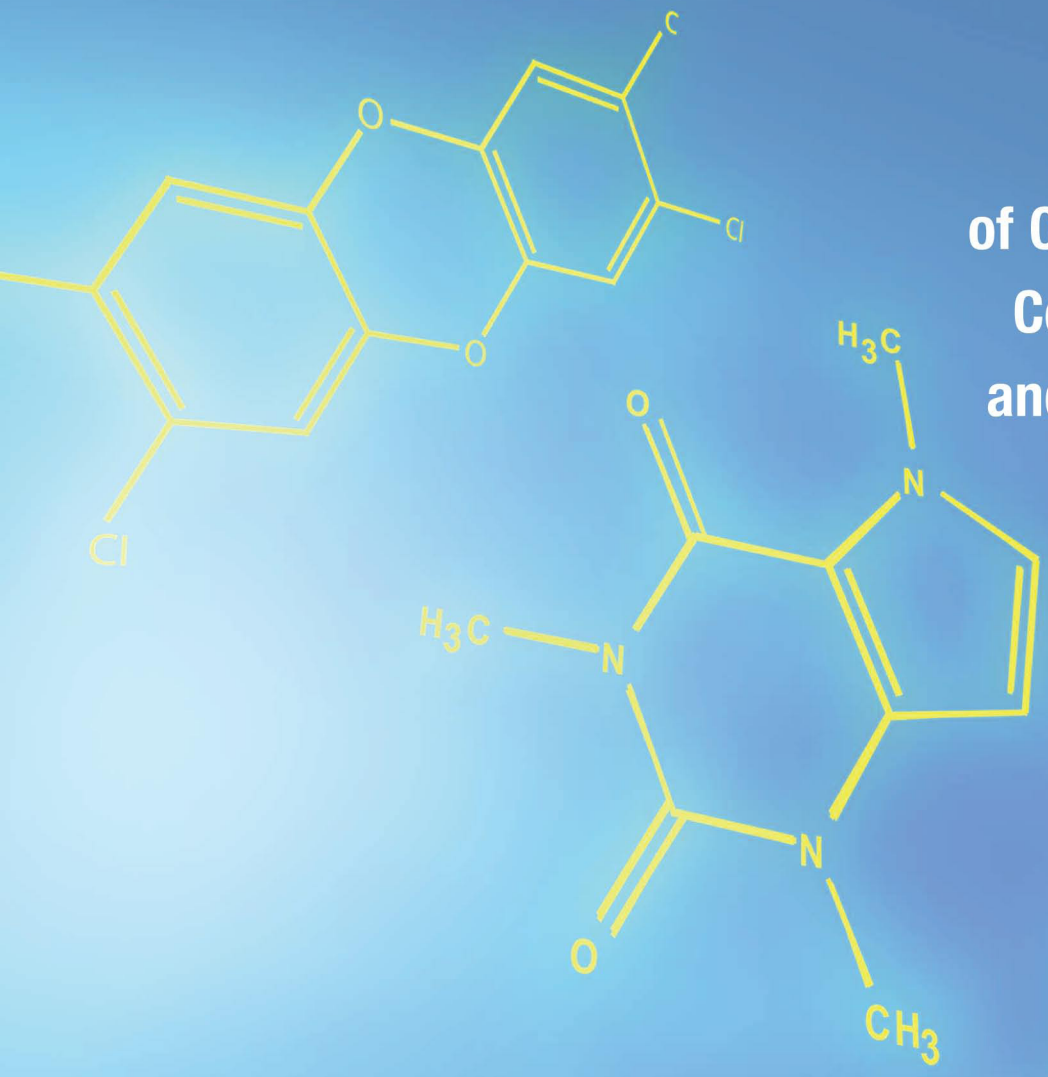
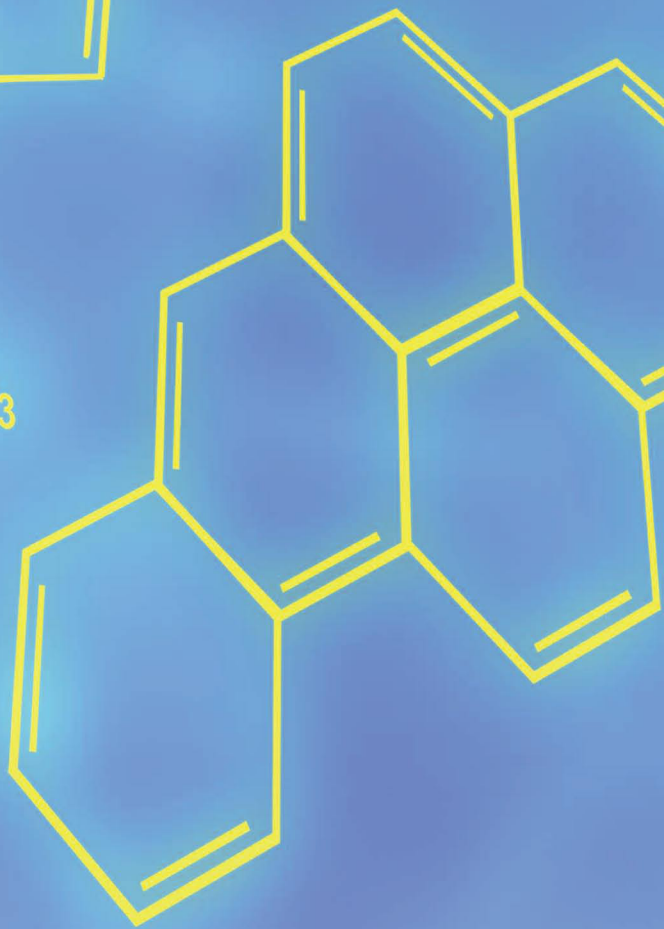
Committees on Toxicity Mutagenicity Carcinogenicity of Chemicals in Food, Consumer Products and the Environment





Committee on TOXICITY

Committee on CARCINOGENICITY

Committee on MUTAGENICITY

Annual Report 2014

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

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About the Committees

This is the twenty-fourth 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, 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 Advisory Committee on Pesticides.

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

COT: http://cot.food.gov.uk
COC: 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 includes the Committees' published statements in full in order to fulfil the obligation to publish statements both electronically and in hard copy.

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

Preface

I am pleased to present this report, which summarises the work of the Committee on Toxicity (COT) during 2014. 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.

This year, we continued our work in support of a review, led by the Scientific Advisory Committee on Nutrition (SACN), of the scientific evidence underpinning the Government's dietary advice for infants and young children. This included publication of statements on various environmentally persistent chemicals that get into the food chain – hexachlorocyclohexanes (previously used as pesticides), perfluorooctane sulphate (at one time widely used in the production of plastics) and tetrabromobisphenol A (which has been used as a flame retardant to promote fire safety).

Also in conjunction with SACN, we considered dietary intakes of vitamin D, and the potential impacts of replacing sodium salts by equivalent compounds of potassium in various food products. While adequate levels of the vitamin D are important for health, over-consumption in dietary supplements can be harmful. Similarly, for sodium replacement, a balance has to be drawn. Reducing intakes of sodium can lower blood pressure and prevent strokes, but increasing potassium intakes might cause health problems in some vulnerable groups.

Domoic acid is a natural toxin that occurs in scallops, and regulations are in place to prevent the sale of scallops containing levels that could threaten health. However, while it is essential to protect the public, it is also important not to restrict the fishing industry unnecessarily, and we have analysed new data to help optimise regulatory controls.

We have also provided critical comment on EFSA consultations regarding acrylamide and bisphenol A; considered possible adverse effects of soya phytoestrogens in people with thyroid disease; and published a major review of possible long-term consequences of exposures to organophosphate insecticides that are insufficient to cause overt poisoning.

I shall shortly be leaving the Committee, and as I move on, I thank the secretariat for their strong support throughout my time as chair, and also the members of the Committee, past and present, who have helped to ensure that our advice to Government has benefitted from timely and thorough scientific consideration.

David Coggon

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

COT evaluations

Adverse effects of high levels of vitamin D

1.1 The Scientific Advisory Committee on Nutrition (SACN) is reviewing recommended daily intakes (dietary reference values) for vitamin D, and asked the COT to advise on possible harmful effects of high intakes, either regularly over prolonged periods, or as single or occasional large doses. SACN also asked COT to consider whether some groups of people might be unusually vulnerable to high intakes of vitamin D (e.g. because of medical disorders).

1.2 Vitamin D is a fat soluble vitamin which is involved in the regulation of calcium within the body. This is important for the health of the bones and function of the nervous system. Vitamin D increases the level of calcium in the blood by increasing its absorption from food, reducing its excretion by the kidney and mobilising it from bone.

1.3 There are two chemical forms of vitamin D: vitamin D2 (ergocalciferol) which is formed in fungi and plant materials when they are exposed to ultraviolet (UV) light; and vitamin D3 (cholecalciferol) which is formed in skin following exposure to UV light. Small quantities of vitamin D are present in the diet – in plant foods such as mushrooms and animal foods such as oily fish and egg yolk. However, people get most of their vitamin D from exposure to sun.

1.4 High intakes of vitamin D from medication or dietary supplements (often over prolonged periods) have caused toxicity in humans, and many cases of such poisoning have been reported. Resultant increases in the levels of calcium in the blood can lead to various symptoms including loss of appetite, nausea, vomiting, weight loss, weakness, lethargy, thirst, excessive urination, constipation and non-specific aches and pains. In addition, the normal rhythm of the heart may be disrupted.

1.5 Some research has suggested other adverse effects of high vitamin D intakes – for example, on the risk of prostatic and pancreatic cancers, and of falls and fractures. However, the evidence for these other effects is less consistent and convincing.

1.6 In considering what would be safe intakes of vitamin D in healthy adults and children, the COT took note of a detailed review that had recently been carried out by the European Food Safety Authority (EFSA), along with other relevant research that had been published subsequently. The Committee endorsed the Tolerable Upper Levels (TULs) for vitamin D that had been proposed by EFSA – i.e. 100 µg (micrograms) per day for adults, 100 µg day for children aged 11-17 years, 50 µg

day for children aged 1-10 years and 25 µg day for infants aged up to 1 year. A TUL is the highest amount of a chemical which, on the basis of available evidence, could be consumed every day over a lifetime without appreciable risk to health The COT agreed that the TUL of 100 µg for adults was appropriate also for the elderly and for pregnant women.

1.7 As regards single or occasional high doses, the Committee concluded that, in adults, a single dose of 7500 µg every three months or less would not be expected to result in harm. However, there was greater uncertainty about the effects of larger doses. There were insufficient data to specify a safe upper limit for single doses in children, but the limited information that was available suggested that toxicity could occur in infants from a dose of 15,000 µg.

1.8 People who may not be adequately protected by the TULs for the general population include those with normocalcaemic hyperparathyroidism, tuberculosis and sarcoidosis.
https://admin.food.gov.uk/committee/committee-on-toxicity/cotstatements/cotstatementsyrs/cotstatements2014/cot-statement-on-vitamin-d

Domoic acid in King Scallops (Pecten Maximus)

1.9 The COT considered the evidence that was available to support shucking (removal of inedible parts) as a scientifically robust and effective method of managing the health risks associated with Amnesic Shellfish Poison (ASP) toxins in scallops. The main toxin of concern is domoic acid (DA). The Committee was asked whether, from data on the distribution of DA in different tissues from King Scallops, it was possible to identify a level of the compound in batches of whole animals that would pose minimal risk to consumers following effective shucking. It was anticipated that such a level would provide the basis for future risk management decisions.

1.10 DA is produced by species of phytoplankton and can be accumulated by filter-feeding shellfish such as scallops. Symptoms in humans following high exposures to DA include vomiting, diarrhoea, confusion, memory loss and in extreme cases, brain damage. The European Food Safety Authority (EFSA) has derived an Acute Reference Dose (ARfD) of 30 µg/kg bw for DA. This is an estimate of the amount of the substance that could be ingested in a period of 24 h or less without appreciable health risks to the consumer. The COT concluded that the EFSA ARfD should be used in its assessment of DA.

1.11 The toxicity of DA is determined by recent exposure, rather than cumulative exposure over a prolonged period. Therefore, for a given concentration of DA in scallops, the greatest potential for risk will be in someone who consumes an

unusually large quantity in a single day. The COT agreed that, as reported by EFSA, 400 g represented a reasonable estimate of the largest portion of scallops that was likely to be consumed over 24 hours.

1.12 Levels of DA in whole scallops vary widely over time and by geographical area, but concentrations in the edible parts (adductor muscle and gonad) are considerably lower than in the whole animal.

1.13 The COT analysed data on DA concentrations in scallops that had been harvested from various locations in the West Coast of Scotland, to determine the levels that might occur in 400g portions of the edible parts. Statistical simulations indicated that fewer than 1% of such portions would contain DA concentrations sufficient to cause exceedance of the ARfD.

1.14 On average, the concentration of DA in edible parts of the scallop is expected to be roughly proportional to the level in the whole animal. The COT used this relationship to estimate the average DA concentrations in whole animals that would lead to exceedance of the EFSA ARfD for no more than 5%, 2.5%, 1%, 0.5% or 0.1% of 400g portions of edible tissues, assuming that shucking was performed according to best practice. The analysis indicated that, at the 1% level, consumption of a 400g portion of adductor muscle plus gonad could lead to exceedance of the ARfD at concentrations of DA in whole scallops that were above 162 mg/kg. For a similarly sized portion of adductor muscle only, exceedance of the ARfD could occur at the 1% level at concentrations in whole scallops that were above 173 mg/kg.

1.15 The efficiency of shucking can vary, and comparison of results for different operators indicated that even among trained and approved processors, this could lead to concentrations of DA in edible tissue (comprising adductor muscle plus gonad) that are at least 4-fold higher than can be achieved by best practice.

1.16 The calculations described provide a basis on which to refine the management of risks from ASP toxins. However, decisions should take into account uncertainties in the analysis, the most important of which relate to the limited number of scallops for which data were available, and the fact that data on variability in the efficiency of shucking were available for only five processors.

1.17 The full COT statement can be found at: http://www.food.gov.uk/sites/default/files/cot-statement-da-scallops.pdf.

European Food Safety Authority (EFSA) consultation on a draft scientific opinion on acrylamide in food

1.18 The COT and COC were asked by the Food Standards Agency (FSA) to respond to an EFSA consultation on a draft scientific opinion concerning acrylamide in

food. The Committees commented on the high quality and comprehensive nature of the scientific opinion and were broadly in agreement with the evaluation and its conclusions. They made recommendations for improvements in a number of areas, particularly relating to other potentially significant sources of exposure.

1.19 Recommendations were made for clarification with respect to the following areas:

- exposure scenarios,
- the importance of non-dietary sources of exposure,
- the potential impact of polymorphisms in cytochrome P450 2E1,
- possible toxicokinetic differences according to routes of exposure,
- the possible contribution of smoking to internal exposure in the epidemiological studies reviewed, and to the observed health outcomes,
- the limitations of dietary exposure assessments based on food frequency questionnaires (FFQs) in the epidemiological studies considered,
- discussion of whether the lack of conclusive evidence of carcinogenicity in the epidemiological studies could be due to exposure misclassification,
- a possible impact of caffeine in the epidemiological studies on pregnancy,
- exposures resulting in neurotoxicity in humans,
- the most important sources of uncertainty,
- the possibility of transgenerational effects.

EFSA Consultation on a draft scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs

1.20 The COT was asked by the FSA to consider a draft EFSA opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs, and to provide comments as a basis for the UK response.

1.21 The COT considered that the draft opinion was an impressive document, and generally agreed with its conclusions. Discussion focussed on changes that would improve the clarity of the opinion, and further explain the rationale for some of the decisions that had been made in its drafting. The COT were not aware of any significant papers which had been missed.

1.22 The COT welcomed the use of the human equivalent dose (HED) approach to extrapolate from experimental animals to humans, adjusting for the differences in

toxicokinetics. In general, the Committee supported the weight-of-evidence approach that had been adopted. Six categories of “likeliness” had been used to classify possible hazards. Hazards classed as “likely” or “very likely” had been taken forward to the hazard characterisation stage. However, the classification system used was a little unusual, and it was unclear how a hazard would be classified if there was no evidence. Where evidence was inadequate, it might be misleading to classify a hazard as being as “as likely as not”. It was unclear why a classification approach such as that used by the International Agency for Research on Cancer had not been employed, which would have included a category for “inadequate evidence”. The COT recommended that the opinion should emphasise more strongly that the classification related solely to hazard identification and not to the quantification of risk, since there was a danger of misinterpretation.

1.23 Overall, the COT considered that the opinion was well structured and comprehensive, and that the conclusions reached were justified on the basis of the available evidence.

1.24 The balance of evidence as presented in the draft EFSA opinion suggested an absence of risk. However, there were some uncertainties, the main source of uncertainty being the relevance of proliferative/developmental changes in the mammary gland. This was currently being addressed by a study in the United States.

FSA-funded research on the effects of soya phytoestrogens in patients with compensated hypogonadism

1.25 The COT discussed the results from a randomised double-blind experimental study, led by scientists at Hull York Medical School, to investigate whether soya protein containing phytoestrogen isoflavones, given in daily divided doses, had any effects on testosterone levels in men with type 2 diabetes who had borderline or subclinical hypogonadism.

1.26 The COT made a number of comments on the results, and made suggestions for improved approaches to analysis of the data that had been obtained. A report of the study will be submitted for publication in a peer-reviewed scientific journal. The minutes of the COT’s discussions have been temporarily withheld from publication whilst this process is on-going. The Committee judged that this delay was acceptable, since the reported absence of significant effects on testosterone levels, including of free testosterone, was reassuring and the results presented did not indicate any need for action to protect the health of the public

FSA-funded research on the effects of soya isoflavones on markers of bone turnover in females in the early menopause

1.27 The COT discussed the results from a randomised, double-blind, parallel study, led by scientists at Hull York Medical School, to examine the effects of soya protein and isoflavones on markers of bone turnover in women within 2 years after the onset of menopause.

1.28 The Committee made a number of comments on the results, and suggested ways in which the analysis of the data might be improved. A report of the study will be submitted for publication in a peer-reviewed scientific journal. The minutes of the COT's discussions have been temporarily withheld from publication whilst this process is on-going. Since the results presented on the markers of bone turnover were consistent with reduced rather than increased risk of bone fracture and the evidence did not suggest that consumption of isoflavones would lead to adverse effects on bone health, the Committee judged that this delay was acceptable.

FSA-funded research on the effect of soya phytoestrogen supplementation on thyroid status and cardiovascular risk

1.29 In 2011 the COT discussed the results of the first two arms of a double-blind placebo-controlled crossover trial, investigating the effect of soya isoflavones on thyroid hormones in subjects with compensated hypothyroidism. The aim of the study was to determine whether soya in the diet could be clinically important in patients with compensated impairment of thyroid function. At that time, the COT agreed that it would consider results from the third and final arm of the study before deciding whether it provided sufficiently strong grounds for advice on phytoestrogen consumption to patients with compensated hypothyroidism, and whether further research was required to resolve outstanding uncertainties.

1.30 In 2014, the COT discussed the results from the third arm of the study, led by scientists at Hull York Medical School, which aimed to clarify whether effects associated with consumption of soya were caused by soya protein. Results from both this and the earlier arms of the study were discussed. The results from the third arm indicated that soya protein alone had no important effect on thyroid function. Thus, the effects observed in the first two arms of the study appeared to have been caused by isoflavones.

1.31 The COT made a number of comments on the results and suggested improved ways of analysing the data that had been obtained. The COT considered it would be prudent to reconsider all the available evidence regarding effects of soya on thyroid function, and concluded that consumption of soya was unlikely to precipitate hypothyroidism unless it had already started to develop. They agreed that, although within the normal range, the consistent changes that had been observed in thyroid hormone levels following consumption of soya protein containing phytoestrogens, both by women within 2 years after the onset of menopause, and by men with type II diabetes and subclinical hypogonadism,

supported the possibility of risks from soya ingestion in people with compensated or overt hypothyroidism

1.32 A report of the study will be submitted for publication in a peer-reviewed scientific journal. The minutes of the COT's discussions have been temporarily withheld from publication whilst this process is on-going. The Committee judged that this delay was acceptable, since the results presented did not indicate any urgent need for action to protect the health of the general public. Although there were uncertainties about dose-response, the COT considered it would be advisable to make people with overt or compensated hypothyroidism aware that increased consumption of soya in their diet or as supplements might exacerbate their condition and alter the treatment that was needed. A COT statement would be drafted that incorporated findings from the three study arms, previously reported results, including from a study in which 132 mg of isoflavones per day were administered, and a review of other relevant literature.

α-, β- and γ-hexachlorocyclohexanes in the infant diet

1.33 The COT was asked by the Scientific Advisory Committee on Nutrition (SACN) to review the risks of toxicity from chemicals in the infant diet. The COT considered that among other things, the review should include chemicals classed as persistent organic pollutants, including α-, β- and γ-hexachlorocyclohexanes (HCHs). None of Government's current dietary recommendations for infants and young children relates to HCHs.

1.34 HCHs were previously used as pesticides, but have been banned from such use because of concerns about their persistence in the environment, and about the safety of operators who applied them. Their environmental persistence means that they can also be present in food. Levels of HCHs in food and published estimates of dietary exposures indicate a reduction over time around the world, consistent with the withdrawal of authorised uses. HCHs have not been detected in recent monitoring of UK infant formula or infant foods

1.35 When administered to experimental animals, γ-HCH has adverse effects on the nervous and immune systems. There is also evidence that it causes cancer in animal studies, but in a way that would not occur in humans. The COT concluded that harmful effects in infants would not be expected when dietary exposures were below a Tolerable Daily Intake (TDI) of 0.04 µg/kg bw. The estimated exposures of infants to γ-HCH from different dietary sources were therefore compared to this TDI.

1.36 The toxicity of α- and β-HCH is less well characterised than that of γ-HCH. The COT concluded that the available information was insufficient to propose a TDI for either of these chemicals, and that it was more appropriate to consider the ratios between the highest doses that had been found not to cause liver toxicity 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 both in the toxicological database and in the estimates of exposure.

1.37 Based on these approaches, and taking into account the evidence that levels in breast milk are declining, the estimated exposure of breastfed infants to HCHs did not indicate a concern.

1.38 For infant formula and food, a lack of quantified data meant that there was substantial uncertainty in exposure estimates. The theoretical maximum exposure to γ-HCH exceeded the TDI, but it was likely that in practice exposures were much lower than this theoretical maximum. For α- and β-HCH, the margins of exposure did not indicate a concern.

1.39 Overall the COT concluded that its evaluation did not provide a basis for recommendations on the infant diet relating to HCHs, particularly as levels in food appeared to be decreasing over time. However, continued monitoring of HCHs in breast milk, infant formula and food, with appropriately sensitive methods, would be useful to confirm that there were unlikely to be any risks.

1.40 The full COT statement can be found at: http://cot.food.gov.uk/sites/default/files/cot/cotstatmhchs.pdf

Long-term neurological, neuropsychological and psychiatric effects of low-level exposure to organophosphates in adults

1.41 Organophosphates are a class of chemicals, some of which can bind to and inactivate an enzyme, acetylcholinesterase, which is important to the function of the nervous system. This property has been exploited in their use as insecticides in agriculture and horticulture, as veterinary medicines to prevent or treat infestations (e.g. sheep dips), as human medicines (malathion only – as a treatment for head lice), and as public hygiene products (e.g. for control of cockroaches). However, it poses a hazard to people who are exposed to them inadvertently during their manufacture or as a consequence of their use. In addition, intentional human poisoning has occurred as a result of deliberate self-harm, and through the use of some organophosphates (different from those in pesticides and medicines) as chemical warfare agents.

1.42 Poisoning by over-exposure to organophosphates that bind acetylcholinesterase causes rapid onset of illness, which in severe cases can be fatal. Moreover, people who survive such poisoning are at increased risk of subtle, long-term effects on brain function.

1.43 The COT considered whether long-term, harmful effects on the nervous system can result from exposure of adults to lower levels of cholinesterase-inhibiting organophosphates that are insufficient to cause overt short-term poisoning. When

this question had last been considered by the COT as part of a report published in 1999, the evidence was judged to be inconclusive.

1.44 A COT working group carried out a systematic review of relevant research that had been published in peer-reviewed scientific journals up to September 2013. Preliminary consideration indicated that the most pertinent evidence would come from epidemiological investigations in human populations, and that toxicological studies in animals and in vitro would be less telling. The search was therefore limited to studies in humans, and reports of other types of research were not reviewed systematically.

1.45 Since 1999, 13 new papers had been published on the relation of low-level exposure to organophosphates to peripheral neuropathy (i.e. impaired function of the nerves outside the brain and spinal cord). These added to 13 studies that were already available at the time of the previous COT report. The balance of evidence suggested that there was no long-term risk of clearly demonstrable peripheral neuropathy from exposure to organophosphates that does not cause overt short-term poisoning; a conclusion that had strengthened with the passage of time.

1.46 There was uncertainty as to whether long-term low level exposure to organophosphates causes detectable impairment of people's ability to perceive sensory stimuli (such as light touch, hot and cold), but if there were an effect then it was likely to be small.

1.47 Few studies had looked for effects of low-level exposure to organophosphates on background patterns of electrical activity in the brain (electroencephalography or EEG), patterns of brain activity in response to standardised sensory stimuli (event-related evoked potentials), or the electrical activity in muscles (electromyography or EMG). In general, these studies did not suggest a hazard, but the evidence base was slim. One study had suggested impairment in the brain's processing of auditory information, but without independent replication, little could be drawn from this isolated finding.

1.48 Since the previous COT review, 22 investigations had been published that looked for neuropsychological consequences of low-level exposure to organophosphates, adding to the nine that were available in 1999. Overall, there was no consistent evidence that low-level exposure to organophosphates has adverse effects on any specific aspect of cognitive function. If organophosphates do cause long-term neuropsychological impairment in the absence of overt poisoning, then the effects, at least in the large majority of cases, must be minor and subtle.

1.49 Evidence on whether, in the absence of acute poisoning, low-level exposure to organophosphates can cause long-term structural changes in the brain was insufficient for any firm conclusions.

1.50 The overall balance of evidence from 11 studies suggested no increased risk of Parkinson's disease from exposure to organophosphates that was insufficient to cause overt acute poisoning, although a small elevation of risk could not be ruled out.

1.51 Findings from the only two studies on the relation of organophosphates to later dementia were not strongly suggestive of a hazard, but pointed to a need for further research.

1.52 Fourteen studies (including 10 published since 1999) had investigated the association of low-level exposure to organophosphates with depression and anxiety. Overall, there was no consistent evidence of a link. The balance of evidence suggested that low-level exposure to organophosphates does not lead to an increased risk of suicide.

1.53 Despite limitations of individual studies, evidence suggested that there is an excess of multiple neuropsychiatric symptoms in people who have been exposed to organophosphates at levels insufficient to cause overt acute poisoning. However, it did not support the existence of a specific syndrome of "chronic organophosphate-induced neuropsychiatric disorder (COPIND)", as had previously been hypothesised. It was unclear whether the observed excess of symptoms was a consequence of chemical toxicity or occurred through psychological mechanisms, and it was possible that people who were aware of having been exposed to potentially toxic chemicals were more inclined to notice and report symptoms. Studies on the relationship of symptoms to differences in people's capacity to metabolise organophosphates had not clearly established a causal link with poorer ability to detoxify organophosphate compounds, as might be expected if the illness were a consequence of toxicity.

1.54 Collectively, the evidence reviewed was reassuring. It suggested that exposures to cholinesterase-inhibiting organophosphates that are insufficient to cause overt acute poisoning do not cause important long-term neurological toxicity in adults, and that if toxic effects on the nervous system do occur then they are minor and subtle.

1.55 The most important gap in the current evidence base concerned the relation between low-level exposure to organophosphates and later dementia. An association of such exposure with dementia had some biological plausibility, and was suggested (although not strongly) by the two studies that had looked at the question to date. Moreover, dementia was a major and growing public health problem, and even a small proportionate increase in risk could have important implications at a population level. However, further research on this should be conducted only through studies with adequate rigour that were statistically robust.

1.56 Given the evidence that was now available, it seemed unlikely that further research on neurophysiological, neuropsychological and psychiatric outcomes would identify any important hazard from low-level exposure to organophosphates. Research to explore the possibility of more subtle, minor effects would require rigorous assessment of exposure, and better methods for assessment of the health outcomes than were currently available.

Perfluorooctane sulfonate (PFOS) in the infant diet

1.57 The COT considered perfluorooctane sulfonate (PFOS) as part of its review of the risks of toxicity from chemicals in the infant diet on behalf of SACN. None of the Government's current dietary recommendations for infants and young children relates to PFOS.

1.58 PFOS has been used extensively in plastics, electronic equipment and textiles and as a result it has become widely distributed in the environment, which means that it can also be present in food. Almost all uses have now been banned, although a few have been allowed to continue until suitable alternative products are available.

1.59 The COT and also the European Food Safety Authority (EFSA) have previously set guidelines for daily exposures to PFOS that are not expected to harm health, even if they are experienced over a prolonged period of time.

1.60 The COT considered possible dietary exposure of infants to PFOS from breast milk, infant formula (including water used in its reconstitution) and foods that are offered to infants to complement milk feed. Additional exposure to PFOS might arise from related chemicals that have the potential to break down to form PFOS. However these are likely to make only a minor contribution to total exposure.

1.61 Estimated dietary exposures of infants to PFOS were lower than the guidelines set by COT and EFSA, and therefore the COT concluded that there was no need for dietary recommendations to protect the health of infants.

1.62 The COT noted that EFSA was currently reviewing the possible health effects of PFOS and, depending on the outcome of the EFSA review, the above conclusion might be reconsidered in the future.

1.63 The full COT statement can be found at: http://cot.food.gov.uk/sites/default/files/cot/cotstatmpfos.pdf

Recommendations of the Bystander Risk Assessment Working Group report concerning skin sensitisation from exposure to pesticides

1.64 In 2012 the COT and the Advisory Committee on Pesticides (ACP) published a report of the joint Bystander Risk Assessment Working Group (BRAWG) on the methods used in regulatory risk assessment of potential health risks to bystanders and residents from the application of pesticides. The BRAWG had noted a concern that some individuals might become sensitised to pesticides. The working group had been concerned that risk factors for dermal sensitisation were not well understood, and considered that further work was needed to characterise and quantify the potential of pesticide formulations to induce skin sensitisation.

1.65 The BRAWG report had made the following recommendations: that research be conducted on the extent to which current or new formulations might affect the ability of chemicals to act as sensitisers; further work on characterising the potency of formulations using the local lymph node assay (LLNA), and on clarifying the relationship between potency estimates and human risk; and work on the influence of co-formulants on sensitisation. The Government had subsequently asked for the COT's views on how these recommendations might be taken forward. In considering this topic the COT were advised by two experts on skin sensitisation.

1.66 The mouse LLNA was now the main test used to determine whether a chemical might be a skin sensitiser. Recent EU regulations required that data to support approvals for plant protection products include information on the potential of active substances and formulations to cause sensitisation, and that the LLNA be the test used. A key advantage of the LLNA was that it gave a quantitative estimate of the relative potency of sensitisers: Estimated Concentration 3 (EC3) values, often expressed as a percentage, gave an indication of the amount of sensitiser needed to induce a sensitisation response, and made it possible to discriminate between strong and weak sensitisers.

1.67 The current regulatory approach was that if a pesticide active substance was classed as a sensitiser, but was diluted to less than 1% in a product, then the product was not considered to be a sensitiser. On the other hand, if the concentration was more than 1%, the product would also be classified as a sensitiser. The BRAWG had concluded that this approach needed to be supported by empirical data. A product that was classed as a sensitiser could not be approved for non-professional use, but it might be approved for use by professional operators with a specification that appropriate personal protective equipment must be used. Some pesticides, for example captan, were known to cause skin sensitisation in humans.

1.68 The Committee asked whether there had been any documented cases of skin sensitisation in operators caused by pesticide products that had not been labelled as sensitisers, and whether there had been any documented cases at all of skin sensitisation in re-entry workers, bystanders, residents or non-professional pesticide users. The COT was advised by an expert in skin sensitisation that

occupational allergic contact dermatitis caused by pesticides was extremely rare and that he was not aware of any cases in bystanders, residents or non-professional users, but the Health and Safety Executive (HSE) Chemicals Regulation Directorate (CRD) would be asked to check.

1.69 The COT discussed in vitro methods, noting that while these were not fully quantitative they might perhaps be used to rank potency. However, they could not be used to test formulations and there would be a need to take into account factors such as skin penetration. The COT were advised by an expert on skin sensitisation that draft OECD guidelines had been prepared on two alternative methods of assessment and a third was under preparation. These were likely to be combined to give a dichotomous hazard classification and there were ideas on how the methods might be further developed to assess potency. However, he did not foresee their practical application in assessment of potency in the near future.

1.70 Dose per unit area of skin was the metric most relevant to dermal sensitisation, although the Committee was advised that the relationship to this measure weakened when only very small areas of skin, less than a few mm in diameter (e.g. from minor splashes), were exposed. Exposure of such small areas was insufficient to induce sensitisation. The duration of exposure and repetition of exposures also influenced responses. If a chemical was immediately washed off the skin, risk would be determined by the remaining residue.

1.71 Regarding validation of estimates of potency using the LLNA, the COT were advised that a study had classified 131 chemicals into six grades of potency, based on human experimentation, and compared the rankings with results from the LLNA. The study had found that the LLNA could be benchmarked against human potency. The chemicals considered were mostly ingredients of cosmetics rather than pesticides, but provided the relevant chemistry was represented, it would be reasonable to extrapolate the findings to other chemicals. Furthermore the LLNA had been validated a number of years ago and found to have good sensitivity and specificity.

1.72 The COT agreed that it might be useful to conduct a study using the LLNA to compare the sensitising potency of active substances with that of different formulations containing them. However, the information obtained would need to be of sufficient value to justify the use of laboratory animals that the research would entail.

1.73 The COT was advised that the use of different vehicles appeared to have a relatively limited effect on the potency of a substance: at most one order of magnitude, and more commonly 3-4 fold, though it was unclear how well the vehicles that had been tested would represent the chemicals in pesticide formulations. The available data did not indicate a way by which the effect of co-formulants on the sensitising potency of a substance could be predicted from their

chemical properties. While a substance which enhanced skin penetration might often be expected to increase sensitising potency, it might sometimes reduce it by causing the exposure of the skin to be more transient. Studies could be performed using the same active substance and varying the vehicle. The COT considered that such research would be worth conducting, although not necessarily for pesticides. Whether it was worth focusing on pesticides would depend on the frequency of any pesticide-related skin sensitisation in relation to products that were not currently classed as sensitisers.

1.74 The COT concluded that further work to characterise the relative sensitising potency of active substances was not necessary if using the LLNA.

1.75 The COT agreed that there was no need to develop a more detailed classification of preparations based on the concentrations and sensitising potency of their ingredients, unless there was evidence of sensitisation in re-entry workers, bystanders, residents or non-professional pesticide users. If there was no evidence that such sensitisation occurred then it could be concluded that the current approach to risk assessment was adequate to protect bystanders and residents. It was noted that one of the skin sensitisation experts had advised that he considered the 1% trigger for classification of formulations as sensitisers to be reasonable. If cases of skin sensitisation were shown to have occurred in re-entry workers, bystanders, residents or non-professional pesticide users then the Committee would need to reconsider this.

1.76 The COT considered research that had been done on modelling of skin sensitisation, and noted that modelling approaches were not yet sufficiently developed for application in regulatory risk assessment. It concluded that unless there was evidence of skin sensitisation in bystanders or residents, further work to develop such methods was not a priority for pesticides, although they might be useful for other categories of chemical. The COT was advised that there were a large number of ongoing projects related to cosmetics.

Tetrabromobisphenol A (TBBPA) in the infant diet

1.77 The COT considered brominated flame retardants (BRFs), including tetrabromobisphenol A (TBBPA) as part of its review of the risks of toxicity from chemicals in the infant diet on behalf of SACN. None of the Government's current dietary recommendations for infants and young children relates to TBBPA.

1.78 The COT reviewed information on the toxicology of TBBPA that had been published by the COT in 2004, and by EFSA in 2011, and from more recent research, together with estimates of the exposures of UK infants from various sources, including air, dust, soil, food, drinking water, breast milk, infant formulae and complementary foods.

1.79 TBBPA derivatives were considered a possible additional source of TBBPA, and were noted to be of varied structure, with some likely to be more lipophilic than TBBPA itself. Metabolism to TBBPA was to be expected, but it was not possible to predict the extent of such metabolism. It was noted that bioavailability was reported for one derivative and was much lower (2.2%) than that of TBBPA (~70%). The lack of information on uptake of the derivatives and their potential for metabolism to TBBPA was a major uncertainty in the risk assessment. It would also be important to know whether the analytical methods used to quantify TBBPA would also detect derivatives, since some methods incorporated an enzymatic cleavage step.

1.80 A new study conducted by the US National Toxicology Program provided good evidence that TBBPA was carcinogenic, but in view of the negative findings in genotoxicity studies, this effect was likely to occur only at doses above a threshold. It was plausible that the testicular and uterine tumours which had been observed were secondary to hormonal effects, and that the increased incidence of liver tumours was a consequence of enzyme induction. In the absence of information on mode of action, it should be assumed that the tumours were relevant to humans. Pre-neoplastic changes were reported at all dose levels, and therefore it was not possible to identify a no observed adverse effect level (NOAEL) that could be used as a basis for a revised TDI or a margin of exposure (MOE) approach. Furthermore, the inconsistent dose-response relationship meant that the data were not suitable for dose-response modelling. A lack of information about possible immunotoxicity was noted as a data gap.

1.81 Exposure to TBBPA via dust and air was thought likely to be relatively unimportant compared to that via food, since TBBPA is lipophilic. Little information was available on exposure to TBBPA derivatives.

1.82 Overall, the COT concluded that neither the TDI previously established by the COT nor the reference point used by EFSA were now appropriate for use in risk assessment. An assessment of maximum potential exposures to TBBPA might be possible, using the limits of quantification where residues had not been detected, and from the available information it seemed likely that exposures were low. However, it was not currently possible to perform a risk assessment that included TBBPA derivatives.

1.83 Key areas for further toxicological research included studies on the mechanisms by which TBBPA affected the liver and levels of thyroid hormones. It was hypothesised that changes in the liver might include the induction of enzymes involved in the metabolism of thyroid hormones, leading to reduced circulating levels.

1.84 Further recommendations were to investigate the bioavailability of TBBPA derivatives, and the fractions of these compounds that convert to TBBPA.

Information on the toxicity of derivative compounds was also required. In vitro studies were suggested as an option to investigate their potential for hormonal effects.

1.85 Further data on the occurrence of TBBPA and its derivatives were needed. The European Commission had recently announced that it would ask Member States to gather additional information on levels of brominated flame retardents (BFRs) in food. For the derivatives, it was suggested that information might be available from the relative quantities manufactured, but that this would only be crude. The Committee recommended that FSA should inquire whether any studies of occurrence or exposure were underway or planned by authorities in the USA.

1.86 The Committee agreed that it would be appropriate to revisit TBBPA and its derivatives later, after it had considered other groups of BFRs as part of its work on infant diet.

Committee procedures

Horizon Scanning

1.87 At their February 2014 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.

1.88 Members noted the list of agenda items that were planned or underway for 2014, and discussed several other topics that might also be considered.

Risks associated with the consumption of Lactobacillus rhamnosus GG (LGG) as a component of fully hydrolysed infant formula by cows' milk-allergic children under 6 months of age

1.89 The FSA had been asked to consider potential risks from the addition of LGG to infant formula, and the proposed claim that consumption would reduce the risk of developing cows' milk allergy. Members were asked to advise whether it was within the remit of the Committee to assess such risks, and to suggest an alternative Committee if they judged it was not. It was proposed that an *ad hoc* Working Group be set up to evaluate the evidence for risks and benefits, and that relevant expertise would include allergy, diet, paediatrics and microbiology.

Update on Tox21 and ToxCast

1.90 A brief overview of recent developments in these American initiatives was presented. 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. 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. It was noted that PHE would be interested in presenting detailed results of the ToxCast project to the Committee in the future.

Modelling kinetics

1.91 Recent publications stemming from European-wide cooperation in the areas of physiologically-based toxicokinetic modelling were presented. These covered: available (including freely-available) models; the generation of supporting data for such models; and the use of such models to aid the incorporation of *in vitro* data into risk assessment.

1.92 Members had not had experience with the freely-available models but speculated that they might be rather complex for inexperienced users. The Committee agreed that a presentation on developments in the field would be interesting, and that it would be useful if such a presentation provided examples of different methods with their pros and cons. However, this was not viewed as a high priority.

Guidance on COT procedures

1.93 Members were advised that the sister Committees on Carcinogenicity and Mutagenicity had produced guidance statements on the approaches they follow in risk assessment. Those guidance statements had taken the form of an overall strategy with more detailed guidance on individual aspects published as separate web-based documents.

1.94 It was noted that in general, the COT follow WHO principles and methods for risk assessment (EHC 240, 2009). The COT consider a wider variety of questions than the other two Committees, covering more diverse topics, and often have incomplete data on which to draw in making risk assessments. This impacted on the approaches used. Members considered that drawing up guidance statements on their methods might in theory have benefits in transparency and promoting consistency, but that because of the complexity, the benefits would in practice be limited and insufficient to justify the use of Committee time.

Balance of expertise on the Committee

1.95 The COT confirmed that the expertise required for some or all of its evaluations was as listed in the table below.

Analytical techniques	Biochemistry
Bioinformatics	Cell biology
Clinical practice	Dietary exposure assessment

Endocrinology	Environmental exposure assessment
Epidemiology	Human toxicology
Immunology	Mathematical Modelling
Mechanistic toxicology	Molecular biology
Neurotoxicology	Nutrition
Paediatrics	Pharmacokinetics
Pharmacology	Probabilistic modelling
Reproductive toxicology	Respiratory toxicology
Risk assessment	Statistical aspects of experimental design
Statistics	Systems biology
Toxicogenomics	Toxicological pathology
Xenobiotic metabolism	

1.96 It was noted that the Committee lacked specific expertise in paediatrics, and that this gap had been covered on a case-by-case basis by a Member of SACN. The need for expertise in predictive toxicology and psychology was also considered, but it was agreed that Members had sufficient knowledge to identify when further expertise in these areas was required on an ad hoc basis.

Ongoing work

Assessment of the adequacy of the 10-fold uncertainty factor to allow for interspecies variation in developmental toxicity

1.97 The COT had considered this topic in 2013 and concluded that there were strong indications that the 10-fold uncertainty factor for interspecies variation was not always adequate in relation to developmental toxicity. It was not currently possible to conclude how often the factor was inadequate, or how the situation compared for other endpoints. The COT had requested additional information, including on endpoints other than developmental toxicity, and considered this in 2014.

1.98 The COT observed that animal studies did not always identify the type and severity of adverse developmental effects that could occur in humans, and that substances with large ratios between LOAELs in animals and in humans had no obvious features in common. Older pharmaceuticals tended to have larger ratios between LOAELs than newer products, which might be because older molecules tended to have more off-target effects or because new pharmaceuticals under development which were found to be developmental toxicants were now less likely to reach the market.

1.99 The COT confirmed its conclusion from 2013 that there were strong indications that the 10-fold uncertainty factor for interspecies variation in developmental toxicity was not always adequate, and having considered the data on effects other

than in utero developmental toxicity, extended this conclusion to non-developmental outcomes. A key question was the frequency of exceptions that was tolerable.

1.100 The COT 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.

Effects of soya phytoestrogen supplementation on thyroid status

1.101 A 2003 COT report on phytoestrogens and health had identified individuals with hypothyroidism as a subgroup of the population of potential concern regarding adverse effects of phytoestrogens in soya, and made recommendations for research. During 2014 the Committee considered the results of several FSA-funded research studies on phytoestrogens, and made recommendations for a review of related evidence published since 2003. The COT is considering possible health effects of soya phytoestrogens on thyroid function in different groups of the population and will publish a statement on this topic in 2015.

Toxicity of chemicals in the infant diet

1.102 The COT is continuing its reviews of the potential toxicity of chemicals in the infant diet, in support of a SACN review of Government's dietary recommendations for infants and young children. Further statements will be published in 2015:

Hexabromocyclododecanes (HBCDDs) in the infant diet

1.103 There are currently no Government dietary recommendations for infants and young children that relate to hexabromocyclododecanes (HBCDDs). Technical mixtures of HBCDDs have been widely used as additive flame retardants in fabrics and in polystyrene products in the building and electronics industries. Most uses have now been restricted but they remain in the environment. The COT is considering possible health risks from the exposure of infants to HBCDDs in breast milk, dust and food.

Polybrominated biphenyls (PBBs) in the infant diet

1.104 There are currently no Government dietary recommendations for infants and young children that relate to polybrominated biphenyls (PBBs). Over the past four decades, the production and use of PBBs has been restricted progressively across the world, but they remain in the environment. The COT is considering possible health risks from the exposure of infants to PBBs in breast milk, dust and food.

Polybrominated diphenyl ethers (PBDEs) in the infant diet

1.105 There are currently no Government dietary recommendations for infants and young children that relate to polybrominated diphenyl ethers (PBDEs). They are

widely distributed in the environment although international agreements on bans and regulations on production and use of technical mixtures of PBDEs have been introduced since 2004, leading to declining levels in the environment. The COT is considering possible health risks from the exposure of infants to HCHs in breast milk, infant formula, complementary foods and from non-dietary sources.

Potassium-based salt replacers

1.106 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).

1.107 The COT are continuing to review papers on the adverse effects of increased levels of potassium in potentially vulnerable groups.

1.108 It is anticipated that the COT's views will be submitted to SACN in spring 2015.

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

1.109 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. This is in support of a review SACN are undertaking on the UK Government's dietary recommendations for infants and young children. Systematic reviews of the available, published, scientific literature have been commissioned by the FSA and will be discussed by the COT in 2015.

2014 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

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Dr L Kent (from April 2014)	
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Ms F Hill BSc (Hons) MSc	
Mr B Maycock BSc (Hons) MSc	
Dr D Parker BSc (Hons) MSc PhD (until June 2014)	
Dr D Hedley (from March 2014)	

DECLARATION OF MEMBERS INTERESTS DURING THE PERIOD OF THIS REPORT

Professor David Coggon OBE		
Personal Interest		**Non Personal Interest**
Shareholder Halifax/Lloyds Standard Life		**Trustee** Colt Foundation
Mr Derek Bodey		
Personal Interest		**Non Personal Interest**
None		**Member** COC FHRS steering group
Dr Roger Brimblecombe		
Personal Interest		**Non Personal Interest**
Member Home Office Advisory Council on the Misuse of Drugs		**Member** British Pharmacological Society British Toxicology Society Society for Medicines Research
Misc Consultant Editor Drug Discovery World		**Trustee & Treasurer** Bath & NE Somerset Volunteer Centre
Professor Janet Cade		
Personal Interest		**Non Personal Interest**
None		Kellogg - PhD student
Dr René Crevel		
Personal Interest		**Non Personal Interest**
Shareholder Unilever Centrica BG Group National Grid Lloyds		None

Employee Unilever		
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Employee MG Toxicology Consulting Ltd		None
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Employee Imperial College London: Small Area Health Statistics Unit, Department of Epidemiology & Biostatistics		**Research Grant** Defra **Misc**
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Shareholder Ryboquin Ltd Benenox Ltd		**Research collaboration** Cytosystems Ltd MRC Technology Ltd Cancer Research UK European Commission Carnegie Trust
Misc NHS Lothian University of Cambridge Cunningham Trust		**Misc** Office of the Scottish Charity Regulator - Board member **Fellowships** College of American Pathologists Royal College of Pathologists Royal College of Surgeons, Edinburgh Royal College of Physicians, Edinburgh

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Consultancy Kind Abdulaziz University (Saudi Arabia)		
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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

Dr John Thompson		
Personal Interest		**Non Personal Interest**
None		None

Professor Faith Williams (joined 1 April 2012)		
Personal Interest		**Non Personal Interest**
Shareholding Rio Tinto National Grid Vodaphone BP SSE Aviva		**Member** Commission on Human Medicines (currently invited expert) EMA Ad Hoc Group 3Rs ILSI Expert Working Group
		Current and recent research funding Astra Zeneca Syngenta HPA Department of health BBSRC Pfizer

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

Preface

I am pleased to present this report, which summarises the work of the Committee on Mutagenicity (COM) during 2014.

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 Committee 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 2014, the Committee published a Guidance note on the current knowledge on Mutational Spectra and their potential use in the interpretation of genotoxicity testing result. It discussed the ToxTracker assay, received a presentation on the assay by one of its developers and considered the possible role of the assay and what further work might be needed on it.

The Committee considered an updated review of the mutagenicity of alcohol and its primary metabolite acetaldehyde following a request from the COC to support its review of alcohol-induced carcinogenicity. As part of this review it initiated an overview of the potential role of oxidative damage as a mechanism of the genotoxicity of alcohol. 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. Unfortunately, the COM had to cancel one of its meetings in 2014 because of problems arising from Public Health England (PHE), who provide the scientific secretariat to the COM, being unable to fill vacant staff positions. This meant that it did not have a formal session on Horizon Scanning in 2014. However, topics for future consideration were identified during the other meetings and will be brought forward for discussion at the Committee's first meeting in 2015.

I am grateful for the support of the secretariat, who maintained their usual high standard of work despite the difficulties they faced because of the staff shortages 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

Mutational spectra

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 transversions).

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. From this evaluation and discussion, a statement was generated.

2.3 A variety of test systems were evaluated. *In vitro* systems included bacterial, human, rodent and transgenic cell lines. *In vivo* systems identified were primarily transgenic models from which genes were more easily isolated and sequenced (i.e. Muta^{TM} mouse, Big Blue and gpt delta mice). The COM agreed that the main value of MS was in evaluating a chemical's mode of carcinogenic action, and in understanding cancer aetiology, including the types of adducts and mutation involved in cancer.

2.4 The COM were of the opinion that the selectable genes in the Ames test Salmonella strains and genes such as the *hprt, gpt and tk* loci, in mammalian cells, whilst good systems for identifying chemically induced mutations, are not suitable for use in identification of MS. This is because mutations in such diagnostic genes in bacteria or cells are identified following selection through growth advantage and hence may not be representative of the overall pattern of mutation. Thus, MS are most appropriately identified in phenotypically neutral genes.

2.5 The COM noted that the analysis of p53 across different models was of value in evaluating chemically-induced mutations as it has been shown that mutation patterns are conserved in different test systems and species. Mutations in p53 are seen following exposure to PAH's in animals and these are correlated with those seen in some human cancers, for example in smokers, as detailed in an IARC database.

2.6 The human p53 knock-in (Hupki) mouse model was also considered. Important limitations in using *in vitro* systems were noted. For example, DNA damage and mutation are more likely to occur *in vitro* than *in vivo* due to the greater potential for oxidative damage and therefore results from cell lines being possibly unrepresentative of untransformed diploid cells.

2.7 The COM advised that currently, there were only a few good examples of mutation spectra that could be associated with certain cancer causative agents. These agents are; UV light, aflatoxin B1, tobacco smoke and aristolochic acid. The MS of

aflatoxin B1 is distinct in human liver tumours. It was noted that a number of factors could also affect mutation spectra for aflatoxin and other chemicals, such as the effect of viruses (e.g. hepatitis B for aflatoxin) and the time at which spectra are measured (i.e. mutation spectra may change over time after the initial chemical exposure).

2.8 Aristolochic acid was considered to generate an unusual tumour and distinct MS. It was considered to be the best example of a specific chemically induced MS. A distinct MS may also be apparent for smoking related exposures, when the sample or measurement was taken at the right time and in the right tissue.

2.9 The COM agreed that the development of 'next generation sequencing' technologies, where the whole genome could be sequenced would provide a substantial amount of new data that could be very useful for evaluating and understanding the role of mutation patterns in cancer development.

2.10 The COM considered the use of MS from transgenic animal models in interpreting the significance of a positive *in vitro* genotoxicity result and a negative *in vivo* genotoxicity test results, where a chronic carcinogenicity assay was positive. It was suggested that in such cases, any differences in metabolism and target tissues exposure would be considered.

2.11 In conclusion, Members agreed:

- Despite an extensive literature describing studies which examine chemically induced mutation spectra in a wide variety of *in vitro* and *in vivo* systems, there are still very few examples where a specific mutation spectrum clearly establishes a specific genotoxic mode of action for a chemically-induced human tumour. Of those highlighted, there is still some uncertainty surrounding the robustness of the spectrum for AFB1 and liver cancer, and although the relationship between smoking, B[a]P exposure and the induced spectrum is characterised, causality remains unproven Aristolochic acid appears to provide the best example for a diagnostic mutation for a human cancer induced by a chemical.
- Mutation signatures using current, single gene, approaches may, on a case-by-case basis, provide useful mechanistic insight into genotoxic modes of action.
- The embryonic stem cells cultured from the HUPKI mouse do not always reflect human p53 mutation response, but as an *in vitro* model they do appear to offer some advantages over other models.
- Major advances in understanding the processes of mutagenesis and carcinogenesis are anticipated when data from studies using next generation sequencing become available. Data to evaluate whether this is the case are awaited.

The full statement is published on the COM website.

TOX Tracker Assay

2.12 The ToxTracker assay is a new genotoxicity test system comprised of a set of reporter cell lines where 6 identified genes reflecting key pathways have been cloned into mouse embryonic stem cells. The COM reviewed the papers published describing the development of the test system and proof of concept exercises and the validation data from the test system published to date. Members were also given a presentation by the director of laboratories responsible for developing the assay

2.13 The COM Members agreed that the assay appeared to be an interesting approach to identifying genotoxicants and would be potentially useful in evaluating mode of genotoxic action, although it was noted that the selection of the genes used in the test system could have been chosen on an empirical basis rather than on a mechanistic basis. Chemically induced genotoxicity, could be detected by the induction of Green fluorescent protein (GFP) determined by flow cytometry.

2.14 According to the Tox Tracker website the entire system comprising six cell lines would be required for the assay to be of sufficient value. Validation data from only two of the cell lines had been published namely the Bscl2 reporter cell line responding to genotoxins and the Srxn1 reporter cell line, responding to pro-oxidants. The COM was not aware of published validation data for the other cell lines, namely Rtkn, Blvrb, Ddit3 and Btg2. The small number of chemicals tested in the presence of S9; a lack of evaluation of the effects of S9 on the expressed genes; and the unexpected results for methyl methanesulphonate (i.e. did not indicate a predominantly genotoxic response); were all considered to be limitations of the data. Currently, the apparent high sensitivity of the test system indicated on the website could not be verified from the published data.

2.15 The COM considered that pro-oxidants have genotoxic potential i.e. if the degree of oxidation is sufficient then genotoxicity may occur. It was noted that processes that lead to oxidative stress generated *in vitro* can be very different to those generated *in vivo* (which may also be attributable to immune driven or inflammatory responses).

2.16 At a later date, Dr Giel Hendriks from the University of Leiden, was invited to the COM and gave a presentation on ToxTracker. Dr Hendriks provided further insight into advantages of this genotoxicity assay over standard *in vitro* test systems and some details of the practical aspects of the assay.

2.17 Different types of genotoxicity could be detected by certain reporter or biomarker genes related to certain cellular pathways and related biological damage (e.g. DNA damage detected by Bacl2 and Rtkn; oxidative stress detected by Srxn1 and Blvrb; and protein stress by Ddit3). Thus Toxtracker has the capacity to provide some insight into the mechanism of genotoxicity. For validation of the assay, the

developers used the ECVAM-suggested library for carcinogens and non-carcinogens and the USA Toxcast library.

2.18 Optimum sampling time was considered to be 24 hours after initial exposure, a time point sufficiently long to detect aneugenic activity, which was considered to be a later event. The cut off point for a positive genotoxicity result was chosen as a 1.5 fold increase in the induction of GFP, which was 5 times the standard deviation. All compounds could be tested in the test system with the addition of S9, which is considered to be the most effective method for the inclusion of metabolic activation. Using specifically designed software , the fold increase in GFP induction was used to determine an overall positive genotoxicity response, calculated at a certain degree of cytotoxicity (50% cytotoxicity was selected as the optimum value).

2.19 The COM considered the role of this assay in a testing strategy. It was suggested that the current view was that it would be useful as an early screen before *in vivo* testing or as a biomarker assay as it does not directly address one of the three mutagenic endpoints (i.e. aneuploidy). ToxTracker may help with the overall interpretation of a scenario where there was a positive *in vitro* genotoxicity result, considered to be weak or a misleading positive and it may be potentially useful in a genotoxicity testing strategy where *in vivo* testing is not permitted, such as in the testing of cosmetics. The committee considered that an inter-laboratory trial for the use of this assay would be useful, but queried how costly and resource demanding the assay would be to use.

2.20 The COM agreed that there was a need to gain a better understanding of what the gene expression changes meant in terms of the mechanism of genotoxicity (i.e. what the genes were doing or reflecting) and that an inter-laboratory trial for the assay would be useful.

Ongoing work

Review of the Mutagenicity of Alcohol

2.21 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 (see section Alcohol and cancer para 3.6). This review would provide insight to COC regarding possible mechanisms of cancer causally associated with the consumption of alcoholic drinks.

2.22 Two papers were considered by the COM in 2014: a review of the new evidence on genotoxic effects of alcohol, alcoholic beverages and acetaldehyde; and a preliminary overview of alcohol and oxidative DNA damage.

This topic will continue in 2015, as the Committee will discuss and publish a statement.

OECD Test Guidelines Programme

2.23 During the year COM commented on several OECD genotoxicity Test Guidelines (TG).

- Draft TG in vitro Syrian hamster embryo (SHE) cell transformation assay
- Draft TG474 Mammalian erythrocyte micronucleus test
- Draft TG475 Mammalian bone marrow chromosomal aberration test
- Draft TG473 in vitro Mammalian chromosome aberration test
- Draft TG487 in vitro Mammalian cell micronucleus test
- Draft TG in vivo Mammalian alkaline comet assay
- Draft Guidance document on the genotoxicity testing for manufactured nanomaterials

Horizon Scanning

2.24 The horizon scanning exercise provides information which can be used by Government Departments/Regulatory Agencies to identify important areas for future work. There was no formal horizon scan exercise in 2014. Aspects from 2013 were taken forward in 2014.

DECLARATION OF 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 G Clare	Covance AstraZeneca Diageo HBOS Marks & Spencer Shell Research Ltd Astra Zeneca	Consultant Shareholder 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
P Hardwick	Unilever plc	Pension	None	None
Professor G Jenkins	None	None	Hoffman-LaRoche	Research Grant 2008 – 2010 Consultancy 2008

Member	Personal Interest		*Non-Personal Interest*	
	Company	Interest	Company	Interest
			Unilever CEFIC/ECETOC	Research Grant 2008 - 2010 Honorarium 2008
Professor D Kirkland	Kirkland Consulting GSK 3i Standard Life Corning Covance ILSI HESI ECVAM ESAC	Principal Shareholder Shareholder Shareholder Shareholder Shareholder and share option holder Committee member Member of peer-review panel	None	None
Dr A Lynch	GlaxoSmithKline	Salary Shareholder	None	None
Professor F Martin	Cable & Wireless	Shareholder		
Professor M O'Donovan	O'Donovan GT Consulting LTD	Director	None	None
Professor D H Phillips	Aviva Banco Santander BG Group Bradford & Bingley Centrica National Grid Takeda	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultant		
Professor M J Rennie	None	None	None	None
Professor S H Doak	None	None	Astra Zeneca Unilever Hoffman-LaRoche	PhD studentship grants 2009-2016 PhD studentship grants 2010-2017 Research Grant 2008 – 2010

Member	**Personal Interest**		***Non-Personal Interest***	
	Company	Interest	Company	Interest
			Unilever	Research Grant 2008 - 2010

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

Preface

The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) evaluates chemicals for their carcinogenic potential in humans at the request of UK Government Departments and Agencies. The membership of the Committee, agendas and minutes of meetings, and statements are all published on the internet (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 2014. There were two continuing major items on which the committee's advice was requested during the year. These were the substantial update of the 2010 review by the WHO International Agency for Research on Cancer (IARC) review of the risk of cancer from consuming alcohol, and our series of Guidance Statements on the risk assessment of chemical carcinogens. Advice was also sought by the FSA on the results of a trial which indicated an increased risk of cancer from taking Vitamin E supplements and on an opinion by the European Food Safety Authority's Contaminants' Panel on acrylamide. Also, Professor Heather Wallace gave the rest of the committee an interesting presentation on the use of zebrafish in biomedical research, which was much appreciated.

As always, I am grateful to members of the committee for the invaluable advice they have provided during the year and to the secretariat for its support. I look forward to working with them on yet more challenges in 2015.

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Professor David H Phillips
BA PhD DSc FRCPath

COC Evaluations

Consultation of the European Food Safety Authority on a Draft Scientific Opinion on Acrylamide in Food

3.1 At the July meeting, Members were asked for their views on a draft Scientific Opinion on acrylamide in food issued for public consultation by the European Food Safety Authority (EFSA). The COC had not previously performed a risk assessment on acrylamide. The comments were combined with those of the COT before submission to EFSA. The combined comments can be found in paragraph 1.18.

Horizon Scanning

3.2 Following the horizon scanning exercise in 2013, the Committee agreed the following list of priorities for consideration:

High priority:
- Alcohol and cancer
- Alternatives in risk assessment

Medium-high Priority
- Mode of action framework

Medium Priority
- Thresholds of Genotoxicity – keep informed of COM work
- Nanomaterials – presentation of research on inhalation of nanomaterials
- Dose response modelling in epidemiology studies - this will be covered as part of the Guidance Statement series G2 (Interpretation of Evidence of Carcinogenicity in Humans)
- *In vitro* cell lines - to be undertaken when resource allows
- ETS Exposure in Childhood and Cancer Risk - to be undertaken when resource allows

Low Priority
- Mechanistic studies in Zebrafish

3.3 Due to the volume of work currently being considered by the COC, some of which was addressing topics from this list, no horizon scanning paper was prepared for the Committee to discuss in 2014. However, Members were reminded that topics of relevance to the Committee could be raised with the Secretariat at any time.

3.4 The Committee has continued to work on a number of the topics.
- Alcohol and cancer is discussed in paragraph 3.6.
- Alternatives in Risk Assessment will form section D of Guidance Statement G07 but this sectionwill be drafted after sections A (in vivo assays) and B (cell transformation assays) are agreed, probably in 2015.
- A presentation was given on Mechanistic studies in Zebrafish and this is described below.

Zebrafish

3.5 At the March meeting, Professor Heather Wallace gave a short presentation to the Committee on the use of Zebrafish (*Danio rerio*) in biomedical research. This topic had previously been raised during horizon scanning because of the increased use of Zebrafish as a model in toxicological research and development. The presentation described the fish model and the benefits of the fish i.e. they are transparent and generate a large supply of eggs so that statistically meaningful

studies are easily designed. Also, they are small in size, easily manipulated and can be grown in 96-well or 384-well plates. The main disadvantages are that the fish lack some mammalian organs, are diverse from man on the evolutionary tree, and that, because the compound under investigation is administered in the water, it is not possible to carry out studies on absorption, metabolism, distribution or pharmacokinetics. It was also noted that Zebrafish are prone to parasitic infections. Preliminary trials have shown that they can be used to investigate toxicity endpoints. General toxicity, and some organ specific toxicity (liver), can be identified. Zebrafish express some enzymes that are also found in humans. There are numerous other general uses, including in cancer biology but, in general, they are considered useful for preliminary screening only.

Ongoing work

Alcohol and cancer

3.6 The need for an updated review of alcohol and cancer was identified by the Committee during the Horizon Scanning exercise at its meeting in November 2012 and it was considered that a statement generated from such a review would provide useful information for both Public Health England (PHE) and the Department of Health (DH).

3.7 Following on from the papers reviewed by the COC in 2013, in 2014 papers were presented to the Committee on:

- alcohol consumption and pancreatic cancer risk
- alcohol consumption and liver cancer risk
- alcohol consumption and breast cancer risk
- alcohol consumption and colorectal cancer risk
- effect of cessation of alcohol consumption on oesophageal and head and neck cancer risk
- cessation of alcohol consumption and effect on liver cancer risk
- publications suggesting a decrease in risk among drinkers compared to non-drinkers for Hodgkin's and non-Hodgkin's lymphoma, extra-hepatic bile system cancer and renal cancer
- a strategy to calculate burden of cancer attributable to alcohol consumption.

In addition, further papers on the ongoing review by the UK's Chief Medical Officers were discussed as reserved business as the results had not yet been published.

The review of alcohol and cancer risk is ongoing, with a number of further papers expected in 2015.

IGF-1 and cancer risk

3.8 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.

3.9 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 2014. It is hoped that it will be progressed in 2015.

Vitamin E and the risk of prostate cancer

3.10 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.

3.11 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. A first draft statement was produced in 2013. In 2014, the Committee considered two further drafts of the statement, which will be published in 2015.

Guidance statements

3.12 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.

3.13 During 2014, the COC published guidance statement G05 "Points of Departure and Potency Estimates", which discusses various methods for identifying a level of (no) effect or a point of departure from the dose-response curve which can be used as a basis for risk characterisation.

3.14 Work began on Guidance statement G03: "Hazard identification and characterisation: Conduct and Interpretation of Animal Carcinogenicity Studies'. This is expected to be published early in 2015.

3.15 The Committee discussed further drafts of statement G07: "Alternatives to the 2-year bioassay", particularly on Section A, which discusses alternative *in vivo* studies. It is intended to publish this and Section B in 2015 with two further sections to follow.

Declaration of 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	AstraZeneca Covance Diageo Marks & Spencer Shell Research Ltd	Shareholder, deferred pension Cytogenetic consultant Shareholder Shareholder Pension		
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 Biotie Therapies Inc., S. San Francisco, USA	Consultant		

Member	**Personal Interest**		**Non-personal Interest**	
	Company	Interest	Company	Interest
	Experimental Pathology Laboratories Inc., Sterling, Virginia, USA Johnson & Johnson Pharmaceutical Research & Development LLC, Raritan, New Jersey, USA Shire Pharmaceutical Development Ltd, Basingstoke, UK and USA Actelion Pharmaceuticals Ltd, Allschwil, Switzerland. Arena Pharmaceuticals, Inc., San Diego, California Astellas Pharma Europe Ltd Daiichi Sankyo, Edison, New Jersey GlaxoSmithKline, Ware Hyperion Therapeutics, Inc., San Francisco, California Novo Nordisk,A/S, Malov, Denmark Sun Coast Tox Inc., San Diego, California.			
Prof Ray Kemp BA MSc PhD	Ray Kemp Consulting Ltd	Shareholder	ARPANSA	Chair of the Radiation

Member	**Personal Interest**		**Non-personal Interest**	
	Company	Interest	Company	Interest
MRTPI				Health and Safety Advisory Council
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
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	Friends Provident Northern Rock Epidemiological Advice relating to dermatitis study to Unilever. Epidemiological advice on study to Transport and	Share holder Shareholder Consultancy Consultancy	CONCAWE (Conservation of Clean Air and Water Europe) CEFIC (European Chemistry Council) Other grants	Research support Research support Research support

Member	**Personal Interest**		**Non-personal Interest**	
	Company	Interest	Company	Interest
	General Workers Union Epidemiological review of occupational causes of malignant melanoma.	Expert witness	from UK government agencies & departments e.g. Food Standards Agency, Health & Safety Executive. ECETOC Scientific Committee ECPA Scientific Advisory Board on Epidemiology	External Committee member Member
Dr Heather Wallace BSc Hons PhD FRCPath FBTS	Bank Santander SA BT Group NovaBiotics Antoxis Precious Cells Cell ProTx	Shareholder Shareholder Shareholder Shareholder Shareholder Director	None	None
Dr Rosemary Waring PhD DSc FRCPath	Centrica and National Grid	Shareholder	Ministry of Defence	Research Support
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
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 2013/14 the budget for the COT, excluding Secretariat resources was £35,550. 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[1].
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.

[1] 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).

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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.[++]

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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/

+ Available on the COC website at 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/

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