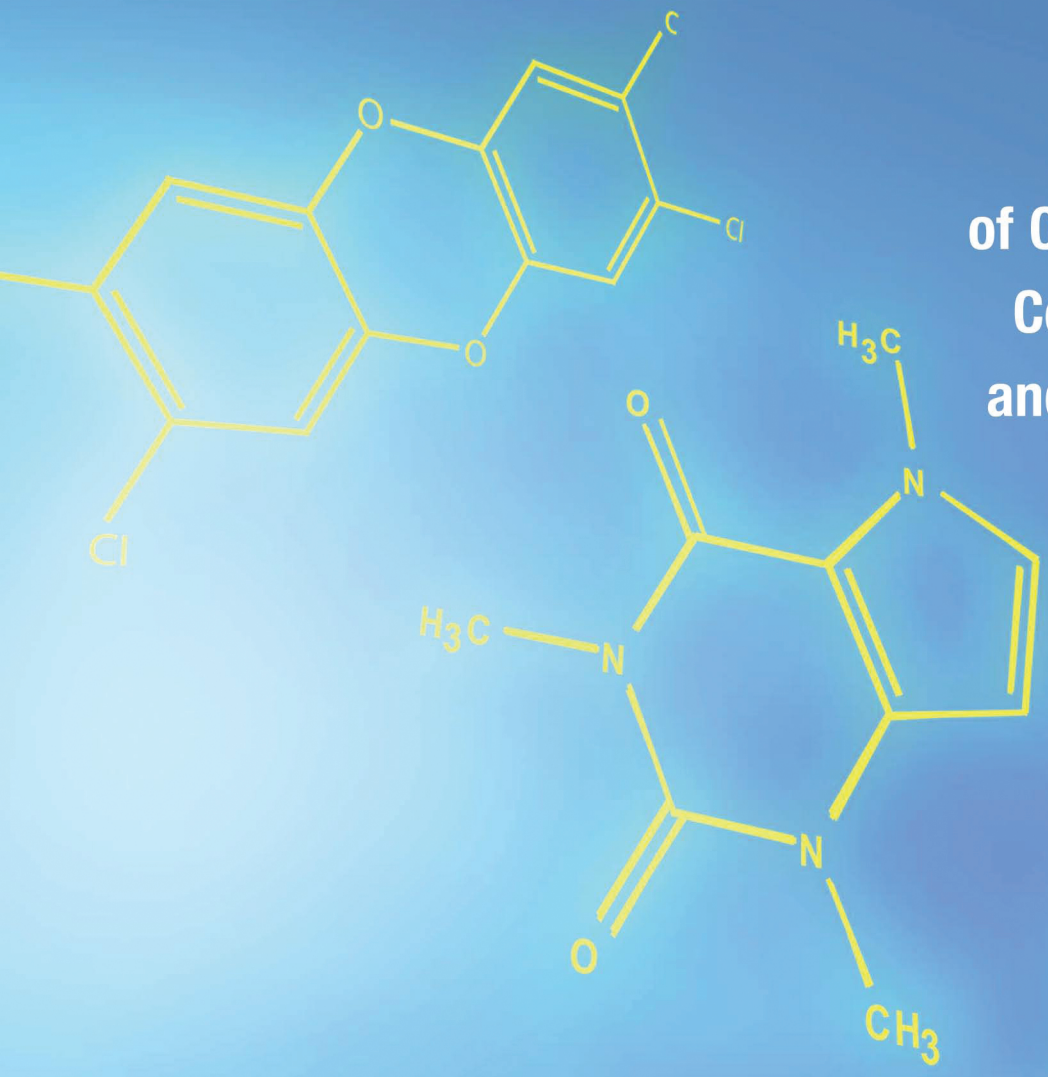
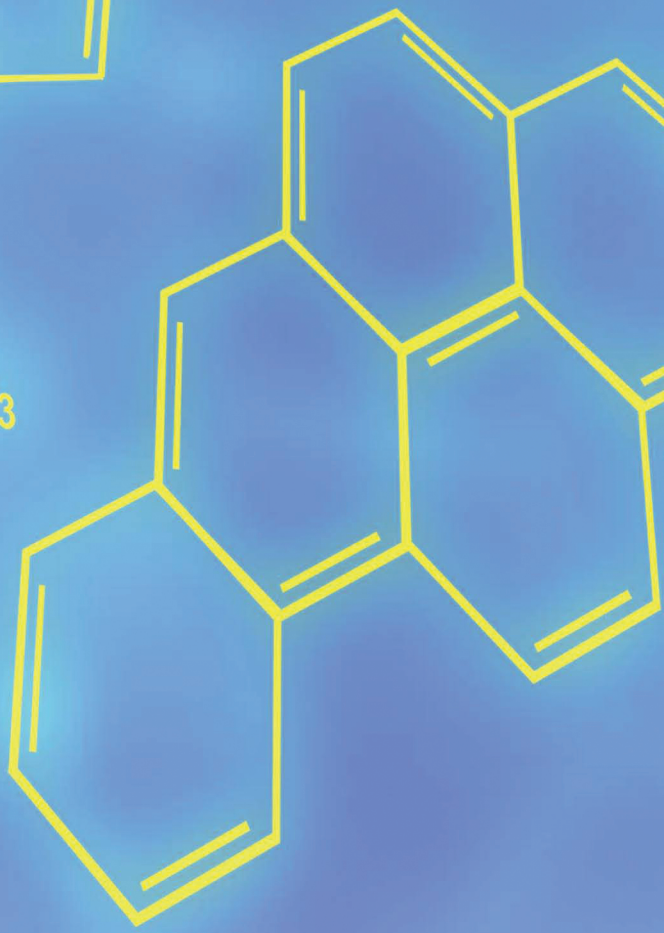
Committees on Toxicity Mutagenicity Carcinogenicity of Chemicals in Food, Consumer Products and the Environment





Committee on TOXICITY

Committee on CARCINOGENICITY

Committee on MUTAGENICITY

Annual Report 2016

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

Annual Report 2016

Contents

About the Committees

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

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

In common with other independent advisory committees, Committee members are required to follow a Code of Conduct which also gives guidance on how commercial interests should be declared. Members are required to declare any commercial interests on appointment and, again during meetings if a topic arises in which they have an interest. If a member declares a specific interest in a topic under discussion, and it is considered to be a conflict of interest, he or she may, at the Chairman's discretion be allowed to take part in the discussion, but is excluded from decision-making. Annex 1 contains the terms of reference under which the Committees were set up. The Code of Conduct is at Annex 2 and Annex 3 describes the Committees' policy on openness. Annex 4 is the Good Practice Agreement for Scientific Advisory Committees. Annex 5 contains a glossary of technical terms used in the text. Annex 6 is an alphabetical index to subjects and substances considered in previous reports. Previous publications of the Committees are listed at Annex 7.

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

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

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

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

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

Preface

I am pleased to present this report, which summarises the work of the Committee on Toxicity (COT) during 2016. The COT assesses chemicals for their potential to harm human health. Evaluations are carried out at the request of the Food Standards Agency, Department of Health, Public Health England, and other Government Departments and Regulatory Authorities, and are published on the Internet as statements or shorter position papers. Details of membership, agendas and minutes are also published on the Internet.

During 2016, the Committee held six meetings. The Committee continued its review of the risks to infants and young children from a variety of contaminants, based on new information on exposure, some of which was from the 2014 Survey of Metals and Other Elements in Infant Foods. Contaminants reviewed included arsenic, acrylamide, lead, aluminium, nickel, polybrominated diphenyl ethers and hexabromocyclododecanes. Work on arsenic, acrylamide, lead and aluminium was completed during the year, and statements were published on these topics. Work on PBDEs, HBCDDs and nickel will be completed in 2017. The Committee also reviewed risks to infants and young children from iodine and vitamin A in the diet. This work will be completed in 2017.

The Committee continued its evaluation of a series of systematic reviews on the role of the infant diet and the development of atopic and autoimmune disease. It also reviewed the results of a related study funded by the FSA: EAT - A randomized trial of the early introduction of allergenic foods in breastfed infants. The Committee finalised its work on hydrolysed cows' milk formulae and on the timing of introduction of allergenic foods into the infant diet. Statements were published on these topics. Work on the remaining aspects will be completed in 2017. As part of this, a joint working group of COT and SACN was established to undertake a benefit-risk assessment of the timing of introduction of allergenic foods into the infant diet to enable consensus advice to be provided to government. This work will be completed in 2017. The contents of the systematic reviews have been published in the peer reviewed literature or will be submitted for publication in due course.

The Committee updated its consideration of the risks from potassium-based replacements for sodium chloride. The combined sub-group with SACN completed its benefit-risk assessment, to ensure the advice provided adequately reflects both the positive and negative consequences of replacement of sodium salt with potassium salt. A joint report on this benefit-risk assessment will be finalised and published in 2017.

The Committee commenced work on evaluating the absolute and relative risks from the use of electronic nicotine delivery systems (e-cigarettes) and novel heat-not-burn tobacco products. In the first instance COT undertook scoping reviews of these products and identified follow-up work for consideration at future meetings. Work on heat-not-burn products will be completed in 2017. The Committee also discussed concerns arising from the use of shisha pipes in public spaces.

The joint COT/COC Synthesising Epidemiological Evidence Sub-group was established in 2015 to review the approaches to synthesising epidemiological evidence used by the committees in their chemical risk assessments and to make recommendations to the committees on guidance. The sub-group has now finalised its proposed guidance and recommendations, for consideration by COC and COT. The committees will conclude this work in 2017.

The COT participated in an FSA *ad hoc* working group: Developing Proportionate Controls for Risky Foods. The working group developed a framework for this purpose which was considered and adopted by the FSA Board. The Framework has been published on the FSA website.

The COT provided comments to the EFSA on its updated draft guidance on the use of the benchmark dose.

The Committee discussed several scientific areas of potential relevance, including emerging non-animal methods for toxicity testing and their "validation", physiologically-based toxicokinetic modelling, trans- and multigenerational toxicity, endocrine disrupting chemicals, and the microbiome. A watching brief will be kept on these topics for developments relevant to the work of the Committee and updates will be provided as appropriate.

2016 saw the passing of a former member (2008-2010), Dr Cliff Elcombe. Dr Elcombe's expertise and research contributions were invaluable to the work of the Committee and he will be sadly missed.

During 2016, Ms Frances Pollitt's attended her last meeting as the PHE Scientific Secretary, as she was retiring. I thank her for all of the work she did in supporting the work of the Committee and wish her well for the future. The Committee welcomed Ms Britta Gadeberg as the new PHE Scientific Secretary in 2016.

A member of the Committee, Prof David Harrison, was appointed to the Chair of the Committee on Carcinogenicity (COC). I congratulate him on his appointment and wish him every success in the role.

I would like to thank all members of the Committee and the secretariat for their support and hard work over the year. It helped make my task as chair much easier.

Professor A Boobis (Chairman)
OBE PhD CBiol FRSB FBTS FBPhS

COT evaluations

Acrylamide in the diet of infants and young children

1.1 The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that will inform the Government's dietary recommendations for infants (0 to 12 months) and young children (1 to 5 years). The COT was asked to review the risks of toxicity from chemicals in the diet of infants. This document gives an overview of the potential risks from acrylamide. There are currently no Government dietary recommendations for infants and young children relating to acrylamide.

1.2 Acrylamide forms naturally in starchy food products during cooking at high temperatures, such as frying, baking, roasting and also during industrial processing. Its presence in food was first reported in 2002, although it is very likely that it has been present in food since cooking began. Acrylamide also has industrial uses, particularly in the production of polyacrylamide. Acrylamide is present in tobacco smoke.

1.3 The key toxicological effects of acrylamide in laboratory studies are:

- changes in the genetic material of cells;
- induction of cancer;
- damage to the nervous system;
- alterations in the male reproductive system.

1.4 Although the results of human studies provide no reliable evidence that acrylamide causes cancer in humans, based on what is known about the way it causes cancer in animals it is possible that it could also cause cancer in humans.

1.5 The COT assessed the possible health risks arising from acrylamide exposure from different sources. Acrylamide has the potential to pass from the mother's blood into breast milk, but only at very low levels, which are unlikely to represent a risk to the breast-fed infant.

1.6 For infant formula and foods eaten by infants and young children, the assessment indicated a potential concern for cancer risk as in other age groups. However the currently available scientific information does not allow quantification of any risk. The levels in food do not indicate a concern for the other effects of acrylamide such as those on the nervous system or reproductive system.

1.7 The major sources of dietary exposure to acrylamide include potatoes (particularly home cooked potatoes), other cooked vegetables and cereal-containing foods (such as breakfast cereals and sweet biscuits). Dietary acrylamide exposure of infants and young children in the UK is similar to that in other European countries.

1.8 There have been efforts in the UK and Europe to reduce concentrations of acrylamide in food over recent years, but the evidence so far is not sufficient to demonstrate whether these have resulted in a decrease in dietary exposure. Therefore, efforts to reduce acrylamide exposure should be continued, with respect to both home cooked and commercially produced food.

1.9 Acrylamide concentrations in soil, water and air are low and therefore exposures from these sources are likely to be low in comparison to dietary exposure. There is a lack of information on potential exposure of infants and young children from some other sources; for example exposure from passive smoking could be an important contributor for some children.

The COT statement is available here:
https://admin.food.gov.uk/sites/default/files/finalacrylamidestatement.pdf

Aluminium in the diet of infants and young children

1.10 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 diet of infants (age 0-12 months) and young children (aged 1-5 years). The COT issued a statement in 2013 on the potential risks from aluminium in the infant diet [http://cot.food.gov.uk/pdfs/statealuminium.pdf]. In 2016, the COT issued an addendum to its 2013 statement, which extended the assessment to young children and updated the assessment for infants, based on the most recent data on exposure [https://admin.food.gov.uk/sites/default/files/finalaluminiumaddendum.pdf].

1.11 This lay summary has been updated to provide an overview of the information in the two COT documents.

1.12 Infants and young children 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.

1.13 Aluminium is present in the 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.

1.14 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 specifically in infants or young children. 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

1.15 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 considers 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.

1.16 The COT has estimated exposure to aluminium based on levels in breast milk, infant formula, water, food, and soil reported in the scientific literature or in Food Standards Agency surveys, together with data on consumption by infants and young children. The combined exposure from these different sources were also considered.

1.17 Dietary exposures of all age groups up to 5 years were well below the PTWI and do not indicate any toxicological concern. This includes exposure through soya-based infant formula and other soya drinks used in older infants and children, which contain higher levels of aluminium than non soya-based foods.

1.18 Combined exposures from breast milk, diet (including water), and soil/dust are up to almost 3 times the PTWI. This is due to the high levels of aluminium present in soil and the assumption that similar levels might also be present in dust. Taking into account that much of the aluminium in soil is likely to be less well absorbed into the body than that in food, and that the PTWI was established from a study on aluminium citrate, which is a more readily absorbed form of aluminium, these exceedances of the PTWI are not clearly of concern.

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

The 2013 COT statement can be found at: http://cot.food.gov.uk/pdfs/statealuminium.pdf
The 2016 addendum can be found at:
https://admin.food.gov.uk/sites/default/files/finalaluminiumaddendum.pdf

Arsenic in the diet of infants and young children

1.20 The SACN is reviewing the scientific evidence that bears on the Government's dietary recommendations for infants and young children. The COT was asked to review the risks of toxicity from chemicals in the diet of infants (aged 0-12 months) and young children (aged 1-5 years). This statement addresses the risks from arsenic in the diet of these age groups. There is one Government dietary recommendation for infants and young children relating to arsenic, specifying that toddlers and young children (aged 1 to 4.5 years) should not be given rice drinks as a substitute for breast milk, infant formula or cows' milk. This is due to the potential for rice drinks to contain high levels of arsenic. Furthermore, cows' milk or alternatives are not suitable as drinks for infants under 12 months old.

1.21 Arsenic occurs in the environment in a variety of organic and inorganic forms[1] as the result of natural and human activity. As it is widely accepted that inorganic arsenic compounds are more toxic than organic arsenic compounds, the COT focused its review on the potential risks from exposure to inorganic arsenic. Where specific information was not available, it was assumed that all arsenic present in that source of exposure was in the inorganic form.

1.22 People are exposed to inorganic arsenic through food, drinking water, air, soil and dust; infants and young children can also be exposed through breast milk and infant formula. Food and water are generally the major sources of exposure to inorganic arsenic.

1.23 The amount of arsenic taken up from the gut varies depending on the chemical form, its solubility, and the material (e.g. type of food) in which it is present. Once absorbed, inorganic arsenic is rapidly cleared from the blood and widely distributed throughout the body before being metabolised and eliminated via urinary excretion.

1.24 The effects of inorganic arsenic depend on total exposure from all sources. Long-term exposure to inorganic arsenic can cause skin lesions, and cancer of the lung, urinary bladder, and skin. Consequently, it is important to consider combined exposures throughout life from food, water, and non-dietary sources. However, dietary sources generally contribute more to total exposure than non-dietary sources such as soil and dust. Exposures from air are considered negligible. Therefore efforts to reduce the levels of inorganic arsenic in food and water should continue.

1.25 The Committee considered the possible risks from exposures of UK infants and young children to inorganic arsenic from different dietary sources. For infants aged

[1]In this context, the term organic refers to the forms of arsenic that are commonly found in fish, seafood and other marine organisms.

0 to 4 months old who are fed only on breast milk, ready-to-feed formula, and powder formula made with water containing typical inorganic arsenic concentrations, exposures were considered of low concern. There could be a small risk when powder formula is prepared with water containing inorganic arsenic at the upper end of the concentration range in public water supplies. It was not possible to estimate likely exposures in those relying on private water supplies, as suitable information was not available. Similarly, with the introduction of complementary feeding, there could be a small risk for some older infants and young children, particularly when water contains higher levels of inorganic arsenic.

1.26 The Committee concluded that the estimates of exposure to inorganic arsenic from rice drinks support the advice not to use rice drinks as a substitute for breast milk, infant formula or cows' milk, and that this advice should therefore remain in place. However, consumption of up to 50 mL of rice drink per day by those aged 1-5 years would not make much difference to total dietary exposure to inorganic arsenic.

1.27 The Committee also assessed exposure to inorganic arsenic from the consumption of infant and 'adult' rice cakes by those aged 0 to 5 years, and concluded that neither would result in an increased risk.

The 2016 COT statement can be found at:
https://admin.food.gov.uk/sites/default/files/finalstatementonarsenic.pdf

Hexabromocyclododecanes (HBCDDs) in the diet of infants and young children

1.28 The Scientific Advisory Committee on Nutrition (SACN) is reviewing the scientific evidence that bears on the Government's dietary recommendations for infants and young children. The Committee on Toxicity (COT) was asked to review the risks of toxicity from chemicals in the diet of infants (aged 0-12 months) and young children (aged 1-5 years). The COT issued a statement on the possible risks from hexabromocyclododecanes (HBCDDs) in the infant diet in 2015. In 2016, the COT issued an addendum to its 2015 statement, which extended the assessment to young children and updated the assessment for infants, based on the most recent data on exposure. This lay summary has been updated to provide an overview of the information in the two COT documents.

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

1.30 Infants and young children can be exposed to HBCDDs through their presence in breast milk as well as other foods. In older infants and young children, swallowed domestic dust is also a source of exposure to HBCDDs.

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

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

1.33 There are a number of uncertainties in the assessment so a generally conservative approach is taken.

1.34 Overall the analysis indicated that estimated exposures via breast milk and food, including infant formula and commercially produced infant foods, are not a cause for concern. No data are available on potential exposures in the UK from drinking water. New data on HBCDD levels in dust have been published since the 2015 statement. Average (median) and high (97.5th percentile) levels of HBCDDs in dust are not a cause for concern but sporadic extremes, which might be found in a few houses, could be.

1.35 Given that most uses of HBCDDs are being phased out, and that the main source of exposure to residual environmental HBCDDs is ingested domestic dust, the priority for further research is continued monitoring of HBCDDs levels in house dust to ensure that they are declining as expected.

The 2015 COT statement can be found at:
https://admin.food.gov.uk/sites/default/files/HBCDDsstatementfinal.pdf

The 2016 COT statement addendum can be found at:
https://admin.food.gov.uk/sites/default/files/finaladdendumonhbcdds.pdf

Histamine in food

1.27 Histamine (scombrotoxin) poisoning is a well-established phenomenon arising from consumption of foods most notably scombroid fish, such as fresh tuna and anchovies and fermented fish products, which have become contaminated with the biogenic amine histamine as a result of bacterial spoilage. Although the

concerns about histamine toxicity initially related to fish, biogenic amines such as histamine also occur in fermented products such as cheese or sausage with the FSA having received a number of incident reports related to excess levels of histamine in cheese over the last few years.

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

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

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

1.31 The COT was asked to comment on the EFSA opinion and the current FSA approach to incidents involving histamine in cheese. The Committees concluded that:

- The effects of histamine poisoning can be quite severe and unpleasant but were short-lived.

- Analysis of data from incidents involving histamine in cheese that were dealt with by the FSA, show that most of the individuals in whom symptoms of poisoning were reported were toddlers and young children. It is unclear whether this observation is evidence that young children are more sensitive to the effects of exogenous histamine, or whether the data had been subject to reporting bias (i.e. as multiple children were affected simultaneously, the likelihood of a diagnosis of histamine poisoning was increased). In general the cheese involved in such incidents tended to be mature and produced by larger manufacturers, rather than by artisan producers.

- The ARfD (50 mg of histamine per meal per healthy adult) that was established by the EFSA Panel, was sensible and conservative. It was adequately protective as it had been based on the responses of healthy and sensitive individuals. Although the ARfD did not take into account the possible modulation of histamine sensitivity by other factors such as medication, management of such risks may be better achieved through education of consumers or patients, as is done in the case of tyramine.

- The FSA's approach to assessing the risk from histamine in cheese was sensible and well-founded as it took into account the appropriate measures of exposure, including data from the National Diet and Nutrition Survey (NDNS), and adjusted the EFSA ARfD for toddlers and children by scaling for bodyweight. It is appropriate to build on the risk assessment already established for biogenic amines in fish, but it would be prudent for the FSA to adopt a case-by-case approach when considering histamine in cheese. There is currently too much heterogeneity in the levels of histamine in cheese to establish an 'action' or guidance level that could inform the FSA's approach to risk assessments.

Hydrolysed cows' milk formulae: role in influencing the development of atopic outcomes and autoimmune disease

1.36 The COT were asked for their opinion on a systematic review looking at the use of hydrolysed cows' milk formulae in infants at a high risk of developing atopic outcomes or autoimmune disease. This review was commissioned by the Food Standards Agency and will be used to direct future policy in this area.

1.37 The COT agreed that the use of hydrolysed infant formula did not reduce the risk of developing atopic outcomes or autoimmune disease in high-risk infants.

The 2016 COT statement can be found at:
https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cot-statement-on-hydrolysed-cows-milk-formulae

Irritant sprays

1.38 The COT previously reviewed the safety-in-use of irritant sprays containing pelargonyl vanillylamide (nonivamide, or PAVA) or 2-chlorobenzylidene malononitrile (CS) in various solvents (in 1998, 1999, 2005, 2013 and 2015), and considered combined exposure to PAVA and sprays in 2006. In 2016, the COT provided advice on a reformulated PAVA irritant spray. This was taken as reserved business as it contained commercially-sensitive information.

Lead in the diet of infants and young children

1.39 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 diet of infants (aged 0-12 months) and young children (aged 1-5 years). The COT issued a statement in 2013 on the potential risks from lead in the infant diet [http://cot.food.gov.uk/pdfs/cotstatlead.pdf]. In 2016, the COT issued an addendum to its 2013 statement, which extended the assessment to young children and updated the assessment for infants, based on the most recent data on exposure [https://admin.food.gov.uk/sites/default/files/finaladdendumonlead.pdf].This lay

summary has been updated to provide an overview of the information in the two COT documents.

1.40 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 young 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.

1.41 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.

1.42 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 results also in the release of lead from the bone.

1.43 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, and the developing brain is 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.

1.44 The Committee concluded that assessment of the potential risks from exposure of infants and young children to lead should be made by reference to an exposure value of 0.5 micrograms per kilogram body weight per day, which the European Food Safety Authority (EFSA) had estimated would produce less than a 1 point decrement in IQ. Exposure below this value indicates that the health risk is small.

1.45 The Committee calculated estimates of exposure of UK infants and young children to lead from different sources and compared them to the exposure value identified by EFSA. For infants aged 0 to 6 months old who are fed breast milk, ready to feed drinks and powder formula made with water containing typical lead concentrations, any risk would be small. A small risk cannot be ruled out for infants of this age exclusively fed on infant formula prepared with water containing lead at the upper end of the concentration range of lead in public water supplies. It was not possible to estimate likely exposure in those relying on private water supply.

1.46 For older infants, and for young children, any risk from diet alone will also be small. However, the effects of lead 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. When the possible contribution from soil and dust is taken into account, a risk at the population level and to some infants and young children cannot be ruled out. Exposures from air are negligible.

1.47 There are a number of uncertainties in the assessment of risks from lead exposure and generally conservative assumptions have been made in estimating risk. The COT previously noted the decreasing trends in dietary exposure to lead and blood lead levels in recent decades. Nevertheless, the absence of an identified threshold for neurodevelopmental effects of lead and the exposures identified in this assessment emphasise the need for continued efforts to control lead in the environment.

The 2013 COT statement can be found at:http://cot.food.gov.uk/pdfs/cotstatlead.pdf

The 2016 addendum can be found at:
https://admin.food.gov.uk/sites/default/files/finaladdendumonlead.pdf

Polybrominated diphenylethers (PBDEs) in the diet of infants andyoung children

1.48 The Scientific Advisory Committee on Nutrition (SACN) is reviewing the scientific evidence that bears on the Government's dietary recommendations for infants and young children. The Committee on Toxicity (COT) was asked to review the risks of toxicity from chemicals in the diet of infants (aged 0-12 months) and young children (aged 1-5 years). The COT issued a statement on the possible risks from polybrominated diphenyl ethers (PBDEs) in the infant diet in 2015

1.49 A discussion paper TOX/2016/22 provided estimates of PBDE exposures for chidren in the UK aged 1-5 years and also an updated exposure assessment for infants aged 0 to 12 months as new data had become available since the 2015 COT statement. These estimates were drafted into an addendum to the COT 2015 statement along with comments regarding whether levels of PBDEs were increasing or decreasing in European Union countries since their ban. The addendum to statement will be finalised in 2017

Timing of introduction of allergenic foods to the infant diet and influence on the risk of development of atopic outcomes and autoimmune disease

1.50 The COT were asked for their opinion on a systematic review looking at the timing of introduction of allergenic foods into the infant diet and the influence on the risk

of developing atopic outcomes and autoimmune disease. This review was commissioned by the Food Standards Agency and will be used to direct future policy in this area. The COT also considered the results from the EAT study[2], also commissioned by the FSA and included as part of the systematic review.

1.51 The COT agreed with the findings of the systematic review that for egg and peanut allergy, early introduction (at 4-6 months for egg and 4-11 months for peanut) of these two foods reduces subsequent development of an allergy to that food.

The 2016 COT statement can be found at:
https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cot-statements-2016/statement-on-the-timing-of-introduction-of-allergenic-foods-to-the-infant-diet-and-influence-on-the-risk-of-development-of-atopic-outcomes-and-autoimmune-disease

Committee procedures

EFSA consultation on draft guidance document on the use of the benchmark dose in risk assessment

1.52 The COT was invited to comment on this draft guidance document and more generally the benchmark dose (BMD) approach and its implications for the work of the Committee. The draft guidance document was an edited update of the previous EFSA guidance document on benchmark dose modelling, which had been published in 2009. The key changes were largely to the methodology, and were primarily on the way that models were used and assessed for goodness of fit; the use of model averaging; and describing how to use either the benchmark dose software (BMDS) developed by the United States Environmental Protection Agency, or PROAST which was developed by the Netherlands National Institute for Public Health and the Environment (RIVM).

1.53 Members considered the document clear and useful to understand how benchmark dose modelling results were calculated and used. Members recognised that benchmark dose modelling was scientifically superior to the use of the no-observed-adverse-effect-level (NOAEL). However, one advantage of the NOAEL approach was that since the NOAEL had to be one of the dose levels tested, most experts would agree the same value for the NOAEL. Since different benchmark dose models might be used, with different judgements on whether to constrain the models, and different uses of model averaging, different scientific committees and bodies might arrive at different reference points, losing consistency between these committees/bodies. Transparency was needed, and it was pointed out that the

[2] Perkin et al (2016) Randomized trial of introduction of allergenic foods in breast-fed infants. NEJM 374 1733-43.

draft guidance document provided a template for reporting benchmark dose modelling results.

1.54 The Committee noted the conclusion of the document that study guidelines should be changed to increase the number of dose levels tested without increasing the total number of animals used in the experiment. It had been argued that no statistical power is lost when using the same number of animals over more dose groups. However, while this was the case for dose-response modelling, the power would be reduced for hazard identification in the case of low potency substances. In addition, if no effects were observed then benchmark dose modelling could not be performed whereas it would still be possible to identify a NOAEL.

1.55 It was agreed that the Committee itself would not submit a response to the consultation. However, Members were encouraged to respond to the consultation individually if they had any comments

Horizon scanning

1.56 At their February 2016 meeting, the COT were invited to consider emerging or developing topics of importance within the COT remit, which might be included in future agendas for detailed discussion. Members noted the list of agenda items that were planned or underway for 2016, and discussed several other topics that might also be considered.

1.57 The Committee considered that since there was much current research activity in read across and predictive toxicology (e.g. Tox21 and ToxCast in the USA; SURAT 1 and EU-ToxRisk in the EU; OECD adverse outcome pathway program), and which was likely to influence the future of toxicity testing a workshop in this area would be useful. The Committee noted there was a need for an international consensus on how best to determine the validity of *in vitro* methods for risk assessment since the current validation process was increasingly considered to be too slow.

1.58 The Committee noted that the application of physiologically based toxicokinetic modelling (PBTK) in risk assessment had shown little recent progress, although there were some developments, such as a tool for non-expert use, and in-house modelling by the pharmaceutical industry. It was agreed that the COT would keep a watching brief on this topic.

1.59 Members agreed that a systematic review of the health effects of endocrine disrupting chemicals (EDCs) would be useful but recognised that this would be a major task. A similar task had been conducted by the World Health Organization (WHO) but more focussed questions would have been helpful. Without a coordinated systematic review to understand the evidence base (possibly an

"umbrella" review of reviews to obviate author selection bias) the impact of EDCs was uncertain. In the first instance, Members agreed that a paper on the evidence gaps would be helpful; this would be prepared by PHE.

1.60 The COT decided that it would be timely to review the toxicity of both nicotine-containing and nicotine-free electronic delivery systems. The Medicines and Healthcare Products Regulatory Agency (MHRA) had licenced at least one nicotine-containing product. However, most products were currently largely unregulated, but this would change with implementation of the Tobacco Products Directive, in May 2016. The aspects related to carcinogenicity could be worked on jointly with COC and COM, while COT could consider the added flavourings and exposure to vapours and particulates, including bystander exposure. A risk-benefit assessment of E-cigarettes would not be within the COT remit.

Update on the COT 2008 Trans and multigenerational toxicity statement

1.61 Members noted that the knowledge base trans and multigenerational toxicity had moved on since the last COT statement was published in 2008. The COT agreed that the statement should be updated, with input from PHE as appropriate.

1.62 The COT agreed that since the importance of the microbiome in many areas of health and disease was becoming increasingly apparent, the effects of xenobiotics on the microbiota and of the microbiota on xenobiotics should be considered. Both the makeup of the microbiological population, i.e. the species of bacteria and other microorganisms present, and its functional makeup, i.e. the biochemical pathways contributed by the total mass of microorganisms, should be taken into account, along with other potential interactions, for example between air pollution, microorganisms in the respiratory tract and the development of asthma.

Balance of expertise on the Committee

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

Analytical techniques	Biochemistry
Bioinformatics	Biomonitoring
Cell biology	Clinical practice
Dietary exposure assessment	Endocrinology
Environmental exposure assessment	Epigenetics
Epidemiology	Human toxicology
Immunology	Mathematical Modelling
Mechanistic toxicology	Molecular biology
Neurotoxicology	Nutrition
Occupational health epidemiology	Paediatrics

Pharmacokinetics	Pharmacology
Probabilistic modelling	Reproductive toxicology
Respiratory toxicology	Risk assessment
Statistical aspects of experimental design	Statistics
Systems biology	Toxicogenomics
Toxicological pathology	Xenobiotic metabolism

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

Peer review by EU-ANSA agencies

1.65 Due to the there being insufficient time for discussion, Members were requested to send in any comments on this paper by email. If required, this item could be brought back to the next meeting for a full Committee discussion.

Working Groups

COT/COC Subgroup on synthesising epidemiological evidence

1.66 The COT and COC set up a subgroup to review the approaches to synthesising epidemiological evidence that are used by the Committees in chemical risk assessments and to make recommendations for COT/COC guidance. The terms of reference are to provide guidance that can be used by expert advisory committees for synthesis of epidemiological evidence, to review recent practice by expert advisory committees for synthesis of epidemiological evidence, with a focus on systematic reviews, to identify key points of current best practice methodologies used in systematic review and meta-analysis, and to identify and make recommendations for areas requiring further work. Further information on the subgroup can be found at: http://cot.food.gov.uk/cotwg/cot-coc-epi-sub-group. The subgroup is expected to complete its work in 2017.

COT/SACN Subgroup on potassium-based replacement for sodium chloride and sodium based additives

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

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

The subgroup is expected to complete its work in 2017.

COT/SACN Subgroup on the timing of introduction of allergenic foods into the infant diet

1.68 A joint COT and SACN subgroup was set up to consider the risk-benefit advice on the timing of introduction of allergenic foods into the infant diet and the development of atopic outcomes or autoimmune diseases. This subgroup is expected to complete its work in 2017.

Ongoing work

Developmental toxicity and the uncertainty factor for interspecies extrapolation

1.69 The Committee had considered papers on this topic in 2013 and 2014. It had agreed that a paper should be produced for publication in a peer-reviewed journal. A short COT statement could then be produced, based on the paper. The Committee considered further the development of a paper on this topic in 2015 and advised on the approach to take. It requested that a toxicologist and an epidemiologist should be sought as collaborators to evaluate the data critically for the identified candidate chemicals.

1.70 The COT did not discuss this topic further in 2016. It is anticipated that the Committee will consider a draft manuscript in 2017.

Maternal and infant dietary exposures and risk of development of atopic outcomes and autoimmune disease

1.71 The COT was asked for their opinion on a systematic review looking at maternal and infant dietary exposures and the development of atopic outcomes or autoimmune disease. This review was commissioned by the Food Standards Agency and will be used to direct future policy in this area.

1.72 This item is ongoing as the contractors are yet to publish their findings in the peer-reviewed literature

Potential risks from electronic nicotine (or non-nicotine) device systems in users and non-users (bystanders): a focused overview

1.73 During the horizon scanning session in 2016, the Committee agreed that possible human health effects of electronic cigarettes was a topic of concern that should be evaluated by the Committee. A scoping paper was subsequently discussed. This work will be taken forward in 2017 after the discussion of novel tobacco products.

Survey of metals and other elements in infant foods

1.74 In 2014, the FSA completed a survey of 15 metals and other elements in infant formula, commercial infant foods, and other foods (i.e. those which were not specifically manufactured or intended for infants and young children but were known to be or could be consumed by them such as bread, fruit and vegetables). The results of the FSA's survey had provided information on the concentrations of aluminium, antimony, arsenic (including inorganic arsenic), cadmium, chromium, copper, iodine, iron, lead, manganese, mercury, nickel, selenium, tin and zinc in these foods. Based on these concentration data, and food consumption data from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC), dietary exposures to these elements had been estimated for UK infants and young children aged 4 to 18 months.

1.75 Discussion paper TOX/2016/29 provided the aforementioned concentration data and exposure estimates, alongside brief summaries of the toxicology of each element and comparisons of the exposure estimates with the relevant health-based guidance values. A statement will be finalised in 2017 and a Food Surveillance Information Sheet (FSIS) will be drafted by the FSA with a view to publishing later in 2017; the FSIS will incorporate the COT's comments and conclusions.

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

1.76 The COT has been asked to consider aspects of the toxicity of chemicals in the diet of infants and of young children aged 1 to 5 years, in support of the SACN review of Government recommendations on complementary and young child feeding. The COT reviews aim to identify whether current advice is appropriate in relation to potential toxicity, or whether there is a need for new or revised advice. Between 2012 and 2016 statements had been produced for a number of chemicals in relation to the infant diet. Reviews of vitamin A, iodine and nickel commenced in 2016 and will continue in 2017. Further evaluation will also be conducted.

Toxicological evaluation of novel heat-not-burn commercial products:

1.77 COT has been requested by DH and PHE to assess the risk of novel tobacco products to provide a general opinion on the absolute and relative toxicological risks of these types of product. A scoping paper was discussed in 2016 and further work will be undertaken on this topic in 2017.

The item is being taken as reserved business as the Committee has been provided with commercially sensitive information.

2016 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

CHAIRMAN

Professor Alan Boobis OBE PhD CBiol FRSB FBTS
Professor of Biochemical Pharmacology and Director of the Toxicology Unit (supported by Public Health England and the Department of Health) in the Faculty of Medicine at Imperial College London

MEMBERS

Mr Derek Bodey MA
Public Interest Representative

Dr Roger Brimblecombe BSc MSc PhD DSc FRCPath FSB CBiol (until 31 March 2016)
Neuropharmacologist

Professor Janet Cade BSc PhD
Professor of Nutritional Epidemiology and Public Health, University of Leeds

Dr James Coulson Bsc MBBCh Dip Med Tox Dip Therapeutics MD MRCP ERT *Clinical Senior Lecturer at Cardiff University*

Dr René Crevel
Science Leader - Allergy & Immunology, Safety and Environmental Assurance Centre, Unilever

Dr Mark Graham BSc PhD
Director, MG Toxicology Consulting Ltd

Dr Anna Hansell MSc MB BCh MRCP FFPH PhD
Reader in environmental epidemiology Fellow, Imperial College London

Dr Caroline Harris PhD, CChem, FRSC
Practice Director and Principal Scientist, Exponent International Ltd

Professor David Harrison BSc MDB FRCPath FRCPEd FRCSEd
Professor of Pathology, University of Edinburgh Medical School

Professor Roy Harrison OBE PhD DSc C.Chem FRSC FRMetS HonFFOM HonMFPH
Professor of Environmental Health, School of Geography, Earth & Environmental Sciences, University of Birmingham

Professor Brian Houston BSc PhD DSc
Professor of Drug Metabolism and Pharmacokinetics, University of Manchester
Director of Centre for Pharmacokinetic Research, University of Manchester

Professor Brian G Lake BSc PhD DSc FBTS
Head of Molecular Sciences Department, Leatherhead Food Research

Professor Ian Morris BPharm PhD DSc
Emeritus Professor of Pharmacology and Physiology
Hull York Medical School

Dr Nicholas Plant BSc PhD
Senior Lecturer in Molecular Toxicology, University of Surrey

Professor Robert Smith BA MSc PhD
Public Interest Representative
Emeritus Professor, University of Huddersfield

Dr John Thompson MB ChB BMedSc FRCP FBTS
Senior Lecturer in Clinical Pharmacology, Cardiff University
Director, National Poisons Information Service, Cardiff

Professor Faith M Williams MA PhD FBTS
Professor of Toxicology, Medical Toxicology Centre and Institute of Cellular Medicine, Newcastle University

SECRETARIAT

Dr D Benford BSc (Hons) PhD	Scientific Secretary
Ms H Gbormittah	Administrative Secretary
Ms F Pollitt MA DipRCPath (until April 2016)	Scientific – PHE
Dr O Sepai BSc (Hons) MSc PhD CChem FRSC (from May 2016)	Scientific – PHE

Dr D Gott BSc (Hons) PhD
Ms R Acheampong BSc (Hons) MSc
Ms L Buckley BSc (Hons) MSc
Dr D Hedley BSc (Hons) MSc PhD
Ms F Hill BSc (Hons) MSc
Dr L Kent BSc (Hons) MSc PhD (until May 2016)
Mr B Maycock BSc (Hons) MSc
Ms C A Mulholland BSc (Hons)
Ms C Potter BSc (Hons) MSc
Mr A Sbaiti BSc (Hons) MSc (until September 2016)
Dr J Shavila BSc (Hons) MSc PhD
Ms K Sturgeon BSc (Hons) MSc

Declaration of members interests during the period of this report

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

Department of Epidemiology & Biostatistics		**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
Shareholder Exponent Inc		
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 Lifesciense 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)		
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

Personal Interest		**Non Personal Interest**
Emeritus Professor of Toxicology, Institute of Cellular Medicine, The Medical School, Newcastle University		ILSI Working Group
		Current and recent research funding None

COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Preface

I am pleased to present this report, which provides a summary of the work of the Committee on Mutagenicity (COM) during 2016. The COM would be happy to receive any feedback from readers of this report.

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. Recommendations for further studies are, on occasions, made.

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

During 2016, the Committee reviewed a number of topics: the genotoxicity of parachloroaniline, assays used to evaluate germ cell DNA integrity, germ cell Adverse Outcome Pathways (AOPs) and a scoping paper on human germ cell mutagens. It discussed recent work on epigenetics and the potential transgenerational effects of Vinclozolin. It commented upon a systematic review on the health effects of emissions to air from municipal waste incinerators. It began a consideration of new quantitative approaches being proposed for the assessment of genotoxicity data. The Committee also carried out its annual Horizon scanning exercise, identifying a number of potential topics for future work. The COM is interested in obtaining information from Government Departments on how its advice is acted upon.

Throughout 2016 the COM continued to take an active interest in the work of the OECD (Organisation for Economic Cooperation and Development) on test guidelines. It commented on the OECD's review of old test guidelines (TGs) and the development of new TG's. It also commented on the OECD's Guidance Document on Revisions to OECD Genetic Toxicology Test Guidelines. The COM also discussed the possible implications of Brexit on its work and noted that there was uncertainty in how this may affect the regulatory environment and the UK's relationship with international organisations.

I am again grateful for the support of the secretariat and the Department of Health Toxicology Unit, who maintained their usual high standard of work despite the difficulties and uncertainties throughout the year and to the members of the committee for their expert advice and support throughout the year.

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

COM Evaluations

MUT/2016/01 Assays used to evaluate germ cell DNA integrity in human fertility investigations

2.1 COM had previously considered germ cell mutation assays, the paternal age effect (an increase in mutations in aging human sperm) and a paper on radiation induced transgenerational effects. As part of the review the suggestion that air pollution should be classified as a human germ cell mutagen was noted and it was decided to perform a review of the literature to examine this claim. During the literature review it was noted that many studies of the effects of air pollution utilised assays for DNA integrity developed for use in assisted reproductive technologies (ART). Their use as markers of DNA damage in human sperm had not been validated and therefore it was considered appropriate for the COM to assess these assays before addressing the claim that air pollution is a germ cell mutagen.

2.2 The paper provided an overview of the sperm chromatin structure assay (SCSA) and the TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labelling) assays and their potential for investigating germ cell mutagenesis in humans. It was noted that both the SCCA and the TUNEL detect DNA strand breaks and therefore should be considered only as indicator assays. It was considered that they did not inform on the consequences of the DNA damage; whether they lead to a mutation or apoptosis; or whether damage would be repaired. It was not clear whether the reported reduced fertility was due to a genotoxic or toxic effect. It was noted that the two assays measured different types of DNA stand breaks and may not be directly comparable. It was possible that the observed DNA fragmentation could have arisen as a result of chemical induced oxidative stress, apoptosis, or another process not involving genotoxicity. There also appeared to be a relatively high background level which would make it difficult to detect a chemically induced increase in DNA fragmentation. Furthermore, it was not clear at what point in spermatogenesis the DNA damage occurs.

2.3 The COM considered that these assays may provide some evidence of chemically induced DNA damage, but there were a number of uncertainties which made both the SCSA and the TUNEL assays difficult to interpret in terms of germ cell mutagenicity. For example, there was a lack of consistency between some of the data and the test methods used; uncertainty over the underlying biology leading to the formation of DNA strand breaks and resultant downstream effects; a large variation in background levels and a lack of validation of the test methods. It would be useful to harmonise these methodologies and for the validation of these assays to be undertaken prior to their use in evaluating human germ cell mutagenicity.

MUT/2016/02 Germ cell adverse outcome pathways

2.4 COM had been made aware of recent papers by a group from Health Canada regarding adverse outcome pathways (AOP) for germ cell endpoints (Yauk et al. 2015

Environ.Mol.Mut 56(9) 724-50 and Marchetti et al. 2015 Environ.Mol.Mut 57(2) 87-113) and these were evaluated as part of the ongoing review of germ cell mutagenesis. An individual AOP is developed for a specific molecular initiating event, is not chemical specific and has key toxicological effects, which should be measurable.

2.5 The DNA alkylation AOP (Yauk et al., 2015) focused on premeiotic germ cell DNA alkylation using ethylnitrosourea as a model alkylating agent. Unique features of germ cells suggest that they should be considered separately from somatic cells. The AOP makes the assumption that the processes of DNA repair and damage are conserved across eukaryotic cells. The tubulin binding AOP (Marchetti et al. 2015) used colchicine as a model example, the majority of evidence is generated from rodents. It was noted that benzimidazoles induce this AOP.

2.6 COM agreed that the two AOPs provided were very specific and more qualitative than quantitative but provide a useful framework for capturing and clarifying information obtained from systems biology approaches. They also provide frameworks to aid in the communication of mode of actions, but further development was required before they could be used in chemical safety evaluation. It was noted that one of the main difficulties was that there was no consensus on terminology across toxicology disciplines which would need to be addressed; it was noted that systems biology may facilitate this, as it already had a number of agreed terms.

2.7 COM agreed that currently, AOPs could not be used to evaluate mixtures of chemicals or in risk assessment. It was noted that the COM 2007 statement on benzimidazoles, where a ‘common mechanism’ of toxicity had been identified used terminology a little different to that used in the AOP but that there were sufficient similarities and that the statement remained valid and did not need updating. It was agreed that COM would keep a watching brief on the development of AOPs for mutagenicity.

MUT/2016/04Draft discussion paper: genotoxicity of parachloroaniline

2.8 RESERVED BUSINESS

MUT/2016/05 Epigenetics

2.9 Transgenerational epigenetics was first examined by the COM in 2006 when the Advisory Committee on Pesticides (ACP) had requested an opinion on a paper investigating the pesticide vinclozolin. The topic was raised again during a Horizon scanning exercises and the COM expressed an interest in examining the topic further, particularly with regards to the impact on risk assessment strategies.

2.10 Dr Emma Marczylo (PHE), presented details and discussion of a recent literature review carried out by PHE and the associated publication (Marczylo E et al., 2016. Critical Reviews in Toxicology) which evaluated environmentally induced epigenetic changes. Firstly she addressed the role of epigenetic mechanisms involved in the mammalian life cycle, particularly highlighting stages that might be vulnerable to epigenetic changes; Dr Marczylo also examined current evidence for environmentally induced epigenetic toxicity

from human cohort studies and animal (rodent) studies. This included adverse outcomes, such as reproductive toxicity, developmental toxicity, metabolic disorders and behavioural changes. The third part of the review considered how potential epigenetic toxicity may affect public health. This included potential implications for regulatory toxicology.

2.11 Regarding the future, Dr Marczylo suggested that more research was required. Improved human bio-monitoring of chemical exposure may help determine the levels of chemicals that humans are exposed to environmentally before establishing whether relevant effects occur at these levels. There was also a need for improved molecular study designs to identify mechanisms for transgenerational effects using additional models (e.g. zebra fish), and to understand the normal variation of epigenetic change. Depending on such information, future test guidelines including epigenetic endpoints could be developed, which may be useful and could have benefits in terms of the 3Rs (reduction, replacement, refinement of animal use). For example, early epigenetic markers of adverse effect may result in a study being stopped early and no further testing being needed.

Epigenetics: The Transgenerational Effects Of Vinclozolin (MUT/2016/05)

2.12 The COM also considered a paper which provided an overview of epigenetics and studies specifically investigating the transgenerational effects of vinclozolin, which had been published since the last review (MUT/2016/05). A number of studies which had demonstrated a variety of vinclozalin induced effects using a dosing protocol of high intraperitoneal doses (100 mg/kg/day) to pregnant rats on days 8-14 of gestation were evaluated together with others using which had aimed to examine these findings. The COM noted that the epigenetic changes observed following the use of inconsistent methods (including different doses and different timing of doses) and different animal crosses made comparison difficult.

2.13 The studies using very high doses and intraperitoneal administration were not considered to be relevant to human environmental exposure. Different time points of exposure could be important because methylation patterns change ‘naturally’ over time in response to environmental pressures. It was noted that some of the results could be an artefact from the use of outbred animals and variation in the strains of animals use. Furthermore, inconsistencies may be the consequence of researchers investigating specific or novel aspects of the research and not necessarily due to an underlying inconsistency in results or findings.

2.14 COM noted that it will be important to identify and separate out the key epigenetic changes that could lead to adverse effects from the large ‘natural’ variation. The identification of epigenetic biomarkers and endpoints was also considered important. There is a need for greater reproducibility and consistency within studies (i.e. validation) and COM suggested that some currently available assays could be used or adapted, although it was agreed that it was not likely that existing test guidelines would be changed to include epigenetic endpoints in the foreseeable future. It was suggested that it would be useful to create a ‘safe harbour’ for epigenetic data that could receive data from industry, similar to that created for ‘omics’ data by the USA Food and Drug Administration. This could be made available, facilitating a broad evaluation which could allow regulatory

bodies and industry to determine what endpoints and types data may be useful and which could be realistically obtained and added to existing toxicity studies.

2.15 The COM also noted that it was important to consider other chemical groups that can be added to DNA, rather than just methyl groups (e.g. carboxyl, formyl etc.) and that further distinctions, such as between 5-methylation and 5- hydroxyl-methylation, should be made. It was noted that epigenetic changes may up-regulate some genes; down-regulate others; and have no effects on other genes. It was noted that it was currently unknown whether there is a threshold for adverse epigenetic effects. COM considered that it would be important to identify any impacts that epigenetics could have on standard genotoxicity studies.

2.16 Overall, it was considered that areas of epigenetics relevant to the remit of the COM include potential mechanisms for genetic damage and inheritance. There was a need for validation of studies before epigenetics could be considered in risk assessment and chemical regulation.

MUT/2016/06 Systematic review on the health effects of emissions to air from municipal waste incinerators

2.17 RESERVED

MUT/2016/07Quantitative approaches to the assessment of genotoxicity data.

2.18 COM were aware of work being conducted by a number of groups developing quantitative approaches to assessing genotoxic dose responses. The topic was addressed in a special issue of Mutagenesis published in June 2016 following an ILSI/HESI Genetic Toxicology Technical committee (GTTC) and European Environmental Mutagen Society /UKEMS workshop held in Lancaster in July 2014. The International Workshop on Genotoxicity Testing (IWGT) working group on Quantitative Genetic Toxicology Risk Assessment (the QWG) had also published the outcome of its discussions and consensus views.

2.19 The COM considered a scoping paper outlining these current approaches and evaluated the potential for data, from *in vivo* genotoxicity studies, to be used in a margin of exposure (MoE) approach to risk assessment, similar to that utilised in the interpretation of carcinogenicity data. A presentation was given by Dr George Johnson from Swansea University who presented some of the work that had been undertaken by ILSI/HESI GTTC and IWGT groups on these quantitative approaches. The presentation covered the derivation of Points of departure (POD) using a variety of metrics; the No Observed Genotoxic Effect Level (NOGEL), the Breakpoint dose (BPD), the Slope transition Dose (STD) and Benchmark Dose (BMD); and how PODs could be used to determine human exposure levels expected to present a low or negligible risk to health. A number of case studies were considered, including *in vivo* genotoxicity data sets for alkylating agents and benzo(a)pyrene. Consensus was reached by the study group that use of the BMD was the preferred option. It was noted that there are currently two different software packages used which differ somewhat in their approaches. The US Environmental Protection

Agency (EPA) BMD uses the best transformation of the response data for analyses, whereas the Netherlands National Institute for Public Health and the Environment (RIVM) PROAST model uses the default assumption of a log-normal distribution. Furthermore, the Benchmark Dose Response (BMR) uses an increase relative to a negative control either by one standard deviation (US EPA) or a percentage (e.g. 5 or 10%) increased response (RIVM PROAST).

2.20 The COM agreed that there had been a change in the quality of available *in vivo* genotoxicity data (e.g. more endpoints, tissues and dose groups) and significant developments in dose response modelling that allow *in vivo* genotoxicity data to be analysed quantitatively rather than only qualitatively, but that the analysis needed be conducted on good quality and consistent data to be informative. Aspects that needed to be considered in terms of risk assessment included what test systems and endpoints were the most suitable (e.g. gene mutations or micronuclei), what tissues should be analysed, what critical effect size should be used (e.g. $BMDL_{05}$ or $BMDL_{10}$), and what BMR values were needed for each genotoxicity endpoint. It was also agreed that if quantitative dose-response analysis of *in vivo* genotoxicity is developed and becomes accepted as an approach to estimate human cancer health risks, then there must be confidence that the approach is sufficiently precautionary and protective of health. It was anticipated that quantitative approaches to genotoxicity data should be considered further by the COM at future meetings.

Horizon scanning

2.21 The COM undertakes an annual 'Horizon Scanning' exercise, which provides an opportunity for Members and assessors from Government Departments/Agencies to discuss and suggest topics for further work.

OECD Genotoxicty test guidelines update.

2.22 The Committee continue to be updated and comment on, the review of old test guidelines (TGs) and the development of new TG's.

2.23 The Committee also commented on the Guidance Document on Revisions to OECD Genetic Toxicology Test Guidelines.

Guidance statements

2.24 None

Declaration of members interests during the period of this report

	Personal Interest		Non-Personal Interest	
	Company	**Interest**	**Company**	**Interest**
Dr D P Lovell (Chairman)	National Grid plc	Shareholder		
	Pfizer	Pension Scheme Member		
	ILSI HESI	Committee Member		
	Biometrics Society	Member		
	British Toxicology Society (BTS)	Member		
	Genetics Society	Member		
	Royal Society of Biology (CBiol, FRSB, 2003)	Member		
	Laboratory Animal Science Association (LASA)	Member		
	Royal Statistical Society	Member		
	Statisticians in the Pharmaceutical Industry (PSI)	Member		
	United Kingdom Environmental Mutagen Society (UKEMS)	Member		
	Grant Funding Panel of the UK National Centre for Replacement, Refinement and Reduction of Animals in Research (NC3Rs)	Member		
	MRC EMINENT Project Review Board	Member		
	AstraZeneca	Spouse Shareholder		
	National Grid plc	Spouse Shareholder		
Dr Carol Beevers	Covance	Salary Pension	None	None
	Labcorp	Employee Equity Holder		
Dr Gill Clare	Covance	Consultant	None	None
	AstraZeneca	Shareholder		
	Diageo	Shareholder		
	Marks and Spencer	Shareholder		
	Shell Research Ltd	Pension		

	AstraZeneca	Pension		
Dr Stephen Dean	WIL Research, Europe (Jan – March 2016)	Salary Employee Equity Holder		
	Smithers Viscient (Aug 2016 onwards)	Managing Director		
	UKEMS	Member		
	Standard Life	Shareholder		
	Society of Toxicology	Member		
Prof Shareen Doak	United Kingdom Environmental Mutagen Society (UKEMS)	Member	Unilever	PhD Studentship Grants 2017 – 2020
	British Association for Cancer Research (BACR)	Member	AstraZeneca	PhD Studentship Grants 2009 – 2016
	Royal Society of Biology (FRSB)	Member	Unilever	PhD Studentship Grants 2010 – 2017
	ILSI HESI	Committee Member	Hoffman-LaRoche	Research Grant 2008 – 2010
	British Toxicology Society (BTS)	Member	Unilever	Research Grant 2008 - 2010
Prof Philippa Hardwick	Unilever plc	Pension	None	None
Prof David Harrison (From 1 May 2016)	University of Canberra	Consultant	Cytosystems Ltd	Research Collaboration
	University of Florida	Consultant	Nucana Ltd	Research Collaboration
	University of Edinburgh	Consultant	Office of the Scottish Charity Regulator	Deputy Chair of the Board
	University of Cambridge (examiner)	Consultant		
	Ryboquin Ltd	Consultant		
	NucanBiomed Ltd	Consultant		
	Cytosystems Ltd	Consultant		
	Cunningham Trust	Scientific Adviser		
	Avipero Ltd	Shareholder		
	Melville Trust (cancer research charity)	Trustee		
	Families First St Andrews (children's charity)	Trustee		
	Ryboquin Ltd	Shareholder and Consultant		
	Benenox Ltd	Shareholder and Consultant		
Prof Gareth Jenkins	None	None	Unilever	Research Grant 2008 – 2010
Prof David Kirkland	Kirkland Consulting	Principal	None	None

	GSK	Shareholder		
	Corning	Shareholder		
	Saga	Shareholder		
	ILSI HESI	Steering Committee Member and Workgroup Leader		
	ECVAM/ESAC	Member of peer-review panel		
Dr Antony Lynch (to 30 March 2016)	GlaxoSmithKline	Salary Shareholder	None	None
Prof Francis Martin	ReVivoCell Ltd	Shareholder and Chief Scientific Officer	Crown Paints	Consultancy 2016/2017
	Biocel Ltd	Shareholder and joint Director	Unilever	PhD Studentship 2014 - 2018
			Barfoots	PhD Studentship 2016 - 2019
Dr Michael O'Donovan	O'Donovan GT Consulting Ltd	Director	None	None
	Apconix	Associate		
	AstraZenca	Pension Scheme Member		
	BASF	Pension Scheme Member		
Prof David H Phillips (to 30 April 2016)	Aviva	Shareholder	None	None
	Banco Santander	Shareholder		
	Royal Dutch Shell	Shareholder		
	Centrica	Shareholder		
	National Grid	Shareholder		

COMMITTEE ON THE CARCINOGENCITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Preface

The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) evaluates chemicals for their potential to cause cancer 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 2016. A number of key issues are being studied, including for example the risks associated with new heat-not-burn tobacco products. COC is keen to promote public awareness and understanding, and so will introduce summaries written in non-technical language for its outputs wherever possible. In doing so we hope this will better communicate the work that is being carried out, and emphasise the need for opinion and recommendations to be practical, based on an overview of the best available evidence.

There was also continued preparation of a series of papers to provide guidance on how the potential cancer-causing chemicals (carcinogens) are investigated and reported. In 2016 two parts of a statement on alternatives to a two year animal study for detecting carcinogens was published. Further work will follow on this in 2017. These statements are important to ensure there is a consistent framework within which to best provide advice about new and existing potential threats.

I assumed the role of Chair from Professor David Phillips during 2016. I wish to extend my gratitude to him, to all the Members of the Committee with whom I have worked this year, to the expertise of the Secretariat, and to the Imperial College London Toxicology Unit for its ongoing invaluable support. I also wish to extend special thanks to Ms Frances Pollitt who retired as PHE Scientific Secretary at the end of April 2016.

Professor David Harrison
BSc MB ChB MD DSc FRCPath FRCPEd FRCSEd

COC Evaluations

Alcohol and Cancer risk

3.1 In January 2016, the COC statement on consumption of alcoholic beverages and risk of cancer (CC/2015/S2), which was finalised and reported in the 2015 Annual Report, was published alongside the consultation on the CMOs' new alcohol guidelines.

3.2 The work by the Committee supported the conclusions drawn by the CMOs Guidelines Development Group, and messaging around potential carcinogenicity of alcohol was a significant element of the new Guidelines. Professor Phillips as Chair of COC supported the publication process and attended the Stakeholder briefing on the new guidelines.

3.3 The Committee prepared and submitted a response to the CMOs' consultation on the new guidelines in March 2016, and the Government response and final guidelines were published in August 2016.

Developments in the Mode of Action and Human Relevance Framework

3.4 The COC had last considered the Mode of Action and Human Relevance Framework in 2008, though an update had been given at 2013 horizon scanning discussion.

3.5 There was recognition that the concepts of key events and adverse outcomes are well accepted, but that dose response information is required to distinguish between adaptive responses and adverse outcomes. It was agreed that updates will be made in the guidance statement series where the framework is mentioned to reflect these considerations and to ensure up to date references are provided.

3.6 The Committee noted an interest in the Halifax project cited in this paper, organised by Getting to Know Cancer, and in particular the suggestion that the low levels of exposure to multiple chemicals which individually are not carcinogenic, may cause cancer. This would be considered, along with other recent developments on mixture assessments e.g. from EFSA, as part of the continuing review of the guidance statement series in particular for the mixtures statement and the overarching statement.

Frailty and Cancer

3.7 Cancer genetics and the influence of industrial exposure on cancer incidence had been raised as a horizon scanning topic in 2015 with reference to a particular

paper. This was part of a commentary series of papers on frailty and cancer, where frailty is defined as the variation in risk due to factors that cannot be measured in individuals and includes inherited differences, environmental influences from conception and through life, and random somatic genetic or epigenetic events. A review of the topic, commentary papers and the review authors' response were discussed by the Committee.

3.8 The Committee noted the use of uncertainty factors as a means of addressing known unknowns is well established, but the concept of frailty was interesting from a mechanistic perspective especially considering the mixture of exposures experienced and the diseases acquired through life. It was noted that frailty also covers individual differences in response, whereas uncertainty factors are applied on a population basis. The large variation in individual susceptibility was not always appropriately covered but raised questions about using this kind of information to adopt a more personalised approach, though it was acknowledged that there were a large number of environmental factors, diet and affluence which all affect cancer risk. The link with epigenetics, both in terms of signatures for potential susceptibility and the influence of environmental factors on the epigenome, was noted and frailty could be borne in mind for the joint meeting on epigenetics.

Incinerators

3.9 At the November 2016 meeting, the COC reviewed some unpublished research on health effects around municipal waste incinerators. The COC was asked to comment on the new evidence since its last assessment in 2011. This work is part of a wider research project which had previously been reviewed by COM in October 2016, and will be reviewed by COT in 2017. Once this research is published, each of the Committees' reviews will be made available.

Horizon scanning

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

3.11 In 2016 the Committee discussed the list from the previous year and noted progress on some activities during the year. The list of priority topics in no specific order following this discussion were:

- Applicability of Margins of Exposure for exposure of young children
- Mechanisms incorporating genomics and the Cancer Genome Atlas
- Epigenetics
- *In vitro* systems - to be undertaken when resource allows
- Immunological and stromal cell modulations relevant to cancer risk
- Nanomaterials
- E-cigarettes and novel tobacco products, and effect of early life exposure to cigarettes

3.12 The Committee requested a standing agenda item for future meetings on horizon scanning topics and to update the COC on upcoming topics for IARC and the EU Scientific Committees.

Ongoing work

IGF-I

3.13 Insulin-like 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 had been proposed that exposure to dietary IGF-1 could increase the risk of certain cancers, and the COC is evaluating the evidence on this.

3.14 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. Further data on IGF-I and lung and colorectal cancers were considered. The review of the relevant literature has been completed and a statement is under preparation.

Guidance statements

3.15 The Committee continued to develop the guidance statement series during 2016. In February, two parts of the guidance statement G07 – Alternatives to the 2-year Bioassay were published. These addressed alternative *in vivo* assays, i.e. animal studies, for the 2 year carcinogenicity study, and cell transformation assays, which cited the COM guidance on this.

3.16 Two further parts of the guidance statement on alternatives to the 2-year bioassay were discussed addressing alternative testing strategies for carcinogenicity, which included a presentation on work by the OECD on developing an Integrated Approach to Testing and Assessment (IATA) for non-genotoxic carcinogens, and emerging technologies. It is likely that these will be published in 2017. Further work during the year included discussion of assessing less than lifetime exposures to carcinogens, and an overview of the progress on the series as a whole.

2016 Membership of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

CHAIRMAN

Professor David Harrison BSc MB ChB MD DSc FRCPath FRCPEd FRCSEd (from 1 May 2016)
Professor of Pathology, University of St Andrews

Professor David H Phillips BA PhD DSc FRCPath (to 30 April 2016)
Professor of Environmental Carcinogenesis, King's College London

MEMBERS

Mr Derek Bodey MA
Public Interest Representative

Dr Gill Clare BSc PhD
Public Interest Representative

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

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

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

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

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

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

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

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

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

Dr Rosemary H Waring PhD DSc FRCPath

Honorary Reader in Human Toxicology, University of Birmingham

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

SECRETARIAT

Ms F Pollitt MA DipRCPath	PHE Scientific Secretary (until 30 April 2016)
Miss B Gadeberg BSc(Hons) MSc	PHE Scientific Secretary (from 1 November 2016)
Dr D Benford BSc(Hons) PhD	FSA Scientific Secretary
Mrs N Blowfield	Administrative Secretary

Declaration of members interests during the period of this report

Member	Personal Interest		Non-Personal Interest	
	Company	**Interest**	**Company**	**Interest**
Professor David Harrison (Chair from 1 May 2016)	University of Canberra	Consultant	Melville Trust (cancer research charity)	Trustee
	University of Florida	Consultant	Families First St Andrew's (children's charity)	Trustee
	University of Cambridge (examiner)	Consultant	Cytosystems Ltd	Research Collaboration
	Ryboquin Ltd	Consultant	Nucanan Ltd	Research Collaboration
	NucanBiomed Ltd	Consultant	Office of the Scottish Charity Regulator	Deputy Chair of the Board
	Cytosystems Ltd	Consultant		
	Cunningham Trust	Scientific Adviser		
	Avipero Ltd	Shareholder		
	Ryboquin Ltd	Shareholder and Consultant		
	Benenox Ltd	Shareholder and Consultant		
Professor David H Phillips (Chair to 30 April 2016)	Aviva	Shareholder		
	Banco Santander	Shareholder		
	Centrica	Shareholder		
	National Grid	Shareholder		
	Royal Dutch Shell	Shareholder		
Mr Derek Bodey	None		None	
Dr Gill Clare BSc PhD	Covance	Consultant	None	
	AstraZeneca	Shareholder		
	Diageo	Shareholder		
	Marks and Spencer	Shareholder		
	Shell Research Ltd	Pension		
	AstraZeneca	Pension		
Dr John Doe PhD Dip R C Path	Parker Doe Partnership	Partner		
	ILSI	Member of Steering Group for RISK 21 project		
	Syngenta	Pension		

	ECETOC	Chairman of Task Force - Bringing Potency into Classification for Carcinogenicity and DART		
Dr Peter Greaves	Astellas Pharma Europe, Leiden	Consultant		
	Bristol-Myers Squibb, Princeton, NJ, USA	Consultant		
	Eisa Inc, Woodclife Lake, NJ, USA	Consultant		
	Gedeon Richter Plc, Budapest	Consultant		
	Myokardia Inc, San Francisco, USA	Consultant		
	NeuroVia Inc, San Francisco, USA	Consultant		
	Novartis Pharma AG, Basel	Consultant		
	Novo Nordisk A/S, Måløv, Denmark	Consultant		
	UCB Biopharma SA, Brussels, Belgium	Consultant		
	Verona Pharma Plc, London	Consultant		
Professor Ray Kemp BA	Ray Kemp Consulting	Shareholder		
Dr David Lovell PhD BSc (Hons) FSS FIBiol Cstat Cbiol	National Grid	Shareholder		
	Pfizer	Pension Scheme Member		
	ILSI HESI	Committee Member		
	Biometrics Society	Member		
	AstraZeneca	Spouse Shareholder		
	National Grid plc	Spouse Shareholder		
	British Toxicology Society (BTS)	Member		
	Genetics Society	Member		
	Royal Society of Biology (CBiol FRSB, 2003)	Member		
	Laboratory Animal Science Association (LASA)	Member		
	Royal Statistical Society	Member		

	Statisticians in the Pharmaceutical Industry (PSI)	Member		
	United Kingdon Environment Mutagen Society (UKEMS)	Member		
	Grant Funding Panel of the UK National Centre of Replacement, Refinement and Reduction of Animals in Research (NC3Rs)	Member		
	MRC EMINENT Project Review Board	Member		
Professor Neil Pearce	None	None	None	None
Professor Julian Peto MA MSc DSc FMedSci	None	None	None	None
Dr Christopher Powell	GlaxoSmithKline	Shareholder and Salary	None	None
Dr Lesley Rushton OBE BA MSc PhD Cstat	Epidemiological Advice relating to dermatitis study to Unilever.	Consultancy	CONCAWE (Conservation of Clean Air and Water Europe)	Research Support
	Epidemiological advice on study to Transport and General Workers Union	Consultancy	CEFIC (European Chemistry Council)	Research Support
	Epidemiological review of occupational causes of malignant melanoma.	Expert Witness	Other grants from UK government agencies & departments e.g. Food Standards Agency, Health & Safety Executive.	Research Support
	ECETOC Scientific Committee	External Committee Member	Cuadrilla	Research Support
	ECPA Scientific Advisory Board on Epidemiology	Member		
Professor Heather Wallace BSc Hons PhD FRCPath FBTS	Bank Santander SA	Shareholder		
	EFSA	Contam Panel		
	BT Group	Shareholder		
	NovaBiotics	Shareholder		
	Antoxis	Shareholder		
	Precious Cells	Shareholder		

	Cell ProTx	Director		
	EUROTOX	President-Elect		
	Paediatric Medicines Expert Advisory Group – MHRA	Member		
	Herbal Medicines Advisory Committee – MHRA	Member		
Dr Rosemary Waring PhD DSc FRCPath	Centrica and National Grid	Shareholder	None	None
	Tharos	Director and Shareholder		
	Ateria Health	Shareholder		
Professor Kasturi Warnakulasuriya FDS, PhD, DSc	National Grid plc	Shareholder		
	Post Office Ltd	Shareholder		
	BDHF	Panel Member		
	Ben Walton Trust	Medical/Scientific Advisor		

ANNEX 1 - Terms of Reference

To advise at the request of:
Food Standards Agency
Food Standards Scotland
Public Health England
Department of Health
Department for Business, Innovation & Skills
Department of Transport, Local Government and the Regions
Health and Safety Executive
Veterinary Medicines Directorate
Medicines and Healthcare products Regulatory Agency
Home Office
Scottish Executive
National Assembly for Wales
Northern Ireland Assembly
Other Government Departments and Agencies

1. To assess and advise on the toxic risk to man of substances which are:

a. used or proposed to be used as food additives, or used in such a way that they might contaminate food through their use or natural occurrence in agriculture, including horticulture and veterinary practice or in the distribution, storage, preparation, processing or packaging of food;

b. used or proposed to be used or manufactured or produced in industry, agriculture, food storage or any other workplace;

c. used or proposed to be used as household goods or toilet goods and preparations;

d. used or proposed to be used as drugs, when advice is requested by the Medicines and Healthcare products Regulatory Agency;

e. used or proposed to be used or disposed of in such a way as to result in pollution of the environment.

2. To advise on important general principles or new scientific discoveries in connection with toxic risks, to co-ordinate with other bodies concerned with the assessment of toxic risks and to present recommendations for toxicity testing.

ANNEX 2 - Code of Conduct for members of the COC/COM/COT

Public service values

Members of the COC/COM/COT (hereafter referred to as “the Committee”) must at all times:

· observe the highest standards of **impartiality**, **integrity** and **objectivity** in relation to the advice they provide and to the management of their Committee;

· be **accountable**, through the Chair of the Food Standards Agency and the Chief Medical Officers, to Ministers, Parliament and the public for its activities and for the standard of advice it provides;

· in accordance with Government policy on **openness**, fully comply with the Freedom of Information Act 2000

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

Standards in Public Life

Members are expected to:

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

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

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

· follow the Seven Principles of Public Life set out by the Committee on Standards in Public Life (http://www.public-standards.gov.uk/).

Selflessness

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

Integrity

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

Objectivity

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

Accountability

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

Openness

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

Honesty

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

Leadership

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

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

Role of Members

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

Members must:

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

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

If members believe the committee's method of working is not rigorous or thorough enough, they have the right to ask that any remaining concerns they have be put on the record. Individual members should inform the Chair (or the Secretariat on his or her behalf) if they are invited to speak in public in their capacity as a Committee member. Communications between members and the Food Standards Agency (FSA) Board, CMOs and/or Ministers will generally be through the Chair except where the Chair has agreed that an individual member should act on its behalf. Nevertheless, any member has the right of access to the FSA Board and/or the CMO on any matter that he or she believes raises important issues relating to his or her duties as a Committee member. In such cases the agreement of the rest of the Committee should normally be sought.

Committee appointments can be terminated early by either party, by giving 3 months notice, in writing. Should the Committee be disbanded before the end of the period of appointment, appointments will terminate on dissolution.

In the event that a member is found guilty of grave misconduct their appointment will be terminated immediately, in the case of the COT by the Chair of the FSA. The Department of Health has delegated the powers for appointments to the COC and COM to the NHS Appointments Commission and it will terminate appointments in consultation with the PHE/DH.

Role of the Chair

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

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

Role of the Deputy Chair

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

Role of the Secretariat

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

The Secretariat is also a source of advice and guidance to members on procedures and processes. The Secretariat is drawn from staff of the Food Standards Agency and Public Health England. However, it is the responsibility of the Secretariat to be an impartial and disinterested reporter and at all times to respect the Committee's independent role. The Secretariat is required to guard against introducing bias during the preparation of papers, during meetings, or in the reporting of the Committee's deliberations. Current contact details for each of the Secretariats are shown on the back page of this report.

Role of the Assessor

Meetings of the Committee (and working groups) may be attended by Assessors. The Assessors are nominated by, and drawn from, the Agencies and Departments that sponsor the Committee, receive its advice, or have other relevant policy interests. Assessors are not members of the Committee and do not participate in Committee business in the manner of members.

The role of an Assessor is to keep their parent Department or Agency informed about the Committee's work and act as a conduit for the exchange of information. They do this by: · advising the Committee on relevant policy developments and the implications of Committee proposals;
· informing the Committee work through the provision of information
· being informed by the Committee on matters of mutual interest.
· sharing with the Secretariat the responsibility of ensuring that information is not needlessly withheld from the Committee. Assessors should make the Committee aware of the existence of any information that has been withheld from the Committee on the basis

that it is exempt from disclosure under Freedom of Information legislation unless that legislation provides a basis for not doing so.
· ensuring that their parent Department or Agency is promptly informed of any matters which may require a response from Government.

Role of other Officials, Invited Experts and Contractors

Officials from Government Departments (not departmental assessors), Regulatory Agencies and Devolved Administrations may be called upon to advise the Committee on relevant developments in order to help the Committee formulate its advice. Invited experts and contractors may also bring particular technical expertise, which may be requested by the Committee on some occasions. In the event of an official, invited expert or contractor not being able to attend written submissions may be sent via the Secretariat.

Role of Observers

Members of the public and other interested parties may attend meetings as observers. However, they should not attempt to participate in Committee discussions. If an interested party wishes to provide information relevant to a topic for consideration by the Committee, they should be submitted in writing to the Secretariat at **least** seven(7) working days before the meeting. The Secretariat will discuss with the Chair the most appropriate way to present the information to the committee and the Chair's decision will be final.
Observers who have submitted information in advance of the meeting **may** be invited to provide further explanation or to make brief comments at the discretion of the Chair.
Observers and/or organisations must not interfere in the work of the Secretariat or input from invited experts, contractors, officials from Government Departments and Agencies in any way which, in the view of the Chair, constitutes harassment and/or might hinder the work of the Committee. Observers and/or organisations must allow other observers and other interested parties to attend items free from interference before, during and after a meeting.

Observers and/or organisations are required to respect the work of the Committee. The Committee's discussions represent the development of its view and any comments made in developing the agreed Committee view should not be attributed to individuals. Where a subject will be considered over several meetings, observers are asked to maintain the confidentiality of the discussion until an agreed Committee opinion is finalised. The Committee's conclusions are not finalised until completion of any necessary consultation and publication of a statement or report.

Under no circumstances will Observers be permitted to record Committee proceedings, on the basis that this might inhibit free discussion. The published minutes of the meeting would provide a record of the proceedings.

Failure to observe this code of conduct may lead to exclusion of individual observers and/or organisations from meetings of the Committee.

All observers and/or organisations are requested to read follow the Committees Openness policy (Annex 3)

Declaration of Members' Interests

Definitions

In this Code, 'the industry' means:
· Companies, partnerships or individuals who are involved with the production, manufacture, sale or supply of products subject to the following legislation;
General Food Regulations 2004
The Food Safety Act 1990 (Amendment) Regulations 2004
The Medicines Acts 1968 and 1971, 1981, 1986 & 2003
The Food and Environmental Protection Act 1985
The Consumer Protection Act 1987
The Cosmetic (Safety) (Amendment) Regulations 2008
Registration, Evaluation, Authorisation and Restriction of Chemicals (EC1970/2006)
· Trade associations representing companies involved with such products;
· Companies, partnerships or individuals who are directly concerned with research, development or marketing of a product which is being considered by the Committees on Toxicity, Mutagenicity, or Carcinogenicity of Chemicals in Food, Consumer Products and the Environment.
· 'the Secretariat' means the Secretariat of the COC, COM and COT;
· 'the Agency' means either the Food Standards Agency or the Health Protection Agency; and
· references to "member(s)" includes the Chair.

Different types of Interest

The following is intended as a guide to the kinds of interests which should be declared. Where members are uncertain as to whether an interest should be declared, they should seek guidance from the Secretariat or, where it may concern a particular product which is to be considered at a meeting, from the Chair at that meeting.

If members have interests not specified in these notes but which they believe could be regarded as influencing their advice they should declare them.

However, neither the members nor the Secretariat are under any obligation to search out links of which they might *reasonably* not be aware. This Code suggests that interests of close family members are declared, members have in the past limited such declarations to personal partners, parents, children (minor and adult), brothers, sisters and the personal partners of any of these with the emphasis on disclosure only where the interest may, or may be perceived (by a reasonable member of the public) to influence a members' judgement.

The Secretariat is required to publish an up-to-date register of members' interests and these can be found on the relevant Committees website.

Personal Interests

A personal interest involves the member personally. The main examples are:

· **Consultancies and/or direct employment:** any consultancy, directorship, position in or work for industry which attracts regular or occasional payments in cash or kind;
· **Fee-Paid Work:** any work commissioned by industry for which the member is paid in cash or kind;
· **Shareholdings:** any shareholding in or other beneficial interest in shares of industry. This does not include shareholdings through unit trusts or similar arrangements where the member has no influence on financial management;
· **Membership or Affiliation:** any membership role or affiliation that you or a close family member has to clubs or organisations with an interest or involvement in the work of the Agency.

Non-Personal Interests

A non-personal interest involves payment which benefits the organisation in which the member works, but is not received by the member personally. The main examples are:
· **Fellowships:** the holding of a fellowship endowed by industry;
· **Support by Industry:** any payment, other support or sponsorship which
does not convey any pecuniary or material benefit to a member personally, but which does benefit their position or organisation, e.g.
i) a grant for the running of a unit or department for which the member is responsible;
ii) a grant or fellowship or other payment to sponsor a post or a member of staff or a post graduate research programme for which the member is responsible. This does not include financial assistance for students;
iii) the commissioning of research or other work by, or advice from, staff who work in a unit for which the member is responsible.
Members are under no obligation to seek out knowledge of work done for, or on behalf of, the industry or other relevant bodies by departments in which they work, if they would not normally expect to be informed.
· **Trusteeships**: where a member is a trustee of a charity with investments in industry, the Secretariat can agree with the member a general declaration to cover this interest rather than draw up a detailed portfolio.
At meetings members are required to declare relevant interests and to state whether they are personal or non-personal interests and whether they are specific or nonspecific to the matter, product or substance under consideration.

Specific Interests

A member must declare a *personal specific* interest if they have at any time worked on a matter, product or substance under consideration and have personally received payment for that work, in any form.

A member must declare a *non-personal specific* interest if they are aware that the organisation in which they work has at any time worked on the matter, product or substance under consideration but they have not personally received payment for that work, in any form.

Non-specific Interests

A member must declare a *personal non-specific* interest if they have a **current** personal interest in a company concerned with a matter, product or substance under consideration, which does not relate specifically to the matter, product or substance under discussion. A member must declare a *non-personal non-specific* interest if they are aware that the organisation in which they work is **currently** receiving payment from the company concerned which does not relate specifically to the matter, product or substance under discussion.

If a member is aware that a substance, product or matter under consideration is or may become a competitor of a substance, product or matter manufactured, sold or supplied by a company in which the member has a *current personal* interest, they should declare their interest in the company marketing the rival product, substance or matter.

Handling conflicts of interests

The purpose of these provisions is to avoid any danger of Committee members being influenced, or appearing to be influenced, by their private interests in the exercise of their public duties. All members should declare any personal or business interest which may, or may be *perceived* (by a reasonable member of the public) to, influence their judgement. A guide to the types of interest that should be declared is mentioned above.

(i) Declaration of Interests to the Secretariat

Members are required to inform the Agency in writing prior to appoint of their *current personal and non-personal* interests, including the principal position(s) held. Members are not required to disclose the amount of any salary, fee, shareholding, grant etc. An interest is current if the member has an on-going financial involvement e.g. if he or she holds shares in industry, has a consultancy contract, or if they or the organisation for which they are responsible is in the process of carrying out work for the industry.

Following appointment members are asked to inform the Secretariat at the time of any change in their *personal* interests. However, the Secretariat will contact each member on an annual basis to update their declaration of interests. Changes in *non-personal* interests can be reported annually, and those involving less than £1000 from a particular company in the previous year need not be declared. The register of interests is kept up-to-date and open to the public via the website.

(ii) **Declaration of Interest at Meetings**

Members of the Committee are required to verbally declare any direct interests relating to salaried employment or consultancies, or those of close family [8] members in matters under discussion at each meeting, and if items are taken by correspondence between meetings. The declaration should note whether the interest is *personal or nonpersonal*, whether it is *specific* to the item under discussion, or *non-specific* and whether it is current or lapsed. Having fully explained the nature of their interest the Chair will, decide whether and to what extent the member should participate in the discussion and determination of the issue and it should be recorded in the minutes of the meeting.

Withdrawal from meetings

If a declaration of interest has been made and the Committee decides that the member should not participate in the discussion and should withdraw from the meeting (even if held in public) and it should be recorded in the minutes of the meeting. The Chair may first allow them to make a statement on the item under discussion.

Personal liability of Committee members

The Department of Health has a formal statement of indemnity for its advisory committee members, which includes the COC and COM, its guidance is taken from the Cabinet Office "Model Code of Practice for Board Members of Advisory Non-Departmental Public Bodies" and states that *"Legal proceedings by a third party against individual board members of advisory bodies are very exceptional. A board member may be personally liable if he or she makes a fraudulent or negligent statement which result in a loss to a third party; or may commit a breach of confidence under common law or criminal offence under insider dealing legislation, if he or she misuses information gained through their position. However, the Government has indicated that individual board members who have acted honestly, reasonably, in good faith and without negligence will not have to meet out of their own personal resources any personal civil liability which is incurred in execution or purported execution of their board functions. Board members who need further advice should consult the sponsor department."*[9] except where the person has acted recklessly.

The FSA has also drawn up a formal statement of indemnity for its advisory committee members.

INDEMNITY BY THE FOOD STANDARDS AGENCY TO MEMBERS OF THE COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Food Standards Agency hereby undertakes with the members (including the Chair) of the Committee on Toxicity of Chemicals in food, Consumer products and the environment (COT) 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.

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 and if an action or claim is brought, the Food Standards Agency shall be entitled to take conduct of the defence, dispute, compromise or appeal of the action or claim and of any incidental negotiations relating to the action or claim.

The Food Standards Agency shall notify the Members as soon as practicable if it intends to so take conduct and the Members shall then provide to the Food Standards 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 so take conduct the

Members shall keep the Food Standards Agency fully informed of the progress of the action or claim and any consequent legal proceedings and consult with the Food Standards Agency as and when required by the Food Standards Agency concerning the action or claim.

The indemnity 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 without the knowledge or consent of the Food Standards Agency 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 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 2015/16 the budget for the COT, excluding Secretariat resources was £37,000. Costs were met by the Food Standards Agency (FSA).

19. Committee members may claim a fee for Committee meetings:
COC and COM Committee Chair £198 per day
COC and COM Committee Member £153 per day
COT Committee Chair £205 per day
COT Committee Member £160 per day

Where COT members are unable to attend a meeting but contribute in writing, a £50.00 reading fee is paid.

Review of fee rates

20. Fees in respect of the COT are set by the FSA and for COC and COM by the Department of Health. The FSA will review and revise COT rates every 2 years with the intention that rates should rise in line with the recommendations of the Senior Salaries Review Board with regard to pay in the Senior Civil Service. The FSA will also take into account comparisons with rates paid in similar advisory bodies in the UK.

Travel and other expenses

21. Committee members are entitled to reimbursement of reasonable travel and subsistence expenses necessarily incurred on official committee business. Members must seek value for money and are encouraged to use the most cost effective and environmentally sustainable options for travel and accommodation.

Working Groups

22. The Committee may establish Working Groups to consider particular topics in depth or to make brief assessments of particular issues and advise the main Committee on the possible need for further action. Such Groups contain a number of Committee members (supplemented, as necessary, by external expertise in the particular subject being considered). A Committee Chair will play a leading role in deciding which Committee members should be invited to join such groups, which may meet on a number of occasions in a particular year. Committee members may claim an allowance for participating on a Working Group.

Terms and conditions of appointment

23. Appointments of members may be staggered so that only a proportion retire or are re-appointed each year, to help ensure continuity. (Note: The COC/COM/COT Chairs are *ex officio* members of General Advisory Committee on Science (GACS) for the term of their appointment as the COC/COM/COT Chair. COC and COM Chairs are *ex officio* members of each other's Committees.)

24. COC and COM members are usually expected to attend 3 meetings in a year. COT members are expected to attend 7 meetings in a year. Members should allow appropriate preparation time. Meetings will usually be in London.

25. The COC/COM/COT Chair must also be available for a number of other activities including: attending, with the FSA Chief Scientist, the FSA Board's annual discussion of the Agency's science; engaging with the media on any high-profile relating to the Committee's work, and discussion with the Agency Chief Scientist and GACS Secretariat in planning and developing the Committee's work (including discussing and agreeing with the Agency's Chief Scientist a framework for providing assurance on the work of the Scientific Advisory Committees in providing advice to the Agency). It is expected that these additional activities might require 5-10 days input per year.

Feedback on performance

26. The COT Chair and members are asked to provide brief feedback on their experience on the committee each year to help the Agency ensure that the Committee operates effectively and identify any areas for improvement.

27. Committee members are normally appointed for a term of 3 years (a maximum 10 years/3 terms per member). The COT uses the feedback self assessment form as one of the tools used to determine whether or not a committee member should be reappointed at the end of their (3 year) term.

ANNEX 4 – Good Practice Agreement for Scientific Advisory Committees

INTRODUCTION

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

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

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

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

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

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

- Advisory Committee on Animal Feedingstuffs
- Advisory Committee on Microbiological Safety of Foods
- Advisory Committee on Novel Foods and Processes
- Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment
- Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment
- Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
- Science Council
- Social Science Research Committee

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

All these committees share important characteristics. They:

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

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

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

Twenty nine principles of good practice have been developed. However, the different committees have different duties and discharge those duties in different ways. Therefore, not all of the principles set out below will be applicable to all of the committees, all of the time.

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

PRINCIPLES

Defining the problem and the approach

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

Seeking input

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

Validation

9. Study design, methods of measurement and the way that analysis of data has been carried out will be assessed by the SAC.
10. Data will be assessed by the committee in accordance with the relevant principles of good practice, e.g. qualitative social science data will be assessed with reference to guidance from the Government's Chief Social Researcher[3].
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.

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

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

Uncertainty

14. When reporting outcomes, SACs will make explicit the level and type of uncertainty (both limitations on the quality of the available data and lack of knowledge) associated with their advice.
15. Any assumptions made by the SAC will be clearly spelled out, and, in reviews, previous assumptions will be challenged.
16. Data gaps will be identified and their impact on uncertainty assessed by the SAC.
17. An indication will be given by the SAC about whether the evidence base is changing or static, and if appropriate, how developments in the evidence base might affect key assumptions and conclusions.

Drawing conclusions

18. The SAC will be broad-minded, acknowledging where conflicting views exist and considering whether alternative interpretations fit the same evidence.
19. Where both risks and benefits have been considered, the committee will address each with the same rigour, as far as possible; it will make clear the degree of rigour and uncertainty, and any important constraints, in reporting its conclusions.
20. SAC decisions will include an explanation of where differences of opinion have arisen during discussions, specifically where there are unresolved issues, and why conclusions have been reached. If it is not possible to reach a consensus, a minority report may be appended to the main report, setting out the differences in interpretation and conclusions, and the reasons for these, and the names of those supporting the minority report.
21. The SAC's interpretation of results, recommended actions or advice will be consistent with the quantitative and/or qualitative evidence and the degree of uncertainty associated with it.
22. SACs will make recommendations about general issues that may have relevance for other committees.

Communicating SACs' conclusions

23. Conclusions will be expressed by the SAC in clear, simple terms and use the minimum caveats consistent with accuracy.
24. It will be made clear by the SAC where assessments have been based on the work of other bodies and where the SAC has started afresh and there will be a clear statement of how the current conclusions compare with previous assessments.
25. The conclusions will be supported by a statement about their robustness and the extent to which judgement has had to be used.
26. As standard practice, the SAC secretariat will publish a full set of references (including the data used as the basis for risk assessment and other SAC opinions) at as early a stage as possible to support openness and transparency of decision-making. Where this is not possible, reasons will be clearly set out, explained and a commitment made to future publication wherever possible.

27. The amount of material withheld by the SAC or FSA as being confidential will be kept to a minimum. Where it is not possible to release material, the reasons will be clearly set out, explained and a commitment made to future publication wherever possible.
28. Where proposals or papers being considered by the FSA Board rest on scientific evidence produced by a SAC, the Chair of the SAC (or a nominated expert member) will be invited to the table at the Open Board meetings at which the paper is discussed. To maintain appropriate separation of risk assessment and risk management processes, the role of the Chairs will be limited to providing an independent view and assurance on how their committee's advice has been reflected in the relevant policy proposals, and to answer Board Members' questions on the science. The Chairs may also, where appropriate, be invited to provide factual briefing to Board members about particular issues within their committees' remits, in advance of discussion at open Board meetings.
29. The SAC will seek (and FSA will provide) timely feedback on actions taken (or not taken) in response to the SAC's advice, and the rationale for these.

Annex 5 – Glossary of Terms

a priori: The formulation of a hypothesis before undertaking an investigation or experiment.

Absorption (biological): Process of active or passive transport of a substance into an organism, in humans this is usually through the lungs, gastrointestinal tract or skin

Acceptable Daily Intake (ADI): Estimate of the amount of a substance in food or drink, expressed on a bodyweight basis (e.g. mg/kg bodyweight), that can be ingested daily over a lifetime by humans without appreciable health risk.

Acceptable Risk: Probability of suffering disease or injury which is considered to be sufficiently small to be “negligible”

Acute: Short term, in relation to exposure or effect.

Acute reference dose (ARfD): Estimate of the amount of a substance in food or drink, expressed on a body weight basis that can be ingested in a period of 24 hours or less without appreciable health risk.

Acute toxicity: Adverse effects that occur over a short period of time (up to 14 days) immediately following exposure.

Adduct: A chemical grouping which is covalently bound (see covalent binding) to a large molecule such as DNA (qv) or protein.

Adenoma: A benign neoplasm arising from a gland forming epithelial tissue such as colon, stomach or respiratory tract.

Adverse effect: Change in morphology, physiology, biochemistry, growth, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences.

Aetiology: study of causation or origination

Ah receptor: The Ah (Aromatic hydrocarbon) receptor protein regulates some specific gene expressions associated with toxicity. The identity of the natural endogenous chemicals which bind to the Ah receptor is unknown. Binding to the Ah receptor is an integral part of the toxicological mechanism of a range of chemicals, such as chlorinated dibenzodioxins and polychlorinated biphenyls.

Alkylating agents: Chemicals which leave an alkyl group covalently bound to biologically important molecules such as proteins and nucleic acids (see adduct). Many alkylating agents are mutagenic, carcinogenic and immunosuppressive.

Allele: Alternative form of a gene.

Allergen: Substance capable of stimulating an allergic reaction.

Allergy: The adverse health effects that may result from the stimulation of a specific immune response.

Allergic reaction: an adverse reaction elicited by exposure to a previously sensitised individual to the relevant antigen.

Ames test: *In vitro* (qv) assay for bacterial gene mutations (qv) using strains of *Salmonella typhimurium* developed by Ames and his colleagues.

Androgen: The generic term for any natural or synthetic compound that can interact with and activate the androgen receptor. In mammals, androgens (for example, androstenedione and testosterone) are synthesised by the adrenal glands and the testes and promote development and maintenance of male secondary sexual characteristics.

Aneugenic: Inducing aneuploidy (qv).

Aneuploidy: The circumstances in which the total number of chromosomes within a cell is not an exact multiple of the normal haploid (see 'polyploidy') number. Chromosomes may be lost or gained during cell division.

Apoptosis: A form of active cell death resulting in fragmentation of the cell into membrane-bound fragments (apoptotic bodies). These are usually rapidly removed *in vivo* by engulfment by phagocytic cells. Apoptosis can occur normally during development, but is often triggered by toxic stimuli.

ARfD: see Acute reference dose

Base pair (bp): Two complementary nucleotide (qv) bases joined together by chemical bonds.

Benchmark dose (BMD) modelling: An approach to dose-response assessment that aims to be more quantitative than the NOAEL process. This approach constructs mathematical models to fit all data points in the dose-response study and uses the best fitting model to interpolate an estimate of the dose that corresponds to a particular level of response (a benchmark response), often 10%. A measure of uncertainty is also calculated, and the lower confidence limit on the benchmark dose is called the BMDL. The BMDL accounts for the uncertainty in the estimate of the dose-response that is due to characteristics of the experimental design such as sample size. The BMDL can be used as the point of departure for derivation of a health-based guidance value or a margin of exposure.

Bias: In the context of epidemiological studies, an interference which at any stage of an investigation tends to produce results that depart systematically from the true values (to be distinguished from random error). The term does not necessarily carry an imputation of prejudice or any other subjective factor such as the experimenter's desire for a particular outcome.

Bioavailability: A term referring to the proportion of a substance which reaches the systemic circulation unchanged after a particular route of administration.

Bioinformatics: The science of informatics as applied to biological research. Informatics is the management and analysis of data using advanced computing techniques. Bioinformatics is particularly important as an adjunct to genomics research, because of the large amount of complex data this research generates.

Biomarker: Observable change (not necessarily pathological) in an organism, related to a specific exposure or effect.

Body burden: Total amount of a chemical present in an organism at a given time.

Bradford Hill Criteria: Sir Austin Bradford-Hill established criteria that may be used to assist in the interpretation of associations reported from epidemiological studies:-

- Strength – The stronger the association the more likely it is causal. The COC has previously noted that the relative risks of ‹3 need careful assessment for effects of bias or confounding.

- Consistency – The association has been consistently identified by studies using different approaches and is also seen in different populations with exposure to the chemical under consideration.

- Specificity – Limitation of the association to specific exposure groups or to specific types of disease increases likelihood that the association is causal.

- Temporality – The association must demonstrate that exposure leads to disease.

The relationship of time since first exposure, duration of exposure and time since last exposure are all important in assessing causality.

- Biological gradient – If an association reveals a biological gradient or doseresponse curve, then this evidence is of particular importance in assessing causality.

- Plausibility – Is there appropriate data to suggest a mechanism by which exposure could lead to concern? However, even if an observed association may be new to science or medicine it should not be dismissed.

- Coherence – Cause and effect interpretation of data should not seriously conflict with generally known facts.

- Experiment – Can the association be demonstrated? Evidence from experimental animals may assist in some cases. Evidence that removal of the exposure leads to a decrease in risk may be relevant.

- Analogy – Have other closely related chemicals been associated with the disease?

Bronchial: Relating to the air passages conducting air from the trachea (windpipe) to the lungs.

C. elegans: *Caenorhabditis elegans*, a nematode or roundworm, the first animal to have its genome completely sequenced and all the genes fully characterised.

Cancer: Synonym for a malignant neoplasm – that is, a tumour (qv) that grows progressively, invades local tissues and spreads to distant sites (see also tumour and metastasis).

Candidate gene: A gene that has been implicated in causing or contributing to the development of a particular disease.

Carcinogenesis: The origin, causation and development of tumours (qv). The term applies to benign as well as malignant neoplasms and not just to carcinomas (qv).

Carcinogenicity bioassay: Tests carried out in laboratory animals, usually rats and mice, to determine whether a substance is carcinogenic. The test material is given throughout life to groups of animals at different dose levels.

Carcinogen: The causal agents which induce tumours. They include external factors (chemicals, physical agents, viruses) and internal factors such as hormones. Chemical carcinogens are structurally diverse and include naturally-occurring substances as well as synthetic compounds. An important distinction can be drawn between *genotoxic* (qv) carcinogens which have been shown to react with and mutate DNA, and *nongenotoxic* carcinogens which act through other mechanisms. The activity of genotoxic carcinogens can often be predicted from their chemical structure - either of the parent compound or of active metabolites (qv). Most chemical carcinogens exert their effects after prolonged exposure, show a dose-response relationship and tend to act on a limited range of susceptible target tissues. Carcinogens are sometimes species or sex-specific and the term should be qualified by the appropriate descriptive adjectives to aid clarity. Several different chemical and other carcinogens may interact, and constitutional factors (genetic susceptibility, hormonal status) may also contribute, emphasising the multifactorial nature of the carcinogenic process.

Carcinoma: Malignant tumour arising from epithelial cells lining, for example, the alimentary, respiratory and urogenital tracts and from epidermis, also from solid viscera such as the liver, pancreas, kidneys and some endocrine glands. (See also 'tumour').

Case-control study: (Synonyms - case comparison study, case referent study, retrospective study) A comparison is made of the proportion of cases who have been exposed to a particular hazard (e.g. a carcinogen) with the proportion of controls who have been exposed to the hazard.

Cell transformation: The process by which a normal cell acquires the capacity for neoplastic growth. Complete transformation occurs in several stages both *in vitro* and *in vivo*. One step which has been identified *in vitro* is 'immortalisation' by which a cell acquires the ability to divide indefinitely in culture. Such cells do not have the capacity to form tumours in animals, but can be induced to do so by extended passage *in vitro*, by treatment with chemicals, or by transfection with oncogene DNA. The transformed

phenotype so generated is usually, but not always, associated with the ability of the cells to grow in soft agar and to form tumours when transplanted into animals. It should be noted that each of these stages of transformation can involve multiple events which may or may not be genetic. The order in which these events take place, if they occur at all, *in vivo* is not known.

Chromosomal aberrations: Collective term of particular types of chromosome damage induced after exposure to exogenous chemical or physical agents which damage the DNA. (see clastogen).

Chromosome: In simple prokaryotic organisms, such as bacteria and most viruses, the chromosome consists of a single circular molecule of DNA containing the entire genetic material of the cell. In eukaryotic cells, the chromosomes are thread-like structures, composed mainly of DNA and protein, which are present within the nuclei of every cell. They occur in pairs, the numbers varying from one to more than 100 per nucleus in different species. Normal somatic cells in humans have 23 pairs of chromosomes, each consisting of linear sequences of DNA which are known as genes (qv).

Chronic effect: Consequence which develops slowly and has a long-lasting course (often but not always irreversible).

Chronic exposure: Continued exposures occurring over an extended period of time, or a significant fraction of the life-time of a human or test animal.

Clastogen: An agent that produces chromosome breaks and other structural aberrations such as translocations. Clastogens may be viruses or physical agents as well as chemicals. Clastogenic events play an important part in the development of some tumours.

Clearance: Volume of blood or plasma, or mass of an organ, effectively cleared of a substance by elimination (metabolism and excretion) in a given time interval. Total clearance is the sum or the clearances for each eliminating organ or tissue.

Clone: A term which is applied to genes, cells, or entire organisms which are derived from - and are genetically identical to - a single common ancestor gene, cell, or organism, respectively. Cloning of genes and cells to create many copies in the laboratory is a common procedure essential for biomedical research.

Coding regions: those parts of the DNA that contain the information needed to form proteins. Other parts of the DNA may have non-coding functions (e.g. start-stop, pointing or timer functions) or as yet unresolved functions or maybe even ‘noise’.

Codon: a set of three nucleotide bases in a DNA or RNA sequence, which together code for a unique amino acid.

Cohort: A defined population that continues to exist through time.

Cohort study: (Synonyms - follow-up, longitudinal study) The study of a group of people defined at a particular point in time (the cohort), who have particular characteristics in common, such as a particular exposure. They are then observed over a period of time for

the occurrence of disease. The rate at which the disease develops in the cohort is compared with the rate in a comparison population, in which the characteristics (e.g. exposure) are absent.

Complementary DNA (cDNA): cDNA is DNA that is synthesised in the laboratory from mRNA by reverse transcription. A cDNA is so-called because its sequence is the complement of the original mRNA sequence.

Confounding variable: (synonym - confounder) An extraneous variable that satisfies BOTH of 2 conditions: (1) it is a risk factor for the disease under study (2) it is associated with the study exposure but is not a consequence of exposure. For example cigarette smoking is a confounding variable with respect to an association between alcohol consumption and heart disease. Failure to adjust for a confounding variable results in distortion of the apparent magnitude of the effect of the exposure under study. (In the example, smoking is a risk factor for heart disease and is associated with alcohol consumption but is not a consequence of alcohol consumption.)

Congeners: Related compounds varying in chemical structure but with similar biological properties.

Covalent binding: Chemical bonding formed by the sharing of an electron pair between two atoms. Molecules are combinations of atoms bound together by covalent bonds.

Cytochrome P450 (CYP): An extensive family of haem-containing proteins involved in enzymic oxidation of a wide range of endogenous and xenobiotic (qv) substances and their conversion to forms that may be more easily excreted. In some cases the metabolites produced may be reactive and may have increased toxicity. In other cases the substances may be natural precursors of hormones (e.g. steroids).

Cytogenetic: Concerning chromosomes, their origin, structure and function.

Deletion: A chromosomal aberration in which a proportion of the chromosome is lost. Deletions may range in size from a single nucleotide (qv) to an entire chromosome. Such deletions may be harmless, may result in disease, or may in rare cases be beneficial.

DNA (Deoxyribonucleic Acid): The carrier of genetic information for all living organisms except the group of RNA viruses. Each of the 46 chromosomes in normal human cells consists of 2 strands of DNA containing up to 100,000 nucleotides, specific sequences of which make up genes (qv). DNA itself is composed of two interwound chains of linked nucleotides (qv).

DNA probe: A piece of single-stranded DNA, typically labelled so that it can be detected (for example, a radioactive or fluorescent label can be used), which can single out and bind with (and only with) another specific piece of DNA. DNA probes can be used to determine which sequences are present in a given length of DNA or which genes are present in a sample of DNA.

DNA repair genes: Genes which code for proteins that correct damage in DNA sequences. When these genes are altered, mutations may be able to accumulate in the genome, ultimately resulting in disease.

Dominant lethal assay: See Dominant Lethal mutation.

Dominant lethal mutation: A dominant mutation that causes death of an early embryo.

Dose: Total amount of a substance administered to, taken or absorbed by an organism.

Endocrine modulator (synonym – endocrine disruptor): A chemical, which can be naturally occurring or man-made, that causes adverse health effects in an organism, as a result of changes in hormonal function.

Endonuclease: An enzyme that cleaves its nucleic acid substrate at internal sites in the nucleotide sequence.

Enterohepatic circulation: Cyclical process involving intestinal re-absorption of a substance that has been excreted through bile followed by transfer back to the liver, making it available for biliary excretion again.

Epidemiology: Study of factors determining the causes, frequency, distribution, and control of diseases in a human population.

Epithelium: The tissue covering the outer surface of the body, the mucous membranes and cavities of the body.

Erythema: Reddening of the skin due to congestion of blood or increased blood flow in the skin.

Erythrocyte: Red blood cell.

Estrogen: Sex hormone or other substance capable of developing and maintaining female characteristics of the body.

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

Exogenous: Arising outside the body.

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

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

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

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

Forestomach: (See glandular stomach).

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

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

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

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

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

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

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

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

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

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

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

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

Genomics: The study of genes and their function.

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

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

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

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

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

Hepatic: Pertaining to the liver.

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

Hepatotoxic: Causing toxicity to the liver.

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

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

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

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

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

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

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

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

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

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

Intraperitoneal: Within the abdominal cavity.

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

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

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

LC50: The theoretical lethal concentration for 50% of a group of organisms

LD50: The dose of a toxic compound that causes death in 50% of a group of experimental animals to which it is administered. It can be used to assess the acute toxicity of a compound, but is being superseded by more refined methods.

Leukaemia: A group of neoplastic disorders (see tumour) affecting blood-forming elements in the bone marrow, characterised by uncontrolled proliferation and disordered differentiation or maturation. Examples include the lymphocytic leukaemia's which develop from lymphoid cells and the myeloid leukaemia's which are derived from myeloid cells (producing red blood cells, mainly in bone marrow).

Ligand: A molecule which binds to a receptor.

Lipids: Fats, substances containing a fatty acid and soluble in alcohols or ether, but insoluble in water.

Lipophilic: 'Lipid liking' - a substance which has a tendency to partition into fatty materials.

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

Lymphocyte: A type of white blood cell that plays central roles in adaptive immune responses.

Lymphoma: Malignant tumours arising from lymphoid tissues. They are usually multifocal, involving lymph nodes, spleen, thymus and sometimes bone marrow, and other sites outside the anatomically defined lymphoid system. (See also 'tumour').

Malignancy: See 'tumour'.

Margin of exposure (MOE) approach: A methodology that allows the comparison of the risks posed by different genotoxic and carcinogenic substances. The MOE approach uses a reference point, often taken from an animal study and corresponding to a dose that causes a low but measurable response in animals. This reference point is then compared with various dietary intake estimates in humans, taking into account differences in consumption patterns. It is also used for contaminants for which there is insufficient information to set a Tolerable Daily Intake (qv).

Messenger RNA (mRNA): The DNA of a gene is transcribed (see transcription) into mRNA molecules, which then serve as a template for the synthesis of proteins.

Meta-analysis: In the context of epidemiology, a statistical analysis of the results from independent studies, which aims to produce a single estimate of an effect.

Metabolic activation: Metabolism of a compound leading to an increase in its activity, whether beneficial (e.g. activation of a pro-drug) or deleterious (e.g. activation to a toxic metabolite).

Metabolic activation system: A cell-free preparation (e.g. from the livers of rats pretreated

with an inducing agent (qv)) added to *in vitro* tests to mimic the metabolic activation typical of mammals.

Metabolism: Chemical modification of a compound by enzymes within the body, for example by reactions such as hydroxylation (see cytochrome P450), epoxidation or conjugation. Metabolism may result in activation, inactivation, accumulation or excretion of the compound.

Metabolite: Product formed by metabolism of a compound.

Metabonomics: Techniques available to identify the presence and concentrations of metabolites in a biological sample.

Metaphase: Stage of cell division (mitosis and meiosis) during which the chromosomes are arranged on the equator of the nuclear spindle (the collection of microtubule filaments which are responsible for the movement of chromosomes during cell division). As the chromosomes are most easily examined in metaphase, cells are arrested at this stage for microscopical examination for chromosomal aberrations (qv) - known as metaphase analysis.

Metastasis: The process whereby malignant cells become detached from the primary tumour mass, disseminate (mainly in the blood stream or in lymph vessels) and 'seed out' in distant sites where they form secondary or metastatic tumours. Such tumours tend to develop at specific sites and their anatomical distribution is often characteristic; it is non-random.

µg: Microgram

Micronuclei: Isolated or broken chromosome fragments which are not expelled when the nucleus is lost during cell division, but remain in the body of the cell forming micronuclei. Centromere positive micronuclei contain DNA and/or protein material derived from the centromere. The presence of centromere positive micronuclei following exposure to chemicals can be used to evaluate the aneugenic (qv) potential of chemicals.

Micronucleus test: See Micronuclei.

Mitogen: A stimulus which provokes cell division in somatic cells.

Mitosis: The type of cell division which occurs in somatic cells when they proliferate. Each daughter cell has the same complement of chromosomes as the parent cell.

Mouse lymphoma assay: An *in vitro* assay for gene mutation in mammalian cells using a mouse lymphoma cell line L5178Y, which is heterozygous for the gene (carries only one functional gene rather than a pair) for the enzyme thymidine kinase ($TK^{+/-}$). Mutation of that single gene is measured by resistance to toxic trifluorothymidine. Mutant cells produce two forms of colony - large, which represent mutations within the gene and small, which represent large genetic changes in the chromosome such as chromosome aberrations. Thus this assay can provide additional information about the type of mutation which has occurred if colony size is scored.

Mouse spot test: An *in vivo* test for mutation, in which pregnant mice are dosed with the test compound and mutations are detected by changes (spots) in coat colour of the offspring. Mutations in the melanocytes (skin pigment cells) of the developing fetus are measured.

Mucosal: Regarding the mucosa or mucous membranes, consisting of epithelium (qv) containing glands secreting mucus, with underlying layers of connective tissue and muscle.

Murine: Often taken to mean “of the mouse”, but strictly speaking means of the Family Muridae which includes rats and squirrels.

Mutagen: is a physical or chemical agent that changes the genetic information (usually DNA) of an organism

Mutation: A permanent change in the amount or structure of the genetic material in an organism or cell, which can result in a change in phenotypic characteristics. The alteration may involve a single gene, a block of genes, or a whole chromosome. Mutations involving single genes may be a consequence of effects on single DNA bases (point mutations) or of large changes, including deletions, within the gene. Changes involving whole chromosomes may be numerical or structural. A mutation in the germ cells of sexually reproducing organisms may be transmitted to the offspring, whereas a mutation that occurs in somatic cells may be transferred only to descendent daughter cells.

Mycotoxin: Toxic compound produced by a fungus.

Neoplasm: See 'tumour'.

Neoplastic: Abnormal cells, the growth of which is more rapid that that of other cells.

Nephrotoxicity: Toxicity to the kidney.

Neurobehavioural: Of behaviour determined by the nervous system.

Neurotoxicity: Toxicity to the nervous system.

NOAEL: No observed adverse effect level. The highest administered dose at which no adverse (qv) effect has been observed.

Non-genotoxic: See 'carcinogens'.

Non-Hodgkin lymphomas: (NHLs) are a diverse group of hematologic cancers which encompass any lymphoma other than Hodgkin's Lymphoma

Nucleic acid: One of the family of molecules which includes the DNA and RNA molecules. Nucleic acids were so named because they were originally discovered within the nucleus of cells, but they have since been found to exist outside the nucleus as well.

Nucleotide: the "building block" of nucleic acids, such as the DNA molecule. A nucleotide consists of one of four bases - adenine, guanine, cytosine, or thymine - attached to a phosphate-sugar group. In DNA the sugar group is deoxyribose, while in RNA (a DNA-related molecule which helps to translate genetic information into proteins), the sugar group is ribose, and the base uracil substitutes for thymine. Each group of three nucleotides in a gene is known as a codon. A nucleic acid is a long chain of nucleotides joined together, and therefore is sometimes referred to as a "polynucleotide."

Null allele: inactive form of a gene.

Odds ratio (OR): The odds of disease in an exposed group divided by the odds of disease in an unexposed group.

OECD: Organisation for Economic Cooperation and Development

Oedema: Excessive accumulation of fluid in body tissues.

Oestrogen: (See estrogen)

Oligonucleotide: A molecule made up of a small number of nucleotides, typically fewer than 25.

Oncogene: A gene which is associated with the development of cancer (see protooncogene).

Organochlorine: A group of chemical compounds, containing multiple chlorine atoms, that are usually of concern as environmental pollutants. Some organochlorines have been manufactured as pesticides or coolants and others arise as contaminants of manufacturing processes or incineration.

Pharmacokinetics: Description of the fate of drugs in the body, including a mathematical account of their absorption, distribution, metabolism and excretion (see toxicokinetics).

Pharmacogenomics: The science of understanding the correlation between an individual patient's genetic make-up (genotype) and their response to drug treatment. Some drugs work well in some patient populations and not as well in others. Studying the genetic basis of patient response to therapeutics allows drug developers to design therapeutic treatments more effectively.

Phenotype: The observable physical, biochemical and physiological characteristics of a cell, tissue, organ or individual, as determined by its genotype and the environment in which it develops.

Phytoestrogen: Any plant substance or metabolite that induces biological responses in vertebrates and can mimic or modulate the actions of endogenous estrogens usually by binding to estrogen receptors.

Plasmid: A structure composed of DNA that is separate from the cell's genome (qv). In bacteria, plasmids confer a variety of traits and can be exchanged between individuals, even those of different species. Plasmids can be manipulated in the laboratory to deliver specific genetic sequences into a cell.

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

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

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

Polymorphism: (see genetic polymorphism)

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

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

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

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

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

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

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

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

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

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

Renal: Relating to the kidney.

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

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

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

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

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

SAHSU: Small Area Health Statistics Unit

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

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

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

Single nucleotide polymorphism (SNP): DNA sequence variations that occur when a single nucleotide in the genome sequence is altered. For example, a SNP might change the DNA sequence A**A**GGCTAA to A**T**GGCTAA. By convention, SNPs occur in at least 1% of the population.

Sister chromatid exchange (SCE): Exchange of genetic material between two subunits of a replicated chromosome.

Stakeholder: A person or organisation representing the interests and opinions of a group with an interest in the outcome of (for example) a review or policy decision.

Suppressor gene: A gene which helps to reverse the effects of damage to an individual's genetic material, typically effects which might lead to uncontrolled cell growth (as would occur in cancer). A suppressor gene may, for example, code for a protein which checks genes for misspellings, and/or which triggers a cell's selfdestruction if too much DNA damage has occurred.

Surfactant: Also called: surface-active agent. A substance, such as a detergent, that can reduce the surface tension of a liquid and thus allow it to foam or penetrate solids; a wetting agent.

Systematic review: A review that has been prepared using a documented systematic approach to minimising biases and random errors.

TDI: See 'Tolerable Daily Intake'.

Teratogen: A substance which, when administered to a pregnant woman or animal, can cause congenital malformations (structural defects) in the baby or offspring.

Testicular Dysgenesis Syndrome (TDS): The hypothesis that maldevelopment (dysgenesis) of the fetal testis results in hormonal or other malfunctions of the testicular somatic cells which in turn predispose a male to the disorders that comprise the TDS, i.e. congenital malformations (cryptorchidism and hypospadias) in babies and testis cancer and low sperm counts in young men.

Threshold: Dose or exposure concentration below which an effect is not expected.

Tolerable Daily Intake (TDI): An estimate of the amount of contaminant, expressed on a body weight basis (e.g. mg/kg bodyweight), that can be ingested daily over a lifetime without appreciable health risk.

Toxic Equivalency Factor (TEF): A measure of relative toxicological potency of a chemical compared to a well characterised reference compound. TEFs can be used to sum the toxicological potency of a mixture of chemicals which are all members of the same chemical class, having common structural, toxicological and biochemical properties. TEF systems have been published for the chlorinated dibenzodioxins, dibenzofurans and dioxin-like polychlorinated biphenyls, and for polycyclic aromatic hydrocarbons.

Total Toxic Equivalent (TEQ): Is a method of comparing the total relative toxicological potency within a sample. It is calculated as the sum of the products of the concentration of each congener multiplied by the toxic equivalency factor (TEF).

Toxicodynamics: The process of interaction of chemical substances with target sites and the subsequent reactions leading to adverse effects.

Toxicogenic: producing or capable of producing a toxin.

Toxicogenomics: A scientific subdiscipline that combines the emerging technologies of genomics and bioinformatics to identify and characterise mechanisms of action of known and suspected toxicants. Currently, the premier toxicogenomic tools are the DNA microarray and the DNA chip, which are used for the simultaneous monitoring of expression levels of hundreds to thousands of genes.

Toxicokinetics: The description of the fate of chemicals in the body, including a mathematical account of their absorption, distribution, metabolism and excretion. (see pharmacokinetics)

Transcription: the process during which the information in a length of DNA (qv) is used to construct an mRNA (qv) molecule.

Transcriptomics: Techniques available to identify mRNA from actively transcribed genes.

Transfer RNA (tRNA): RNA molecules which bond with amino acids and transfer them to ribosomes, where protein synthesis is completed.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Xenobiotic: A chemical foreign to the biologic system.

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

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

Review of toxicogenomics, COT/COC/COM	2004	144
Review of the mutagenicity of alcohol	2015	35
Review of current approaches to germ cell mutagenicity testing	2013	45
Rhizoxin – newlase analytical method to detect	2000 2002 2004	17 11 10
Risk assessment of carcinogens, Revised guidance	2003	197
COC guidance on a strategy for the	2004	188
Risk assessment of *in vivo* mutagens (and genotoxic mutagens)	2001	107
Risk Assessment of Mixtures of Pesticides (and similar substances)	2000 2002	25 19
Risks arising from the infant diet and the development of atopic and autoimmune disease	2012	21
'Risk assessment methodologies and approaches for mutagenic and carcinogenic substances', Preliminary Report by the EU Scientific Committees on Consumer Products, on Health and Environmental Risks, and on Emerging and Newly-Identified Risks on	2008	280
Risk assessment strategies Guidelines for exposure assessment practice for human health	2003	19
Mixtures of food contaminants and additives	2004	15
Physiologically-based pharmacokinetic modelling	2003	19
RCEP study on pesticides and bystander exposure	2004	18
Reassessment of the toxicological testing of tobacco	2004	19
Royal society study on nanoscience and nanotechnology	2004	20
Uncertainty factors: their use in human health risk assessment by UK government	2003	20
Uncertainty in chemical exposure assessment	2004	21
Use of toxicogenomics in toxicology (update on statement published in 2002).	2004	22
Risk communication	2007	182
Risks of chemical toxicity and allergic disease in relation to infant diet	2012	14
Risk procedures used by the Government's Advisory Committees dealing with food safety	2000	22, 110
Risks associated with exposure to low levels of air pollution	2003	193
RNA Interference	2005	16
RNA related effects as a mechanism of carcinogenicity	2009	228
Royal society study on nanoscience and nanotechnology	2004	20
SACN report on Iron and Health,	2009	226
Toxicological aspects	2009	29
SACN Review of Vitamin D	2011 2012 2013	28 21 31

ANNEX 7 – Previous Publications

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2014 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Food Standards Agency/Department of Health, November 2015.

2015 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 2016.

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/

If you require any further information about the work of the committees, or the contents of this report, please write to the committee's administrative secretary at the following address:

COT Secretariat
Food Standards Agency
Aviation House
Kingsway
London WC2B 6NH

Tel: 020 7276 8522
Email: COT@foodstandards.gsi.gov.uk
http://cot.food.gov.uk

COC/COM Secretariat
Health Protection Agency
Centre for Radiation and Chemical Hazards
Chemical Hazards and Poisons Division (Head Office)
Chilton Didcot
Oxon OX11 0RQ

Tel: +44 (0)1235 822836
Fax: +44 (0)1235 841478
Email: Sue.Kennedy@hpa.org.uk
http://www.iacoc.org.uk/index.htm
http://www.iacom.org.uk/index.htm

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