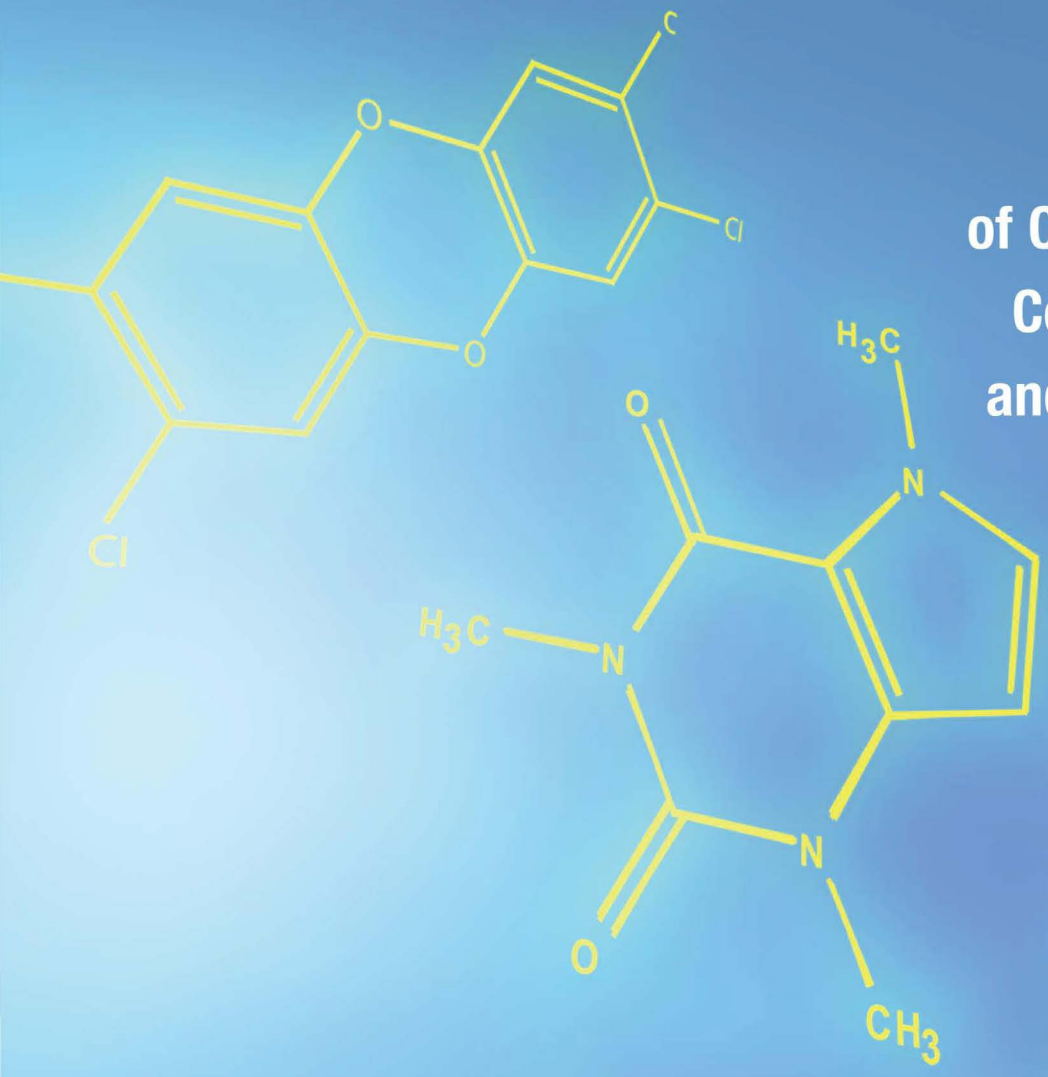
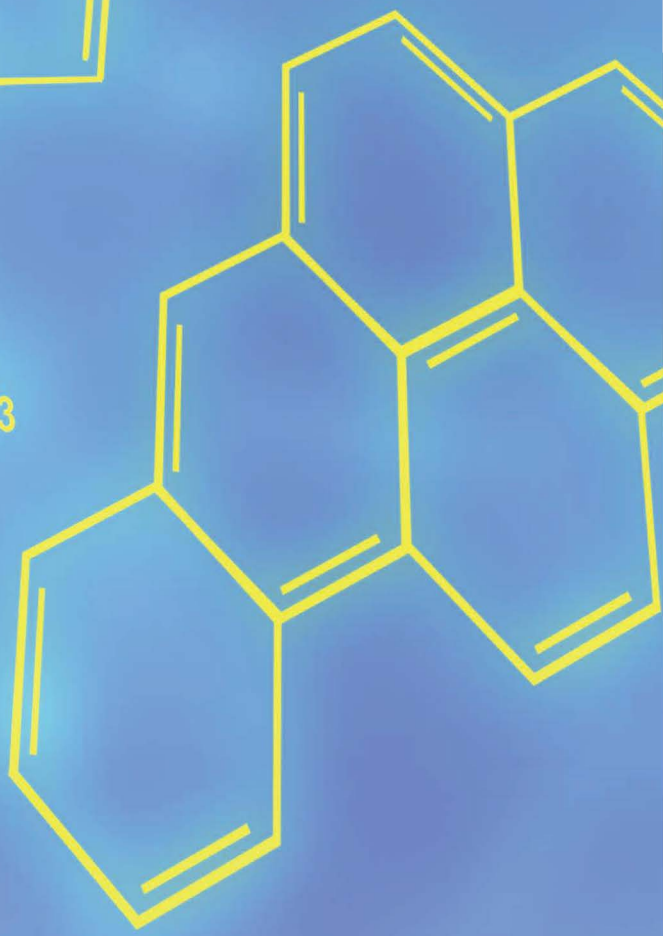
Committees on Toxicity Mutagenicity Carcinogenicity of Chemicals in Food, Consumer Products and the Environment





Committee on TOXICITY

Committee on CARCINOGENICITY

Committee on MUTAGENICITY

Annual Report 2013

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

Annual Report 2013

Contents

About the Committees

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

The aim of these reports is to provide a brief toxicological background to the Committees' decisions. Those seeking further information on a particular subject can obtain relevant references from the Committee's administrative secretary or from the internet sites listed below.

In common with other independent advisory committees, Committee members are required to follow a Code of Conduct which also gives guidance on how commercial interests should be declared. Members are required to declare any commercial interests on appointment and, again during meetings if a topic arises in which they have an interest. If a member declares a specific interest in a topic under discussion, he or she 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: http://www.iacoc.org.uk/index.htm
COM: http://www.iacom.org.uk/index.htm

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

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

Preface

I am pleased to present this report, which summarises the work of the Committee on Toxicity (COT) during 2013. 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.

Much of the recent work of the Committee has been in support an ongoing review, led by the Scientific Advisory Committee on Nutrition (SACN), of the scientific evidence unperpinning Government's dietary recommendations for infants and young children. SACN asked COT to advise on possible toxic effects of chmicals in the infant diet, and as part of this, during 2013, the Committee published statements on aluminium, lead and vitamin A.

The Committee also published two position papers, one on contamination of air in the cabins of commercial aircraft by engine oils and their combustion on products, and the other on the artificial sweetener, aspartame. In both cases, a critical question was whether illness that has been reported to occur immediately following exposure is a toxic effect, or arises through psychological mechanisms.

In addition, the Committee provided advice to help inform Government policy on incapacitant sprays used by the police, and the regulatory assessment and classification of contaminated land.

Other topics covered during the year included possible chemical causes of obesity, standards for composting and anaerobic digestion of waste, and the adequacy of methods of testing for toxicity of chemicals in juveniles.

As ever, I am grateful for the support of the secretariat, who maintained their usual high standard and output of work despite staff shortages.

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

COT evaluations

Adequacy of testing methods for juveniles

1.1 The Committee on Toxicity (COT) received a presentation on the adequacy of testing methods for juveniles by Professor Aldert Piersma of the National Institute for Public health and the Environment (RIVM), The Netherlands. The presentation was in response to the Committee's continuing interest in advances in developmental immunotoxicity and more recently, in review articles on juvenile animal testing which included immunotoxicity. It had been suggested that the review should be broadened to encompass the concept of juveniles as a sensitive group more generally.

1.2 The presentation provided an overview of current knowledge in the area, and included description of relevant tests available in the current Organisation for Economic Cooperation and Development (OECD) test guideline 443 (extended one-generation reproductive toxicity study). It then focussed on explanations for findings on developmental immunotoxicity that had been obtained by Professor Piersma and his colleagues using various exposure designs, and the observation that effects occurred at lower doses when exposure commenced in juvenile animals than when their mothers were exposed pre-mating. The Committee noted that this observation would require further consideration when developing drugs specifically targeted to children.

1.3 The inclusion of immune end points in current tests was particularly important for assessment of immune status in juvenile animals, as it is not possible to extrapolate from end points for adult animals. However, the significance of changes in some immune markers for hazard assessment needed further consideration. Testing with a wider spectrum of compounds was needed to gain further insight into the specificity of the observed responses in the test species and their relevance to adult animals.

1.4 The OECD were considering the inclusion of new technologies in more contemporary study designs but this was at a more advanced stage with respect to the assessment of sensitisation than for other endpoints. The Committee concluded that in absence of a dose-response relationship and a mechanism, the reported experimental findings on immune parameters following chemical challenge should be regarded as preliminary, particularly as the link to human disease was not obvious.

Aircraft cabin air environment

1.5 For some years, there have been concerns about possible adverse health effects, both short- and long-term, in the crew of commercial aircraft, as a consequence of episodes in which cabin air becomes contaminated by components and/or combustion products of engine oils (fume events).

1.6 At its meetings on 17 September and 29 October 2013, the Committee on Toxicity (COT) discussed reports of four research projects (Cranfield University 2008, 2009; Institute of Environment and Health 2011a/b; Institute of Occupational Medicine 2012) that had been commissioned by the Department for Transport (DfT) in response to recommendations that had been made by the Committee in 2007 (COT, 2007). These projects aimed to assess airborne concentrations and surface deposition of chemical pollutants in the cabins of commercial aircraft, and to investigate operational parameters associated with fume events. The Committee also considered papers that had been published in the peer-reviewed scientific literature since 2007, concerning exposures to chemical pollutants in aircraft cabins.

1.7 A position paper was produced summarising the Committee's evaluation of the four reports, the conclusions that could be drawn from the evidence that it had considered to date, the scientific uncertainties that remained, and options for further research to address these continuing uncertainties.

1.8 The first of the four projects was a preliminary study to test air-sampling devices that might be used to monitor cabin air (Cranfield University, 2008). It highlighted several problems that would need to be overcome in an air-monitoring study. These included a need for correct orientation of sampling tubes, better standardisation of methods (inter-laboratory agreement on quantitative measurements was poor), further validation of the analytical methods, and adaptation of the methods to measure compounds up to C17. It also indicated that one method – diffusive SPME fibres – was unsuitable. Measurements during a perceived fume event revealed a transient increase in ultra-fine particle concentration, lasting only a few seconds. With the technology that is available, peak concentrations of such short duration would be difficult to detect for many pollutants, unless the increases above background were extremely large.

1.9 These findings were taken into account in the design of a subsequent air-sampling study (Institute of Environment and Health, 2011a/b), although quality assurance was still less than desirable. The specific flights that were monitored were determined by practical considerations, but the study design ensured that various types of aircraft and engine were covered, including some about which (based on anecdotal reports) there had been a priori concern. No major fume events

occurred during the sampling. Only a limited range of analytes were measured, although retained gas chromatography traces would allow assessment of others if required. Visual inspection suggested that in the absence of a major fume event, there was little correlation between pollutants in the temporal fluctuation of airborne concentrations (i.e. they did not all tend to go up or down at the same time). However, this was not examined by formal statistical methods.

1.10 Conclusions that could be drawn from the study were:

i. Prospective monitoring of cabin air by the methods that were employed in this investigation is difficult because of the limited space in the flight deck and the need to accommodate both equipment and an operator. Given the rarity of major fume events, it would be extremely expensive to conduct such monitoring on sufficient flights to be confident of obtaining useful information about the patterns and levels of pollution during such incidents.

ii. For the types of aircraft studied, and in the absence of a major fume event, airborne concentrations of the pollutants that were measured in the study are likely to be very low (well below the levels that might cause symptoms) during most flights. The data did not rule out the possibility of higher concentrations on some flights (only a limited sample of aircraft could be tested), or of higher concentrations of other pollutants that were not measured.

1.11 The study also provided data which had been useful in interpretation of the surface residues study (see below).

1.12 COT members did not identify any scientific questions of high priority that could be addressed by further analysis of data from the study.

1.13 A study on surface residues (Institute of Occupational Medicine, 2012) looked at an even smaller number of chemicals – four organophosphate compounds selected because they were common additives in aircraft lubricants and fluids, and had been a source of concern because of their potential neurotoxicity. However, the methods used could be extended to other non-volatile pollutants. The 17 aircraft studied had not been subject to any major fume events, and the levels of chemicals that were measured were all low. The authors of the report concluded that the levels appeared consistent with those from the cabin air-sampling study. However, this assumed a single value for deposition velocity applicable to all particles, and that that all of the contaminant was present as particles and not vapour, which may not be justified.

1.14 A statistical analysis of reported incidents (Cranfield University, 2009) was limited by lack of information about the timing of fume events during the flights that were

analysed. Thus parameters that were statistically associated with flights in which incidents occurred may have reflected the pilot's response to the incident rather than aspects of function that predict the occurrence of a fume event. The study did, however, demonstrate the feasibility of this type of statistical analysis, which with some refinement and simplification might usefully be applied in further research (see below).

1.15 The review of recently published literature on chemical pollutants in aircraft cabin air was consistent with the results of the studies commissioned by DfT in showing only low levels of pollutants in the absence of any major fume event. Of particular note was a biomonitoring study by Schindler et al (2013) in which urine samples had been collected from pilots and cabin crew members who reported fume/odour during their last flight. None of the samples contained ortho tricresyl phosphate (o-TCP) above the limit of detection (0.5 µg/l), and while the fume incidents may only have been minor, the study demonstrated the feasibility of collecting meaningful data in this way. A study by Liyasova et al. (2011) who monitored adducts of a TCP metabolite with butyrlycholinesterase in blood, illustrated another biomarker of exposure that might be used. Adducts were detected in six out of 12 jet plane passengers, but only at very low levels.

1.16 Taking into account information that it had considered previously (COT, 2007), along with the results from the new research that had now been reviewed, the Committee agreed several conclusions:

i. Contamination of cabin air by components and/or combustion products of engine oils, including triaryl phosphates, does occur, and peaks of higher exposure have been recorded during episodes that lasted for seconds.

ii. Episodes of acute illness, sometimes severely incapacitating, have occurred in temporal relation to perceived episodes of such contamination.

iii. There are a number of air crew with long-term disabling illness, which they attribute to contamination of cabin air by engine oils or their combustion products.

iv. The acute illness which has occurred in relation to perceived episodes of contamination might reflect a toxic effect of one or more chemicals, but it could also have occurred through nocebo effects.

v. While there is strong scientific evidence that nocebo effects can lead to (sometimes severely disabling) illness from environmental exposures that are perceived as hazardous, there is no simple and reliable way of establishing that nocebo responses are responsible for individual cases of illness. However, they are a plausible alternative explanation if toxicity

seems unlikely. Distinguishing whether acute illness from fume events is likely to arise from toxicity or nocebo responses depends on: assessment of the patterns of symptoms and clinical abnormalities in affected individuals; the levels of relevant chemicals to which they might have been exposed; and what is known about the toxic effects of those chemicals and the levels of exposure at which such toxic effects occur (including the possibility that some individuals might be unusually sensitive).

vi. The patterns of illness that have been reported following fume events do not conform with that which would be expected from exposure to triaryl phosphates such as o-TCP (which differs from the pattern of illness that occurs with over-exposure to organophosphate insecticides and nerve agents). Over-exposure to tricresyl phosphates would be expected to cause delayed peripheral neuropathy. Given the short duration of reported fume incidents, in order to cause such toxicity, peak exposures would have to be much higher than those which have been indicated by monitoring to date. For example, the current short-term exposure limit averaged over a 15 minute period) for o-TCP is 300 µg/m3, whereas the maximum concentration of the compound that was recorded in the cabin air-sampling study was 22.8 $\mu g/m^3$. Assuming that a peak of exposure was sustained for a minute, it would need to exceed 4000 $\mu g/m^3$ to breech the short-term limit.

vii. More generally, the Committee considered that a toxic mechanism for the illness that had been reported in temporal relation to fume incidents was unlikely. Many different chemicals have been identified in the bleed air from aircraft engines, but to cause serious acute toxicity, they would have to occur at very much higher concentrations than have been found to date (although lower concentrations of some might cause an odour or minor irritation of the eyes or airways). Furthermore, the symptoms that have been reported following fume incidents have been wide-ranging (including headache, hot flushes, nausea, vomiting, chest pain, respiratory problems, dizziness and light-headedness), whereas toxic effects of chemicals tend to be more specific. However, uncertainties remain, and a toxic mechanism for symptoms cannot confidently be ruled out.

viii. Decisions to undertake further research will need to balance the likelihood that it will usefully inform further management of the problem against the costs of undertaking the work.

ix. One possibility would be to collect better information about the incidence and nature of fume incidents, and the circumstances in which they occur. This would require airlines to record and retain a limited set of information on all flights that they operate, including the place, date and time of departure and arrival; the type and age of aircraft and engines; the relevant service history of the engines; and whether a fume incident was

reported during the flight. In addition, for the small minority of flights on which fume incidents were reported, information would be collected on the stage of the flight at which the incident occurred; its nature and duration; and any consequences (e.g. health effects in crew). This information could then be used to determine the incidence of contamination episodes by type and severity, and to assess their association with different features of flights (which might provide clues to methods of prevention and assist planning of further studies). Such associations could be explored using a case-control approach. Importantly, a study of this type would not require collation of all of the collected information in a single dataset. For example, one database might hold routine information about times and places of departure and arrival for each flight, and the identity of the plane. A second database might record details of each plane and its engines, including year of manufacture and service history. A third database could cover fume incidents, including the places and times of departure and arrival and identity of the plane, as well as information about the nature, timing and consequences of the fume incident. Information could then be abstracted from these databases and linked, but only for flights in which fume incidents occurred and a representative sample of control flights (a few hundred at the most).

x. As an extension to the above study, a case-control approach could also be used to investigate associations of fume incidents with operational parameters of the sort that were ascertained in the project previously commissioned by DfT, but this time restricted to those measured before the incident occurred. This might give further clues to aspects of engine operation that predispose to fume events.

xi. Another possible extension to a systematic study of fume incidents would be to collect and store samples of urine, and possibly blood, from crew members within 48 hours (the earlier the better) after such events. These could then be analysed for biomarkers of potential toxic pollutants, as in the studies by Schindler at al. (2013) and Liyasova et al. (2011). Again, this could provide evidence of exceptionally high levels of chemical contamination that might be sufficient to cause acute toxicity.

xii. Since 2007, there have been significant advances in the technology that is available for air-monitoring, and in theory it should now be possible to develop a compact, battery-powered automated system, in which a particle counter would run continuously, and trigger other sampling instruments if and when a fume incident occurred. The samples collected could then be used to identify any chemicals that occurred at exceptionally high concentrations during the fume incident, and the levels at which they occurred. To have a good chance of detecting at least one major fume incident, sampling would need to be carried out in many aircraft over many

flights, and this would make data collection extremely expensive (possibly >£10m). Costs would be importantly reduced, however, if a way could be found to induce fume events experimentally, or if circumstances could be identified in which their incidence was much higher than the overall average.

xiii. All of the options for research that have been described would require care in design and execution, and if wished, members of the COT with relevant expertise would be pleased to advise on the specification of calls for proposals and to provide peer-review of proposals that were received.

1.17 Finally, it should be emphasised that illness can be disabling whether it occurs through toxicity or through nocebo effects, and therefore there is a continuing imperative to minimise the risk of fume incidents that give rise to symptoms.

Aluminium in the infant diet

1.18 The COT were asked by the Scientific Advisory Committee on Nutrition (SACN) to review the risks of toxicity from chemicals in the infant diet. This statement focussed on the potential risks from aluminium

1.19 Infants may be exposed to aluminium compounds through inhalation of dust, ingestion of soil and from the diet. Use of aluminium-containing cosmetic products is unlikely in this age group. The diet is likely to be the main source of exposure.

1.20 Aluminium is present in the infant diet as a result of its natural occurrence in foods, its presence in drinking water (either naturally or from water treatment) that is used to reconstitute infant formula or consumed directly, and possibly through contact with food containers such as cans, cookware, utensils and food wrappings. In addition, although aluminium-containing food additives are not permitted in infant formulae or processed foods for infants, they may be present in some foods fed to infants, and additional aluminium may come from the use of aluminium-containing food contact materials in the home.

1.21 Aluminium is taken up from the gut, but absorption is low (generally 0.5% of intake or less). The presence of citrate (citric acid) in some foods, increases absorption. No data are available on the absorption of aluminium in infants specifically. There is evidence that aluminium accumulates in the human body with levels in tissues tending to increase with age. The primary route by which aluminium is eliminated from the body is urinary excretion. Since kidney function is not fully developed at birth, lower rates of elimination would be expected in infants than in adults.

1.22 The main toxic effects of aluminium are on the brain and nervous system and on the kidney, although these have not been shown conclusively to result from dietary exposure in humans. The World Health Organization (WHO) has established a Provisional Tolerable Weekly Intake (PTWI) of 2 mg/kg body weight (expressed as aluminium) for all aluminium compounds in food, including food

additives. The COT considered that the derivation of this PTWI was sound and that it should be used in assessing potential risks from dietary exposure to aluminium. The PTWI is a level of intake below which there is reasonable confidence that consumption every week over a lifetime would not cause harm to health.

1.23 From the small number of available studies, it appears that exposure to aluminium in exclusively breastfed infants is less than 10% of the PTWI.

1.24 Exposure of infants fed exclusively with infant formula is similar to, or a bit higher than that of exclusively breastfed infants, the highest potential exposure being from soya-based formula. This could amount to some 21% of the PTWI, and in the worst case, the water used in reconstitution of powdered formulae could contribute a further 12% of the PTWI.

1.25 Estimates of exposure of older infants to aluminium from infant formula combined with commercial infant foods are up to 39% of the PTWI, without taking into account water used in reconstitution or consumed separately. However, even unusually high water concentrations of aluminium are unlikely to take total intake above the PTWI. Exposure from foods not specifically marketed for infants, which may contain aluminium-based food additives, is currently unknown. Further information on this may become available from a new survey (the UK Dietary and Nutrition Survey of Infants and Young Children), data from which were being analysed at the time the COT statement was finalised.

1.26 Overall, the estimated exposures of infants to aluminium from the dietary sources that have been considered do not indicate toxicological concerns or a need for modified Government advice.

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

Aspartame: response to EFSA consultation on a draft scientific opinion

1.28 The COT was asked by the Food Standards Agency to consider a draft European Food Safety Authority (EFSA) opinion on the re-evaluation of aspartame, and to provide comments as a basis for the UK response.

1.29 The COT considered that the draft opinion was based on a very thorough and critical review of relevant evidence, not only on the parent compound but also on metabolites and breakdown products. The COT were not aware of any significant papers which had been missed.

1.30 The COT welcomed the use of the IPCS Mode of Action framework for a non-cancer end-point and considered that its application was thorough and well described. The approach used by the EFSA Panel for blood level modelling and

consideration of peak plasma levels was appropriate and the approach to chronic end-points acceptable. Thus the data did not indicate a need to revise the Acceptable Daily Intake (ADI).

1.31 The COT considered that the opinion was well structured, comprehensive and the conclusions reached were justified on the basis of the available evidence. However the COT suggested that several points could have been strengthened, amplified or clarified. In particular, despite not being conducted to current standards, the animal studies provide no evidence that aspartame presents a risk of carcinogenicity, reproductive or developmental toxicity and this is supported by the available human data.

Aspartame: FSA-funded research on a pilot double blind placebo crossover study of the symptoms of aspartame in subjects who have reported symptoms in the past compared to controls

1.32 The COT discussed the results from a study led by scientists at Hull York Medical School, in which a cereal bar containing aspartame and a control bar with similar flavour but containing no aspartame, were administered to participants in randomised order. The participants included individuals who had previously experienced symptoms which they attributed to aspartame and others with no known or suspected sensitivity to the chemical. Outcomes assessed following ingestion of the cereal bars included various symptoms and biochemical measures. At the time of data collection, neither the participants nor the researchers were aware of which cereal bars contained aspartame.

1.33 The COT made a number of comments on the results and made suggestions on improved analytical approaches to the data obtained. A report of the study has been 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 need for action to protect the health of the public.

Combined use of CS (2-chloro-benzylidene malonitrile) and PAVA (nonivamide) (captor 2) irritant sprays

1.34 This item was presented by the Home Office. The Committee had previously considered the potential effects of combined exposure to 2-chlorobenzylidene malonitrile (CS) and pelargonic acid vanillylamide (PAVA) in 2006 (http://cot.food.gov.uk/pdfs/cotstatementcspava0604.pdf). Based on the information available at that time, Members had considered that if the substances interacted, then at most, an additive effect could arise from combined exposure. In 2006, the Committee also recommended areas where additional data gathering would be useful to risk assessment in the future.

1.35 During 2013, Members revisited this topic at their September meeting. The meeting was held in reserved session pending the publication of a revised policy on the topic. One of the recommendations of the COT in 2013 was to undertake an extended study, which the Home Office planned to commission. It is intended that the minutes of the Committee's discussion in 2013 of the combined use of CS and PAVA will be published on its website in due course.

Contaminants in soil: new screening levels

1.36 Members were asked to consider the development of new screening levels for contaminants in soil at their May 2013 meeting. The supporting discussion paper had been introduced by the Department for Environment, Food and Rural Affairs (Defra). Specifically, the Committee's view was sought on a revised toxicological framework to aid the development of new screening levels for contaminated land risk assessment. Revisions to the relevant Statutory Guidance had occured in 2012 and the framework was being revised in light of that.

1.37 Land would be determined to fall into one of four categories with the fourth being the land of lowest concern. Water and boreholes would be dealt with separately. Part of the process for working out if land could fall into the fourth category would be to assess levels of chemicals against the Low Level of Toxicological Concern (LLTC), which was intended to represent an exposure of low health concern.

1.38 Defra had initially selected six contaminants for consideration on the basis that they covered the majority of exposure pathways and would therefore be an adequate test of the methodology. The choice had been supported by stakeholders when consulted. Sufficient dose-response information had been available to quantify risk at specific levels of exposure for the six contaminants examined, and the Contractors' use of probability density functions in the risk analysis had been a refinement. It was noted that although some contaminants were data-rich, that would not always apply. Following development of the framework it would be implemented by various organisations.

1.39 The broad approach was noted to be reasonable. However, it was also observed that what was deemed acceptable for Screening Levels would depend on subjective value judgements about uncertainties made by different organisations. Without centralised implimentation, there could be inconsistency in the approach to different chemicals. The potential effects of mixtures of chemicals were not addressed specifically but could be explored if relevant data were available.

1.40 Approximately thirty to forty chemicals had existing Soil Guideline Values (SGVs) and/or Generic Assessment Criteria. In those cases, previous methods of evaluation would continue to be used unless new toxicolological or exposure data arose that needed to be taken into account, or new risk management decisions were taken. In terms of clarifying the guidelines on soil sampling, the Committee

made the point that the potential for localised hot spots of higher contamination should be taken into account.

1.41 While in general, Members agreed that the report was good, some concern was expressed about the specification of thresholds that were above minimal risk. Currently, toxicological evaluation was used to derive minimal effect levels, known as Health Criteria Values (HCVs), and then a judgement was made by Local Authorities to apply less stringent criteria when deciding whether the levels of contaminant at a site were acceptable. However, it appeared that minimal effect levels were not the starting point in the new approach, and it was felt that this should be the case. In response, it was explained that within the new framework minimal risk levels would still be defined.

1.42 The definition of “contaminated land” was set out in legislation and would not be changing. However, the screening levels that were introduced in the new Statutory Guidance would change how assessments were carried out, in a way that was intended to reduce the number of detailed, *ad hoc* assessments and improve consistency. Hence, both exposure and toxicological assessments were modified from minimal risk. Under the current system based only on SGVs, it was not clear what should be done in cases where SGVs were slightly exceeded. The new screening levels aimed to provide a better scientific basis for decision-making.

1.43 It was not intended for existing HCV and SGV values to be updated. However, the Committee stated that they would like to see the minimal risk HCVs updated and made publicly available. There was also a question as to whether the new framework would be more resource intensive, and whether more expertise would be required to perform individual assessments. It was pointed out that setting a Category 4 Screening Level for a new contaminant need only be done once, and could be carried out centrally, but that the process of evaluating quantitative dose-response relationships in key toxicology data would require toxicology expertise. It was felt that more transparent wording of the framework was needed to ensure clarity for lay readers.

1.44 Some members were concerned that there were references to policy-based decisions, and emphasised that the new screening levels should be set purely on a scientific basis. In response, the contractors explained that the aim of the framework was to enable more scientifically informed policy decisions. In setting screening levels above minimal risk, the definition of ‘low risk’ and choice of safety margins entailed risk management as well as risk assessment. It was envisaged that scientists and policy-makers would need to work together in a transparent way when making these risk management decisions.

1.45 The test cases had focussed on human population-based controlled exposure studies from occupational settings within authoritative guidance reviews. Other literature on smaller scale human ‘toxicology’ studies could be considered if

available. The framework had a strong emphasis on updated exposure data, which prompted the question as to whether enough exposure data were available. For example, in the case of cadmium, absorption from dermal exposure was assumed to be similar to that from oral exposure. Members were informed that a few data had been available with which to update the exposure model, and where this was possible it had been done. There were some data on exposures by inhalation and orally, but few on dermal exposures.

1.46 Lead was an example for which overlapping dose response curves existed for different endpoints. Benchmark dose values had been calculated for three lead endpoints (neurodevelopmental effects on children, blood pressure and renal effects in adults). Within this framework the most sensitive endpoint was used and cross-checked against risks of other endpoints. Members cautioned that if benchmark dose lower confidence limits were used, then selection of the most sensitive endpoint might be influenced by the size of the relevant datasets.

1.47 It was suggested that if there were only 6 to 10 important contaminants then reports of original research should be evaluated, and not just authoritative reviews by bodies such as the WHO and the EFSA etc. It was confirmed that where possible, the Contractors had gone back to the original study reports cited within reviews.

1.48 The Committee were informed that Defra planned to organise peer-review of the framework which had been developed for the six contaminants. It was suggested that to ensure transparency, expert panels should be used for the peer-review rather than individual advisors.

1.49 The Committee provided responses to five questions:

i. The Committee felt that the “low level” in the new term, “LLTC”, might be overlooked by the public, who would focus more on the “toxicological concern”. Members recommended that sociological research on how the public would perceive the term would be useful.

ii. Members commented that the approach adopted in the project was consistent with that applied in many other areas of toxicological risk assessment for chemicals. However, there was some concern about the proposed method for developing LLTCs, as regards setting and maintaining the margin between SGVs and Category 4 Screening Levels. It was also recommended that some of the current minimal risk HCVs should be revised to take account of newer data.

iii. The committee agreed that the use of a chemical-specific margin approach, which paralleled the margin of exposure approach, was appropriate to derive an LLTC for non-threshold chemicals. However,

defining an acceptable margin entailed value judgements, and was not purely scientific. It involved an element of risk management, and careful consideration should be given as to how risk assessment and risk management could be brought together without the possibility of misuse. Specific criteria were needed by which to define the levels of margins, supporting the need for a central discussion rather than *ad hoc* local decisions.

iv. In the context of cancer and the use of an Excess Lifetime Cancer Risk (ELCR) higher than 1 in 100,000 to define a LLTC, the Committee commented that a level of exposure associated with a 1 in 100,000 excess risk could not be established scientifically, and therefore it was necessary to consider margins on exposures that caused larger effects. The Committee recommended that further advice on this should be sought from the COC. ELCRs were used by other bodies internationally and so could not be ignored. However, it is a risk management decision to define an acceptable level of risk. Members agreed that it was important that transparency be maintained in making such decisions.

v. The Committee advised that in finalising this research project, differences in the absorption of contaminants from different routes of exposure should be accounted for in the toxicological assessment rather than the exposure assessment.

Endosulfan, pentachlorobenzene and chlordecone in the infant diet

1.50 The Committee on Toxicity (COT) was asked by the Scientific Advisory Committee on Nutrition (SACN) to review the risks of toxicity from chemicals in the infant diet. This statement focuses on possible risks from four persistent organic pollutants (POPs) - two endosulfan isomers, pentachlorobenzene (PeCB) and chlordecone.

1.51 Food is the main source of exposure to POPs in the general population, and infants can be exposed to such chemicals through their presence in breast milk as well as other foods.

1.52 Endosulfan has been used as an insecticide and a wood preservative. It has been banned in the EU since 2005 and significant residues in food are not expected. When administered to experimental animals, endosulfan has shown effects on the nervous system, liver, kidney and immune system. Reproductive and developmental effects have also been reported. A health-based guideline of 6 µg/kg body weight (bw) has been set for endosulfan. This is an amount that would not be expected to cause any appreciable health risk if consumed daily over a lifetime. The limited available data indicate that infants' dietary exposures to endosulfan are below the health-based guideline, and thus do not pose a risk to health.

1.53 PeCB was used in the past as a flame retardant and in dyeing of polyester fibres, and could be found at low levels as an impurity in several pesticides. In experimental animals, PeCB has shown effects on the liver, kidney and adrenal glands. High concentrations of PeCB in animal feed are reported also to cause changes in red and white blood cells. Health Canada has established a health-based guideline of 0.5 µg/kg bw for PeCB. Currently there is no information on levels of PeCB in food, or on exposures to PeCB in the UK population, although such data are being obtained. Reported levels of PeCB in breast milk samples imply exposures to infants substantially less than the health-based guideline, and do not indicate a health concern.

1.54 Chlordecone was used as an agriculture insecticide, miticide and fungicide. In the UK, it was legally banned in 1977, but it is unclear whether it was ever used before then. Animal studies have shown that chlordecone can cause adverse effects in the nervous and immune systems, and on the liver and reproductive function. Available information indicates that even if chlordecone was used in the UK in the past, any current exposures are likely to be extremely low and decreasing. Thus, despite its known toxicity and there being no reported measurements of chlordecone in food or human breast milk in the UK, the Committee consider that adverse health effects in infants from dietary exposures are unlikely.

1.55 Overall, the Committee concluded that the available information on exposures of infants to endosulfan isomers, PeCB and chlordecone did not indicate a toxicological concern. Further research is unlikely to change this view and is therefore not a priority.

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

Lead in the infant diet

1.57 The COT were asked by the Scientific Advisory Committee on Nutrition (SACN) to review the risks of toxicity from chemicals in the infant diet. This statement focussed on possible risks from lead.

1.58 People are exposed to lead through food, drinking water, air, soil and dust. Food and water are the major sources of exposure to lead, although in infants and small children, ingestion of soil and dust can also contribute importantly. In addition, lead can be transferred to the infant from the mother in breast milk. Exposure to lead in the UK has decreased substantially over recent decades.

1.59 The proportion of ingested lead which is absorbed into the body is higher in children than in adults. Inadequate intakes of calcium, iron and zinc have been

shown to increase lead absorption, and higher levels of fat in the diet may lead to higher blood levels of lead.

1.60 Absorbed lead is transported in the blood, and then deposited in soft tissues and bone, where it tends to accumulate with age. During pregnancy and breastfeeding, calcium in the mother's bones is released to meet the needs of her baby, and this result also in the release of lead from the bone.

1.61 Concerns about adverse effects from lead in the diet and environment relate principally to long-term cumulative exposures. The kidney and cardiovascular systems can be adversely affected by lead exposure in adults. However, epidemiological studies have demonstrated effects on the brain at lower levels of exposure, the developing brain being more vulnerable than the mature brain. In particular, there is strong evidence that lead can impair intelligence (as measured by IQ). It has not been possible to demonstrate a threshold level of exposure below which adverse effects on the infant brain are absent.

1.62 The Committee concluded that assessment of the potential risks from infants' exposure to lead should be made by reference to an exposure value of 0.5 micrograms per kilogram body weight per day, which the EFSA had estimated would produce less than a 1 point decrement in IQ. Exposure below this value indicates that the health risk is low.

1.63 The Committee calculated estimates of exposure of UK infants to lead from different sources and compared them to the exposure value identified by EFSA. Based on the maximum concentration of lead measured in breast milk in a study of UK women published in 2004, exposure of babies to lead via mothers' milk was considered not to represent a health risk. Nor would health problems be expected from other dietary exposures in infants, except perhaps where water concentrations of lead were at the highest end of the measured range in the UK.

1.64 Toxicity will depend on total exposure to lead from all sources so it is important to consider combined exposures from food, water, and also non-dietary sources. Exposures from air are negligible. However, there could be some risk from ingestion of soil and house dust where lead concentrations are unusually high.

1.65 There are uncertainties in the assessment of risks to infants from lead since the epidemiological studies looking at cognitive development may not have assessed exposures with complete accuracy or fully taken into account other factors which influence IQ. Moreover, the populations studied may not have been representative of the UK. Also, the contribution to exposure from foods not specifically marketed for infants is currently unknown, although information on this may be available soon.

1.66 Even when allowance is made for these uncertainties, it appears that total exposure to lead is unlikely to pose a material risk to the health of the large majority of UK infants. However, there remains a concern that adverse effects could occur where concentrations of lead in water or soil and house dust are unusually high.

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

Obesogen hypothesis

1.68 Over the last two decades, the prevalence of obesity and associated metabolic syndrome diseases has risen dramatically. Increased caloric intake and decreased physical activity are believed to represent the root causes of this rise. However, more recently some researchers have suggested the possible involvement of environmental obesogens, xenobiotic chemicals that can disrupt the normal developmental and homeostatic controls over adipogenesis and energy balance. This has been referred to as the "obesogen hypothesis".

1.69 The environmental obesogen hypothesis predicts that inappropriate receptor activation by certain chemicals will lead directly to adipocyte differentiation and a predisposition to obesity and/or will sensitize exposed individuals to obesity and related metabolic disorders under the influence of the typical high-calorie, high-fat Western diet. Obesogenic chemicals might act in various ways to disrupt adipose tissue biology.

1.70 Further research to investigate the obesogen theory is on-going internationally. A report was published in 2012 of a 2011 state-of-the-science workshop entitled "Role of Environmental Chemicals in the Development of Diabetes and Obesity" which had been organised by the National Institute of Environmental Health Sciences (NIEHS) Division of the US National Toxicology Program (NTP) to look at ways of investigating the theory. The COT used this publication and several other recent reviews as an opportunity to evaluate the current evidence for the theory and proposed research strategies.

1.71 The NTP workshop evaluated the literature for evidence of associations between certain chemicals and risk of diabetes and/or obesity through an expert elicitation exercise. This evaluated the current literature for consistency and biological plausibility and provided advice on developing a research programme. The specific environmental exposures evaluated were arsenic, maternal smoking during pregnancy/nicotine, organic tin compounds ("organotins"), phthalates, bisphenol A (BPA), pesticides, and various persistent organic pollutants (POPs). Since obesity is a major risk factor for metabolic syndrome and type 2 diabetes, all three of these outcomes were reviewed in relation to the environmental exposures evaluated, although the primary focus and context varied for specific exposures.

1.72 The COT understood why the National Institutes of Health (NIH) had gone about the workshop in this way but it made it harder to form conclusions. A better approach would have been to look at individual endpoints and then consider the interrelationships. The Committee agreed with the conclusions of the NIH workshop that the existing literature supported the plausibility of the "obesogen" hypothesis, although many significant data gaps remain, and that linkages between type 2 diabetes and exposure to certain chemical classes e.g. high arsenic exposure were not inconsistent. The strongest evidence for a developmental obesogen in humans was for nicotine based on a consistent pattern of overweight and/or obesity observed in epidemiological studies of children of mothers who smoked during pregnancy supported by findings from laboratory animals exposed to nicotine during prenatal development. There were possible associations but the relationships were not necessarily causal and for many chemicals considered the data were too limited to draw meaningful conclusions. Obesity needed to be distinguished from type 2 diabetes. A critical data gap was that very little research had been undertaken on understanding associations between environmental exposures and type 1 diabetes.

1.73 In March 2012 Chem Trust published a review it had commissioned on the links between chemical exposures and obesity and diabetes.

1.74 The authors concluded based on a significant and growing number of mechanistic studies and animal experiments, as well as on some clinical and epidemiological studies, that chemicals in the environment may be partly responsible for the increasing occurrence of obesity in human populations. They considered the weight of evidence compelling, although it was difficult to prove such associations in human studies.

1.75 The report commissioned by Chem Trust provided a fairly comprehensive review, which identified large data gaps and included few negative studies. Therefore the conclusions were based on a sparse data set which did not appear to have included a critical evaluation of the whole literature.

1.76 A series of four short papers, which were published in the Journal of Obesity in June 2013 set out arguments for and against the hypothesis and ways to explore it, and also highlighted the complexity by showing how the same data could be used to support both arguments. Epidemiological studies had not collected information on calorie intake which could be confounding, or might be part of the causal pathway. In animal studies pair feeding would be needed, but had not been included in most reported studies. There were significant data gaps which needed to be addressed before conclusions could be reached.

1.77 The OBELIX ("OBesogenic Endocrine disrupting chemicals: Linking prenatal eXposure to the development of obesity later in life") project funded by the European Community's Seventh Framework Programme was considered

promising. The OBELIX project was scheduled to finish this year and the report should be completed soon afterwards. This should be monitored as it might provide an appropriate opportunity to reconsider the evidence base.

1.78 Members agreed that a more detailed evaluation of the obesogens hypothesis was not required at this time, and that there was insufficient new information for a workshop. The secretariat would continue to monitor the subject and update the Committee on developments.

Soy phytoestrogens in the infant diet

1.79 The Committee on Toxicity (COT) were asked by the Scientific Advisory Committee on Nutrition (SACN) to review the risks of toxicity from chemicals in the infant diet. This statement focuses on potential risks from soya phytoestrogens, and particularly from a group of soya phytoestrogens known as isoflavones.

1.80 Soya-based infant formula and weaning food products containing soya are the main source of isoflavone exposure in infants. In addition, isoflavones can be transferred from the mother to the infant via breast milk, with the highest concentrations in breast milk of mothers who follow vegetarian or vegan diets.

1.81 Isoflavones occur in foods in the form of glycosides (in which they are chemically combined with sugars), and these can undergo chemical modification in the gut to become biologically active “aglycones”. Aglycones (daidzein, genistein and glycitein) are more readily absorbed, and are then transported to tissues, being excreted in urine or bile. They can also be further metabolised in the body. For example, daidzein can be converted to a more potent compound, equol.

1.82 Concerns about adverse effects from isoflavones in the infant diet relate principally to their ability to mimic the female hormone, oestrogen, and therefore their potential impact on development and reproduction. Other possible toxic effects relate to immune and thyroid function.

1.83 There are uncertainties in the assessment of risks to infants from exposure to isoflavones. Epidemiological and clinical studies have produced conflicting results, and while the balance of evidence from the small number of epidemiological studies does not suggest important adverse effects of soy infant formula on reproductive development, they are too limited to provide strong reassurance of safety. Animal studies looking at similar levels of exposure to those reported in infants have suggested developmental and reproductive changes later in life. However, differences in the chemical handling of isoflavones, and in the timing of sexual development, make it difficult to extrapolate findings from animals to humans. No guidelines have been published on the highest intakes of isoflavones that are thought unlikely to cause adverse health effects in humans.

1.84 Isoflavone exposure of infants fed exclusively with breast milk (even where mothers consume vegetarian or vegan diets) or cows' milk formula is highly unlikely to present a health problem. Exposure to isoflavones from complementary foods containing soya is higher but unlikely to be harmful.

1.85 The highest potential exposures of infants to isoflavones come from exclusive consumption of soya-based infant formula. While the small number of available epidemiological studies does not suggest that such consumption leads to adverse health effects in humans, the results of animal studies indicate a possible concern, and there is thus some uncertainty about the safety of soya-based infant formula.

1.86 The COT concluded that there is no scientific basis for changing the current government advice – namely, that there is no substantive medical need for, nor health benefit arising from the use of soya-based infant formula, and that it should be used only in exceptional circumstances to ensure adequate nutrition.

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

Vitamin A in the infant diet

1.88 The Committee on Toxicity (COT) were asked by the Scientific Advisory Committee on Nutrition (SACN) to review the risks of toxicity from chemicals in the infant diet. SACN will use the COT advice in determining whether the Government's dietary recommendations for infants and young children should be revised. This statement focuses on possible risks from high levels of vitamin A in the infant diet. It does not deal with risks associated with insufficient intakes of vitamin A.

1.89 It is currently recommended that if solid foods are introduced before age 6 months then liver should be avoided. Children over the age of 6 months (and also adults) are recommended not to eat more than one portion of liver per week, because the vitamin A content in the liver can be harmful in large amounts

1.90 There are two dietary sources of vitamin A – preformed vitamin A in foods of animal origin, and provitamin A carotenoids in fruit and vegetables. The food with the highest concentration of vitamin A is liver. Preformed vitamin A is more active biologically than provitamin A carotenoids.

1.91 Vitamin A toxicity arises from high intakes of preformed vitamin A, and does not result from high intakes of provitamin A carotenoids. Depending on the level of

intake, possible adverse effects in infants include bulging fontanelles[1], loss of appetite, dry skin and damage to the liver.

1.92 The COT concluded that the adverse effect of vitamin A which occurs most readily in infants (i.e. at the lowest doses) is bulging of fontanelles, and that a Tolerable Upper Level (TUL) of exposure should be established below which this effect would not be expected to occur. There have been a number of reports of infants developing bulging fontanelles following vitamin A supplementation at doses of about 800 µg RE/kg bw/day[2], but not (except in children with certain rare diseases) at lower intakes. This value was divided by a factor of 4 to allow for uncertainties because the number of case studies that were available was small and they related to exposures of only limited duration. Thus, a TUL of 200 µg RE/kg bw/day was determined.

1.93 Where mothers are not taking vitamin A supplements, the estimated exposure of exclusively breastfed infants is below the TUL, and not a health concern. Maternal use of dietary supplements could increase the vitamin A content of breast milk by a small amount. However, with the supplements available on the UK market, any resultant exceedance of the TUL would only be minor. Moreover, it would be for only a short period of time.

1.94 Estimated exposures based on reported concentrations of vitamin A in infant formula are below the TUL and not a health concern. However if vitamin A were present in formula at the maximum legally permitted level (180 µg RE/100 mL), resulting exposures could exceed the TUL by up to about 80 %.

1.95 Data on total exposures to vitamin A from breast milk, infant formula and complementary foods in UK infants indicate that the TUL could be exceeded by up to about 25% at high levels of intake. However, this exceedance is small, and at most is likely to occur only rarely. Thus, while the possibility of adverse effects cannot be excluded, they would not be expected to occur in other than a very small proportion of infants, if at all.

1.96 There is evidence that a very small proportion of infants eat foods containing liver. Frequently consuming liver at the levels reported could lead to the TUL being exceeded. Therefore the current Government recommendation that infants over the age of 6 months should not have more than one portion of liver per week is appropriate.

[1] Fontanelles are the soft spots on babies' heads where the bones of the skull have not yet fully formed.

[2] Micrograms of retinol equivalent per kilogram bodyweight per day. Retinol equivalents are a measure of dose that take into account the varying biological activity of different forms of vitamin A.

1.97 Dietary multivitamin supplements marketed for infants in the UK were also evaluated. The brand with the highest recommended dosage could produce an estimated exposure of more than half the TUL. This could result in total intake above the TUL for exclusively breastfed infants, and increase the potential for exceedance of the TUL for formula-fed infants, and infants consuming large amounts of complementary foods rich in vitamin A. The recommended dosage provided under the Healthy Start scheme would give a lower exposure, and any resultant exceedances of the TUL are likely to be minor.

1.98 Overall the COT concluded that there is potential for some infants to exceed the TUL under the following circumstances:

- if exclusively breastfed by mothers taking dietary supplements containing high levels of vitamin A,
- if fed with infant formula at the upper limit of the retinol content allowed by regulation,
- if given high dose vitamin A supplements
- if consuming liver more than once per week

The possibility of adverse effects from such exceedances cannot be excluded, but if they do occur, it is likely to be in only a very small proportion of infants.
The full COT statement can be found at: http://cot.food.gov.uk/pdfs/cotstavita.pdf

Waste and Resources Action Programme (WRAP)

1.99 In 2009 and 2010, COT had discussed two draft reports carried out for the Waste and Resources Action Programme (WRAP) on the use of source segregated composts in agriculture and the Scottish Livestock Sector in 2009 and 2010 These reports had also been considered by the Advisory Committee on the Microbiological Safety of Food (ACMSF). A number of comments had been made on the risk assessments and reports, and the COT had indicated that it would like to see the revised reports before agreeing its conclusions.

1.100 In 2011, the Committee had considered a further report on anaerobic digestates in agriculture. The COT had agreed with the conclusion of that report that risks from allergens in the food chain would be negligible, and also with its conclusions on chemical risks, although only for the range of chemicals considered in the report. COT had also accepted the overall conclusion that any risks associated with the use of PAS 110-compliant anaerobic digestates in agriculture would be similar to those from other materials used for these purposes.

1.101 In addition to the revised reports on the use of source segregated composts in agriculture and the Scottish Livestock Sector, WRAP now provided two additional papers on Risk-based Guidance for the use of Source-Segregated Anaerobic Digestates in GB Agriculture and Making the Best Use of Renewable Fertilisers.

1.102 The COT noted the approach to exposure assessment was acceptable and the list of chemicals considered in the assessment was reasonable. The COT had some reservations that appropriate reference doses had not always been used in the report and that the terminology used in the reports was not always consistent with that used elsewhere. The COT considered that the risk assessments for mixtures of dioxin-like PCBs and PAHs were not consistent with current scientific methodology applied to these mixtures.

1.103 The COT agreed that it would not be necessary for future work to take greater account of pesticides and natural toxins, since only food waste would be used in digestates, and therefore high levels of pesticides would not be expected. Moreover, significant concentration would not be expected to occur during the digestion process.

1.104 The COT agreed with the overall conclusions of the reports that any risks associated with the use of PAS 100-compliant composts and PAS 110-compliant anaerobic digestates in agriculture would be similar to those from other materials used for the same purpose.

Committee procedures

Horizon Scanning

1.105 At their February 2013 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.

1.106 Possible topics that had been discussed in the 2012 horizon scanning were discussed and prioritised. High priorities for work in 2013 were consideration of whether the 10-fold uncertainty factor for interspecies extrapolation is sufficient for developmental toxicity, and the obesogen hypothesis. The issue of plant micro RNAs was considered a low priority because there was no evidence that exposure had increased recently, and other committees (the Advisory Committee on Novel Foods and Processes (ACNFP), and the Advisory Committee on Releases to the Environment [ACRE]) were addressing this topic.

1.107 Immunotoxic effects of environmental chemicals had also been mentioned previously as a possible discussion topic. It was observed that there is a very small number of established human immunotoxicants, and that immunotoxicity is rarely the most sensitive toxic parameter for a chemical. It was agreed that an external expert would be invited to give a presentation to the COT on the susceptibility of juveniles to immunotoxicity.

1.108 In considering the toxicity of chemicals in the infant diet, the COT had previously observed that intakes of methylmercury by infants were well within the provisional

tolerable weekly intake (PTWI) of 1.6 µg/kg bw/week recommended by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). However, the Committee had been aware that the EFSA Panel on Contaminants in the Food Chain (CONTAM) was re-evaluating methylmercury. The EFSA CONTAM Panel had since completed its re-evaluation and had recommended a lower tolerable weekly intake (TWI) of 1.3 µg/kg bw/week. The reduction was due to a more recent analysis of one of the key epidemiological studies, which included adjustment of the results for confounding by the nutritional benefits of oily fish on neurodevelopment. The Committee reviewed the EFSA evaluation and concluded that the previous COT advice on methylmercury in the infant diet would not change since estimated intakes in infants were approximately three-fold lower than the EFSA TWI.

1.109 The COT considered the balance of expertise among the current membership of the Committee. It was judged to be appropriate, and it was noted that additional expertise could be sought on an ad hoc basis in connection with specific topics. Members also discussed the need for younger scientists to become involved with the Committee in order to develop potential future COT members..

1.110 Members were reminded that they may draw particular issues to the attention of the Secretariat at any time.

Working groups

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

1.111 The COT had considered a draft review of the epidemiological literature on organophosphates and health outcomes related to the nervous system at its September 2012 meeting. The Committee had agreed to establish a Working Group to consider the review in detail. External experts with expertise in epidemiology, psychiatry, epidemiological psychiatry, neurophysiology and neurology had been recruited to the Working Group, in addition to COT members with expertise in epidemiology. The objective of the Working Group was to produce a draft COT Statement, assessing whether there are long-term adverse neurological effects from levels of exposure to organophosphates which are insufficient to cause overt acute toxicity. The COT had previously concluded, in its report on organophosphates published in 1999, that overt acute poisoning by organophosphates could cause long-term neurological impairment, and regulatory risk assessment already aimed to prevent acute poisoning.

1.112 The Working Group allocated tasks to individual members of the Working Group, corresponded by email, and held two meetings in 2013. The draft Statement will be considered by the full Committee in early 2014.

Ongoing work

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

1.113 As part of its discussions on horizon scanning at its meetings in February 2012 and 2013, COT had discussed the possibility of evaluating the adequacy of the 10-fold uncertainty factor for interspecies variation in relation to developmental toxicity. Reviews in the literature had indicated that humans were typically more susceptible than rats, mice and rabbits to known human developmental toxicants, and a 10-fold uncertainty factor applied to the most sensitive of these species did not appear to be adequate for a number of substances. The differences between humans and non-human primates, where data were available, were typically much smaller, but chemicals in food and the environment are usually only studied for developmental toxicity in rats and rabbits. The Committee had agreed that it would be useful to investigate this subject further.

1.114 The COT considered a paper in which estimates of LOAELs for developmental toxicity in humans, rats, rabbits and non-human primates had been compared. Useful comparable data had been identified for 41 human developmental toxicants, though not in all of the species for all of the substances. The results indicated that the 10-fold factor, applied to the most sensitive of either rats or rabbits, would be adequate to extrapolate to humans for some substances, but for some the ratios of the lowest LOAELs from either rats or rabbits to humans were much greater than 10.

1.115 The COT observed the limitations in the estimates of the human LOAELs and that the LOAELs were estimated from epidemiological studies in some cases and from case reports in others. The interpretation of these two types of data was potentially different as there would be limitations to the sensitivity of epidemiological studies whereas case-reports could potentially include reports of effects in particularly sensitive individuals, even if these were rare.

1.116 It was possible that where the human LOAELs were based on case reports it would be necessary to compare the ratios of LOAELs to the value of the total uncertainty factor of 100. Thus, if there were documented cases of toxicity in humans at dose levels more than 100 times lower than the LOAEL in animals, this would indicate that a 100-fold total uncertainty factor would not provide adequate protection. However, it was also observed that for some substances, e.g. phenytoin, while there were large ratios between the LOAELs in rats or rabbits and humans, the ratio was much smaller between non-human primates and humans, which indicated that the magnitude of the ratio between LOAELs in rats or rabbits and humans was not entirely due to the human data also reflecting inter-individual variation, and was at least in part due to large species differences.

1.117 The COT observed that there were no similarities, either chemically or toxicologically, between the substances with ratios greater than 10. The COT considered that toxicokinetic variation may partly explain some of the large ratios between rats or rabbits and humans, but not entirely.

1.118 Overall, the COT concluded that there were strong indications that the 10-fold uncertainty factor for interspecies variation in relation to developmental toxicity was not always adequate. It was not currently possible to conclude how often the factor was inadequate, or how the situation compared for other toxic endpoints. The COT requested additional information in order to consider this topic further in 2014. In addition, an initial consideration should be given to what data were available for non-developmental outcomes.

Infant feeding and allergy

1.119 In 2012, the Committee provided advice to the SACN on what risks of toxicity may need consideration during their review of dietary recommendations for infants and young children (http://cot.food.gov.uk/pdfs/cotstatementoverarch201203.pdf). Scientific evidence concerning the influence of infant diet on risks of allergic and autoimmune disease would also be addressed.

1.120 During 2013, Members received an update on the review of infant feeding and allergy at their May meeting. The meeting was held in reserved session whilst study protocols for literature reviews were being considered and submitted for peer review. It is intended that the minutes of the Committee's discussion in 2013 of infant feeding and allergy will be published on its website in due course.

Potassium salt replacers in vulnerable groups

1.121 The COT have been asked by SACN to provide advice on the potential effects of increased potassium intakes in vulnerable groups in support of a SACN review of the use of potassium-based salt replacers as part of the Government's overall salt reduction strategy. Currently, the use of potassium-based salt replacers is not recommended since it is considered preferable gradually to reduce salt levels in food products to allow the palates of consumers to become used 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 could 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 had 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.

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

1.123 It is anticipated that the COT's views will be submitted to SACN in spring 2014.

SACN review of dietary guidelines for vitamin D

1.124 The SACN are undertaking a review of their recommendations on appropriate levels of vitamin D intake. As part of this process, COT were asked to provide SACN with advice on the effects of high levels of vitamin D intake. The SACN review began in 2011, will be completed in 2015 and will include a period of public consultation.

1.125 The COT are continuing to review the potential toxicity of vitamin D as evidenced by adverse effects occurring at high levels of vitamin D intake, and in relation to high blood vitamin D concentrations. The COT have considered papers on hypercalcaemia, dose-response relationships and the effects of high vitamin D intakes on potential vulnerable groups and individuals with certain medical conditions.

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

1.127 It is anticipated that the COT review will be submitted to SACN by the spring of 2014 with further updates as required.

Soy phytoestrogens in hypogonadism and hypothyroidism

1.128 The COT discussed the initial results from a study on soy phytoestrogens in patients with compensated hypogonadism, led by scientists at Hull York Medical School, and made suggestions for aspects which needed further clarification in finalising the report. In 2011 the COT considered the results of the first two arms of a study by the same scientist on soy phytoestrogens in patients with compensated hypothyroidism, and agreed to reconsider these data when the third arm was completed. The Committee will consider both these completed studies in 2014.

Toxicity of chemicals in the infant diet

1.129 The COT has been asked to consider 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. The COT reviews aim to assess whether current advice is appropriate with regard to potential toxicity, or whether

there is a need for new or revised advice. Further statements will be published in 2014:

Potential risks from α-, β- and γ-hexachlorocyclohexanes in the infant diet

1.130 There are currently no Government dietary recommendations for infants and young children that relate to α-, β- and γ-hexachlorocyclohexanes (HCHs). They are widely distributed in the environment and since 2009 have been designated as a Persistent Organic Pollutants under the Stockholm Convention. The COT is considering possible health risks of the exposure of infants to HCHs from breast milk, infant formula, complementary foods and non-dietary exposures.

Potential risks from perfluorooctane sulphonate in the infant diet

1.131 There are currently no Government dietary recommendations for infants and young children feeding that relate to perfluorooctane sulphonate (PFOS). The chemical is widely distributed in the environment and since 2009 has been designated as a Persistent Organic Pollutant under the Stockholm Convention. The COT is considering estimates of the exposure of infants to PFOS from breast milk, infant formula, complementary foods and non-dietary exposures, in the light of Tolerable Daily Intakes previously set by the COT and EFSA.

2013 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

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Senior Lecturer in Clinical Pharmacology, Cardiff University
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Professor of Toxicology, Medical Toxicology Centre and Institute of Cellular Medicine, Newcastle University

SECRETARIAT

Dr D Benford BSc (Hons) PhD	Scientific Secretary
Ms J Shroff BA (Hons)	Administrative Secretary (until March 2013)
Ms H Gbormittah	Administrative Secretary (from June 2013)
Ms Frances Pollitt MA DipRCPath	Scientific – HPA
Dr D Gott BSc (Hons) PhD	
Ms C A Mulholland BSc (Hons)	
Dr C Baskaran BSc MSc PhD (until July 2013)	
Dr E Cemeli BSc PhD	
Ms C Potter BSc MSc	
Dr M Kurzawa-Zegota MSc (Hons) PhD	
Mrs F Hill BSc (Hons) MSc	
Mr B Maycock BSc (Hons) MSc	
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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		
Membership/affiliation ILSI Food Allergy Task Force: Chair		
Dr Mark Graham		
Personal Interest		**Non Personal Interest**
Employee MG Toxicology Consulting Ltd		None
Dr Anna Hansell		
Personal Interest		**Non Personal Interest**
Employee Imperial College London: Small Area Health Statistics Unit, Department of Epidemiology & Biostatistics		**Research Grant** Defra **Misc**
Shareholder Halifax		
Membership International Society for Environmental Epidemiology British Thoracic Society American Thoracic Society Society for Social Medicine Greenpeace		
Dr Caroline Harris		
Personal Interest		**Non Personal Interest**
Employee Exponent International Ltd		**Fellowships** Royal Society of Chemistry
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Member International Union of Pure and Applied Chemistry		**Misc** Advisory Committee on Pesticides Steering Committee for ACROPOLIS

Professor David Harrison		
Personal Interest		**Non Personal Interest**
Consultant University of Canberra University of Florida Quintiles		**Trustee** Medical Research Scotland Melville Trust Scottish Lifescienses Association
Shareholder Avipero		**Research collaboration** Myriad Genetics Cytosystems Antoxis Ltd Biopta Ltd MDX Health Nucana Ltd
		Misc Office of the Scottish Charity Regulator - Board member
Professor Roy Harrison OBE (joined 1 April 2012)		
Personal Interest		**Non Personal Interest**
Employee University of Birmingham		**Member** Royal Society of Chemistry Royal Meteorological Society Faculty of Public Health (honorary) Faculty of Occupational Medicine (honorary) Chartered Institute of Environmental Health (honorary)
Consultancy Kind Abdulaziz University (Saudi Arabia)		
Shareholder Halifax/Lloyds		
Member Defra Air Quality Expert Group Dept. of Health Committee on the Medical Effects of Air Pollutants		
Professor Brian Houston		

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

Professor Brian Lake

Personal Interest		Non Personal Interest
Employee Leatherhead Food Research(LFR)		**Member** British Toxicology Society Society of Toxicology
		Member of the editorial board Food and Chemical Toxicology Xenobiotica
		Misc Various pharmaceutical and other companies - Contract research at LFR and consultancy

Professor Ian Morris

Personal Interest		Non Personal Interest
Employee Universities of Hull and York		**Member**
Membership British Society for Toxicology Society for Endocrinology Society for Medicines Research Society for study of Fertility		**Misc**

Dr Nicholas Plant

Personal Interest		Non Personal Interest

Employee University of Surrey		**Research Funding** AstraZeneca - GlaxoSmithKline Pfizer
		Member International Society for the Study of Xenobiotics (ISSX) MHRA Pharmacovigilance Expert Advisory Group
		Misc Xenobiotica - Associate Editor Frontiers in Predictive Toxicology – Editorial Board British Toxicology Society – Secretary of Education sub-committee

Professor Robert Smith

Personal Interest		**Non Personal Interest**
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

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.

During 2013, the Committee published a Guidance note on the human health significance of chemical-induced mutagenicity, produced a statement on photogenotoxicity testing and reviewed current approaches to germ cell mutagenicity testing. It assessed the potential risks from swimming pool disinfection by-products. Statements on these topics were also published on the COM website. It updated its review of the potential of toxicogenomics as a tool for identifying genotoxic carcinogens and concluded that its present statement did not need to be updated. The Committee received an update on the development and validation of the PigA gene mutation assay.

The COM considered a Food Standards Agency funded research project on the combined effects of aneugenic benzimidazoles, other aneugens and other substances in the *in vitro* micronucleus assay. Throughout the year the Committee monitored the development of revised OECD Test Guidelines for *in vitro* and *in vivo* genotoxicity tests and cell transformation assays. Horizon Scanning was discussed at the June 2013 meeting.

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

FSA-funded research on the combined effects of aneugenic benzimidazoles, other aneugens and other substances in the *in vitro* micronucleus assay

2.1 In 2006-7, the COM considered the approach to the risk assessment of the combined exposure to a number of aneugenic benzimidazoles. Benzimidazoles are a group of substances used as pesticides (fungicides) and veterinary medicines (anthelmintics). They can occur as residues in both plant- and animal-derived foods. Most have been demonstrated to be aneugenic as a result of binding to tubulin and inhibiting its polymerisation and thereby inhibiting microtubule assembly.

2.2 The COT had advised that the default assumption in the risk assessment of combined exposure to chemicals with the same mode of action is that dose-addition would occur, based on the consideration of data for several types of non-genotoxic chemicals. Similar conclusions have subsequently been drawn by other international risk assessment committees and bodies. Under the dose-addition principle, every chemical in the mixture would contribute to the combined effect in proportion to its dose and individual potency. Dose-addition occurs across the full dose-response curve, therefore a key implication for risk assessment is that the combined exposure to a number of similar acting chemicals may be above the threshold for an adverse effect, even if individual exposure to each substance in the mixture is below its individual threshold for an adverse effect.

2.3 The COM recommended that combined exposure to a number of individual benzimidazoles could be assumed to act in accordance with dose addition. However, it also recommended research to confirm this by testing combinations of benzimidazoles in the *in vitro* micronucleus assay. Furthermore, COT recommended that the combined exposure to benzimidazoles along with other aneugens should also be tested. The Food Standards Agency (FSA) funded a research project to address this recommendation and the final report was presented to COM for its consideration.

2.4 The Committee had been asked specific questions on this study and considered the following:

i) The Committee agreed that the study results supported the use of the principle of dose addition as a protective approach in the setting of acceptable residue levels of benzimidazoles in foods, but considered that *in vivo* data would be required to assess more accurately the risks from exceeding such levels. Members suggested that an *in vivo* mixture study be undertaken.

ii) The Committee agreed that a definitive conclusion could not be drawn at present on whether the principle of dose addition should be extended to combined exposure to all aneugens that act by inhibiting tubulin polymerisation. The results indicated that an assumption of independent action would not be sufficiently protective; therefore one possibility was to err on the side of caution and set acceptable residue levels based on the principle of dose addition, or alternatively

more data could be generated to gain a better understanding. It was concluded that further analysis of the existing data based on a scoring of micronuclei in both mononucleate and binucleate cells may allow firmer conclusions to be drawn.

iii) The Committee agreed that, in the absence of convincing mechanistic data, it would not be appropriate to extend the principle of dose addition to combined exposure to all aneugens regardless of their mechanisms.

iv) Members agreed that there were insufficient data to conclude whether dose addition would occur between aneugens and clastogens, or between clastogens that act by different modes of DNA action. Members recommended that further research be conducted on mixtures of clastogens *in vitro*, testing mixtures of chemicals that act by different modes of DNA action to cause clastogenicity in p53 competent cells.

Statement on photogenotoxicity testing

2.5 The Chemicals Regulations Directorate (CRD) of the Health and Safety Executive (HSE) had asked the COM for a view on photogenotoxicity testing. In particular, the molar extinction coefficient required to trigger photogenotoxicity assessment and the photogenotoxicity testing strategy that should be adopted in the absence of any OECD/EU photogenotoxicity test. The referral arose as a result of proposed EU data requirements for the phototoxicity testing of chemical pesticide active ingredients.

2.6 The Committee agreed with the conclusions reached by the IWGT working group regarding the use of photogenotoxicity data in the overall safety assessment of chemicals that there should be no requirement for photosafety assessment of chemicals with a molar extinction coefficient (MEC) below 1000 $Lmol^{-1}$ cm^{-1}. A tiered approach to testing should be used and thus if an *in vitro* 3T3 NRU phototoxicity test was negative there would be no need for photogenotoxicity testing. Also, the Committee agreed with the IWGT working group conclusion that photogenotoxicity testing had a negligible impact in the overall assessment for potential of photocarcinogenicity. Follow up *in vivo* testing in the case of chemicals which gave positive results for 3T3 NRU assay would involve *in vivo* phototoxicity testing. It would not be necessary to undertake photocarcinogenicity testing if *in vivo* phototoxicity studies were negative.

2.7 The COM reached the following conclusions

i) Photogenotoxicity testing need not be undertaken routinely as part of a photosafety assessment and would only be required when the MEC was >1000 $Lmol^{-1}$ cm^{-1}.

ii) The prediction of photocarcinogenic potential should involve *in vitro* and *in vivo* phototoxicity tests where permitted, but this would only apply to chemicals with an MEC >1000 $Lmol^{-1}$ cm^{-1} which absorb light and which are likely to be present in/on skin and/or eye.

iii) We recommend a revision of OECD guideline TG 432 to require phototoxicity assessment if the ultraviolet/visible molar extinction /absorption coefficient of the active substance and its major metabolites is greater than 1000 $Lmol^{-1}$ cm^{-1}.

The full statement can be obtained at:
https://www.gov.uk/government/publications/statement-on-photogenotoxicity-testing

Swimming pool disinfection by-products and genotoxicity assessment

2.8 This topic was identified by members from the 2011 horizon scanning exercise as an item for further discussion. The Health Protection Agency had expressed an interest in this topic with regard to the public health aspects in relation to swimmers.

2.9 The aim of swimming pool disinfection is to minimise the number of micro-organisms and thus protect against the spread of water borne disease. Disinfection by-products (DBPs) are generated through the reaction of various disinfectants with organic material in the water, which can be present from the use of sunscreens, cosmetics, and from natural organic matter (e.g. urine, sweat, skin cells, hair etc.).

2.10 Members considered information on the levels and identity of various disinfection by-products (DBPs) detected in swimming pool water, which included the most predominant DBPs, such as trihalomethanes (THMs), haloacetic acids, and chloramines, and numerous other species including haloacetonitriles, haloketones, halonitromethanes etc. There was limited genotoxicity data on pool water extracts and the limited biomonitoring of exposure to DBPs in swimmers and pool workers indicated that inhalation and dermal were the main routes of uptake. Only one study investigating genotoxic effects in swimmers was retrieved. This study found that exposure to the DBPs (as measured by exposure to trihalomethanes (THMs)) was not associated with DNA damage as detected by the comet assay, following 40 minutes of swimming in a chlorinated pool. No significant associations were found between swimming and exposure to DBPs (as measured by exposure to THMs) and micronuclei in exfoliated urothelial cells. However, the frequency of micronucleated peripheral blood lymphocytes increased after swimming in association with higher exhaled brominated THMs (i.e. bromodichloromethane, dibromochloromethane, and bromoform), but not for the chlorinated trihalomethane chloroform. Urine mutagenicity increased significantly after swimming in association with the higher concentration of exhaled bromoform.

2.11 Members agreed that the positive genotoxicity test results reported for fractions taken from extracts of swimming pool water could not be interpreted in terms of genotoxic hazard to humans and did not provide any important new data. Members noted that the study in swimmers found a negative result for DNA damage in peripheral blood lymphocytes as measured by the comet assay. There was an increase in micronuclei detected in the peripheral blood lymphocytes and the urothelial cells, but Members could not interpret the significance of these findings in the absence of data on background levels of micronuclei. Furthermore, there was potential for confounding factors due to the known effect of exercise in increasing DNA damage, for example due to oxidative stress. One Member advised the Committee that this study was being progressed further. Members considered the

COC conclusion that the epidemiological evidence for a causal association between exposure to chlorinated DBPs in drinking water and cancer was limited and any such association for exposure through swimming in chlorinated pools was unlikely to be strong.

2.12 Based on the current evidence, the Committee concluded any potential genotoxic risk to swimmers from swimming pool water DBPs was likely to be negligible providing good practice was adopted regarding swimming pool water disinfection and management.

Guidance statement on the human health significance of chemical induced mutagenicity

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

2.14 The full guidance statement can be found at: https://www.gov.uk/government/publications/the-significance-of-chemical-induced-mutation-for-human-health

Review of current approaches to germ cell mutagenicity testing

2.15 In the horizon scanning exercise 2012, COM members requested a review of the current approaches and new developments in germ cell mutagenicity assessment. The COM previously considered germ cell mutagenicity during its update of the guidance on a strategy for genotoxicity testing for chemicals published in 2011. However, at that time a full assessment of new approaches to germ cell testing was not undertaken.

2.16 Heritable mutations are recognised as potentially detrimental to offspring; however, testing strategies for the initial screening of compounds for genotoxicity do not include assays specifically for germ cell mutations. Chemicals that are recognised as *in vivo* somatic cell mutagens are assumed to be both potential genotoxic carcinogens and potential germ cell mutagens, and no further genotoxicity testing is performed.

2.17 The Committee agreed that suggestions by Health Canada on when to consider testing specifically for germ cell mutagenicity were reasonable i.e. Where there were *in vitro* test results and positive evidence for mutagenicity in somatic cells *in vivo* and either

1) evidence from pharmacokinetic/tissue, or distribution studies that test materials and/or metabolites reach the gonads, or
2) evidence from sub-chronic or chronic treatment studies of gonadal pathology indicating germ cell damage, or

3) evidence for reproductive/developmental effects showing reduced numbers of pregnancies, reduced litter size, or an increased time to mating following treatment. However, it was noted that such information is not always available.

2.18 Overall, Members considered that there were insufficient data available to draw conclusions on any potential differences between somatic cell assays and between the various germ cell assays (e.g. in terms of potency and sensitivity). It was noted that the ability to detect aneuploidy was important and that this could vary between the different assays with the micronucleus assay being useful for this. The Committee agreed that the use of the expanded simple tandem repeat (ESTR) assay was an interesting new development, but it needed validation before any definitive conclusions could be drawn.

2.18 Regarding the different type of assays, Members considered that there were currently insufficient data to determine which assays had the most potential for future use. The FISH assay in sperm uses different probes making comparison of studies difficult, although this assay may be better for detecting aneuploidy than the micronucleus assay. More information was required on the number of cells that were being scored. Members also noted that, with the exception of the use of the ESTR, the assays would not detect all three mutagenicity endpoints. Therefore, a combination of assays would be required. Whole genome sequencing has the potential to detect all three mutagenicity endpoints, but currently this technique was too expensive.

2.19 Members agreed that further validation work was needed before germ cell assays could be incorporated into general genotoxicity testing. There were a number of difficulties such as DNA extraction and good study design was crucial. The Committee were aware that various groups were including germ cell assays in toxicity studies using 28 days of dosing followed by 28 days off dosing in, for example, the Big Blue transgenic assay, but it was currently not clear whether this would be a practical approach. Sampling and treatment times were important and needed careful consideration for the detection of germ cell mutations.

2.20 Regarding potential triggers for specific germ cell genotoxicity testing, Members considered that there was a need to establish first whether there was evidence for chemicals that were uniquely genotoxic in germ cells and thought that the outcome of the upcoming October 2013 IWGT meeting on this topic would be useful in this regard. Members also agreed that reproductive/developmental toxicity testing had not traditionally been a trigger for mutagenicity testing and that the role of genetic effects in embryo or fetal deaths was not understood. The Committee commented that currently the COM guidance on mutagenicity testing was adequate but welcomed further information on the results of germ cell testing.

Toxicogenomics as a tool for identifying genotoxic carcinogens

2.21 In the Horizon scanning exercise at the October 2012 COM meeting, it was suggested that the Committee review the use of gene expression technologies in genetic toxicology. The COM considered an outline of the development of toxicogenomics and a summary of studies published since the last review (February 2009). This included studies that looked at gene expression profiles to

identify genotoxic chemicals or to distinguish between genotoxic and non-genotoxic chemicals. Some studies comparing different cell lines were considered and some utilising human peripheral blood lymphocytes were also reviewed. An update on the current statement was not considered necessary.

2.22 The COM concluded that some good science had been conducted in the area of toxicogenomics for assessing genotoxicity, but it was not yet ready for regulatory purposes or for use in human biomonitoring. Currently the ontology was inconclusive and there were substantial variations in the methods used e.g. different microarrays; different genes selected to identify a genotoxic response; criteria for differentially expressed genes; cell lines used; exposure time etc. This high degree of variability along with the rapid changes within this field of investigation made it difficult to compare studies and draw overall conclusions. Members considered that information from toxicogenomics is potentially useful for evaluating mode of genotoxic action and may give a better mechanistic understanding of carcinogenicity. The move towards using human cell lines (e.g. HepG2) was supported. Members questioned the use of p53 deficient cells It was noted that cell lines which are deficient in p53 (e.g. mouse lymphoma) are probably not relevant for the evaluation of genotoxicity in toxicogenomic studies, because increased expression of p53 controlled genes is common after treatment with genotoxic chemicals. There was a need to develop a framework for a more harmonised approach, which would aid the validation of the use of toxicogenomics in assessing genotoxicity.

Horizon Scanning

2.23 The horizon scanning exercise provides information which can be used by Government Departments/Regulatory Agencies to identify important areas for future work.

2.24 In the 2013 horizon scanning exercise the Committee considered that an important area for consideration was the interpretation of negative data from two *in vitro* mammalian cell tests following a positive Ames test, and whether the *in vitro* mammalian cell results alter the view of the Ames result. This would be important under REACH where a database of experimental data is now being generated.

2.25 The Committee suggested that it would be useful to review current practices of incorporating genotoxicity testing into existing toxicity tests for example, integration of the micronucleus test and the comet assay into repeat dose toxicity testing to reduce the overall numbers of animals tested and the use of transgenic animals in 28 day toxicity studies to evaluate transgenic mutations. Another possible consideration was how high the maximum tested dose should be and what constituted a biologically significant response, for example a fold increase above background. Further, the use of genotoxicity data in an approach to risk assessment similar to that used with toxicological risk assessments was considered important. Members were also aware of work being conducted by ILSI on quantifying genotoxic responses and assessing non-linear dose-response relationships and that the potential importance of this work may need to be considered. It was also noted that many environmental chemicals do not have carcinogenicity data; therefore the possibility of developing a semi-quantitative

approach to dose-response data from *in vivo* genotoxicity studies, similar to a margin of exposure (MoE) approach adopted for the interpretation of carcinogenicity data was discussed.

2.26 Another topic suggested was epigenetics and epimutations. Members considered that there will be a need to understand and measure epigenetic effects and epimutations in the future and suggested histone and genome stability and genotoxic effects caused by epigenetic mechanisms as particular topics for consideration. Members were informed that a speaker on the topic of epigenetics to update the Committee could be arranged.

2.27 The Committee agreed that 3D tissue models may be of increasing importance in the future and therefore it would be useful to consider the validation and the potential utility of these models. It was noted that they may be particularly useful with respect to cosmetics in assessing genotoxicity in the skin.

2.28 Overall, Members agreed the following topics in order of priority as part of the horizon scanning activity for the upcoming year: the quantification of mutagenicity data including consideration of the biological significance of mutation, a review of 3D tissue models, a review of the use of combined genotoxicity and toxicity studies and 28 day studies in transgenic animals, and a consideration of epigenetics and epimutations.

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 C Allen (retired 31 March 13)	NONE	None	None	None
Dr B Burlinson (retired 31 March 13)	Huntingdon Life Sciences	Salary Employee Share Option Holder	None	None
Dr G Clare (joined 1 June 13)	Covance AstraZeneca Diageo HBOS Marks & Spencer	Consultant Shareholder Shareholder Shareholder Shareholder	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
Dr D Gatehouse (retired 31 March 13)	GlaxoSmithKline	Pension Share Option Holder Shareholder	None	None
Mrs R Glazebrook (retired 31 March 13)	BT Group Lloyds TSB National Grid	Shareholder Shareholder Shareholder	None	None
P Hardwick (joined 1 June 13)	Unilever plc	Pension	None	None
Professor G Jenkins	None	None	Hoffman-LaRoche Unilever CEFIC/ECETOC	Research Grant 2008 – 2010 Consultancy 2008 Research Grant 2008 - 2010 Honorarium 2008
Professor D Kirkland	Kirkland Consulting GSK	Principal Shareholder	None	None

Member	Personal Interest		Non-Personal Interest	
	Company	**Interest**	**Company**	**Interest**
	3i Standard Life Corning Covance ILSI HESI	Shareholder Shareholder Shareholder Shareholder and share option holder Committee member		
Dr A Lynch	GlaxoSmithKline	Salary Shareholder	None	None
Professor F Martin	Cable & Wireless	Shareholder		
Professor M O'Donovan (joined 1 June 13)	AstraZeneca	Shareholder	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 (joined 1 June 13)	None	None	None	None

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 2013. After extensive review of the evidence, we provided advice to the Department for Education on the relative vulnerability of children to asbestos. We also considered the following topics:

- The role of epigenetics in carcinogenesis.
- The influence of vitamin E on risk of prostate cancer.
- A study on the interpretation of margins of exposure for genotoxic carcinogens.
- The development of new screening levels for contaminants in soil.
- We began a review of the current evidence on alcohol and cancer risk.
- We continued our review of guidance statements on carcinogen risk assessment and published one on biomarkers.

As always, I am grateful to members of the committee for the invaluable advice and expertise they have provided during the year and to the secretariat for their support. I look forward to working with them on more topics and challenges in 2014.

Professor David H Phillips
BA PhD DSc FRCPath

COC Evaluations

Relative vulnerability of children to asbestos

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

3.2 The review extended into 2012 and 2013, when a statement was published with the following conclusions:

a) Asbestos is classified by the International Agency for Research on Cancer (IARC) as a group 1 carcinogen, i.e. it is carcinogenic to humans. Asbestos causes mesothelioma, and cancer of the lung, larynx, and ovary. In their recent evaluation, IARC also considered that there is evidence (in some cases limited) in humans for positive associations between exposure to asbestos and cancer of the pharynx, stomach and colorectum.

b) In general terms, the levels of respirable asbestos fibres in air range from lowest to highest in the following order:

- background outdoor ambient levels (lowest levels)
- background indoor ambient levels in buildings not built with asbestos
- levels in buildings built with asbestos where the asbestos is in good condition
- levels in buildings built with asbestos where the asbestos has been disturbed or damaged and/or is in bad condition (highest levels)

c) The data in general suggest that the levels of asbestos found in schools with no asbestos in their construction are of the same order of magnitude as indoor asbestos levels in other buildings. When asbestos is present and is disturbed or damaged, the data indicate that exposure to asbestos fibres can increase. However, the information on levels found in schools is largely historical and there is a lack of contemporary data on asbestos in schools. In view of the importance of this issue, there would be a benefit in generating new exposure data.

d) There is also potential for children to be exposed to asbestos in their home environment in homes where asbestos-containing products (ACPs) were used in their construction. In general, the reported levels of asbestos found in traditionally

built houses and flats are of the same order of magnitude as ambient indoor levels. However, activities such as maintenance can disturb asbestos and increase exposure both at home and at school.

e) From an epidemiological perspective, there is good evidence that childhood exposure to asbestos can cause mesothelioma in later life. However, the epidemiological data are too limited to assess differential susceptibility between children and adults. We recognise the effect of increased life expectancy of children compared to adults and the increased likelihood of mesothelioma as a result of the long latency period for this cancer. Because of differences in life expectancy, for a given dose of asbestos, the lifetime risk of developing mesothelioma is predicted to be about 3.5 times greater for a child first exposed to asbestos at age 5 compared to an adult first exposed at age 25 and about 5 times greater when compared to an adult first exposed at age 30.

f) There are respiratory and immunological differences between adults and children but their impact on the susceptibility of children to asbestos-induced cancer is unclear. We were informed that the juvenile lung is particularly susceptible to injury and that any lung damage received in the first 4 years of life, in terms of air flow obstruction, would remain for life. However, it is not possible to determine what effect fibre inhalation before the age of 5 would have on lung function, and whether any effect would persist. Some physiological differences (e.g. respiratory rates, total volume, and airway dimension) have the potential to modify the susceptibility of children compared to adults to asbestos. However, modelling of fibre deposition in children has indicated that children are unlikely to inhale more fibres than adults.

g) While the available relevant animal study provides data on age-related susceptibility to asbestos in rodents, it does not offer any significant insight into the relative vulnerability of children compared to adults to asbestos.

h) From the available data, it is not possible to say that children are intrinsically more susceptible to asbestos-related injury. However, it is well recognised by this Committee that, due to the increased life expectancy of children compared to adults, there is an increased lifetime risk of mesothelioma as a result of the long latency period of the disease. In reaching our conclusion and taking into consideration that there are a number of uncertainties and data gaps, we conclude that exposure of children to asbestos is likely to render them more vulnerable to developing mesothelioma than exposure of adults to an equivalent asbestos dose.

The COC's statement on the Relative Vulnerability of Children to Asbestos is available at: https://www.gov.uk/government/collections/coc-guidance-statements#statements.

Epigenetics in carcinogenesis

3.3 Epigenetics is the modification of gene expression or cell phenotype caused by mechanisms other than a direct change in the DNA sequence. It is known to be involved with many regulatory processes in the cell, including cell growth and transformation. Epigenetics and its role in carcinogenesis was first considered by the Committee at the Horizon Scanning meeting in November 2010, and in 2013

the COC considered two papers and a presentation by Professor Tim Gant which provided a background and introduction to epigenetics.

3.4 One key question raised was whether epigenetic changes were the cause or consequence of the carcinogenic process. Changes in the methylation status of gene promoter regions during tumour formation had been identified, however it was noted that it was the resultant change in gene expression which could progress to tumour formation. The importance of looking at the gene level rather than global methylation state was highlighted.

3.5 The COC considered evidence of epigenetic effects following exposure to arsenic or benzene. There was also a brief discussion of the impact of endocrine disruptors on epigenetics but it was noted there was little information on cancer. Any assessment of epigenetic changes and cancer associated with endocrine disruptors would need to be based on a systematic review of the literature rather than undertaking an evaluation on a study by study basis.

3.6 It was noted that there were data gaps in the published epigenetic studies.This included a lack of study replication that the human relevance of animal studies was not clear, and often epidemiological evidence was not available. It was queried whether methylation of DNA would be preserved during sample storage as this would enable investigation of epigenetics using some of the large cohort studies collecting and storing relevant biological samples.

3.7 Overall, the Committee considered that it was possible that epigenetic changes contribute to the carcinogenic action of arsenic and benzene but much more work would be required to assess this. It was agreed that epigenetic changes could be considered on a case-by-case basis when undertaking a carcinogen risk assessment, though it was noted that epigenetic changes could be causal for tumour development or an effect of tumour development.

It was agreed that the Committee would be kept up to date with developments in the epigenetics field, particularly where relevant to carcinogenicity.

The development of new screening levels for contaminants in soil

3.8 At the September 2013 meeting, the COC was asked by the Depatment for Evironment, Food and Rural Affairs (Defra) to consider a revised toxicological framework to aid the development of new screening levels for contaminated land risk assessment which were more pragmatic, although still strongly precautionary than the existing levels, termed Soil Guideline Levels (SGVs). The new screening levels are termed ‘Category 4 Screening Levels (C4SLs) and are derived from an intake dose that would represent ‘low risk’, termed a Lower Level of Toxicological Concern (LLTC). C4SLs are intended to provide a simple test for deciding when land is suitable for use and definitely not contaminated land. The project had been assessed by the COT and further information is provided in paragraphs 1.36-1.49. The COT had recommended that the COC could provide further advice on whether it was appropriate to use an Excess Lifetime Cancer Risk (ELCR) higher than 1 in 100,000 to define low risk.

3.9 The COC made a number of comments on the report and the contaminated land regime as a whole, including comparing the revised framework with the existing approach of using Health Criteria Values to define Soil Guideline Values.

3.10 In the context of contaminated land, the Committee discussed whether the use of an ELCR higher than 1 in 100,000 (e.g. 1 in 10,000 to 1 in 50,000) was appropriate to define a LLTC and hence a C4SL. Given the uncertainties involved, it was difficult to make a generic judgement and factors such as cancer site, data quality and animal versus human data would need to be considered. It was noted that the specific data for each of the six contaminants analysed in the project would have been helpful to the Committee's consideration. In general, the COC favours a minimal risk approach and would not like to see the threshold go higher than 1 in 100,000 ELCR. It was emphasised that the Committee already had a banding system for Margins of Exposure (MOEs) to aid risk communication and the derivation of the descriptors for each band had involved in depth discussion by the Committee in 2007. Further discussion is provided in paragraph 3.17 of this report. The term "Low Risk" was not used in the COC MOE banding.

3.11 The Committee noted that, when assessing contaminated land, consideration was not currently given to exposures to mixtures of contaminants, except in the case of polyaromatic hydrocarbons. Another potential approach was suggested, which would be to sum up the agreed level of risk for each of the contaminants present in the soil sample in question to get an indication whether there is a risk.

3.12 The Committee discussed the need for transparency and consistency between Local Authorities and other stakeholders using the framework to identify C4SLs. In the final reports to Defra for each contaminant, a number of different possible C4SLs had been presented for each exposure scenario, so Defra could determine how precautionary or conservative the values should be, and the Committee noted the need for risk management in such a decision. The Committee was advised that Local Authorities have to produce a risk summary document stating how land was categorised and the implications for landowners. The COC considered it important to have guidance to go with the C4SLs explaining the levels of risk. It was noted that the complex nature of the methodology could lead to uncertainty.

3.13 Overall, the Committee concluded that there was no scientific basis for using a default margin smaller than those currently recommended by the COC to derive an LLTC and advised the consortium to refer to the current COC bandings for the appropriate communication of the margin.

3.14 In addition, the COC noted that there were no plans to update the current SGVs but that the SGV for lead had been withdrawn by EA in light of the scientific data which had been published recently. Therefore, Local Authorities would not have any basis on which to assess the health risks from lead in land that may be contaminated. This could result in difficulties in determining the land as contaminated land. The Chair subsequently wrote to Defra expressing this concern and requesting feedback on the support being provided to Local Authorities.

Food Standards Agency funded research project on Interpretation of Margins of Exposure for Genotoxic Carcinogens (T01051)

3.15 Also at the September 2013 meeting, the COC was asked to review the final report of a research project funded by the FSA on “Interpretation of Margins of Exposure for Genotoxic Carcinogens”.

3.16 The general approach to genotoxic carcinogens has been to reduce exposure to levels that are "as low as reasonably practicable" (ALARP) or "as low as reasonably achievable" (ALARA), but this does not provide a clear basis for deciding on the urgency or extent of risk management actions. To address this, a series of international initiatives have recommended adopting a "Margin of Exposure" approach (MOE), for assessing risks from chemical substances in food that are genotoxic and carcinogenic. In this approach, a point of departure is generated by modelling the dose response data from an animal carcinogenicity study. The point of departure used is usually the lower 95% confidence limit of the BMD for a 10% response over control levels ($BMDL_{10}$). The margins between this value and estimates of exposure to the chemical are then calculated. A judgement can be made on the basis of the magnitude of these MOE.

3.17 The COC has previously concluded that the MOE approach could be useful for risk management action and communicating relative levels of concern. MOEs less than 10,000 were considered to be of possible concern, those between 10,000 and 1,000,000 were considered unlikely to be of concern, and those above 1,000,000 were considered highly unlikely to be of concern.

3.18 In view of the lack of international consensus on interpreting the level of concern for an MOE on the basis of uncertainty factors related to species differences, the FSA commissioned a research project (T01051) to support the establishment of levels of concern for the MOE or assist the development of alternative approaches. The project approach focussed on systematic review of evidence and elicitation of expert opinion on dose-response relationships for genotoxic carcinogens, development of a statistical framework to inform the definition of levels of concern, and comparison of the results with data on a number of known or potential human carcinogens. The draft final report was provided to COC as part of the review process.

3.19 Members acknowledged the final draft report was well-structured and reflected a large amount of work by the contractors. However, the small number of carcinogens for which both animal and human quantitative data were available limited the analyses that could be undertaken. Members commented that studies based on the mechanism of action could have provided information on the shape of the dose-response relationship at low doses in animal and human cells *in vitro*, to aid low dose extrapolation from carcinogenicity studies. Despite this limitation, Members agreed the research project adequately addressed its objectives. The overall conclusion of the research project was that it was not possible to establish with certainty the level of concern for a MOE of 10,000. Some of the case studies indicated that an MOE of 10,000 is a low concern whereas, for others, the uncertainties in the assessments were such that conclusions could not be drawn. The Committee agreed that on the basis of the outcomes of this project there was

no need to alter the previous conclusions on the MOE approach. It encouraged further studies addressing the mechanism of action in order to determine the shape of the dose response relationship at low doses which might support developments in the MOE approach.

Horizon Scanning

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

3.21 In 2013, the Committee considered the outstanding items from previous years, and one new discussion topic. Following these discussions, the list of priority topics was agreed as:

High priority:

- Alcohol and cancer - this work is ongoing
- Alternatives in Risk assessment

Medium-high Priority

- Mode of action framework

Medium Priority

- Thresholds of Genotoxicity – keep informed of COM work
- Nanomaterials – presentation on research on inhalation of nanomaterials
- Dose response modelling in epidemiology studies - this will be covered as part of the Guidance series G2 (Interpretation of Evidence of Carcinogenicity in Humans)
- *In vitro* 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

Ongoing work

Vitamin E and risk of prostate cancer – 1st draft statement

3.22 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.

3.23 The Food Standards Agency has asked the Committee to review the information available on vitamin E and prostate cancer, including epidemiological, animal and *in vitro* studies on this topic. In 2013, the Committee considered further information on the placebo used in the SELECT study published by the study authors. The review is ongoing and it is hoped it will be completed in 2014.

Alcohol and cancer risk

3.24 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).

3.25 In 2013, the COC considered a strategy to take forward a review of alcohol and cancer risk and agreed that the principal outcome of the review should be to inform risk reduction strategies. Investigations of dose-responses and patterns of intake (e.g. binge drinking) were considered essential to the review as this information could be directly related to the public's drinking habits, in contrast to reviews by the International Agency for Research on Cancer which are more focused on cumulative exposure. It was agreed the COC should review the epidemiological data and assess the overall burden of alcohol on cancer incidence in the UK. The COC would also consider interactions of alcohol and smoking. Two other interactions 1) caffeine and alcohol and 2) obesity and alcohol were also suggested.

3.26 It was noted that an evidence-based review on alcohol was ongoing by the UK's Chief Medical Officers (CMOs) and is due to be published in 2014. The Committee discussed a pre-publication report relating to this work, and further liaison with the groups undertaking the CMOs' review will take place in 2014

3.27 The COC was also provided with a paper on alcohol consumption and trends. The Committee found the information on the proportion of adults drinking above government guidelines helpful. It was also noted that data from the survey of children indicated an overall reduction in the numbers of 11-15 year olds drinking alcohol and the amount they consumed in recent years. Overall, the information was considered useful for the Committee to move forward and consider the impact of alcohol consumption on cancer burden in the UK.

The review of alcohol and cancer risk is ongoing, with a number of further papers expected in 2014.

IGF-1 and cancer risk

3.28 Interleukin Growth Factor 1 (IGF-1) is a growth factor which has a variety of biological effects including the promotion of cell division and growth. It has been proposed that exposure to dietary IGF-1 could increase the risk of certain cancers. The COC is considering an extensive range of data which covers dietary absorption, levels of IGF-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 2013. It is hoped that it will be progressed in 2014.

Guidance statements

3.29 During 2010, the COC adopted a proposal to change the way in which technical guidance on the risk assessment of carcinogens is presented on the COC website

3.30 At present, guidance is presented in a stand-alone booklet and is also spread throughout minutes and certain statements, which has several drawbacks. The proposed changes aim to improve accessibility of up-to-date advice, ease timely review, and make it easier to reference specific parts of COC guidance. The new system will comprise an overarching statement which will provide an 'executive summary' of the advice, and a series of guidance statements on specific aspects of the risk assessment of carcinogens. The overarching statement will undergo regular updates as each detailed guidance statement is revised to reflect the best available scientific practice as it evolves.

3.31 During 2013, the COC published guidance statement G04: The Use of Biomarkers in Carcinogenic Risk Assessment. This discusses biomarkers of effect and their use to assess mode of action of a carcinogen, and the application and value of different biomarkers of exposure

3.32 Guidance statements G05: Points of Departure and Potency Estimates, and G07: Alternatives to the 2-Year Bioassay, were discussed in November 2013 and are expected to be published in 2014.

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 Bradford & Bingley Centrica National Grid Takeda	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultancy		
Dr Carolyn Allen (until 31 March 13)	None	None	None	None
Mr Derek Bodey MA (from 1 June 13)	None	None	None	None
Prof Alan Boobis OBE (until 31 March 13)	Bank Santander Barclays Bank BG Group BT Group Centrica Iberdrola SA National Grid Lloyds Endura Fine Chemicals Astra Zeneca GlaxoSmithKline DuaneMorris Coca-Cola (from Oct 2012)	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultancies	Food Standards Agency Department of Health Health Protection Agency Medical Research Council European Chemical Industry Council – Long range Initiative Medical Research Council GlaxoSmithKline ILSI, ILSI HESI & ILSI Europe Board of Trustees/ Directors ILSI HESI Risk 21 project ILSI HESI, ILSI Europe & ILSI Research Foundation Working Groups on generic risk assessment issues.	Research Contracts PhD studentship Trustee/Director (non-remunerated) (past Chair of HESI) Vice-president of ILSI Europe Co-Chair Member

Member	Personal Interest		Non-personal Interest	
	Company	**Interest**	**Company**	**Interest**
			JMPR JECFA (vet drugs) EFSA CONTAM Panel (Panel on chemical contaminants in the food chain) EFSA PPR Panel Working Groups on Cumulative Assessment Groups for Pesticides; Risk Assessment of Pesticide Metabolites EFSA working group on Identification of Emerging Risks EFSA Scientific Committee Working Group on Threshold of Toxicogical Concern DG SANCO SCHER Working Group on Mixtures of Chemicals WHO IPCS Working Groups on Chemical Mixtures and on Mode of Action FP7 COSMOS Project Scientific Advisory Board of FP6/7 projects: PREDICT – IV ACROPOLIS and HEROIC Science Advisory Board, Swiss Centre for Applied Human Toxicology, Basel, Switzerland.	Chair/Member
Dr Phil Carthew (until 31 March 13)	Unilever	Salary	None	None

Member	Personal Interest		Non-personal Interest	
	Company	**Interest**	**Company**	**Interest**
Dr Gill Clare BSc PhD (from 1 June 13)	AstraZeneca Covance Diageo Marks & Spencer Shell Research Ltd	Shareholder, deferred pension Cytogenetic consultant Shareholder Shareholder Pension		
Dr John Doe PhD Dip R C Path (from 1 June 13)	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
Mrs Rosie Glazebrook (until 31 March 13)	BT Group Lloyds TSB National Grid	Shareholder Shareholder Shareholder	NONE	NONE
Dr Peter Greaves	Actelion Pharmaceuticals Ltd, Allschwil, Switzerland. Arena Pharmaceuticals, Inc., San Diego, California Astellas Pharma Europe Ltd Daiichi Sankyo, Edison, New Jersey Experimental Pathology Laboratories Inc., Sterling, Virginia GlaxoSmithKline, Ware Hyperion Therapeutics, Inc., San Francisco, California Johnson & Johnson Pharmaceutical Research & Development LLC, Raritan, New Jersey Novo Nordisk,A/S, Malov, Denmark Shire Pharmaceutical Development Ltd, Basingstoke, UK Sun Coast Tox Inc., San Diego, California. Biotie Therapies Inc., S. San Francisco	Consultant	EFSA ILSI	Member of Scientific Panel Committee Member

Member	Personal Interest		Non-personal Interest	
	Company	**Interest**	**Company**	**Interest**
Prof Ray Kemp BA MSc PhD MRTPI (from 1 June 13)	Ray Kemp Consulting Ltd	Shareholder	ARPANSA	Member of the Radiation Health Advisory Council
Dr David Lovell PhD BSc (Hons) FSS FIBiol CStat CBiol	National Grid plc	Shareholder	AstraZeneca National Grid plc EFSA EFSA member ECVAM ESAC	Spouse shareholder Member & Vice Chair Working Group on Threshold of Toxicological Concern Working Group on Genotoxicity Testing Strategies Working Group on Statistical Approaches (Member & Chair) Member of various working Group Peer Review panels
Dr Brian G Miller 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 General Workers Union Epidemiological review of occupational causes of malignant melanoma.	Share holder Shareholder Consultancy Consultancy Expert witness	CONCAWE (Conservation of Clean Air and Water Europe) CEFIC (European Chemistry Council) Other grants from UK government agencies & departments e.g. Food Standards Agency, Health & Safety Executive. ECETOC Scientific Committee	Research support Research support Research support External Committee member
Dr Heather Wallace BSc Hons PhD FRCPath FBTS	Bank Santander SA BT Group	Shareholder Shareholder	None	None

Member	Personal Interest		Non-personal Interest	
	Company	**Interest**	**Company**	**Interest**
Dr N Wallis (until 31 March 13)	Pfizer Bristol Myers Squibb	Shareholder Salary	None	None
Dr Rosemary Waring PhD DSc FRCPath (from 1 June 13)	Centrica and National Grid	Shareholder	Ministry of Defence	Research Support

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

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

Selflessness

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

Integrity

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

Objectivity

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

Accountability

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

Openness

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

Honesty

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

Leadership

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

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

Role of Members

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

Members must:

· engage fully in collective consideration of the issues, taking account of the full range of relevant factors, including any guidance issued by the Food Standards Agency, Health Protection Agency and the Department of Health
· undertake on appointment to comply with the Code of Practice for Scientific Advisory Committees[7]
· not divulge any commercially sensitive information, pre-publication or unpublished research data provided to the Committee
· agree an annual report
· ensure that an appropriate response is provided to complaints and other correspondence, if necessary with reference to the sponsor department; and;
· ensure that the Committee(s) does not exceed its powers or functions.

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

If members believe the committee's method of working is not rigorous or thorough enough, they have the right to ask that any remaining concerns they have be put on the record. Individual members should inform the Chair (or the Secretariat on his or her behalf) if they are invited to speak in public in their capacity as a Committee member. Communications between members and the Food Standards Agency (FSA) Board, 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.

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

Role of the Chair

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

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

Role of the Deputy Chair

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

Role of the Secretariat

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

The Secretariat is also a source of advice and guidance to members on procedures and processes. The Secretariat is drawn from staff of the Food Standards Agency and 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 2012/13 the budget for the COT, excluding Secretariat resources was £39,963. 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*[3] 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*[4] and the *Principles of Scientific Advice to Government*[5] 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[6]

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

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

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

- Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment[4]
- Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment[7]
- 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.

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

PRINCIPLES

Defining the problem and the approach

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

Seeking input

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

Validation

9. Study design, methods of measurement and the way that analysis of data has been carried out will be assessed by the SAC.
10. Data will be assessed by the committee in accordance with the relevant principles of good practice, e.g. qualitative social science data will be assessed with reference to guidance from the Government's Chief Social Researcher[8].
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.

[8] 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.[++]

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

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

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

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

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

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

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

2011 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Food Standards Agency/Department of Health, July 2012

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

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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