist independent of the work so far, assessing the quality of evidence that they were developmental toxicants and their relative potency in humans and laboratory animals.

1.78 The Committee debated how broad the definition of developmental toxicity should be, and agreed that it should not be restricted only to teratogenicity but should be limited to effects of in utero exposure that were manifest at birth.

1.79 Overall the Committee agreed that it was worth pursuing publication of a paper in the peer-reviewed literature, and requested that a toxicologist and an epidemiologist should be sought as collaborators to evaluate the data critically for the identified candidate chemicals and the draft manuscript revised.

Histamine in cheese

1.80 Histamine (scombrotoxin) poisoning is a well-established phenomenon arising from consumption of foods most notably scombroid fish, such as fresh tuna and anchovies and fermented fish products, which have become contaminated with the biogenic amine histamine as a result of bacterial spoilage. Although the concerns about histamine toxicity initially related to fish, biogenic amines such as histamine also occur in fermented products such as cheese or sausage with the FSA having received a number of incident reports related to excess levels of histamine in cheese over the last few years.

1.81 The symptoms of scombrotoxin (histamine) poisoning include flushing, headache, nausea, itching, rash, palpitations and altered blood pressure.

1.82 The histamine levels in scombroid fish and fermented fish products are controlled by legislation which specifies the maximum concentration(s) of histamine that can occur in batches of fish. However, the histamine levels in other foods are not covered by any specific legislation.

1.83 In the absence of specific legislation, the FSA gives advice on histamine incidents on a pragmatic basis, taking into account a number of factors. These include the likely exposure (concentration of histamine and quantity consumed), and the specific population group concerned, with advice reflecting previous experience related to incidents in fish, and the results of volunteer studies of histamine. In 2011, EFSA set a reference dose of 50 mg/meal for biogenic amines; this has also been incorporated into the FSA advice.

1.84 The COT commented on the EFSA opinion and the current FSA approach to incidents involving histamine in cheese but requested additional data on routine monitoring of histamine and the possible supply chain for cheese. The Secretariat are in discussion with the relevant stakeholders and hope to provide additional information to the COT in early 2016.

Infant diet and the development of atopic and autoimmune disease: Hydrolysed formula and risk of allergic or autoimmune outcomes: a systematic review and meta-analysis

1.85 The FSA had commissioned Imperial Consultants to conduct a systematic literature review of the published scientific evidence available on infant formulae containing hydrolysed cows' milk protein and their ability to reduce the risk of infants and young children developing atopic or autoimmune disease.

1.86 The main purpose of this review was to investigate the role of hydrolysed cows' milk formula feeding in place of either standard cows' milk formula or breast milk on a child's future risk of developing atopic or autoimmune disease. Allergic outcomes of interest were asthma, eczema, allergic rhinitis, allergic conjunctivitis, allergic sensitisation and total IgE; autoimmune outcomes of interest were type I diabetes mellitus, coeliac disease, inflammatory bowel disease, autoimmune thyroid disease (Grave's disease, or Hashimoto's thyroiditis), juvenile rheumatoid arthritis, vitiligo or psoriasis.

1.87 A statement will be finalised in 2016 following publication of this review in the peer-reviewed literature.

Potassium-based replacement for sodium chloride and sodium based additives

1.88 The COT have been asked by SACN to advise on the potential effects of increased potassium intakes in vulnerable groups. This is in support of a SACN review of the use of potassium-based replacements for sodium chloride and sodium-based additives as part of the Government's overall salt reduction strategy. Currently, the use of potassium-based replacements for sodium salts is not recommended since it has been considered preferable gradually to reduce salt

levels in food products to allow the palates of consumers to become accustomed to lower salt levels. In addition, increasing potassium levels in food might have adverse effects in some vulnerable groups including very young children, the elderly and individuals with kidney disease, all of whom might be at risk of hyperkalaemia due to immature or impaired kidney function, particularly since many individuals with impaired kidney function may not have been diagnosed. However, industry has asked the Department of Health to reconsider this view, as there are a number of foods for which further reformulation to reduce sodium levels is not possible, particularly where the sodium is present for functional as well as taste purposes (such as in raising agents and preservatives).

1.89 The COT have completed their review of the potential adverse effects of increased levels of potassium and a statement has been finalised. SACN have also completed their consideration of the potential benefits of increased potassium intakes. A COT/SACN sub-group has been formed to prepare integrated risk benefit advice on potassium. Once this work has been completed, all the relevant statements will be published at the same time.

Review of risk arising from the infant diet and the development of atopic and autoimmune disease

1.90 The COT have been asked by SACN to provide advice on risks arising from the diet that are related to the development of atopic and autoimmune disease, in support of a review SACN are undertaking on UK Government recommendations on complementary and young child feeding practices.

1.91 Four separate systematic reviews of the available, published, scientific literature have been commissioned by the FSA:

- Systematic review A will explore the evidence relating to milk feeding and the child's future risk of developing atopic or autoimmune disease
- Systematic review B will explore the evidence concerning the timing of introduction of allergenic foods into the infant diet during the first year of life
- Systematic review C will explore the evidence concerning the avoidance or exposure to specific dietary patterns, food groups or nutrients during infancy, pregnancy and lactation
- Systematic review D will explore the evidence concerning infant formulae containing protein hydrolysates and risk of developing atopic or autoimmune disease

1.92 The reviews will be completed in 2016.

Toxicity of chemicals in the infant diet and the diet of young children aged 1 to 5 years

1.93 The COT has been asked to consider aspects of the toxicity of chemicals in the infant diet and the diet of young children aged 1 to 5 years, in support of the SACN review of Government recommendations on complementary and young child feeding. The SACN's review was being conducted in two stages; focussing first on advice for the feeding of infants aged 0 to 12 months, and then on advice for young children aged 1 to 5 years.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. Between 2012 and 2015 statements had been produced for a number of chemicals in relation to the infant diet. Reviews of certain chemicals in the diet of 1 to 5 year old children and updated exposures for infants aged 0 to 12 months had commenced in 2015.

Addendum to the 2013 COT statement on potential risks from aluminium in the infant diet

1.94 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.The aim of this addendum is to provide an overview of the potential risks from levels of aluminium in the diet of young children aged 1 to 5 years. Since new occurrence data had become available since the statement produced in 2013 (**http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2013/aluminium**), updated exposure assessments for infants had been provided in addition to exposure assessments for young children aged 1 to 5 years.The addendum is to be completed and published in 2016.

Addendum to the 2013 COT statement on potential risks from lead in the infant diet

1.95 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.The aim of this addendum is to provide an overview of the potential risks from levels of lead in the diet of young children aged 1-5 years. Since new occurrence data had become available since the statement produced in 2013 (http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2013/lead), updated exposure assessments for infants had been provided in addition to exposure assessments for young children aged 1 to 5 years. The addendum is to be completed and published in 2016.

2015 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

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Professor of Biochemical Pharmacology and Director of the Toxicology Unit (supported by Public Health England and the Department of Health) in the Faculty of Medicine at Imperial College London

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Declaration of members interests during the period of this report

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Personal Interest		**Non Personal Interest**
Employee Imperial College London, Department of Medicine **Shareholder** Bank Santander Barclays Bank BG Group BT Group Centrica Iberdrola SA National Grid Lloyds **Membership** ILSI & ILSI HESI Board of Trustees ILSI Europe Board of Directors Science Advisory Board of Swiss Centre for Applied Human Toxicology Dept. of Health Committee on the Medical Effects of Air Pollutants ”		**Grants** GSK/MRC CASE PhD studentship CEFIC/LRI Horizon 2020 EUROMIX **Membership** WHO/FAO JMPR WHO/FAO JECFA (vet) WHO TobReg WG10 TC126 (Intense Machine-smoking Regime for Testing Cigarettes) EUROTOX British Pharmacological Society British Toxicology Society Society of Toxicology (USA) SAB of Innovative Medicines Initiative “Drug-Induced Liver Injury”

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Membership/affiliation ILSI Food Allergy Task Force: Chair		
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Consultant University of Canberra University of Florida Quintiles		**Trustee** Medical Research Scotland Melville Trust Scottish Lifesciense Association
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Consultancy Kind Abdulaziz University (Saudi Arabia)		
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Consultancies and Direct Employment Simcyp Xenotech GSK Pfizer		**Support by Industry** GSK Pfizer Lilly Servier
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		Misc Xenobiotica - Associate Editor Frontiers in Predictive Toxicology – Editorial Board British Toxicology Society – Secretary of Education sub-committee
Professor Robert Smith		

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None		None

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Personal Interest		**Non Personal Interest**
None		None

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		Current and recent research funding None

COMMITTEE ON MUTAGENICITY 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 Mutagenicity (COM) during 2015.

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.

The COM also advises on important general principles and new scientific discoveries associated with the assessment of mutagenic risk and makes recommendations on mutagenicity testing. The membership of the Committee, agendas and minutes of meetings, and statements are all published on the internet https://www.gov.uk/government/organisations/committee-on-mutagenicity-of-chemicals-in-food-consumer-products-and-the-environment

During 2015, the COM published a statement on the mutagenicity of alcohol (ethanol) and its metabolite acetaldehyde which provided an update on information published on the topic between 2000- 2014 together with a paper on the potential role of oxidative damage as a mechanism of the genotoxicity of alcohol. This work was carried out to support the Committee on Carcinogenicity (COC)'s review of alcohol-induced carcinogenicity.

The COM considered whether there was evidence for a threshold for mutagenicity for Chromium VI and commented, at the request of the COC, on potential genotoxicity issues associated with the novel food ingredient cycloastragenol.

The COM carried out its annual Horizon scanning exercise, identifying a number of potential topics for future work, and as a part of this, had a presentation and discussion of the present status of 3D tissue models. The Committee also considered scoping papers on the potential effect of age on mutation rate and the evidence for transgenerational effects.

Throughout 2015 the COM continued to take an active interest by commenting on the reviews of the OECD (Organisation for Economic Cooperation and Development) Guidelines for Genotoxicity Testing. The COM also underwent a triennial review of its role and activities undertaken for the Department of Health and provided input into the Public Health England (PHE) review.

I am again grateful for the support of the secretariat and the Imperial College Toxicology Unit funded by PHE, who maintained their usual high standard of work despite the difficulties they experienced through staff shortages and reorganizations and to the members of the committee for their expert advice and support throughout the year.

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

COM Evaluations

Statement on the use of mutation spectra in genetic toxicology: MUT/2015/S1

2.1 The term 'mutation spectra' (MS) refers to the composite of the number, types and sites of all mutations observed in a given sequence. It is also more loosely used in referring to the number and types of mutation found or even the main type of mutation observed (e.g. GC to AT transitions).

2.2 The COM reviewed a selection of papers considered to be a representative cross-section of studies examining mutational fingerprints and hotspots for mutation following carcinogen exposure in 2014. From these evaluations and discussions, a statement was generated and is available: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/500831/COM_statement_on_mutation_spectra.pdf

Review of the mutagenicity of alcohol

Statement on the mutagenicity of alcohol (ethanol) and its metabolite acetaldehyde: update on information published between 2000-2014 (MUT/2015/S2)

2.3 The COM considered an updated review of the mutagenicity of alcohol and its primary metabolite acetaldehyde following a request from COC to support its on-going review of alcohol induced carcinogenicity in 2014. This review provided insight to COC regarding possible mechanisms of cancer causally associated with the consumption of alcoholic drinks.

2.4 A statement summarising these papers and the discussions, including those pertaining to the potential oxidative mechanisms, was published and is available MUT/2015/S2

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/490582/COM_2015_S2_Alcohol_and_Mutagenicity_Statement.pdf

The potential role of oxidative damage in alcohol's mutagenic and carcinogenic mode of action

2.5 As part of the review of the mutagenicity of alcohol, the potential role of oxidative damage in alcohol's mutagenic and carcinogenic mode of action was considered. The COM agreed that the hypothesis that alcohol-induced oxidative stress could be important in alcohol induced liver disease and carcinogenesis was plausible. Reactive oxygen species generated from oxidative metabolism or inflammatory processes could give rise to lipid peroxidation products, which may lead to subsequent mutagenic adducts. Alcohol-induced mechanisms that could lead to

the oxidative damage to DNA, include the generation of reactive oxygen species and induction of CYP2E1.

2.6 The COM noted that ethanol consumption can result in the induction of CYP2E1, primarily in the liver, but also in other tissues, such as the oesophagus and intestine. It was agreed that it was plausible that the induction of CYP2E1 enhanced the metabolism of alcohol to acetaldehyde; the generation of reactive oxygen species; and adduct formation. A correlation between CYP2E1 levels and DNA etheno adducts had been demonstrated in animal models and humans. It was noted that an association between CYP2E1 polymorphisms and alcoholic liver disease/alcohol induced carcinogenesis was not well defined and appeared to be weak.

2.7 Overall, the COM concluded that oxidative damage to DNA was a plausible mode of action for the genotoxic and carcinogenic potential of alcohol and its metabolite acetaldehyde, but that further evidence was required to substantiate the hypothesis.

Chromium VI

2.8 The Environment Agency asked Public Health England whether a paper published by Thompson et al., 2013 (Journal of Applied Toxicology. 34(5): 525-36) and associated work by that group had demonstrated a threshold for the genotoxicity of Chromium (VI) following oral exposure. This paper contends that the mode of action (MOA) for intestinal neoplasms following oral exposure to Cr(VI) involves cytotoxicity and not mutagenicity. Therefore a threshold for carcinogenicity is claimed, and that it is appropriate to derive an oral reference dose (RfD/TDI) from intestinal tumour data. This is contrary to the current UK position that assumes the mutagenic potential of Cr(VI) via oral exposure and therefore, that there is no threshold for its carcinogenicity. Members were asked for their opinion on the evidence for a threshold for the mutagenicity of Cr (VI) following oral exposure.

2.9 The COM considered a number of studies that contributed to the evaluation of the MOA of Cr (VI) induced intestinal neoplasms and overviews of available data relating to the genotoxicity of Cr (VI), including summaries from the European Food Safety Authority (EFSA 2014) and the US Agency for Toxic Substances and Disease Registry (ATSDR 2012). Members noted that there were two separate questions that could be considered. One was whether data provided by Thompson et al., and O'Brien et al., 2013 (Mutation Research. 754: 15 -21) demonstrated a threshold for the mutagenicity of Cr(VI) via oral exposure and the other was whether there was a potential threshold due to the conversion of Cr (VI) to the non-mutagenic Cr (III) in the gastrointestinal tract.

2.10 A number of practical or methodological aspects of the studies used to substantiate the claim for a cytotoxic MOA were examined. The selection of K-

Ras as the most sensitive marker for mutagenicity was queried, and it was suggested that other key mutated genes and K-*Ras* in other tissues (i.e. the small intestine) could be investigated. It was agreed that a key weakness of the investigation was the lack of a suitable positive control, one that could be anticipated to act via the same mechanism (e.g. a direct acting alkylating agent). Furthermore, it was noted that it would be difficult to detect an induced mutagenic effect as the reported background frequency of K-*Ras* mutation was very high. Members were not convinced that the dose related increase in micronuclei in the duodenal villi was solely due to cytotoxicity. It was felt that the use of the paraffin sections as described had insufficient sensitivity for identifying micronuclei.

2.11 The COM was not convinced by the arguments presented in the paper which claimed there were no correlations between K-*Ras* mutations and Cr-DNA binding and that this did not represent pre-mutagenic DNA damage. It was agreed that the authors had not sufficiently negated concern for potential mutation following Cr-DNA binding.

2.12 Overall the COM agreed that whilst the hypothesis was plausible, there were limited data to demonstrate a threshold for genotoxicity for Cr (VI) and was not convinced that there was a clear negative result for genotoxicity at low doses.

Germ cell mutagenesis

2.13 A paper on germ cell mutagenicity testing was considered by the committee in 2013 and it had concluded that further validation work was needed before newly developed germ cell assays could be incorporated into general genotoxicity testing. During the horizon scanning exercise in June 2015, the COM considered a recent suggestion that there is a need to investigate and advise on the existence and implications of human germ cell mutagens in a manner similar to that undertaken by IARC for human carcinogens. In addition, it was noted that the advent of high throughput sequencing methodologies has enabled substantially more detailed analyses of human genome mutations; for example how an increasing rate of *de novo* mutation associated with increasing paternal age can give rise to disease in offspring.

2.14 The COM considered a paper outlining methods for investigating germ cell mutagenesis, the germ cell genome, meiosis and mutagenesis, the paternal age effect and aneuploidy in germ cells with a view to stimulating discussion on chemically induced germ cell mutagenesis. It was noted that it is not known whether unique germ cell mutagens exist (i.e. chemicals that are germ cell mutagens but not somatic cell mutagens). This was mainly due to the underutilisation of the currently accepted tests for assessing germ cell mutagenicity and a lack of investigations examining the possibility. Differences between mitosis and meiosis meant that it was therefore possible that some

chemicals may only be mutagenic in germ cells and this raises some uncertainty over the relevance of somatic cell test endpoints to germ cells.

2.15 The COM noted that DNA damage in germ cells can be associated with spontaneous abortions, infertility or heritable damage in the offspring/subsequent generations. Methotrexate was given as an example of a pharmaceutical, which can cause teratogenicity through an indirect genotoxic mode of action.

2.16 There had been recent papers developing the concept of air pollution being a possible human germ cell mutagen. It was suggested that the COM could investigate this further, although it was noted that measurement of exposure to air pollution can be complex.

2.17 A Health Protection Agency 2013 report (prepared by a sub-group of the Advisory Group on ionising Radiation) on transgenerational effects in human populations exposed to radiation (primarily as a result of radiotherapy) was considered as a possible protocol/proof of principle that could be adopted to address chemical induced germ cell mutagenesis. It considered transgenerational effects that were not due to the inheritance of a conventional DNA mutation or mutations arising in the next generation due to the transmission of damaged DNA through sperm (e.g. epigenetic effects). Members acknowledged that there is some evidence for transgenerational effects in mice, but limited evidence in humans. Members discussed possible mechanisms which could account for the species differences. It was noted that, if embryos with significant chromosome damage were mainly aborted, as may be the case in humans, then adverse effects may occur mainly in terms of impaired fertility or early pregnancy loss rather than as adverse effects in offspring.

2.18 Overall, the committee agreed that this would be an interesting topic to investigate further and that future work could be separated into three key themes: i) test methods to identify hazard to germ cells ii) germ cell mutagenesis and ageing and iii) transgenerational effects.

Evaluation of cycloastragenol

2.19 Cycloastragenol is a novel compound extracted from the root of *Astragalus membranaceus* and intended for use in food supplements. It is reported in the scientific literature that cycloastragenol increases the activity of the enzyme telomerase and thus reduces the number of critically short telomeres but it does not increase mean telomere length. This finding has been reported both in mouse embryonic fibroblasts *in vitro* and in five different types of tissue in mice supplemented with cycloastragenol, as well as in the lymphocytes of human volunteers supplemented with cycloastragenol.

2.20 Following concerns that the available data was not robust enough to demonstrate the safety of cycloastragenol in relation to its carcinogenic potential, cycloastragenol was referred to the Committee on the Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) by the Advisory Committee on Novel Foods and Processes (ACNFP) and subsequently the COM.

2.21 Cycloastragenol was submitted to the ACNFP for authorisation as a novel food. The submitted data indicated that cycloastragenol has low oral bioavailability and is metabolised to a number of oxidised and hydroxylated compounds. A number of genotoxicity studies were also submitted that were considered by the manufacturers to be either equivocal or negative. Although some information on carcinogenicity was supplied, no standard carcinogenicity studies were submitted. The ACNFP had noted that there was a suggestion of a non-statistically significant increase in liver cancer incidence in treated mice in a study by Bernardes de Jesus *et al*., 2011 which was cited by the applicant. However, the study was limited by small numbers and a relatively short duration of exposure as well as having a relatively high background rate of tumours. This prevented any clear conclusions being drawn from the study. Given, the available data and the reported effects on telomeres, the ACNFP requested advice from the COC.

2.22 The COC concluded that the available data were inadequate to demonstrate a lack of carcinogenic potential and that a bioassay or other comparable further work might be needed, although the precise requirements for such work were uncertain given the reported mechanism of the compound. Although the manufacturers considered that the results of the supplied genotoxicity data were either equivocal or negative, the COC requested the COM's view on whether the conducted genotoxicity studies were appropriate to demonstrate a lack of genotoxic potential. The COC were particularly concerned over the *in vitro* chromosome aberration study, which indicated an increase in aberrations at one dose level. A number of suggestions were made for further work regarding genotoxicity that could be conducted. The COC advised that the COM should be consulted regarding potential genotoxicity.

2.23 The COM considered the genotoxicity data that had been submitted and whether the package provided was appropriate given the reported effects of cycloastragenol on telomeres and telomerase

2.24 <u>The COM conclusions</u>

- The genotoxicity data submitted for cycloastragenol gave a valid negative result in the Ames test. The findings of the *in vitro* chromosome aberration test results in V79 Chinese hamster cells were equivocal, but this is likely to be an artefact due to cytotoxicity and did not indicate mutagenic potential in this assay.

- The results of the available *in vitro* tests indicated that only one *in vivo* genotoxicity study would be required. The *in vivo* erythrocyte micronucleus test in mice via intraperitoneal administration gave a negative result and there were no concerns over this negative *in vivo* test result with regard to the design and conduct of the study.

- Overall, the genotoxicity tests conducted on cycloastragenol do not indicate *in vivo* mutagenic potential.

- The transformed cells used in the chromosome aberration assay (Chinese hamster V79 cells) are sensitive to genotoxicity and already have disrupted telomeres, making it more likely that chromosome aberrations would be produced. Cycloastragenol produced a negative result in this assay, but a chromosome aberration test conducted in non-transformed human cells may have been more relevant biologically.

- The potential concern regarding cycloastragenol does not arise from the genotoxicity test results, but from the suggestion of an increase in liver tumours. Therefore, the mode of action in the target tissue could be investigated further. This could be done by an *in vivo* Comet or micronucleus study in the liver to investigate a possible genotoxic mode of action or by studies investigating evidence for a non-genotoxic mode of action for liver tumours.

2.24 Subsequently, an expert on telomere biology was consulted following a recommendation by the COM. The expert in telomere biology was concerned over cycloastragenol if it did what was claimed in the literature, because it could remove a key block on the progression of damaged/ageing cells to malignant cells. This meant that individuals consuming a product containing cycloastragenol could be at an increased risk of cancer, particularly following long-term consumption. The expert on telomere biology also noted that rodent carcinogenicity bioassays would not be biologically representative of humans due to key differences between rodent and human telomere biology. Therefore, rodent carcinogenicity tests would not be informative in assessing the carcinogenicity potential of cycloastragenol in humans.

Horizon Scanning

2.25 The COM undertakes an annual ‘Horizon Scanning’ exercise, which provides an opportunity for Members and assessors from Government Departments/Agencies to discuss and suggest topics for further work. [A formal horizon scanning exercise was not carried out in 2014]. Members considered brief outlines of topics recently reviewed (cell transformation assays; mutation spectra); topics still under consideration and topics proposed for consideration (e.g. gene expression profiling; integration of *in vivo* genotoxicity assays in repeat dose toxicity testing; quantification of genotoxic response; epigenetics and mutations; and 3D tissue models).

2.26 Members noted that integrating genotoxicity testing into repeat dose studies was increasingly becoming standard practice (e.g. including micronucleus assays in toxicity tests) in order to comply with the 3Rs principles and therefore a review was not considered urgent. It was noted that a paper would soon be published on quantitative approaches to genotoxicity which would inform the Committee on this topic. Members were aware of studies investigating mitochondrial DNA mutations; much of the information was on the impact of mutations on health effects (e.g. neurodegenerative diseases, heart conditions, epilepsy and diabetes etc.) and there was only limited data on associations between environmental chemical exposure and mitochondrial mutations. The Committee agreed to keep a watching brief on this topic. Age related germ cell mutagenesis and its impact on disease in off-spring were also considered to be topics of interest.

Presentation on 3D models

2.27 Following discussion at the Horizon scanning exercise, a Member offered to update COM on recent developments in 3D models for genotoxicity. 3D models for genotoxicity have mainly been developed for the skin (e.g. 3D reconstructed skin micronucleus (MN) assay and the 3D reconstructed skin comet assay). The main drivers for the use of such 3D models was the Cosmetics Directive preventing the use of *in vivo* testing for cosmetics and the 3Rs principle requiring the reduction in the use of animal toxicity testing.

2.28 The presentation described recent developments in 3D assays. There are different types of models, ranging from single cell microtissues to multi cell types grown within scaffolds. It is hoped the use of such models will reduce the number of misleading positives and improve the accuracy of predictions. Most of the available data relates to skin models, which have the additional advantage of allowing topical application, more realistic metabolism, and use of a skin barrier. Other endpoints can also be evaluated, such as irritation. The genotoxicity 3D models allow both micronuclei and comet assessments. There is on-going international validation of 3D MN and comet assays. For the 3D reconstructed MN assay, the first phase of evaluation involved optimisation of the protocol, which has been completed. The second phase involved inter- and intra-laboratory reproducibility with 5 coded chemicals, which has also been completed. Phase 3, pre-validation, with 38 coded chemicals was underway.

2.29 Development and evaluation of the 3D comet genotoxicity test has lagged behind that of the MN 3D test and shows relatively poor sensitivity. It was suggested that in terms of regulatory testing of cosmetics, a tiered approach to genotoxicity testing could be used (including the use of the Ames test, *in vitro* mammalian cells and a 3D skin MN/comet).

2.30 Advantages of 3D genotoxicity models include the fact that a greater frequency of micronuclei can be produced than in 2D models (which could be due to a greater

cytochrome P450 enzyme expression) and that they have the potential to assess nano-material genotoxicity via dermal exposure. Current disadvantages of 3D models are that they are relatively expensive; require expertise to conduct; and are at early stages of development requiring further work and validation.

2.31 Members noted that it was likely the 3D MN model would be considered by an IWGT working group in 2017. Overall, the COM noted that progress had been made in the area of 3D genotoxicity models and would follow the developments with interest and provide any comment when necessary.

OECD genotoxicty test guidelines update.

2.32 The Committee continue to be updated and comment on, the review of old test guidelines (TGs) and the development of new TG's. The Committee also commented on the Guidance Document on Revisions to OECD Genetic Toxicology Test Guidelines.

Guidance statements

Statement 2015/S1 – Statement on the use of mutation spectra in genetic toxicology.

Statement 2015/S2 - Statement on the mutagenicity of alcohol (ethanol) and its metabolite acetaldehyde: update on information published between 2000 – 2014

Declaration of members interests during the period of this report

Member	Personal Interest		Non-Personal Interest	
	Company	**Interest**	**Company**	**Interest**
Dr D P Lovell (Chairman)	National Grid plc Pfizer ECVAM ESAC ILSI HESI OECD	Shareholder Pension Scheme Member Member of various Working Group/ Peer Review panels Committee member Consultant	AstraZeneca National Grid plc	Spouse Shareholder Spouse Shareholder
Dr Carol Beevers	Covance LabCorp ILSI HESI	Salary Pension Employee Equity Holder Committee Member	None	None
Dr G Clare	Covance AstraZeneca Diageo Marks & Spencer Shell Research Ltd AstraZeneca	Consultant Shareholder Shareholder Shareholder Pension Deferred Pension	None	none
Dr Stephen Dean	WIL Research, Europe	Salary Employee Equity Holder	None	None
Dr B M Elliott	Syngenta Syngenta AstraZeneca Elliott GT Ltd Regulatory Science Associates	Pension Shareholder Shareholder Director Associate	None	None

Member	Personal Interest		Non-Personal Interest	
	Company	**Interest**	**Company**	**Interest**
P Hardwick	Unilever plc	Pension	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	Kirkland Consulting GSK Corning Saga ILSI HESI ECVAM/ESAC	Principal Shareholder Shareholder Shareholder Steering Committee member and Workgroup leader Member of peer-review panel	None	None
Dr A Lynch	GlaxoSmithKline	Salary Shareholder	None	None
Professor F Martin	Cable & Wireless	Shareholder		
Dr M O'Donovan	O'Donovan GT Consulting Ltd	Director	None	None
Professor D H Phillips	Aviva Banco Santander BG Group Centrica National Grid Takeda Pannone Solicitors	Shareholder Shareholder Shareholder Shareholder Shareholder Consultant Consultant		
Professor M J Rennie	None	None	None	None

Member	Personal Interest		Non-Personal Interest	
	Company	**Interest**	**Company**	**Interest**
Professor S H Doak	None	None	Astra Zeneca Unilever Hoffman-LaRoche Unilever	PhD studentship grants 2009-2016 PhD studentship grants 2010-2017 Research Grant 2008 – 2010 Research Grant 2008 - 2010

COMMITTEE ON THE CARCINOGENCITY 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 (https://www.gov.uk/government/groups/committee-on-carcinogenicity-of-chemicals-in-food-consumer-products-and-the-environment-coc).

The COC held three meetings in 2015. The major item of work this year was the ongoing review of the risk of cancer from consuming alcohol. The statement on this was finalised at the end of the year and published very early in 2016. The year also saw the publication of our statement on Vitamin E and the risk of prostate cancer which we have been considering for some time.

2015 saw a referral from the Advisory Committee on Novel Foods and Processes for advice on the novel food ingredient cycloastragenol. The COC reviewed the carcinogenicity data and advised further referral to the COM for consideration of the mutagenicity data.

There was also continued discussion of the guidance statement series, with publication of the statement on hazard identification and characterization. There will be further statements published in 2016.

As 2015 was my last full year as Chair, I wish to extend my gratitude to all the members of the committee I have worked with for the invaluable advice they have provided and to the secretariat for its support. I wish my successor all the best for the future.

Professor David H Phillips
BA PhD DSc FRCPath

COC Evaluations

Statement CC/2015/S1 – Statement on vitamin E and the risk of prostate cancer.

3.1 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.

3.2 The Food Standards Agency asked the Committee to review the information available on vitamin E and prostate cancer, including epidemiological, animal and in vitro studies on this topic as well as to peer-review the SELECT study. The Committee highlighted a number of shortcomings in the SELECT trial and these are outlined in their statement which was published in 2015. This can be found here: https://www.gov.uk/government/publications/vitamin-e-and-the-risk-of-prostate-cancer

Cycloastragenol

3.3 Cycloastragenol is a novel compound extracted from the root of plants of the genus *Astralagus* (including *Astralagus membranaceus*) and intended for use in food supplements. It is reported in the scientific literature that cycloastragenol increases the activity of the enzyme telomerase and thus reduces the number of critically short telomeres but it does not increase mean telomere length. This finding has been reported both in mouse embryonic fibroblasts *in vitro* and in five different types of tissue in mice supplemented with cycloastragenol, as well as in the lymphocytes of human volunteers supplemented with cycloastragenol.

3.4 Following concerns that the available data was not robust enough to demonstrate the safety of cycloastragenol in relation to its carcinogenic potential, cycloastragenol was referred to the COC by the Advisory Committee on Novel Foods and Processes (ACNFP).

3.5 Cycloastragenol was submitted to the ACNFP for authorisation as a novel food. The submitted data indicated that cycloastragenol has low oral bioavailability and was metabolised to a number of oxidised and hydroxylated compounds. A number of genotoxicity studies were also submitted that were considered by the manufacturers to be either equivocal or negative. Although some information on carcinogenicity was supplied, no standard carcinogenicity studies were submitted. The ACNFP had noted that there was a suggestion of a non-statistically significant increase in liver cancer incidence in treated mice in a study by Bernardes de Jesus *et al*. (2011) which was cited by the applicant. However, the study was limited by small numbers and a relatively short duration of exposure as well as having a relatively high background rate of tumours. This prevented any clear

conclusions being drawn from the study. Given the available data and the reported effects on telomeres, the ACNFP requested advice from the Committee on the Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC).

3.6 The COC considered that there were notable differences in metabolism between rats and humans. Although the compound was stated to have low bioavailability, there was little parent compound present after ingestion, due to rapid absorption and metabolism by hydrolysis and/or oxidation; no data on metabolite concentrations or longevity were presented.

3.7 The Committee had a number of concerns about the study by Bernardes de Jesus *et al*. (2011)[6]. These included the following; the age of death of the animals was not known; the tissues had not been studied; all tumour types had been summed, and; it was not clear whether other organs of relevance had been examined to ascertain that the liver tumours were secondary tumours as they were reported to be. The study was also too small to have sufficient power to show statistical significance, and since the cycloastragenol was only administered for 4 months it was not considered to be an adequate carcinogenicity study.

3.8 The 13 week study repeat dose feeding study was considered to be well conducted. Although outside the remit of the COC, the Committee were concerned that the increase in heart weight observed in that study had been dismissed by the applicant, despite a cardiotonic effect being claimed for the compound.

3.9 The mode of action of telomerase is to produce genetic changes by increasing repeats at the ends of DNA and it was not known whether this effect might also occur elsewhere in the DNA. It was noted that the genotoxicity tests undertaken would not necessarily pick up such effects. The genotoxicity experiments had been done to standard and were well reported but the results seemed to be equivocal and the COC recommended that cycloastragenol be referred to the COM.

3.10 The possibility of increasing telomere length or stopping telomeres shortening was of concern as these factors could increase cancer risk by allowing the proliferation of damaged cells which might otherwise undergo apoptosis. The Committee were concerned about the effects of cycloastragenol in younger people taking it compared to those who are older. Since the precise mode of action was uncertain it was unclear if it might be different in older animals and if other effects could also

[6] Bernardes de Jesus B, Schneeberger K, Vera E, Tejera A, Harley CB and Blasco M (2011) The Telomerase activator TA-65 elongates short telomeres and increases health span of adult/old mice without increasing cancer incidence. Aging Cell, 10, 604-621.

be occurring. There might also be the potential for differences in the effect(s) of cycloastragenol in people with tumour precursors and those without.

COC conclusions

3.11 The Committee has scientifically reviewed the data submitted and agrees that there remains general concern about the use of cycloastragenol. The Committee made the following recommendations:

a) Cycloastragenol should be considered by the COM. In particular, the raw data from the genotoxicity tests should be further examined, and consideration given as to whether another Ames test using a pre-incubation protocol would provide enough weight to establish whether or not a full 2 year bioassay would be required.

b) In the absence of additional appropriate negative mutagenicity data, the Committee would recommend a conventional two year bioassay, or other suitable study to show a lack of effect. The aim should be to identify an observable effect in older animals, but also to check whether any effects are likely to occur in younger people taking cycloastragenol.

Statement CC/2015/02 – Statement on consumption of alcoholic beverages and risk of cancer.

3.12 Since 2013, the Committee has undertaken a programme of work considering the new evidence on alcohol and cancer risk.

The Committee has considered the new papers published since the most recent IARC review of alcohol conducted in 2009 (IARC, 2012). New cohort and case-control studies were considered as well as meta-and pooled analyses. The review focussed on upper aerodigestive tract (combined), oral cavity and pharynx, larynx, oesophagus, female breast, liver and colorectum cancers as IARC considered consumption of alcohol to be causally related to these sites. In addition, the Committee considered the new evidence on pancreatic cancer and alcohol consumption for which an association had been identified by IARC.

3.13 The COC also considered the available evidence on the effect of binge drinking on cancer risk as this was identified as an emerging area of concern, the interaction of alcohol consumption and genotype in cancer risk, the burden of alcohol on cancer, the effect of cessation of alcohol consumption on cancer risk and the potential mechanisms by which alcohol may increase the risk of cancer. Some individual meta-analyses reporting potential inverse effects for some cancer types were also discussed.

3.14 Overall the findings supported the IARC conclusions and suggest that all types of alcoholic beverage can cause cancer with risk increasing the more alcohol a person consumes. Using the two most appropriate available studies investigating

the burden of cancer attributable to alcohol, produces estimates that 4-6% of all new cancers in the UK in 2013 were caused by alcohol consumption.

3.15 The new publications show:

- At **low, medium and high alcohol intakes**, a statistically significant increased risk at the following cancer sites:
  - oral cavity and pharynx (combined)
  - oesophagus (squamous cell carcinoma)
  - female breast
- At **medium and high alcohol intakes** (i.e. generally at intakes >12.5 g ethanol/day, or > approximately 1.5 UK units/day), a statistically significant increased cancer risk at the following cancer sites:
  - Larynx
  - colorectum
- At **high levels of alcohol intake** (i.e. generally at intakes >50 g ethanol/day, or > approximately 6 UK units/day), a statistically significant increased cancer risk for the following cancer sites:
  - Liver
  - Pancreas.

3.16 The risk of getting some alcohol-related cancers gradually decreases over time in people who stop drinking alcohol, but it can take many years for the risk to fall to levels similar to those in people who have never drunk alcohol. It is logical to assume that reducing alcohol consumption would also lead to a reduction in cancer risk.

The full statement, and supporting discussion papers, are available here: https://www.gov.uk/government/publications/consumption-of-alcoholic-beverages-and-risk-of-cancer

Horizon Scanning

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

3.18 In 2015, the Committee considered the items still outstanding from the last horizon scan in 2013, as no horizon scanning was undertaken in 2014 due to the ongoing volume of work. In addition, some new suggestions of topics were made by the

Secretariat as well as Members. Following discussion of these items, the list of priority topics was agreed as:

High priority:

- Alternatives in Risk assessment

Medium-high Priority

- Mode of action framework

Medium Priority

- Applicability of Margins of Exposure for exposure of young children
- Thresholds of Genotoxicity – keep informed of COM work
- Nanomaterials – presentation on research on inhalation of nanomaterials
- Dose response modelling in epidemiology studies - this will be covered as part of the Guidance series G2 (Interpretation of Evidence of Carcinogenicity in Humans)
- In vitro systems - to be undertaken when resource allows
- Studying cancer genomics through next generation DNA sequencing – as relevant papers are published
- Cancer genetics and cancer advancement by industrial exposure

Effect of immunomodulation on cancer susceptibility

Low Priority

- Environmental Tobacco Smoke Exposure in Childhood and Cancer Risk

Ongoing work

IGF-1 and cancer risk

3.19 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.

3.20 The COC is considering an extensive range of data which covers dietary absorption, levels of IGF-1 in food and the association between blood levels of IGF-1 and the risk of certain types of cancer. The review is ongoing, though it was not possible to progress work on it in the period 2014-5. It is hoped that it will be progressed in 2016.

Guidance statements

3.21 In 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. This 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 comprises an overarching statement G01 (which provides 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.

3.22 During 2015, the COC published guidance statement G03 - Hazard Identification and Characterisation: Conduct and Interpretation of Animal Carcinogenicity Studies.

3.23 Guidance statement G07 – Alternatives to the 2 year Bioassay was also discussed. The Introduction, parts A (*in vivo* assays) and B (cell transformation assays) was circulated for final comment from Members towards the end of the year and is expected to be published in early 2016.

3.24 A discussion paper on assessing the risk of acute and short-term exposure to carcinogens which will form the basis of guidance statement G09 was considered and this topic will be discussed further in 2016.

2015 Membership of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

CHAIRMAN

Professor David H Phillips BA PhD DSc FRCPath
Professor of Environmental Carcinogenesis, King's College London

MEMBERS

Mr Derek Bodey MA
Public Interest Representative

Dr Gill Clare BSc PhD
Public Interest Representative

Dr John Doe PhD DipRCPath
Consultant in Toxicology, Parker Doe Partnership

Dr Peter Greaves MBChB FRCPath
Consultant Pathologist and Honorary Senior Lecturer, University of Leicester

Professor Ray Kemp BA MSc PhD MRTPI
Public Interest Representative, Adjunct Professor of Risk and Sustainability

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

Dr Brian G Miller BSc PhD CStat CSci (to 31 March 2015)
Director of Research Operations, Institute of Occupational Medicine (now retired)

Professor Neil Pearce BSc DipSci DipORS PhD DSc FRSNZ FMedSci FFPH (from May 2015)
Professor of Epidemiology and Biostatistics, London School of Hygiene and Tropical Medicine

Professor Julian Peto MA MSc DSc FMedSci
Professor of Epidemiology, London School of Hygiene and Tropical Medicine

Dr Christopher Powell BSc PhD DipRC Path FRC Path FBTS
Vice President Safety Assessment, GlaxoSmithKline

Dr Lesley Rushton OBE BA MSc PhD CStat
Reader in Occupational Epidemiology, Imperial College London

Professor Heather Wallace BSc(Hons) PhD FRCPath FBTS FRSC FSB FBPharmacolS
Professor in Biochemical Pharmacology and Toxicology, University of Aberdeen

Dr Rosemary H Waring PhD DSc FRCPath
Honorary Reader in Human Toxicology, University of Birmingham

Professor Saman Warnakulasuriya BDS, FDSRCS, DipOralMed, PhD, DSc
Professor of Oral Medicine & Experimental Pathology, King's College London

SECRETARIAT

Ms F Pollitt MA DipRCPath	PHE Scientific Secretary
Dr D Benford BSc(Hons) PhD	FSA Scientific Secretary
Mrs N Blowfield	Administrative Secretary
Miss B Gadeberg BSc(Hons) MSc	

Declaration of members interests during 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 Centrica National Grid Takeda Pannone Solicitors	Shareholder Shareholder Shareholder Shareholder Shareholder Consultancy Consultant		
Mr Derek Bodey MA	None	None	None	None
Dr Gill Clare BSc PhD	Covance AstraZeneca Diageo Marks & Spencer Shell Research Ltd AstraZeneca	Consultant Shareholder Shareholder Shareholder Pension Deferred Pension	None	None
Dr John Doe PhD Dip R C Path	Parker Doe Partnership LLP Syngenta	Partner Pension	ILSI ECETOC	Member of Steering Group for RISK 21 project Chairman of Task Force – Bringing Potency into Classification for Carcinogenicity and DART
Dr Peter Greaves	Amicus Therapeutics Inc., Cranbury, New Jersey, USA	Consultant		

Member	Personal Interest		Non-personal Interest	
	Company	Interest	Company	Interest
	Experimental Pathology Laboratories Inc., Astra Zeneca UK Ltd Eisai Inc. Woodclife Lake, NJ, USA Grünenthal GmbH, Aachen, Germany UCB Biopharma SA Brussels, Belgium			
Prof Ray Kemp BA MSc PhD MRTPI	Ray Kemp Consulting Ltd	Shareholder		
Dr David Lovell PhD BSc (Hons) FSS FIBiol CStat CBiol	National Grid plc Pfizer ECVAM ESAC ILSI HESI OECD	Shareholder Pension Scheme Member Member of various Working Group/ Peer Review panels Committee member Consultant	AstraZeneca National Grid plc	Spouse shareholder Spouse shareholder
Dr Brian G Miller BSc PhD CStat CSci	Iberdrola SA	Shareholder	None	None

Member	Personal Interest		Non-personal Interest	
	Company	Interest	Company	Interest
Prof Neil Pearce	None	None	None	None
Prof Julian Peto MA MSc DSc FMedSci	None	None	None	None
Dr Christopher Powell	GlaxoSmithKline	Shareholder and salary	None	None
Dr Lesley Rushton OBE BA MSc PhD CStat	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.	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 ECPA Scientific Advisory Board on Epidemiology Cuadrilla	Research support Research support Research support External Committee member Member Research support.

Member	Personal Interest		Non-personal Interest	
	Company	Interest	Company	Interest
Professor Heather Wallace BSc Hons PhD FRCPath FBTS	Bank Santander SA BT Group NovaBiotics Antoxis Precious Cells Cell ProTx	Shareholder Shareholder Shareholder Shareholder Shareholder Director	EFSA	Contam Panel
Dr Rosemary Waring PhD DSc FRCPath	Centrica and National Grid	Shareholder	None	None
Professor Kasturi Warnakulasuriya FDS, PhD, DSc	National Grid plc Post Office Ltd	Shareholder Shareholder	BDHF Ben Walton Trust	Panel member Medical /Scientific Advisor

ANNEX 1 - Terms of Reference

To advise at the request of:
Food Standards Agency
Food Standards Scotland
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 Officers, 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

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

Standards in Public Life

Members are expected to:

· comply with this Code, and ensure they understand their duties, rights and responsibilities, and that they are familiar with the function and role of their Committee and any relevant statements of Government policy. If necessary members should consider undertaking relevant training to assist them in carrying out their role;

· not misuse information gained in the course of their public service for personal gain or for political purpose, nor seek to use the opportunity of public service to promote their private interests or those of connected persons, firms, businesses or other organisations; and

· not hold any paid or high profile unpaid posts in a political party, and not engage in specific political activities on matters directly affecting the work of the Committee. When engaging in other political activities, Committee members should be conscious of their public role and exercise proper discretion. These restrictions do not apply to MPs (in those cases where MPs are eligible to be appointed), to local councillors, or to Peers in relation to their conduct in the House of Lords.

· follow the Seven Principles of Public Life set out by the Committee on Standards in Public Life (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
· 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, CMOs 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 PHE/DH.

Role of the Chair

The Chair has particular responsibility for providing effective leadership on the issues above. In addition, the Chair is responsible for:
· ensuring that the Committee meets at appropriate intervals,
· ensuring that the minutes of meetings accurately reflect proceedings and any reports to the FSA Board and/or Ministers accurately record the decisions taken
· ensuring that where appropriate, the views of individual members have been recorded;

· representing the views of the Committee to the general public;
· ensuring that new members are briefed on appointment (and their training needs considered), and providing an assessment of their performance, on an annual basis or when members are considered for re-appointment to the Committee or for appointment to the board of some other public body.
· providing urgent advice to the FSA and HPA on issues within the remit of the Committee, in liaison with the Secretariat,

Role of the Deputy Chair

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

Role of the Secretariat

The primary function of the Secretariat is to facilitate the business of the Committee.This includes supporting the Committee by arranging its meetings, assembling and analysing information, and recording conclusions. An important task is ensuring that proceedings of the Committee are properly documented and recorded. Minutes of all Committee meetings will be taken. These will accurately reflect the proceedings and discussions that take place and will be recorded on a non-attributable basis except where the views of one or more individual members need recording (for example, when declaring an interest).

The Secretariat is also a source of advice and guidance to members on procedures and processes. The Secretariat is drawn from staff of the Food Standards Agency and Public Health England. 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 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.

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 2014/15 the budget for the COT, excluding Secretariat resources was £37,000. 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* 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* and the *Principles of Scientific Advice to Government* 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
- Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment
- Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
- 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.

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[7].
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.

[7] 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.

European Food Safety Authority (EFSA): European organisation that provides risk assessments to the European Commission

Exogenous: Arising outside the body.

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

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

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

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

Forestomach: (See glandular stomach).

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

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

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

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

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

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

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

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

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

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

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

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

Genomics: The study of genes and their function.

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

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

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

Half-life: Time in which the concentration of a substance will be reduced by half, assuming a first order elimination process.

Hazard: Set of inherent properties of a substance, mixture of substances or a process involving substances that make it capable of causing adverse effects to organisms or the environment.

Hepatic: Pertaining to the liver.

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

Hepatotoxic: Causing toxicity to the liver.

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

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

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

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

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

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

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

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

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

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

Intraperitoneal: Within the abdominal cavity.

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

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

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

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. It is also used for contaminants for which there is insufficient information to set a Tolerable Daily Intake (qv).

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

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

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

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

Polymorphism: (see genetic polymorphism)

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

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

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

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

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

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

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

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

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

Relative risk: A measure of the association between exposure and outcome. The rate of disease in the exposed population divided by the rate of disease among the unexposed population in a cohort study or a population-based case control study. A relative risk of 2 means that the exposed group has twice the disease risk compared to the unexposed group.

Renal: Relating to the kidney.

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

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

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

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

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

SAHSU: Small Area Health Statistics Unit

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

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

SCF: The European Commission's Scientific Committee on Food (formerly the Scientific Committee for Food). Its role has now been taken on by the European Food Safety Authority (qv).

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 ribosomes, where protein synthesis is completed.

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

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

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

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

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

microscopical appearance, rather than by cause. Some common examples of nomenclature are as follows:

- Tumours arising from epithelia (qv): benign - adenomas, papillomas*;* malignant - adenocarcinomas, papillary carcinomas.

- Tumours arising from connective tissues such as fat, cartilage or bone: benign - lipomas, chondromas, osteomas; malignant - fibrosarcomas, liposarcomas, chondrosarcomas, osteosarcomas.

- Tumours arising from lymphoid tissues are malignant and are called lymphomas (qv); they are often multifocal. Malignant proliferations of bone marrow cells are called leukaemias.

Benign tumours may evolve to the corresponding malignant tumours; examples involve the adenoma → carcinoma sequence in the large bowel in humans, and the papilloma → carcinoma sequence in mouse skin.

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

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

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

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

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

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

Xenobiotic: A chemical foreign to the biologic system.

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

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

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ANNEX 7 – Previous Publications

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2012 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Food Standards Agency/Department of Health, April 2014

2013 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Food Standards Agency/Department of Health, March 2015

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.

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment: Peanut Allergy, Department of Health (1998)**

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment: Organophosphates, Department of Health (1998)**

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment: Adverse Reactions to Food and Food Ingredients, Food Standards Agency (2000)++

Guidance on a Strategy for testing of chemicals for Mutagenicity. Department of Health (2000)*

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment: Risk Assessment of Mixtures of Pesticides and Similar Substances, Food Standards Agency, FSA/0691/0902 (2002).++

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment: Phytoestrogens and Health, Food Standards Agency, FSA/0826/0503 (2002).++

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)+

*Available on the COM website at:
https://www.gov.uk/government/organisations/committee-on-mutagenicity-of-chemicals-in-food-consumer-products-and-the-environment

** Available on the COT archive at:
http://tna.europarchive.org/20130802141804/http://cot.food.gov.uk/cotstatements/

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https://www.gov.uk/government/groups/committee-on-carcinogenicity-of-chemicals-in-food-consumer-products-and-the-environment-coc

++ http://cot.food.gov.uk/cotreports/