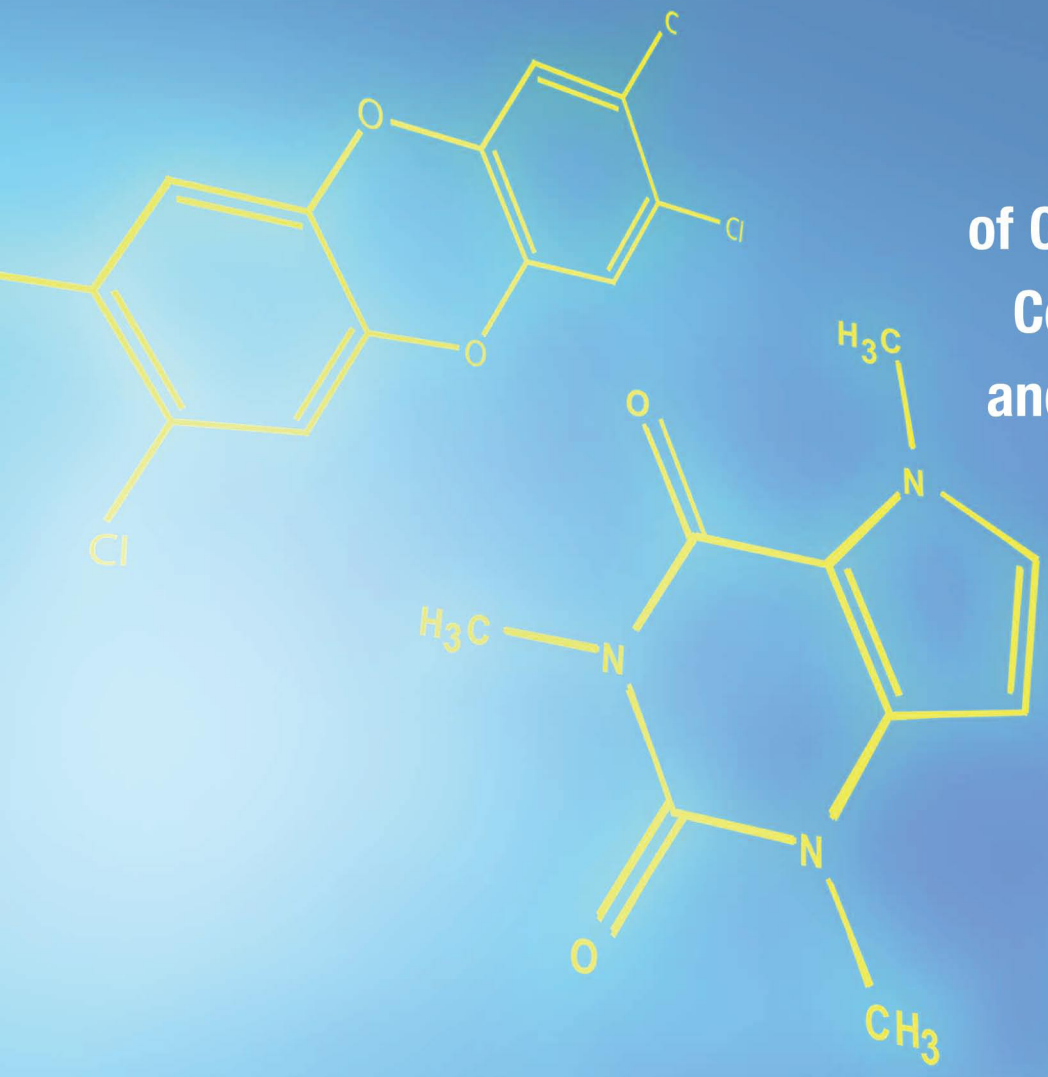
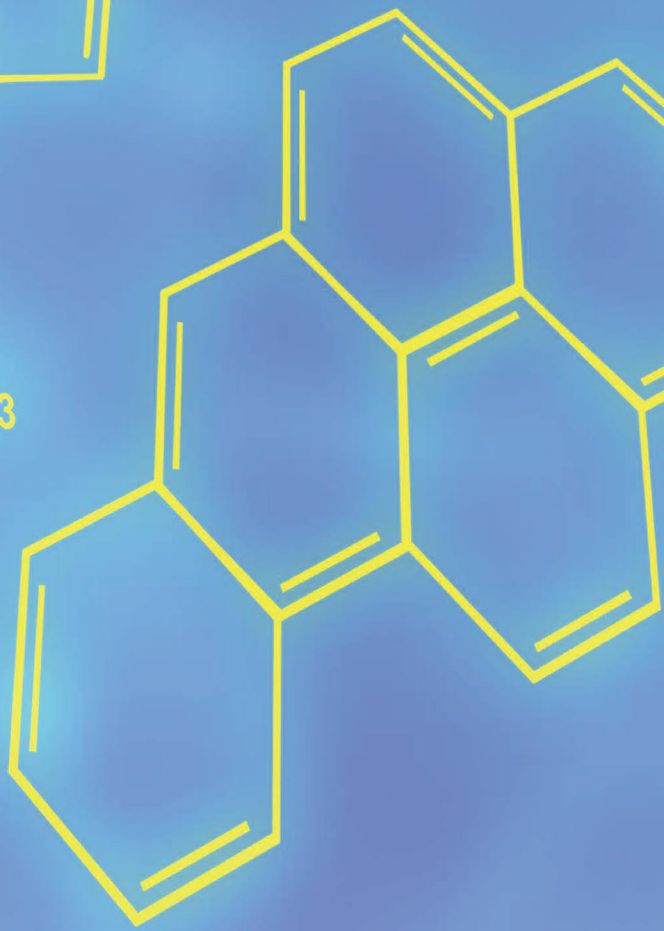
Committees on Toxicity Mutagenicity Carcinogenicity of Chemicals in Food, Consumer Products and the Environment





Committee on TOXICITY

Committee on CARCINOGENICITY

Committee on MUTAGENICITY

Annual Report 2011

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

Annual Report 2011

Contents

About the Committees

This is the twenty-first 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 summary of the Committees' work during the past year. Those seeking further information on a particular subject can access it through the links that are given to published statements, from the Committees' websites (see below), or from the administrative secretary of the relevant Committee.

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 conflict of interest with regard to a topic under discussion, he or she may, at the Chairman's discretion be allowed to take part in the discussion, but is excluded from decision-making. Annex 1 contains the terms of reference under which the Committees were set up. The Code of Conduct is at Annex 2 and Annex 3 describes the Committees' policy on openness. Annex 4 has the Good Practice Agreement for Scientific Advisory Committees. Annex 5 contains a glossary of technical terms used in the text. Annex 6 is an alphabetical index to subjects and substances considered in previous reports. Previous publications of the Committees are located at Annex 7.

These three Committees also provide expert advice to other advisory committees, such as the Advisory Committee on Novel Foods and Processes, and there are links with the General Advisory Committee on Science, Veterinary Products Committee and the Advisory Committee on Pesticides.

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

COT: http://cot.food.gov.uk
COC: http://www.iacoc.org.uk/index.htm
COM: http://www.iacom.org.uk/index.htm

This report provides links to the Committees' published statements in full in order to fulfil the obligation to publish statements both electronically and in hard copy.

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

Preface

I am pleased to present this report, which summarises the work of the Committee on Toxicity (COT) during 2011. The role of the Committee is to assess chemicals for their potential to harm human health. Evaluations are carried out at the request of the Food Standards Agency, Department of Health, Health Protection Agency, and other Government Departments and Regulatory Authorities, and are published as statements on the Internet. Details of membership, agendas and minutes are also published on the Internet.

The work of COT has important practical impacts. For example, our statement on effects of chronic dietary exposure to methanol, published early in 2011, was used by the Scottish Government in responding to a petition for a ban on the artificial sweetener, aspartame. Following our reviews of the validity of new methods of measuring biotoxins in shellfish, these are now being applied routinely in statutory monitoring, reducing the use of tests in laboratory animals. Our assessment of the risks of coeliac disease and diabetes according to the age at which gluten is introduced into the infant diet contributes to a review by the Scientific Advisory Committee on Nutrition (SACN) that will underpin national guidance on feeding for babies and young children. And our evaluation of possible health risks from phthalates has been used by the Health and Safety Executive in responding to a proposal to tighten restrictions on these compounds in the European Union.

The work of the Committee would not be possible without the excellent support that we receive from our secretariat. I would particularly like to thank two members of the FSA team, Dr Natalie Thatcher and Mr Gary Welsh, who left us during 2011 to take up new posts.

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

COT evaluations

Dietary exposure to phthalates – data from the Total Diet Study

Background

1.1 Phthalates (phthalic acid esters) are chemical compounds made from phthalic acid. They have a wide variety of industrial uses that include the manufacture of household and consumer goods such as lubricating oils, solvents, personal care products and food packaging.

1.2 Phthalates may occur in food because of their widespread presence as environmental contaminants and through their release from plastic food packaging. Phthalates can interact with the hormonal (endocrine) control systems of the body, and in particular those that regulate reproductive function.

1.3 In the EU, there is legislation to ensure that materials which come into contact with food (directly or indirectly) do not transfer to food in quantities large enough to endanger human health. EU law limits the use of certain phthalates in plastics that come into contact with food, with specific restrictions on the maximum amount that can transfer (migrate) into foods.

1.4 The safety of dietary exposure to phthalates has previously been evaluated by several independent scientific committees, including the COT.

Introduction

1.5 A recent Food Standards Agency funded study looked for the presence of phthalates in food samples collected as part of the 2007 Total Diet Study (TDS).

1.6 The TDS survey involves the collection of over one hundred types of food from normal retail outlets in twenty four towns across the UK. These food samples represent the average UK diet. The sampled foods are prepared according to normal domestic practice and are then analysed to determine the levels of various different chemicals.

1.7 The Committee was invited to consider the potential risk to consumers from dietary exposures to phthalates estimated from the 2007 TDS samples, and to advise whether the levels detected in foods were a health concern.

Results

1.8 Of the twenty six different phthalates that were looked for in the TDS samples, only eight were detected. These were:

- Diethyl phthalate (DEP)
- Di-isobutyl phthalate (DiBP)
- Di-n-butyl phthalate (DBP)

- Benzyl butyl phthalate (BBP)
- Dicyclohexyl phthalate (DCHP)
- Di-(2-ethylhexyl) phthalate (DEHP)
- Monobutyl phthalate (MBP)
- Mono-(2-ethylhexyl) phthalate (MEHP)

1.9 For each compound, the COT estimated the highest dietary exposures that might occur in different age groups, and compared them to the corresponding Tolerable Daily Intake (TDI) where available. A TDI is the amount of a contaminant that would not be expected to cause appreciable harm in consumers, even if eaten every day, over a whole lifetime. The estimates of dietary exposure were made by combining the measured concentrations of phthalates in different foods with data on patterns of consumption of those foods from the National Diet and Nutrition Survey (NDNS).

1.10 The highest estimated exposures relative to body weight were for toddlers aged between 1½ and 2½ years. The Committee noted that in practice, exposures were likely to be much lower than those estimated, since the assumptions made in the exposure calculation were highly conservative.

1.11 Potential intakes of DBP, DEHP, BBP and DEP, estimated from the levels found in the 2007 TDS food samples, were all below their respective TDIs and did not indicate a risk to human health from dietary exposure.

1.12 To assess the risk from total dietary exposure to phthalates (i.e. from the combination of all phthalates in the diet), the Committee assumed that the toxic effects of each individual phthalate would be similar, and that the combined toxic effect for a mix of phthalates could be estimated by adding together the exposure estimates for individual compounds.

1.13 The Committee compared an estimate of the highest total exposures to all phthalates with the lowest TDI for any of the individual compounds (which was for DBP). The estimated total phthalate exposure was approximately twice the TDI for DBP. The Committee considered this did not indicate a concern for health since a) most of the phthalates are less potent than DBP, b) the TDI for DBP was likely to be very conservative, and c) DBP accounted for only approximately 5% of the total exposure to phthalates.

Conclusion

1.14 Overall the Committee concluded that levels of phthalates found in samples from the 2007 TDS did not indicate a risk to human health from dietary exposure alone. However other, non-dietary, sources of exposure would need to be considered in a full risk assessment for phthalates.

1.15 The full COT statement can be found at:
http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2011/cot201104

Effects of chronic dietary exposure to methanol

1.16 Methanol (methyl alcohol) is a chemical which is similar in structure to ethanol (ethyl alcohol), the alcohol found in alcoholic drinks.

1.17 It is generated in the body as a by-product of protein formation, and is also found in food, particularly fruit and vegetables, from which it is taken up during digestion. Another dietary source is the sweetener aspartame, which breaks down in the body to amino acids and methanol. Some people are exposed to methanol vapour through their work.

1.18 In the body, some methanol is excreted unchanged in urine or breath, but most is broken down through a series of chemical reactions. The methanol is first converted into formaldehyde, then formate or formic acid and finally carbon dioxide.

1.19 High intakes of methanol, usually from consumption of illegally distilled alcoholic drinks or counterfeit drinks made from methylated spirits, can be toxic to the nervous system, particularly to sight, and if enough is consumed can result in permanent blindness or even death. The toxicity is caused by the breakdown product formate. The body's capacity to convert formate to carbon dioxide is limited, and when production of formate exceeds the maximum rate at which it can be eliminated, the formate begins to build up.

1.20 Although the toxicity of methanol at high doses is well established, less is known about whether effects occur from lower levels of exposure that continue over a long time, and it has been suggested that the methanol released from the sweetener aspartame could be harmful.

1.21 The COT was asked to review the scientific evidence on possible effects of long–term, low-level exposure to methanol, and particularly the exposures that might occur from aspartame. The COT considered information on how methanol is absorbed into the body, broken down and excreted. It looked at information on how much methanol is produced by the body, and how much could be taken up from food and drink, including from aspartame. It also looked at data from studies in humans who had consumed or inhaled known amounts of methanol, to see whether there was any evidence that formate levels built up or toxic effects occurred.

1.22 The evidence reviewed indicated that the body itself produces 0.3 to 0.6 g methanol/day and that up to 1 g/day may be consumed in food, particularly fruit and vegetables. The methanol released from aspartame would be a maximum of 0.24 g/day (though survey data suggest it is actually much lower than this).

1.23 Experiments have shown that exposure to aspartame, even at doses well above the maximum that could be expected from food and drink, does not lead to a build-up of formate in the blood. Furthermore, there are no reports of illness associated with long-term occupational exposure to methanol vapour at levels below the permitted maximum concentration of 200 parts per million (although adverse effects have been reported at higher levels). Over an eight-

hour working day, this exposure would give a daily dose of approximately 1.9 g – well in excess of that which could occur from aspartame.

1.24 Uncertainties remain because there have been few studies of long-term repeated exposure to methanol, either in animals or in humans. However, from the evidence available, the COT concluded that amounts of methanol consumed through food, including from aspartame, would not result in build up of formate and so are unlikely to cause harmful health effects.

1.25 The full COT statement can be found at: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2011/cot201102

FSA-funded research and other progress on mixtures of pesticides and similar substances

1.26 A COT report on Risk Assessment of Mixtures of Pesticides and Similar Substances was published in September 2002. This report considered the approaches that should be taken to the risk assessment of multiple residues of pesticides and veterinary medicines in food, and of multiple sources of exposure to these substances. The report is available to download at http://cot.food.gov.uk/cotreports/cotwgreports/cocktailreport.

1.27 The report made a number of recommendations under the headings of "Regulatory", "Surveillance", "Research" and "Public Information". The Food Standards Agency subsequently funded seventeen research projects to address the research recommendations and to provide information that was needed so that some of the other recommendations could be taken forward. The final reports of these research projects were now available and were considered by the COT. The Committee discussed the conclusions that could be drawn from the reports and what the priorities should be for further research.

1.28 In addition, the Committee considered the actions which had taken place to address the non-research recommendations in the report. The Committee's conclusions and recommendations were published as a Statement, which is available at: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2011/cot201107

Gluten - timing of introduction into the infant diet

1.29 In 2010, following publication of a Scientific Opinion by the European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies (NDA) on the appropriate age for the introduction of complementary food into infant diets in the EU, the Department of Health and Food Standards Agency asked the Scientific Advisory Committee on Nutrition (SACN) and the COT to assess the evidence on timing of introduction of gluten into the infant diet and subsequent risk of developing coeliac disease or type 1 diabetes mellitus (T1DM).

1.30 The COT considered the relevant evidence and provisional conclusions were forwarded to SACN. Further discussions took place during 2011.

1.31 SACN and COT agreed the following conclusions on the evidence-base concerning timing of introduction of gluten into the infant diet and risk of coeliac disease and T1DM:

i. The studies cited in the EFSA Opinion provide few data on the later risk of coeliac disease or type 1 diabetes mellitus in relation to the timing of introduction of gluten into the infant diet. The only evidence currently available is from observational studies. This means that there is uncertainty in the conclusions that can be drawn, and the balance of evidence might change in the future as the results of randomised controlled trials become available.

ii. Timing of introduction of gluten into the infant diet and risk of coeliac disease.

- EFSA identified no data directly relating age of introduction of gluten to an increase in the risk of coeliac disease in the general population. However, studies of children with a genetic predisposition to coeliac disease or a family history of T1DM are available.

- The currently available evidence provides an indication that dietary introduction of gluten-containing foods in the period up to and including the first 3 completed months of age is associated with an increased risk of coeliac disease. This is largely based on findings from a single observational study (Norris *et al.,* 2005).

- Relevant evidence on delayed introduction of gluten into the infant diet beyond 6 completed months of age is limited to that provided by two cohort studies (Norris *et al.,* 2005 and Ziegler *et al.,* 2003), with inconsistent findings and limitations in study design. There is therefore insufficient evidence to support a conclusion that the introduction of gluten into the infant diet after 6 completed months of age is associated with an increased risk of coeliac disease.

- A systematic review (Akobeng *et al.,* 2006) reported an association between longer duration of breastfeeding and reduced risk of developing coeliac disease. This systematic review included a meta-analysis of four case-control studies, which indicated that introduction of gluten into the infant diet whilst not breastfeeding is associated with an increased risk of subsequent coeliac disease. However, there is an absence of evidence to determine whether this relationship varies according to the age at which gluten is introduced.

iii. Timing of introduction of gluten into the infant diet and risk of T1DM.

- Currently available evidence on the timing of introduction of gluten into the infant diet and risk of T1DM is weak and does not allow specific conclusions to be drawn.

1.32 Overall currently available evidence on the timing of introduction of gluten into the infant diet and subsequent risk of coeliac disease and T1DM is insufficient to support recommendations about the appropriate timing of introduction of gluten into the infant diet beyond 3 completed months of age, for either the general population or high-risk sub-populations. SACN and COT do not consider the evidence sufficient to support EFSA's conclusion on the introduction of gluten into the infant diet not later than 6 completed months of age with the aim of reducing the risk of subsequent development of coeliac disease and T1DM.

1.33 These conclusions will inform a review to be conducted by SACN on complementary and young child feeding, which will include a critical appraisal of existing recommendations regarding the appropriate timing for introduction of solids. This review is on SACN's work programme and started in early 2011.

1.34 The joint SACN/COT statement is available at http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2011/cot201101

Idiopathic Environmental Intolerance (IEI)

Introduction

1.35 Idiopathic Environmental Intolerance (IEI) (which includes what has sometimes been called multiple chemical sensitivity) is a long-term, disabling disorder, in which symptoms relating to various organs and bodily systems are triggered by exposures to chemicals or other environmental agents at levels well below those which cause adverse effects in the large majority of the population.

1.36 To address a need that had been identified in an earlier COT statement, the Committee reviewed the published scientific literature on possible toxicological mechanisms for IEI linked to environmental chemicals. From consideration of its clinical features (symptoms, triggering exposures and clinical course) and associations with other illness, the Committee concluded that a full explanation of IEI would need to account for:

- The wide and diverse range of chemicals that can trigger symptoms
- The occurrence of symptoms appearing to depend on the triggering exposure being discernible (e.g. by its smell or irritancy), and being more likely when the chemical is perceived as harmful
- The variety of symptoms that are produced - relating to multiple organs and bodily systems

- The triggering of symptoms, in some cases severely disabling, in people who suffer from IEI by levels of exposure to chemicals well below those that are tolerated by the large majority of the population.

- A progressive increase that can occur over time in the number and diversity of chemicals that cause symptoms in an affected individual.

- The association of the disorder with psychiatric illness (although such illness could occur in some cases as a consequence of the distress caused by IEI)

1.37 The COT reviewed the evidence for hypothesised toxicological mechanisms and also heard a presentation on the psychological aspects of IEI given by Professor Omer Van den Bergh, Research Group on Health Psychology, University of Leuven, Belgium.

1.38 The COT reached the following conclusions;

(i) It was unable to identify any toxicological mechanism that could satisfactorily account for all of the clinical features and epidemiology of IEI. In particular, it found no convincing evidence for any biological mechanism that would explain why such diverse symptoms are induced in some individuals by such a wide range of chemicals, at levels of exposure well below those which are tolerated by the majority of people. Nor was there any convincing evidence of genetic differences in IEI patients that pointed to a toxicological mechanism for the disorder. It is conceivable that trigeminal irritancy (an unusual sensitivity to irritation of the nose and throat) could lead to the development of IEI in some individuals. However, not all of the chemicals that trigger symptoms in IEI patients are irritant.

(ii) Whilst an unknown toxicological mechanism cannot be totally discounted, on current evidence, a much more plausible explanation for IEI is that it represents a psychologically mediated response to perceived harmful exposures. In support of this theory, IEI is associated with psychiatric illness, and overlaps clinically with other disorders such as chronic fatigue syndrome that appear also to have a significant psychological component.

(iii) If psychological mechanisms do have a critical role in IEI, this does not preclude the possibility that differences in thresholds for airways irritation might render some individuals more susceptible to the disorder, although the evidence for such predisposition at present is weak.

(iv) Given the plausibility of an important psychological component in IEI, the COT recommend that this should be considered further by the appropriate specialism within the Department of Health (and devolved administrations), as there may be implications for the development of treatments.

1.39 The full COT statement can be found at: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2011/cot201103

Measurement of toxins that cause Paralytic Shellfish Poisoning (PSP)

1.40 The COT had previously agreed that High Performance Liquid Chromatography (HPLC) should replace the use of a Mouse Bio-Assay (MBA) for the official monitoring of Paralytic Shellfish Poisoning (PSP) toxins, provided appropriate quality control measures and suitable method validation studies had been conducted and it could be demonstrated that the HPLC method provided equivalent or better public health protection from paralytic shellfish poisoning than the MBA method. This had already resulted in the implementation of HPLC in quantitative testing for PSP toxins in mussels, cockles, razor clams and hard clams. The COT was presented with three draft reports of new work completed during the past year to extend the scope of the official HPLC method (the Lawrence method) for the quantification of PSP toxins to further UK shellfish species of commercial significance. The COT was asked whether the evidence provided in the three draft reports was sufficient to support a recommendation for the further implementation of HPLC in the official UK monitoring of PSP toxins in oysters, whole scallops and minor clam species

1.41 The COT suggested some minor amendments that should be made before publication of the report of investigations into the effects of oyster matrix on HPLC and MBA PSP results, which would improve the presentation of the information. Previous validation work had highlighted significant differences in method performance between HPLC and MBA when quantifying PSP toxins in oysters. Work conducted in Canada and Norway had indicated specific biological effects in mice in response to zinc and it was thought likely that metals in the oyster matrix might suppress PSP toxicities in the MBA method, especially as it was known that levels of zinc were approximately ten times higher in oysters than in other shellfish species.

1.42 The COT accepted the evidence that MBA analysis of Pacific and native oysters (containing naturally high concentrations of zinc) significantly underestimated PSP toxicity, whereas, higher concentrations of zinc did not have any effect on the performance of the HPLC method. The COT agreed the HPLC method would provide a higher level of public protection and, given its greater accuracy, would be a more appropriate method to use for oysters in the monitoring programme.

1.43 The COT considered a draft report on refinement and validation of the HPLC method for king and queen scallops. As the refined method was so far validated in only a single laboratory, it would be desirable to obtain further inter-laboratory validation. However, as the modifications were only minor amendments to the original Lawrence method and did not constitute a new method, laboratories wishing to use the technique would only need to demonstrate key performance characteristics, rather than a full new method validation exercise. It would be useful for the monitoring programme if at least

one other laboratory were able to perform the method, although this was not essential. COT agreed that the method was fit for purpose and the modified method could be supported for use as the official test for whole scallops.

1.44 The COT discussed a draft report on assessment of the HPLC method for minor clam species. It was not possible to compare the method to the MBA since no positive results for PSP toxins had been found using the MBA method in clams. Therefore, a method verification approach had been adopted based on previous HPLC validation work on other major shellfish species including razor clams and hard clams in which results were compared to those from the MBA method. There was generally good agreement between the two methods for clams. COT agreed with the conclusions of the report. In "surf clams", there was evidence of toxic conversion to decarbamoyl analogues even in homogenised flesh (which confirmed results previously noted in a Portuguese study). COT agreed that if the decarbamoyl toxins were not detected by HPLC, then, there would be confidence that there was no risk of paralytic shellfish poisoning. These data supported use of the HPLC method as the official test for minor clam species.

Para-occupational exposure to pesticides and health outcomes other than cancer

1.45 Following up a recommendation from an earlier statement by the Committees on Toxicity and Carcinogenicity (COT and COC), COT carried out a review of the epidemiological literature on para-occupational exposure to pesticides and health. In this context, para-occupational exposure was defined as exposure which occurs in household members who live with an occupationally exposed worker, but who are not themselves occupationally exposed. Such exposure might occur, for example, when laundering contaminated clothing, or through contact with contaminated surfaces such as taps that have been handled by the exposed worker.

1.46 The review was restricted to health outcomes other than cancer. Possible risks of cancer were considered in a parallel review conducted by COC[a].

1.47 A total of 53 relevant published reports were considered by the Committee, covering neurological and mental health, reproductive health, respiratory health, and possible effects on the eye. In addition, a number of studies were identified, which provided information on levels of para-occupational exposure, assessed by measurement of pesticides or their breakdown products in the blood or urine of people living with farmers or pesticide operators. In these investigations, the highest para-occupational exposures were all lower than the highest occupational exposures recorded in the same study.

[a] Committee on Carcinogenicity of Chemicals in Food Consumer Products and the Environment. Statement on the systematic review of epidemiological literature of para-occupational exposure to pesticides and health outcomes, CC/11/S1 http://www.iacoc.org.uk/statements/documents/ParaoccupationalpesticideCOCfinalstatement2011Editedwlogo.pdf

1.48 The Committee found that the available epidemiological evidence had major limitations. Most studies had investigated exposure to 'pesticides', or to classes of pesticides, such as insecticides, fungicides or herbicides. These broad categories cover a wide variety of chemical compounds which differ from each other substantially in their toxicology, and which therefore would be expected to have different health effects. Combining diverse compounds in a single exposure category would tend to obscure any adverse effects that they produced. At the same time, in studies where exposures to specific compounds were investigated, the numbers of individuals exposed to any one chemical were small, which again limited ability to detect adverse effects.

1.49 In most studies, exposure was self-reported, and in some cases this may have led to bias from errors of recall.

1.50 Selective publication of studies, or of positive findings within studies, may have distorted the overall balance of evidence in the literature.

1.51 Where positive findings were reported, they had often emerged from large analyses in which multiple associations between exposures and health outcomes had been explored, with no strong reason to expect the specific associations that were observed. Such findings can be given little weight unless they are confirmed in other independent studies.

Conclusions

1.52 The Committee reached the following conclusions.

i) Epidemiological studies of para-occupational exposure to pesticides allow investigation of health outcomes that cannot readily be addressed in relation to occupational exposure – for example, possible effects on brain development and allergic disease in children. Moreover, para-occupational exposures may be higher than those that occur in bystanders and residents[b], making it easier to detect adverse effects where they occur (because risks will tend to be higher).

ii) Despite these theoretical advantages, currently available studies of para-occupational exposure to pesticides are limited in number, scope and design, and do not provide strong pointers to any health hazard, either from broad classes of pesticide or from specific compounds.

iii) Most worthy of further investigation are a possible association of miscarriage with para-occupational exposure to fungicides and phenoxy herbicides, and further research on allergic diseases such as asthma and hay fever, in children of farmers who use pesticides. However, studies of pesticides and miscarriage would be better conducted among

[b] Bystanders are persons located within or directly adjacent to an area where a plant protection product is being or has recently been applied, and whose presence is incidental and unrelated to work involving pesticides, but whose position may put them at risk of exposure. Residents are persons who live, work or attend school or any other institution adjacent to an area that is being or has been treated with a plant protection product, and whose presence is incidental and unrelated to work involving pesticides but whose position may put them at risk of exposure.

women with occupational rather than para-occupational exposure, and are more likely to be feasible in countries other than the UK.

1.53 The review did not point to any pesticides that should be a particular priority for biomonitoring studies in bystanders or residents

1.54 The COT Statement is available at: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2011/cot201105

Restriction report: proposal for a restriction: bis(2-ethylhexyl)phthalate (DEHP), benzyl butyl phthalate (BBP), dibutyl phthalate (DBP) and diisobutyl phthalate (DiBP)

Introduction

1.55 Phthalates (phthalic acid esters) are chemical compounds made from phthalic acid. They are used as plasticisers (softening agents) in PVC and other plastics, and have various industrial applications, including the manufacture of household and consumer goods such as vinyl floorings, wallpaper, furniture, paints, varnishes, cosmetics, perfumes, lubricating oils, solvents, and food packaging. They may occur as trace contaminants in food because of their widespread presence as environmental contaminants and through their release from plastic food packaging

1.56 Phthalates can interact with the hormonal (endocrine) control systems of the body, and in particular those that regulate reproductive function.

1.57 In the EU, there is legislation to ensure that materials which come into contact with food (directly or indirectly) do not transfer phthalates to food in quantities large enough to endanger human health.

1.58 The Danish Environmental Protection Agency (EPA), which is the Danish Competent Authority for REACH (Registration Authorisation and restriction of Chemicals) within the European Union (EU), recently drafted a proposal to restrict further the marketing of articles and products containing four of the phthalate esters, namely DEHP, BBP, DBP and DiBP*****.

1.59 The Committee on Toxicity (COT) was asked by the Health and Safety Executive (HSE) to advise on the risk assessment carried out by the Danish EPA.

1.60 The COT had previously considered the toxicology of a number of phthalate esters, and in May 2011 had published a statement on dietary exposure to phthalates, based on data from a Food Standards Agency (FSA) total diet study (TDS).

***** Bis(2-ethylhexyl)phthalate (DEHP), Benzyl butyl phthalate (BBP), Dibutyl phthalate (DBP) and Diisobutyl phthalate (DiBP).

http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2011/cot201104

Overview of Danish EPA Restriction Report

1.61 In their "Restriction Report", the Danish EPA estimated potential exposures to each of the four phthalate esters of concern, from a wide range of sources, including various household articles and products, dust in indoor air, and food. Estimates of the total exposures which might plausibly occur were then compared to "Derived No Effect Levels (DNELs)" for the chemicals. A DNEL is a maximum level of daily exposure at which there is reasonable confidence, based on available toxicological evidence that adverse effects on health would not occur. The authors proposed that the combined toxicity of the four phthalate esters under review could be characterised by calculations assuming "dose addition". This allowed assessment of overall risks from exposure to all four substances.

1.62 The Danish EPA concluded that there was sufficient uncertainty about the safety of potential exposures to justify further regulatory restrictions on the four phthalates. Thus, they proposed that within the EU it should not be permitted to place on the market articles intended for use indoors in unsealed applications, or that might come into direct contact with people's skin or mucous membranes, if they contained one or more of DEHP, BBP, DBP and DiBP at a concentration greater than 0.1% by weight of any plasticised material.

COT consideration and conclusion

1.63 The COT noted that the assessment of risks from combined exposures to DEHP, DBP, BBP and DiBP that was set out in the Danish Restriction Report entailed a number of conservative assumptions. These related both to levels of exposure which might reasonably be expected to occur, and also to the toxicity of one of the chemicals under consideration (DBP). In view of this conservatism, and the calculated ratios of potential exposures to DNELs, which were not so high as to be of major immediate concern, the COT judged that the risk assessment did not necessarily indicate a need for risk reduction measures beyond those that are already in place.

1.64 An alternative would be to refine the risk assessment before deciding whether additional regulatory action was appropriate. To this end, it would be most useful to collect further biomonitoring data from representative samples of people, as a means of better characterising the distribution and determinants of total exposures to phthalates in different sections (e.g. age groups) of the general population. Furthermore, if concerns about safety remained after a more refined risk assessment, there would also be value in carrying out a more thorough risk assessment for other products which might be used as substitutes should additional restrictions be imposed on DEHP, DHP, BBP and DiBP.

1.65 The COT Statement is available at:
http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2011/cot201106

WRAP risk assessment on anaerobic digestates

1.66 In February 2010 Members discussed two risk assessments carried out under the Waste And Resources Action Programme (WRAP) Confidence in Compost Programme. The draft risk assessments were on use of green composts in the Scottish livestock sector study and all composts in all agricultural sectors. The COT provided comments and observations on the two reports. These indicated a need for substantial modifications to the draft reports, and the COT wished to see the final versions of the reports before agreeing its conclusions. The Advisory Committee on the Microbiological Safety of Food (ACMSF) was also considering these two risk assessments plus a further one which only dealt with microbiological risks. The ACMSF comments were finalised in the autumn of 2010. Comments from the two Committees had been forwarded to WRAP and were informing revision of these reports.

1.67 In the meantime, WRAP had also undertaken work on anaerobic digestion, an alternative method of processing waste. The draft WRAP report on the use of anaerobic digestates in agriculture was out for consultation and the FSA had again agreed to consult ACMSF and COT on relevant sections of the report to provide the independent scrutiny that a number of stakeholders had requested. The risk assessments assumed that Publicly Available Standard (PAS) 110-compliant feedstock was being used and were intended to reflect normal conditions of use.

1.68 It was noted that the legislative position regarding the use of waste digestates on land was complex as the specific regulatory status of waste depended on various factors and, for example, could be changed by waste treatment processing. The feedstock was from commercial sources and would not contain silage. The digestate that had been used for analysis of chemical contaminants as part of the risk assessment was not yet PAS 110-compliant, as control of feedstocks had not been demonstrated, but work was being carried out towards compliance.

1.69 Chemical contaminants had been measured in composite samples so that they were representative. The chemicals analysed included polychlorinated biphenyls (PCBs), dioxins, perfluorooctanesulfonate (PFOS) and perfluorooctanoic acid (PFOA). Very few were found above the limits of detection, and thus no further risk assessment had been included in the report. The Committee considered that the sampling had been reasonably representative in that it covered 30% of the plants in England and used triplicate samples taken on two separate occasions, with only one unusual finding. Furthermore, the analyses appeared to have been well conducted. It was agreed that analysis of further samples would be useful once the digestate was PAS 110-compliant. The rationale for the choice of chemicals to be analysed was uncertain but it was possible that they were the ones considered to be of most concern by stakeholders. It seemed unlikely that some of the chemicals selected for study would be present in food at significant levels.

1.70 The digestate output was likely to show some variability because of variation in the feedstock. It would aid risk assessment to know more about what was being

digested, and whether certain types of feedstock were associated with high levels of particular chemicals. It was noted that the input was food-based but also included livestock manure, and that the food component should already be compliant with regulatory limits for contaminants.

1.71 The COT agreed that it would have been helpful to assess a greater range of pesticides and herbicides, particularly if garden waste was being included in the feedstock. It was noted that contaminating herbicides had been considered only in the context of possible damage to crops. Similarly plant alkaloids were assessed only in the context of possible harm to livestock. It would be important to know whether chemicals could be concentrated in the course of the digestion process.

1.72 The calculations in the report were not always clearly set out – for example the conversion of kg/hectare to concentration in dry matter. The use of toxic equivalency factors (TEFs) in the report was also questioned. These had been used for dioxin-like PCBs, but did not appear to have been used for the dioxins themselves.

1.73 It was unclear whether the digestate would be used on ready-to-eat crops. Consumers were advised to wash and peel vegetables but this was to address microbiological rather than chemical risks.

1.74 Exposure to allergens from the digestate was likely to be extremely low. The allergens present were expected to be high molecular weight proteins. Very little evidence was available on whether proteins could be taken up by plants, but based on their physico-chemical properties it was unlikely that proteins would be taken up by passive processes. Exposure of operators to allergens through direct contact was more likely to pose a risk. It was noted that the Committee on the Medical Effects of Air Pollutants (COMEAP) was planning to assess bio-aerosols formed from compost.

1.75 The COT considered that the approaches employed were appropriate and sufficiently rigorous to assess fully the chemical risks associated with application of PAS 110-compliant anaerobic digestates to food-producing land. However, the basis of the draft EU limits for chemicals used in the risk assessment from the draft Sewage Sludge working document (2000) and draft Biowaste Directive (EU 2001) should be checked.

1.76 The COT agreed with the conclusion of the report that risks from allergens in the food chain would be negligible, and also with its conclusions on chemical risks, although only for the range of chemicals considered in the report. COT noted that possible risks to the food chain considered in this programme of work focussed on environmental contaminants and should take greater account of pesticides and natural toxins. COT accepted the overall conclusion that any risks associated with the use of PAS 110-compliant anaerobic digestates in agriculture would be similar to those from other materials used for these purposes.

Committee procedures

EFSA opinion on statistical significance and biological relevance

1.77 The COT received a presentation on a newly released EFSA opinion on concepts related to statistical significance and biological relevance, and were invited to discuss the conclusions and recommendations of the opinion, and their relevance to evaluations conducted by the COT. The EFSA opinion had been developed to assist the EFSA Scientific Panels and Committees in assessment of biologically relevant effects. It is available at http://www.efsa.europa.eu/en/efsajournal/pub/2372.htm.

1.78 The EFSA opinion focussed on frequentist statistical techniques rather than Bayesian approaches, and aimed to guide those submitting and evaluating data. The utility of retrospective power calculations was questioned by the COT, particularly when confidence intervals were available for consideration. The COT agreed that statistical planning and appropriate model selection were important considerations when designing new studies, and that less emphasis should be placed upon reporting of statistical significance and more on estimation with confidence intervals. The COT agreed with the conclusions and recommendations of the EFSA opinion.

Horizon Scanning

1.79 At the February 2011 meeting, Members were provided with papers (TOX/2011/03 and its addendum) listing ongoing topics and potential future agenda items, of which the Secretariat was currently aware.

1.80 Ongoing items scheduled for further discussion at future meetings were identified as:

- Risk assessment of bystander/resident exposure to pesticides – joint working group with the Advisory Committee on Pesticides.
- Review of epidemiological literature on para-occupational exposure to pesticides and health outcomes.
- Waste and Resources Action Programme (WRAP).
- Use of toxicogenomics in toxicology.

1.81 Other topics that were likely to be covered included

- Results of FSA surveys to monitor the safety of food;
- EFSA guidance on risk assessment of nanomaterials;
- Methods used in the UK monitoring programme for marine biotoxins that could cause Paralytic Shellfish Poisoning (PSP).

1.82 *Interaction of caffeine and alcohol:* Following concerns that an interaction between the caffeine in energy drinks and alcohol could result in adverse behavioural or toxic effects, the FSA had asked that the COT review the

available data to establish whether there was evidence for a specific interaction, and whether risk management action might be necessary. Members suggested that in addition to combined toxicity, interactions mediated by behavioural effects (e.g. consumption of caffeine leading to higher intake of alcohol) should be considered. Since a number of studies had been published on behavioural effects, Members suggested that additional expertise in the area of experimental human psychology and psychopharmacology might be needed.

1.83 *Vitamin D:* In 2003, the Expert Group on Vitamins and Minerals had reviewed vitamin D and concluded that there was not enough information to establish a Safe Upper Level, but that a supplementary intake of 25 µg/day was unlikely to result in adverse effects. Some interested parties had criticised this amount as not being nutritionally adequate. In 2011, the Scientific Advisory Committee on Nutrition (SACN) would be commencing a review of the recommendations on vitamin D intake, and as part of this review, COT advice would be required concerning possible adverse effects of high levels of intake.

1.84 *Potassium:* As part of Government salt reduction strategy, manufacturers were being encouraged to reduce the sodium content of their products. However in some products, sodium-based ingredients are functional and have to be replaced rather than reduced or removed. In many cases, potassium-based equivalents are used, resulting in a potential increase in dietary exposure to potassium. Whilst somewhat higher potassium intakes would not be of concern for most people, some individuals with impaired kidney function need to consume a low potassium diet. The Department of Health was considering commissioning research to assess the potential increase in potassium exposure from the use of such ingredients. As part of this process it was likely that the COT would be asked to provide advice on the toxicological implications of increased potassium intake in certain sub-groups of the population.

1.85 *Consideration of whether the 10-fold uncertainty factor for interspecies extrapolation is sufficient in relation to developmental toxicity:* In 2007, the COT concluded in its report on Variability and Uncertainty in Toxicology of Chemicals in Food, Consumer Products and the Environment that ‘Data from the available research in which compounds have been studied in both animals and man suggest that the default uncertainty factor of 10 allows adequately for interspecies differences.’ However, some data, which were not discussed in the report, suggest that the 10-fold factor may not be sufficient for all of the developmental toxicants for which human data are available (e.g. thalidomide), when reference values are based on data from the two laboratory species commonly used for food chemicals – rats and rabbits – and do not take account of data from non-human primates. Members agreed that it would be useful to investigate this subject and that relevant new data should be reviewed. It was noted that human and primate data would be limited, and that comparisons of sensitivity between rodent species could also be considered.

1.86 *State of the science on novel in vitro and in vivo screening and testing methods and endpoints for evaluating endocrine disruptors:* The Organisation for Economic Co-operation and Development (OECD) had developed, validated and established guidelines for test methods to evaluate the endocrine

disrupting potential of chemicals. In order to consider the adverse effects via various hormonal pathways (previous assays focussed primarily on the estrogen, androgen and thyroid hormonal systems), the OECD had begun drafting a Detailed Review Paper (DRP), which would examine the state of the science on novel *in vitro* and *in vivo* test methods and endpoints relevant to various taxa of vertebrates, for detecting and evaluating chemical interactions and potential disturbances in various endocrine and neuroendocrine pathways. Members expressed their wish to be kept informed about progress, and to be consulted on the draft documents.

1.87 *Review of complementary feeding:* The Subgroup on Maternal and Child Nutrition (SMCN) of the Scientific Advisory Committee on Nutrition (SACN) was planning a review of complementary and young child feeding. The COT would provide input on toxicological issues. Members provided comments on the draft terms of reference, including recommendations to consider lipid soluble compounds in breast milk, and other forms of offal in addition to liver. They also observed that rates of development vary between children, and that toddlers have higher exposures to contaminants on a bodyweight basis.

1.88 *Risks to health from climate change:* A letter had been sent to the Committee chair from the Department of Health concerning the possible impacts of climate change on health within the COT's remit. Members were invited to comment on the key issues including the short, medium and long term impacts of climate change and the adaptation measures needed to minimise these impacts. It was agreed that whilst climate change has the potential to alter exposure to contaminants via food and the environment, the Committee could not identify any issues that might merit pre-emptive action. A response was sent to the Department of Health.

1.89 In discussing the balance of expertise on the Committee, it was agreed that while there was no redundant expertise on the Committee, and that most relevant areas of expertise were adequately covered by the existing membership, additional expertise might usefully cover environmental exposure assessment, mathematical modelling and experimental study designs. Expertise in psychology could be included as the need arose.

1.90 Members were invited to make suggestions for future topics and were reminded that they may draw particular issues to the attention of the Secretariat at any time. A Member suggested it would be useful to organise a joint meeting with SACN, in view of the number of topics of mutual interest.

Quinquennial Review of the COT

1.91 At the request of the FSA, the COT underwent a quinquennial review in 2011. Several members, the Chairman, the Administrative and Scientific Secretaries and a number of stakeholders were interviewed by the independent reviewer. At the June 2011 meeting Members were provided with the report of the quinquennial review and discussed its recommendations. A formal response to

the review would be sent to the General Advisory Committee on Science (GACS) and the FSA Board.

1.92 The review and the COT response are available at: http://cot.food.gov.uk/cotreports/cotquinreview/cotquinrev2011. .

Uncertainty framework from a social science perspective

1.93 In 2007 the COT published a report on Variability and Uncertainty in Toxicology of Chemicals in Food, Consumer Products and the Environment (http://cot.food.gov.uk/cotreports/cotwgreports/cotwgvut). One conclusion in the report was that that the development of a framework for transparent expression of uncertainty in hazard characterisation would enable the COT and other committees that perform toxicological evaluations to improve communication of the sources of variability and uncertainty in their risk assessments.

1.94 The FSA commissioned a research project to review existing approaches to qualitative evaluation and expression of uncertainties and assess their suitability for routine use by the COT and other committees. In consultation with the COT, the project developed a framework to make the steps of the risk assessment process easier and more transparent. It was decided that it would be helpful to develop a scale of terms describing different levels of uncertainty, with input from the FSA Social Science Research Committee (SSRC). The FSA had subsequently commissioned research to assess the COT's draft uncertainty framework from a social science perspective.

1.95 In 2011, the COT was presented with the report of the social science research. Discussions highlighted that the way uncertainty is framed (descriptive text used), as well as the context, affects how people interpret uncertainty. That is, some terms are understood to mean something in one context but would not necessarily mean the same in another context. This would make it difficult for the COT to develop consistency of wording when expressing uncertainty. For example, terms developed by the Intergovernmental Panel on Climate Change (IPCC) are not used/understood in the way that the IPPC notes/expects; people's prejudices underlie how they interpret terms. The COT noted that the context is more important than having a consistent way of expressing uncertainty.

1.96 Members affirmed it was important that the major sources of uncertainty and their potential impact on conclusions should be documented in reports, scientific papers and scientific committee opinions. It was suggested that for quantitative questions, uncertainty would best be explained by a range of values within which the parameter of interest might reasonably be expected to lie (say with 95% credibility). For qualitative questions, it might be better to express uncertainty in terms of the strength of evidence underpinning the conclusion and how easily it might be overturned by further research.

1.97 Members agreed there was no immediate need to revise the uncertainty framework in light of the report and discussions.

Working Groups and Workshops

Bystander Risk Assessment Working Group (BRAWG)

1.98 The BRAWG is a joint Working Group with the Advisory Committee on Pesticides (ACP). The COT agreed in 2009 to form this joint working group with the ACP in order to explore issues related to the assessment of risks to bystanders and residents from the application of pesticides. The Group's terms of reference are:

- To agree a definition of operators, workers, bystanders and residents
- To agree the nature of the exposures that require consideration
- To review the current approach to modelling these exposures for bystanders and residents in the light of current knowledge
- To review the approach to assessing the risk arising from these exposures in the light of current knowledge

1.99 The BRAWG held three meetings during 2011. The third meeting, in December, was an open meeting, which discussed the draft report of the Working Group. The draft report will be revised and will be considered by the full Committees during 2012.

Lowermoor Subgroup

1.100 Members had previously been informed that the deaths of two individuals who had lived in the area that received contaminated water following the 1988 Lowermoor Water Pollution Incident had been referred to the West Somerset coroner. The two individuals both had neurodegenerative disease and had been reported to have higher than usual levels of aluminium in the brain.

1.101 The COT was informed that Department of Health lawyers had advised that publication of the Subgroup's report before the Coroner's proceedings were completed could be seen as an attempt to bias the jury and this had led to a delay in publication. The inquest into the death of one individual was held in 2008 and recorded a verdict of death by natural causes. The second inquest began in November 2010 but was adjourned early in 2011

1.102 The Lowermoor Subgroup held a meeting in December 2011 to consider how to proceed in view of the long delay in reconvening the inquest and to review an update of published scientific data on aluminium. Members were informed that the Coroner had just announced that the inquest would reopen in March 2012. The Subgroup decided to delay completion of the report until after the inquest ended. It is expected that the final Subgroup report will be published in 2012.

Ongoing work

Effect of soy phytoestrogen supplementation on thyroid status and cardiovascular risk

1.103 The COT Report on Phytoestrogens and Health (2003) made research recommendations, to address which, FSA has since funded research. Research project (T05029) is a double-blind placebo-controlled crossover trial, investigating the effect of soy isoflavones on thyroid hormones in subjects with compensated hypothyroidism. The aim of the study is to determine whether soy in the diet may be clinically important in patients with compensated impairment of thyroid function.

1.104 The study is being undertaken in three independent arms and the results will be disseminated as such. Each arm is a cross-over, double-blind, placebo-controlled clinical trial involving 60 patients with compensated hypothyroidism. In all the three arms there will be a two month phase one (active or control), followed by a two month wash out period, and then a phase two crossover for a further two month period (control or active).

1.105 The COT was presented with the results from the first arm of the study, in the form of a manuscript which was subsequently published in the Journal of Clinical Endocrinology and Metabolism (Sathyapalan *et* al. 2011[c]), and with pre-publication results from the second arm.

1.106 The COT will consider results from the third and final arm of the study before concluding whether this study provides a sufficiently strong basis for issuing advice on phytoestrogen consumption to patients with compensated hypothyroidism, and whether further research is required to resolve outstanding uncertainties.

Phytoestrogens research programme

1.107 The T05 Phytoestrogen research programme was established in 1997 by the Ministry of Agriculture, Fisheries and Food (MAFF) to improve the assessment of the human health implications (risks and benefits) of dietary phytoestrogens, in order to underpin appropriate information to consumers. During 2000-2003, a COT working group reviewed the available scientific literature, the research funded in the T05 programme and the results of an external review of the T05 research programme conducted in 2001. A COT report, including recommendations for further research, was published in 2003[d]. The T05 Research Programme was subject to a further external review in 2007, together with the FSA T01 Risk Assessment Research Programme.

1.108 A strategic review within the FSA subsequently decided that the scope of the T05 programme extended to areas outwith the Agency's remit and that no

[c] http://jcem.endojournals.org/cgi/content/abstract/jc.2010-2255v1
[d] http://cot.food.gov.uk/cotreports/cotwgreports/phytoestrogensandhealthcot

further research would be funded under this programme. Any future work on the potential risks of phytoestrogens would be commissioned under the Risk Assessment programme (T01).

1.109 The COT is considering the outcomes from the studies on-going at the time of the last external review in 2007 and in combination with the previous external reviews, assessing whether overall the T05 programme met its objectives and provided the Agency with useful information and value for money. A statement will be published in 2012.

SACN Review of Vitamin D

1.110 In 2011, the Scientific Advisory Committee on Nutrition (SACN) established a Working Group to undertake a comprehensive review of vitamin D and health. The Working Group will review the Dietary Reference Values for vitamin D intake and make recommendations. The COT was asked to provide SACN with advice on the effects of high levels of vitamin D intake. The SACN review began in 2011 and the completed draft review will be subject to a period of public consultation.

1.111 Excess levels of vitamin D are associated with the occurrence of hypercalcaemia and hypercalciuria. This occurs because vitamin D promotes the absorption of calcium and resorption of bone, resulting in calcium deposition in soft tissues, diffuse demineralisation of bones and irreversible renal and cardiovascular toxicity

1.112 The effects of high levels of vitamin D intake were previously reviewed by the EU Scientific Committee on Food (SCF) in 2002 and the UK Expert Group on Vitamins and Minerals (EVM) in 2003, which respectively established a Tolerable Upper Level of 50µg/day and a Guidance level of 25µg/day. The most recent review of vitamin D was undertaken in 2011 by the US Institute of Medicine (IOM), who established an Upper Level of 100µg/day vitamin D for adults. Although various toxic endpoints were considered, all of these upper levels were set on the basis of reports of hypercalcaemia in human volunteers taking vitamin D supplements. Vitamin D exposure as a whole is complicated to assess because of the difficulties in quantifying vitamin D formed in the skin from exposure to sunlight.

1.113 The COT review commenced in 2011 and will consider the potential toxicity of vitamin D exposure as adverse effects occurring at high levels of vitamin D intake and at high blood vitamin D concentrations. The COT review will include data from epidemiology studies, human supplementation studies and animal studies as appropriate. It is hoped that the review will be submitted to SACN by the end of 2112 with further updates as required.

Toxicogenomics in toxicology

1.114 The COT's latest consideration of the use of toxicogenomic data in human health risk assessment commenced in September 2011 with discussion of a case study on DBP. It was noted that there are an exceptionally large number of toxicogenomic datasets for DBP, in contrast to most substances that might be evaluated. Even so, it was difficult to draw conclusions of relevance to risk assessment from historical toxicogenomic studies that had been designed for other purposes. Ideally, experiments would be designed to address specific questions in risk assessment, using a range of doses to support dose-response modelling.

1.115 The COT will discuss further papers in 2012 and produce a statement.

2011 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

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Dr C Baskaran BSc MSc PhD	
Dr E Cemeli BSc PhD	*(from 3 October 2011)*
Ms C Potter BSc MSc	*(from 28 November 2011)*
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Mr G Welsh BSc(Hons)	*(up to 16 July 2011)*
Miss T Gray BA(Hons)	

Declaration of COT members' interests during (2011) the period of this report
(an up-to-date version can be found on the COT website)

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

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

Dr John Foster

Personal Interest		Non Personal Interest
Shareholder and Employee AstraZeneca		**Misc** British Toxicology Society – Member of Executive Committee Society of Toxicologic Pathology - Member and Editor in Chief of journal *Toxicologic Pathology*

Dr Mark Graham

Personal Interest		Non Personal Interest
Employee AstraZeneca		None

Dr Anna Hansell

Personal Interest		Non Personal Interest
Employee Department of Epidemiology & Public Health Imperial College, London (includes Small Area Health Statistics Unit)		**Research Grant** AstraZeneca **Misc** ESRC - PhD Studentship
Shareholder Halifax		
Supporter (non-active) Greenpeace		

Professor David Harrison

Personal Interest		Non Personal Interest
Consultant University of Canberra University of Florida Quintiles		**Trustee** Medical Research Scotland Melville Trust
Shareholder Avipero		**Research collaboration** Myriad Genetics Cytosystems Genentech Somalogic Destina Ltd Antoxis Ltd Biopta Ltd

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

Professor Brian Houston

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

Professor Justin Konje

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

Professor Brian Lake

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Employee Leatherhead Food Research(LFR)		**Member** British Toxicology Society Society of Toxicology
		Member of the editorial board Food and Chemical Toxicology Xenobiotica

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

Professor Robert Smith		
Personal Interest		**Non Personal Interest**
Membership Rodenticide Resistance Action Group		**Misc** Support by Industry - Research costs for a student monitoring rodenticide resistance
Dr John Thompson		
Personal Interest		**Non Personal Interest**
None		None

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

Preface

The Committee on Mutagenicity (COM) provides advice on potential mutagenic activity of specific chemicals at the request of UK Government Departments and Agencies. Such requests generally relate to chemicals for which there are incomplete, non-standard or controversial data sets for which independent authoritative advice on potential mutagenic hazards and risks is required. Frequently recommendations for further studies are made.

During 2011, the Committee completed a strategy for testing and assessment for chemicals. This was a major task which involved a world-wide consultation with interested groups. The finalised strategy was published in the new Guidance series of statements on the COM Internet site. The COM also completed guidance for the assessment and testing of chemicals with inadequate genotoxicity data. The Committee completed a further review of genotoxicity data on Fumagillin Dicyclohexylamine.

The Committee has a number of ongoing generic reviews including the use of Quantitative Structure Activity Relationship (QSAR) approaches to mutagenicity evaluation, the genotoxicity testing and assessment of impurities, and a guidance document on the human health significance of mutagenicity. The Committee also considered the genotoxicity of nanomaterials and chlorophenols.

There was insufficient time to discuss the 2011 Horizon scanning paper which will be considered at the March 2012 meeting.

Professor P B Farmer Chair
MA DPhil CChem FRSC

COM evaluations

Fumagillin Dicyclohexylamine

2.1 Fumagillin dicyclohexylamine (fumagillin DCHA) is an antibiotic authorised for use in honey bees for the prevention of infections caused by the *Nosema apis* parasite present in the gut of infected bees (Figure 1). Fumagillin DCHA is fed to the colony in winter over a period of several weeks in a medicated syrup as a supplementary food source to eradicate the parasites. The commercial formulation of fumagillin DCHA is a stabilised water-soluble preparation, Fumidil-B (CEVA Animal Health). Fumidil-B contains the excipient polysorbate 80, sodium phosphate (anhydrous) and sodium acid phosphate (anhydrous). The veterinary medicine Marketing Authorisation Holder (MAH) is CEVA Animal Health.

2.2 The COM recommended the following testing strategy for fumagillin DCHA in 2009.

i) A further *in vivo* mutagenicity study using the same protocol used by Stanimirovic et al. (*Mutat Res* (2007) 628, 1-10) to include sampling of bone marrow for MN and chromosomal aberrations.
ii) A site of contact comet assay using gastrointestinal (stomach) tissue. (The comet assay should also include an appropriate positive control substance).
iii) If any genotoxicity is observed with fumagillin DCHA, more genotoxicity data (*in vitro* chromosomal aberration test in human lymphocytes) should be provided on dicyclohexylamine to evaluate its potential role. (Any study should also include fumagillin DCHA for quantitative comparison).

2.3 The data holder submitted two additional studies:

i) Fumagillin DCHA was tested for its ability to induce chromosome aberrations in the bone marrow of male Crl:CD-1(ICR) mice when administered orally by gavage at 25, 50 and 75 mg/kg bw/day in a dose volume of 10ml/kg water-sugar syrup solution over 7 days.

ii) Fumagillin DCHA (suspended in a sugar/water 1:1 syrup) was administered orally to groups of 5-7 male and female OF1 mice on 8 consecutive days at dose levels of 25 mg/kg bw/day, 50 mg/kg bw/day and 75 mg/kg bw/day in the main study. The animals were killed 3-6 hours after the final dose and bone marrow isolated for micronucleus determination in polychromatic erythrocytes (male and females) and stomach for comet assay (males).

2.4 The COM reached the following conclusions;

i) The newly submitted bone marrow chromosome aberrations and micronucleus tests in mice adequately addressed the data requests

agreed by COM in 2009, and reported negative results. There were limitations in the conduct of the in vivo Comet assay in mice; overall a negative result was reported.

ii) Fumagillin DCHA should be considered as an *in vitro* mutagen.

iii) The weight of evidence available to the COM supports the conclusion that fumagillin DCHA is not an *in vivo* mutagen.

2.5 The full guidance statement can be found at http://www.iacom.org.uk/statements/documents/fumagillinfinalstatement2011_002.pdf

Guidance on a Strategy for Genotoxicity Testing of Chemical Substances

2.6 The COM has a remit to provide UK Government Departments and Agencies with advice on the most suitable approaches to testing chemical substances for genotoxicity. The COM published guidance in 1981, 1989 and again in 2000. A further review was completed during 2011 and the published strategy represents the most appropriate at the time of publication.

2.7 The COM recommended a staged approach to testing:

Stage 0 consists of preliminary considerations which include physico-chemical properties of the test chemical substance, Structure Activity Relationships (SAR), and information from screening tests. However, data from SAR and screening tests should not overrule test data from adequately designed and conducted genotoxicity tests.

Stage 1 consists of *in vitro* genotoxicity tests. The COM recommends a core-test battery of the Ames test combined with the *in vitro* micronucleus test. This combination provides information on three types of genetic damage for which data are required (namely, gene mutation, chromosomal damage and aneuploidy) and gives appropriate sensitivity to detect chemical mutagens. There is no need to independently replicate adequately designed and conducted core *in vitro* tests which are either clearly negative or clearly positive. The strategy document also considers the value which can be attributed to a number of non-core *in vitro* tests.

Stage 2 consists of *in vivo* genotoxicity tests. A case-by-case strategy should be developed to answer one or more of the following specific queries;

1) Investigation of mutagenic end point(s) identified in Stage 1,
2) Investigation of genotoxicity in tumour target tissue(s),
3) Investigation of potential for germ cell genotoxicity,
4) Investigation of *in vivo* mutagenicity for chemicals, which were negative in Stage 1 but where there is high or moderate and prolonged exposure,
5) Investigation of genotoxicity in site of contact tissues.

2.8 The core tests in Stage 2 are the rodent micronucleus/chromosome aberration assays for aneuploidy and clastogenicity, the transgenic rodent gene mutation assay and the rodent Comet assay for DNA damage. Usually negative results obtained in a carefully selected *in vivo* test (possibly studying more than one endpoint and tissue) will be sufficient to address positive results found *in vitro.* However, a further test(s) may be needed if some of the genotoxic effects seen in Stage 1 *in vitro* tests had not been adequately studied *in vivo* (e.g. the chemical affects multiple mutagenic end-points), or other aspects of the genotoxic potential of the chemical had not been fully resolved (e.g. in the case where an investigation of heritable effects was required). The strategy document also considers the value which can be attributed to a number of non-core *in vivo* tests. In most instances information from core *in vivo* tests is sufficient to evaluate the *in vivo* mutagenicity of chemical substances. A supplementary *in vivo* test strategy can provide additional information on a case-by-case basis, to investigate aspects such as further characterisation of germ cell genotoxicity, and DNA adduct data which can provide information to elucidate the mode of genotoxic action of carcinogenic chemicals.

2.9 It is acknowledged that the field of genotoxicology and genotoxicity testing is rapidly developing. A short overview of possible future developments and techniques such as toxicogenomics was provided.

2.10 The full guidance statement can be found at http://www.iacom.org.uk/guidstate/documents/COMGuidanceFINAL2.pdf

Guidance on Mutagenic Hazard Assessment and a Strategy for Genotoxicity Testing of Chemicals with Inadequate Genotoxicity Data

2.11 The purpose of the COM guidance was twofold: firstly, to provide guidance on deriving preliminary conclusions on mutagenic hazard in the absence of full genotoxicity data, and secondly to provide a framework which allows the integration of existing genotoxicity data on a chemical substance with a testing strategy designed to provide data sufficient for mutagenic hazard assessment to be completed, in compliance with the COM testing strategy (see paragraph 2.7 above). This guidance should therefore be read in conjunction with the published COM guidance on a strategy for genotoxicity testing.

2.12 The preliminary hazard assessment consists of a comprehensive literature search to identify available data relevant to genotoxicity, evaluation of the quality of the data and consideration of the completeness of the overall database. The assessment can include data from both core and non-core genotoxicity tests. (A listing of core and non-core tests is provided in the guidance statement). It is important to note that a case-by-case approach is needed using expert judgement to reach conclusions on mutagenic hazard assessment and on a testing strategy to complete the assessment. The COM agreed that genotoxicity tests not included in the guidance statement were not recommended for mutagenic hazard assessment, and considered that little or no weight of evidence should be attached to tests.

2.13 A stepwise approach to genotoxicity data assessment is presented in the guidance statement. Devising a strategy for genotoxicity testing of chemicals with inadequate genotoxicity data commences with the preliminary hazard assessment. If the available evidence is insufficient to reach conclusions on mutagenic hazard, identify key data gaps, taking into account the purpose of the evaluation, and derive a plan for each stage of the COM testing strategy as appropriate (see paragraph 2.7). This may include repeating specific genotoxicity tests from each stage of the COM testing strategy and/or undertaking additional studies from Stages 1 and 2 as appropriate.

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

Ongoing Work

Use of Quantitative Structure Activity Relationships (QSARs) for Mutagenicity

2.15 The COM considered a preliminary assessment of drinking water chemicals using CAESAR and Toxtree. The Committee were unable to reach definite conclusions based on the information provided. A further paper was submitted outlining more information on these two (Q)SAR models. Members agreed that where negative predictions were made, this would provide some reassurance regarding the absence of mutagenic potential. It was also noted that Toxtree, being a rule based system, gave the reasons for its predictions. CAESAR gave the results for six other structural analogues, so some confidence could be obtained in positive predictions if the results for analogues were considered reasonable. Overall the committee agreed that it would be useful for the COM to hear a presentation from a computational toxicologist with expertise in QSARs. A presentation is due to be heard at the March 2012 COM meeting.

Genotoxicity Testing of Impurities

2.16 The Committee considered a draft guidance statement at the March, June and October 2011 meetings. A further draft paper is due for consideration at the March 2012 meeting.

Human Health Significance of Chemical Induced Mutagenicity

2.17 The Committee considered a draft guidance statement at the March 2011 meeting. The document was considered to be a good draft with the target audience being the informed lay reader. There was need for inclusion of figures to explain the involvement of mutation in disease processes and hyperlinks to

explanations of terms used in the document. A revised draft is due for consideration at the March 2012 meeting.

Genotoxicity of Nanomaterials

2.18 A detailed review paper was considered at the October 2011 meeting. A statement is currently being drafted.

Chlorophenols

2.19 A detailed review paper was considered at the October 2011 meeting. A statement is currently being drafted

2011 Membership of the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment

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Ms S Kennedy	Administrative Secretary – Health Protection Agency

Declaration of COM members' interests during (2011) the period of this report

(an up-to-date version can be found on the COM website)

Member	Personal Interest		Non-Personal Interest	
	Company	**Interest**	**Company**	**Interest**
Prof P B Farmer (Chairman)	Santander Foreign & Colonial Friends Provident Torotrak ILSI HESI EFSA	Shareholder Shareholder Shareholder Shareholder Committee Member Member of Scientific Panel	Van Geest Foundation	Research support
Dr C Allen	NONE	NONE	NONE	NONE
Dr B Burlinson	Huntingdon Life Sciences	Salary Employee Share Option Holder	NONE	NONE
Dr G Clare	Covance AstraZeneca Diageo HBOS Marks & Spencer	Consultant Shareholder Shareholder Shareholder Shareholder	NONE	NONE
Dr B M Elliott	Syngenta AstraZeneca Elliott GT Ltd Regulatory Science Associates	Pension Shareholder Director Associate	NONE	NONE
Dr D Gatehouse	GlaxoSmithKline	Pension Share Option Holder Shareholder	NONE	NONE
Mrs R Glazebrook	BT Group Lloyds TSB National Grid	Shareholder Shareholder Shareholder	NONE	NONE
Dr G Jenkins	NONE	NONE	Hoffman-LaRoche Hoffman-LaRoche Unilever CEFIC/ECETOC	Research Grant 2008 – 2010 Consultancy 2008 Research Grant 2008 - 2010 Honorarium 2008
Dr D Kirkland	Kirkland Consulting	Principal	NONE	NONE

Dr D P Lovell	National Grid plc	Shareholder	AstraZeneca National Grid plc	Spouse Shareholder Spouse Shareholder
Dr A Lynch	GlaxoSmithKline	Salary Shareholder	NONE	NONE
Dr E M Parry	F & C M & S Compass BP	Shareholder Shareholder Shareholder Shareholder	NONE	NONE
Prof D H Phillips	Aviva Banco Santander BG Group Bradford & Bingley Centrica National Grid Takeda	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultant		

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

Preface

The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) evaluates chemicals for their carcinogenic potential in humans at the request of UK Government Departments and Agencies. The membership of the Committee, agendas and minutes of meetings, and statements are all published on the internet (http://www.iacoc.org.uk/).

During 2011, the Committee held two meetings and considered a number of items. At the request of the Department for Education, we began a consideration of the relative vulnerability of children to asbestos. This will clearly be a challenging item and I am grateful to the members of the Committee for their suggestions as to how we should go about it, and of information and appropriate individuals to assist us.

The Committee also responded to a request from the Department of Health for its view on the potential effects of climate change on the risk of cancer. I am grateful again to members for the ideas they contributed in response to this request. I also recognise the continued support of the secretariat and the value of the draft papers which they provide. I look forward to working with them on new challenges in 2012.

Professor David H Phillips
BA PhD DSc FRCPath

COC evaluations

Climate change

3.1 During 2011, the COC was asked by the Department of Health to provide advice on climate change. It made a number of suggestions as to both the potential beneficial and adverse effects of climate change on the risk of cancer, as given in the table below. Any impacts on incidence of cancer due to climate change are likely to be long term, due to the protracted natural history of the disease(s).

Consequence of climate change	**Possible beneficial effect**	**Possible adverse effect**
People spend more time outdoors	More scope for exercise	Increased exposure to UV radiation leading to higher rates of skin cancer
	Increased levels of endogenous vitamin D	Increased consumption of food cooked outdoors which may contain carcinogens (eg barbecued food contains relatively high levels of nitrosamines)
	Decreased exposure to indoor air pollution	Increased exposure to outdoor air pollution
		More opportunity to smoke (no smoking ban outdoors)
Changes in air quality	Decrease in emissions due to domestic/indoor heating	Deterioration of urban air quality from industrial and traffic emissions with increasing temperatures. Effect of climate on composition of atmospheric particulates. Increase in emissions due to energy demand for widespread use of air conditioning.
Changes in food grown or available in the UK	Increased availability and consumption of fresh fruit and vegetables Changes in nutritional or residue content of food of animal origin	Increased levels of mycotoxins in food Changes in nutritional or residue content of food of animal origin Availability of different staples e.g. highly spiced foods leading to higher incidence of cancer of GI tract.
		Changes/increases in pesticide use
Spread of parasites from warmer countries	None	Increase in cancer associated with parasitic infection or use of chemicals to destroy parasites
More insect infestations indoors	None	Higher exposure to pesticides used to treat infestations

Major weather incidents e.g. flooding	None	Effects on contaminant dispersion, microorganism growth, water contamination.
Increasing salinity of groundwater and surface water as sea levels rise	None	Increased levels of salt consumption in food and water lead to increased risk of stomach cancer

Dichlorvos

3.2 Dichlorvos (2,2-dichlorovinyl dimethyl phosphate) is an insecticide acting by acetylcholinesterase inhibition. The genotoxicity and carcinogenicity of dichlorvos were evaluated by the COM in 2002, with the assistance of co-opted COC members. Since then, evaluations of dichlorvos have been performed by the US Environmental Protection Agency (EPA) and the Scientific Panel on Plant Health, Plant Protection Products and their Residues (PPR) of the European Food Safety Authority (EFSA) and there are some differences between the three groups in the conclusions on carcinogenicity.

3.3 In 2010, the Health and Safety Executive (HSE) sought the view of the COC as to whether a threshold could be assumed for the carcinogenicity of dichlorvos. Members concluded that there were not sufficient data to support the mode of action (MOA) for forestomach tumours in a US National Toxicology Programme (NTP) mouse gavage study on dichlorvos which was proposed by AMVAC Chemical Company. The Committee's position on the risk assessment of carcinogens is that there needs to be clear evidence of a MOA for tumour formation before it can move away from the default non-threshold assumption for substances that are genotoxic and carcinogenic. The evidence was insufficient in this case and, therefore, it recommended that exposure should be as low as reasonably practicable (ALARP).

3.4 AMVAC subsequently submitted a number of further comments in the form of a technical note. The COC discussed these comments at the April 2011 meeting. The note suggested that studies by Wooder and Wight (Acta Pharmacol et Toxicol, volume 48, suppl V: pp 51-55, 1981) were extremely important in demonstrating that dichlorvos does not react with DNA *in vivo*. This paper was subsequently reviewed by two members with appropriate expertise and they agreed that there was no inconsistency between the results and the conclusion of the COM that dichlorvos should be regarded as an *in vivo* mutagen at the site of contact. Overall, the COC confirmed the conclusions it had made in 2010.

Interaction between genotype and chemicals in the environment on the induction of cancer in risk assessment

3.5 In 2010, the COC considered a scoping paper which reported ongoing activity in the area of genomics, environmental exposure assessment and gene-environment interaction. The paper also discussed the advent of Genome-Wide

Association Studies (GWAS). These are non-hypothesis driven studies that examine genetic variation across a given genome and relate these variants to disease. It was agreed that the next step should be to compare, for a specific endpoint, GWAS studies and good quality studies investigating specific gene-environment interactions.

3.6 At the April 2011 meeting, the Committee discussed a paper on GWAS on bladder cancer and colorectal cancer. In response to specific questions posed in the paper, the Committee concluded as follows:

3.7 Overall, it was thought that GWAS have been useful but it would be difficult to use these data at this stage without clear understanding of the functional links and biological relevance. The research had now begun to focus on Exposure Wide Association Studies (EWAS) or the "Exposome".

3.8 The Committee was not yet clear how GWAS would inform the assessments of the COC other than on a case-by-case basis. For example, in a couple of studies, strong associations have been found between single nucleotide polymorphisms (SNPs) in or close to genes for xenobiotic metabolising enzymes and certain cancer types. This would support the involvement of environmental chemicals in the cancer process. However, there are endogenous substrates for many of these enzymes, so the findings would have to be considered within the broader context of all available information. Such studies are likely to have most impact on the assessments of the COC if the specific genes involved in the associations observed can be identified, and their biological relevance determined. The COC agreed that further development of the studies is needed and that some guidance on interpretation would be helpful.

3.9 Currently, the Committee did not consider that the findings of the GWAS described shed any light on the environmental causes of colorectal or bladder cancer. It was thought that EWAS were more likely to be useful.

3.10 Members were interested to know if GWAS could provide information about the epidemiology of cancer clusters. It was recommended that a watching brief was maintained in this area.

Municipal waste incinerators

3.11 In the late 1990s, the Committee discussed a study by the Small Area Health Statistics Unit (SAHSU) on cancer incidence near municipal waste incinerators (MWI) in Great Britain and published a statement which concluded that *'any potential risk of cancer due to residency near to a municipal solid waste incinerator was exceedingly low and probably not measurable by the most modern epidemiological techniques.''* A second statement was published in 2009 after a review of literature published since 2000 which concluded that *''there is no need to change the advice given in the previous statement in 2000, but the situation should be kept under review''*.

3.12 In 2011, the Committee considered three further papers on this topic published since the 2009 review. One reported a positive association between living near a MWI in Besancon, France and non-Hodgkin's lymphoma (NHL). The other two

studies were based in Italy and Brazil and showed a negative association between living near a MSWI and cancer incidence.

3.13 The COC recalled that it has previously seen papers on the incinerator in Besancon, France and had noted that, for many years, emissions of PCDDs and PCDFs from this incinerator were reported to be far higher than is currently permitted. The Committee noted issues with the methodology in this paper and also commented on the difficulties with histological classification of NHL. The evidence provided was considered to be weak overall. Problems were also noted in the other two studies. Overall, the Committee considered that there was no change in the position given in its previous statement.

Systematic review of the epidemiological literature on para-occupational exposure to pesticides and cancer

3.14 In 2005, the Royal Commission on Environmental Pollution (RCEP) published a report on crop spraying and the health of residents and bystanders. This recommended a "…systematic review of the literature on pesticide spraying and human health…" The COT and COC commented on the RCEP report at the request of the Department for Environment Food and Rural Affairs and the Advisory Committee on Pesticides and published a joint statement in 2006. In this, the COT agreed that an epidemiological review of paraoccupational exposure to pesticides should be undertaken. The COC was therefore asked to review the relevant epidemiological literature on cancer.

3.15 In 2010, the COC considered a systematic review of the relevant literature which included a detailed meta-analysis of the available case-control studies and began to draft a statement. This statement was completed in 2011 and the Committee agreed the following conclusions:

i) There is limited evidence for a weak positive association between para-occupational exposure of children to pesticides and haematopoietic cancer.

ii) Recent meta-analyses support an association between maternal prenatal exposure to pesticides and childhood leukaemia.

iii) There is insufficient evidence to determine whether the observed association is causal, nor the likely candidate pesticides.

iv) The conclusion reached regarding para-occupational exposure to pesticides in this statement related to the exposures considered in the relevant studies and should not be extrapolated to current exposures of residents and bystanders.

v) No specific chemicals or populations were identified that would warrant further investigation by the Advisory Committee on Pesticides at this time.

3.16 The COC statement can be found at:
http://www.iacoc.org.uk/statements/index.htm

The role of miRNA related effects and chemicals on cancer

3.17 Ribonucleic acid (RNA) has a variety of functions in a cell and is found in many organisms. RNA and deoxyribonucleic acid (DNA) differ functionally. DNA primarily serves as the storage material for genetic information. RNAs are versatile molecules capable of an array of functions. In recent years many new small functional RNAs have been found. RNA is usually thought of as messenger RNA that serves as a template for translation of genes into proteins. In contrast, functional and non-coding RNA molecules are transcribed from a DNA sequence but not translated into proteins. The encoding DNA sequence is often referred to as an RNA gene.

3.18 In 2009, the COC considered a review of the role of RNA mechanisms in cancer development. One area of particular interest was the role played by small functional RNA molecules collectively called microRNAs (miRNAs) in carcinogenesis. At the April 2011 meeting, the Committee considered a review of 25 publications which described investigations of the influence of environmental chemicals on miRNA expression in cancer. These studies were considered to give a good picture of the field although there were some uncertainties with regards to interpretation of the studies. Also, it was not clear how the role of miRNA and related effects could be incorporated into cancer risk assessments nor how it would be useful as a diagnostic tool. The Committee considered that, currently, miRNAs would be less sensitive biomarkers of exposure than DNA adducts.

Horizon scanning

3.19 Due to cancellation of the November meeting, the annual horizon scanning item was postponed to January 2012 and will be reported in the 2012 Annual Report.

Ongoing work

Alcohol attributable burden of cancer

3.20 The COC reviewed the carcinogenicity of alcoholic beverages in 1995 as part of the health input to the Interdepartmental Working Group on the Sensible Drinking Message. From 2002 to 2004, the COC conducted a further review on alcoholic beverages and breast cancer. As part of this, the Department of Health commissioned a systematic review and subsequent meta-analyses from Imperial College Department of Epidemiology and Public Health which aimed to determine the magnitude of any association between drinking alcohol and primary breast cancer and to estimate the population attributable risk (PAR). Assuming causality and that 1 unit of alcohol contains 8 g ethanol, it was calculated that 6.0% (confidence interval 3 to 9%) of breast cancers reported in the UK each year could be prevented if drinking was reduced to a very low level (i.e. less than 1 unit/week).

3.21 At the July 2011 meeting, the Committee saw a recently published paper which estimated the alcohol attributable fraction of cancer in eight European countries (Schutze M et al. British Medical Journal, volume 342:d1584 June 2011). The

proportion of cancer cases attributable to former or current alcohol use in men aged >15 years was 10% (confidence interval 7 to 13%) and in women was 3% (confidence interval 1 to 5%). For breast cancer in women, it was 5% (2-8%).

3.22 The paper was considered to be of good quality because it reports the results of a large study with a relatively good exposure assessment and stable estimates. Members were also made aware of another recent publication from a French group which found that current alcohol consumption guidelines are inadequate for the prevention of cancer and that there was no safe level of alcohol consumption. It was suggested that the Committee should issue a statement again in light of the recent publications, to make its position clear.

Asbestos

3.23 Asbestos is a well known carcinogen which can cause both mesothelioma and lung cancer. Asbestos was used in the past in the building of homes, schools and other buildings and hence there is a potential for individuals to be exposed to asbestos from this historical use. At the July meeting, the Committee was informed about an independent advisory group called the "Asbestos in Schools Steering Group" which reports to the Department for Education (DfE). The Steering Group aims to promote effective management of asbestos in schools and to contribute to the development of guidance on such management. Following discussions in this Group, the DfE had asked the Department of Health for a study of the risk of asbestos to children and the Department had facilitated a DfE request for advice from the COC on the relative vulnerability of children to asbestos.

3.24 Initially, the COC was asked to advise on the appropriate strategy to take forward a consideration of this issue. The following approach was agreed:

i) to consider the recent advice of the Health and Safety Executive's scientific advisory committee, the Working Group on Action to Control Chemicals (WATCH), on the risks from low level exposure to asbestos in adults
ii) to consider reviews of any epidemiological literature or case-studies on children exposed to asbestos, of data from developing countries where children are occupationally exposed to asbestos and the development of mesothelioma in later life, and of animal data on the comparative differences between the effects of juvenile versus adult exposure to asbestos (if available)
iii) to review information on the levels of asbestos found in school buildings so as to provide an exposure perspective to the discussions
iv) to consider differences between adults and children in respiratory physiology, immunology and dosimetry
v) to co-opt experts from fields such as juvenile respiratory physiology, differences in inflammatory cell involvement between adults and children in the responsiveness to inhaled fibres, or asbestos epidemiology or pathology.

3.25 A statement is expected in 2012.

The carcinogenicity of carbon nanotubes

3.26 Carbon nanotubes (CNT) are rolled up sheets of carbon atoms only one-atom thick which are densely packed in a honeycomb crystal lattice. They are extremely strong, biopersistent materials which have good thermal and electrical conductivity. There is some concern that carbon nanotubes might have carcinogenic potential analogous to asbestos and in 2010 the COC heard a presentation from Professor Ken Donaldson of Edinburgh University on his work on CNT and discussed this issue with him. In 2011, the COC discussed a then pre-publication paper sent by Professor Donaldson on "Length dependent retention of carobn nanotubes in the pleural space of mice inititates sustained inflammation and progressive fibrosis on the parietal pleura (Americal Journal of Pathology, volume 178(6): pp 2587-2600, June 2011). The Committee considered this to be useful and discussed how it could help with the performance of risk assessments. It expressed continued interest in this work.

Guidance statements

3.27 During 2010, the COC adopted a proposal to change the way in which technical guidance on the risk assessment of carcinogens is presented on the COC website. At present, guidance is presented in a stand-alone booklet and is also spread throughout minutes and certain statements, which has several drawbacks. The proposed changes aim to improve accessibility of up-to-date advice, ease timely review, and make it easier to reference specific parts of COC guidance. The new system will comprise an overarching statement which will provide an 'executive summary' of the advice, and a series of guidance statements on specific aspects of the risk assessment of carcinogens. The overarching statement will undergo regular updates as each detailed guidance statement is revised to reflect the best available scientific practice as it evolves.

3.28 During 2011, the COC made progress with the overarching statement, introducing new concepts such as the Mode of Action, Human Relevance Framework and Margin of Exposure. In the context of this guidance statement, the Committee considered risk assessment paradigms used by different organisations. These describe the individual steps in the risk assessment process. The COC decided to base its paradigm on one published by the US National Academy of Sciences in 1983 which specifies the different stages as hazard identification, hazard characterisation, exposure assessment and risk characterisation.

3.29 The overarching guidance statement will be published in 2012.

2011 Membership of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

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Professor of Environmental Carcinogenesis, King's College London

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Dr L Hetherington BSc PhD	Scientific – Health Protection Agency
Mr J Battershill BSc MSc	Scientific– Health Protection Agency
Ms S Kennedy	Administrative Secretary – Health Protection Agency

Declaration of COC members' interests during (2011) the period of this report

(an up-to-date version can be found on the COC website)

Member	Personal Interest		Non-personal Interest	
	Company	Interest	Company	Interest
Professor D H Phillips (Chairman)	Aviva Banco Santander BG Group Bradford & Bingley Centrica National Grid Takeda	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultancy		
Dr C Allen	NONE	NONE	NONE	NONE
Prof A Boobis OBE	Bank Santander Barclays Bank BG Group BT Group Centrica Iberdrola SA National Grid Lloyds Endura Fine Chemicals Astra Zeneka GlaxoSmithKline DuaneMorris	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultancies	Food Standards Agency Department of Health Health Protection Agency Medical Research Council Medical Research Council GlaxoSmithKline ILSI, ILSI HESI & ILSI Europe Board of Trustees/ Directors ILSI HESI Risk 21 project ILSI HESI, ILSI Europe & ILSI Research Foundation Working Groups on generic risk assessment issues. JMPR JECFA (vet	Research Contracts PhD studentships Trustee/Director (non-remunerated) (past Chair of HESI) Co-Chair Member Chair/Member

			drugs) EFSA CONTAM Panel (Panel on chemical contaminants in the food chain) EFSA PPR Panel Working Groups on Cumulative Assessment Groups for Pesticides; Risk Assessment of Pesticide Metabolites EFSA working group on Identification of Emerging Risks EFSA Scientific Committee Working Group on Threshold of Toxicogical Concern DG SANCO SCHER Working Group on Mixtures of Chemicals WHO IPCS Working Groups on Chemical Mixtures and on Mode of Action FP7 COSMOS Project Scientific Advisory Board of FP6/7 projects: PREDICT – IV ACROPOLIS and HEROIC Science Advisory Board, Swiss Centre for Applied Human Toxicology, Basel, Switzerland.	
Dr P Carthew	Unilever	Salary	Gwathmey, Cambridge USA	Consultancy work

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

Dr David Lovell	National Grid plc Pfizer	Shareholder Shareholder	AstraZeneca National Grid plc	Spouse shareholder
Dr B G Miller	(Iberdrola SA)	Shareholder	NONE	NONE
Dr Christopher Powell	GlaxoSmithKline	Shareholder and salary	NONE	NONE
Dr P Vineis	NONE	NONE	NONE	NONE
Dr N Wallis	Pfizer Merck Serona SA, Geneve	Shareholder Salary	NONE	NONE
Dr Lindsay Wright	AstraZeneca	Salary and shareholder	NONE	NONE

ANNEX 1 - Terms of Reference

To advise at the request of:

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

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

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

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

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

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

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

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

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

Public service values

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

- observe the highest standards of **impartiality**, **integrity** and **objectivity** in relation to the advice they provide and to the management of their Committee;
- be **accountable**, through the Chair of the Food Standards Agency and the Chief Medical Officer, to Ministers, Parliament and the public for its activities and for the standard of advice it provides;
- in accordance with Government policy on **openness**, fully comply with the Freedom of Information Act 2000[5]

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

Standards in Public Life

Members are expected to:

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

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

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

- follow the Seven Principles of Public Life (see overleaf) set out by the Committee on Standards in Public Life[6];

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

[6] http://www.public-standards.gov.uk/

Selflessness

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

Integrity

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

Objectivity

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

Accountability

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

Openness

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

Honesty

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

Leadership

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

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

Role of Members

Members have collective responsibility for the operation of their Committee. Members are appointed as individuals to fulfil the role of their respective Committees, not as representatives of their particular profession, employer or interest group and have a

duty to act in the public interest. Members are appointed on a personal basis, even when they are members of stakeholder groups and organisations. If a member declares an organisation's view rather than a personal view they should make it clear at the time of declaring that view.

Members must:

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

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

If members believe the committee's method of working is not rigorous or thorough enough, they have the right to ask that any remaining concerns they have be put on the record.

Individual members should inform the Chair (or the Secretariat on his or her behalf) if they are invited to speak in public in their capacity as a Committee member.

Communications between members and the Food Standards Agency (FSA) Board, CMO and/or Ministers will generally be through the Chair except where the Chair has agreed that an individual member should act on its behalf. Nevertheless, any member has the right of access to the FSA Board and/or the CMO on any matter that he or she believes raises important issues relating to his or her duties as a Committee member. In such cases the agreement of the rest of the Committee should normally be sought.

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

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

[7]Currently located at: http://www.bis.gov.uk/assets/biscore/goscience/c/cop-scientific-advisory-committees.pdf

Role of the Chair

The Chair has particular responsibility for providing effective leadership on the issues above. In addition, the Chair is responsible for:

- ensuring that the Committee meets at appropriate intervals,
- ensuring that the minutes of meetings accurately reflect proceedings and any reports to the FSA Board and/or Ministers accurately record the decisions taken
- ensuring that where appropriate, the views of individual members have been recorded;
- representing the views of the Committee to the general public;
- ensuring that new members are briefed on appointment (and their training needs considered), and providing an assessment of their performance, on an annual basis or when members are considered for re-appointment to the Committee or for appointment to the board of some other public body.
- providing urgent advice to the FSA and HPA on issues within the remit of the Committee, in liaison with the Secretariat,

Role of the Deputy Chair

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

Role of the Secretariat

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

The Secretariat is also a source of advice and guidance to members on procedures and processes.

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

Role of the Assessor

Meetings of the Committee (and working groups) may be attended by Assessors. The Assessors are nominated by, and drawn from, the Agencies and Departments that sponsor the Committee, receive its advice, or have other relevant policy interests.

Assessors are not members of the Committee and do not participate in Committee business in the manner of members.

The role of an Assessor is to keep their parent Department or Agency informed about the Committee's work and act as a conduit for the exchange of information. They do this by:

- advising the Committee on relevant policy developments and the implications of Committee proposals;
- informing the Committee work through the provision of information
- being informed by the Committee on matters of mutual interest.
- sharing with the Secretariat the responsibility of ensuring that information is not needlessly withheld from the Committee. Assessors should make the Committee aware of the existence of any information that has been withheld from the Committee on the basis that it is exempt from disclosure under Freedom of Information legislation unless that legislation provides a basis for not doing so.
- ensuring that their parent Department or Agency is promptly informed of any matters which may require a response from Government.

Role of other Officials, Invited Experts and Contractors

Officials from Government Departments (not departmental assessors), Regulatory Agencies and Devolved Administrations may be called upon to advise the Committee on relevant developments in order to help the Committee formulate its advice.

Invited experts and contractors may also bring particular technical expertise, which may be requested by the Committee on some occasions.

In the event of an official, invited expert or contractor not being able to attend written submissions may be sent via the Secretariat.

Role of Observers

Members of the public and other interested parties may attend meetings as observers. However, they should not attempt to participate in Committee discussions.

If an interested party wishes to provide information relevant to a topic for consideration by the Committee, they should be submitted in writing to the Secretariat at **least** seven(7) working days before the meeting. The Secretariat will discuss with the Chair the most appropriate way to present the information to the committee and the Chair's decision will be final.

Observers who have submitted information in advance of the meeting **may** be invited to provide further explanation or to make brief comments at the discretion of the Chair.

Observers and/or organisations must not interfere in the work of the Secretariat or input from invited experts, contractors, officials from Government Departments and Agencies in any way which, in the view of the Chair, constitutes harassment and/or might hinder the work of the Committee. Observers and/or organisations must allow

other observers and other interested parties to attend items free from interference before, during and after a meeting.

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

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

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

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

Declaration of Members' Interests

Definitions

In this Code, 'the industry' means:

- Companies, partnerships or individuals who are involved with the production, manufacture, sale or supply of products subject to the following legislation;

  General Food Regulations 2004

  The Food Safety Act 1990 (Amendment) Regulations 2004

  The Medicines Acts 1968 and 1971, 1981, 1986 & 2003

  The Food and Environmental Protection Act 1985

  The Consumer Protection Act 1987

  The Cosmetic (Safety) (Amendment) Regulations 2008

  Registration, Evaluation, Authorisation and Restriction of Chemicals (EC1970/2006)

- Trade associations representing companies involved with such products;

- Companies, partnerships or individuals who are directly concerned with research, development or marketing of a product which is being considered by

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

- 'the Secretariat' means the Secretariat of the COC, COM and COT;

- 'the Agency' means either the Food Standards Agency or the Health Protection Agency; and

- references to "member(s)" includes the Chair.

Different types of Interest

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

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

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

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

Personal Interests

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

- **Consultancies and/or direct employment:** any consultancy, directorship, position in or work for industry which attracts regular or occasional payments in cash or kind;

- **Fee-Paid Work:** any work commissioned by industry for which the member is paid in cash or kind;

- **Shareholdings:** any shareholding in or other beneficial interest in shares of industry. This does not include shareholdings through unit trusts or similar arrangements where the member has no influence on financial management;

- **Membership or Affiliation:** any membership role or affiliation that you or a close family member has to clubs or organisations with an interest or involvement in the work of the Agency.

Non-Personal Interests

A non-personal interest involves payment which benefits the organisation in which the member works, but is not received by the member personally. The main examples are:

- **Fellowships:** the holding of a fellowship endowed by industry;

- **Support by Industry:** any payment, other support or sponsorship which does not convey any pecuniary or material benefit to a member personally, but which does benefit their position or organisation, e.g.

  i) a grant for the running of a unit or department for which the member is responsible;

  ii) a grant or fellowship or other payment to sponsor a post or a member of staff or a post graduate research programme for which the member is responsible. This does not include financial assistance for students;

  iii) the commissioning of research or other work by, or advice from, staff who work in a unit for which the member is responsible.

Members are under no obligation to seek out knowledge of work done for, or on behalf of, the industry or other relevant bodies by departments in which they work, if they would not normally expect to be informed.

- **Trusteeships**: where a member is a trustee of a charity with investments in industry, the Secretariat can agree with the member a general declaration to cover this interest rather than draw up a detailed portfolio.

At meetings members are required to declare relevant interests and to state whether they are personal or non-personal interests and whether they are specific or non-specific 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 non-personal*, 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

[8] Guidance suggests close family members include personal partners, parents, children (minor and adult), brothers, sisters and the personal partners of any of these.

discussion and determination of the issue and it should be recorded in the minutes of the meeting.

Withdrawal from meetings

If a declaration of interest has been made and the Committee decides that the member should not participate in the discussion and should withdraw from the meeting (even if held in public) and it should be recorded in the minutes of the meeting.

The Chair may first allow them to make a statement on the item under discussion.

Personal liability of Committee members

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

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

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

1. Subject as provided in paragraph 3 of this document, the Food Standards Agency hereby undertakes with the Members[10] of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment ("the Members") to indemnify them against all liability in respect of any action or claim which may be brought, or threatened to be brought, against them either individually or collectively by reason of or in connection with the performance of their duties as Members, including

[9] Paragraph 40 Code of Practice for Scientific Advisory Committees http://www.bis.gov.uk/assets/biscore/goscience/c/cop-scientific-advisory-committees.pdf

[10] Members of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment also includes members of Working Groups and other *Ad Hoc* expert groups of that Committee.

all costs, charges and expenses which the Members may properly and reasonably suffer or incur in disputing any such action or claim.

2. The Members shall as soon as practicable notify the Food Standards Agency if any action or claim is brought or threatened to be brought against them in respect of which indemnity may be sought pursuant to paragraph 1, and if an action or claim is brought, the Food Standards Agency shall be entitled to assume the defence. The Agency shall notify the Members as soon as practicable if it intends to assume the defence and the Members shall then provide to the Agency such information and assistance as it shall reasonably request, subject to all out of pocket expenses properly and reasonably incurred by them being reasonably reimbursed. The Food Standards Agency shall, to the extent reasonable and practicable, consult with and keep the Members informed as and when reasonably requested by the Members in respect of any action or claim. If the Food Standards Agency does not assume the defence of such action or claim, the Members shall keep the Agency fully informed on its progress and any consequent legal proceedings and consult with the Agency as and when required concerning the action or claim.

3. The indemnity contained in paragraph 1 shall not extend to any losses, claims, damages, costs, charges, expenses and any other liabilities:

(a) in respect of which the Members are indemnified by or through any defence organisation or insurers or;

(b) which may result from bad faith (including dishonesty), wilful default or recklessness on the part of the Members; or

(c) which may result from any of the following circumstances:

(i) any settlement made or compromise effected on behalf of the Members of any action or claim brought, or threatened to be brought, against the Members; or

(ii) any admission by the Members of any liability or responsibility in respect of any action or claim brought, or threatened to be brought, against them; or

(iii) Members taking action that they we were aware, or ought reasonably to have been aware, might prejudice the successful defence of any action or claim, once the Members had become aware that such an action or claim had been brought or was likely to be brought.

ANNEX 3 – Openness

Introduction

1. The Committee on Toxicity (COT) and its sister committees the Committee on Mutagenicity (COM) and Committee on Carcinogenicity (COC) are non-statutory independent scientific advisory committees which advise the Chair of the Food Standards Agency and the Chief Medical Officers (for England, Scotland, Wales and Northern Ireland) and, through them, the Government on a wide range of matters concerning chemicals in food, consumer products and the environment.

2. The Government is committed to make the operation of scientific advisory committees such as the COT/COM/COC hereafter referred to as "the Committee" more open and to increase accountability. The Committee is aware that the disclosure of information that is of a confidential nature and is communicated in circumstances importing an obligation of confidence is subject to the common law of confidentiality. There are some circumstances making disclosure of confidential information lawful for example, where the individual to whom the information relates has consented; where disclosure is in the public interest; and where there is a legal duty to do so. However, guidance is set out in the Freedom of Information Act 2000[11] which gives any person legal rights of access to information which is held by a public authority.

3. The Committee has agreed to hold open meetings as standard practice. Interest groups, consumer organisations etc can attend (subject to the appropriate procedures for handling commercially sensitive information and research not in the public domain, paragraphs 9-15 refer).

4. The Committee appoints lay/public interest member(s) to help to increase public scrutiny of Committee business.

5. The Committee has agreed to the publication of agendas, draft and finalised minutes, discussion papers and statements on the internet.

6. Statements will summarise all the relevant data, such as information regarding potential hazards/risks for human health in respect of the use of products and chemicals, and any recommendations for further research.

7. The Committee will be asked for an opinion based on the data available at the time of consideration. It is recognised that, for many chemicals, the toxicological information is incomplete and that recommendations for further research to address these gaps may form part of the Committee's advice

8. The release of documents (papers, minutes and statements) where the Committee has agreed an opinion on the available unpublished data but where further additional information is required in order to finalise the Committee's conclusions, needs to be considered on a case-by case basis. The relevant considerations include the likelihood that such additional data would alter the Committee's conclusion, any

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

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 2010/11 the budget for the COT, excluding Secretariat resources was £40,000.00. Costs were met by the Food Standards Agency (FSA).

19. Committee members may claim a fee for Committee meetings:

COC and COM Committee Chair £198 per day

COC and COM Committee Member £153 per day
COT Committee Chair £205 per day
COT Committee Member £160 per day

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

Review of fee rates

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

Travel and other expenses

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

Working Groups

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

Terms and conditions of appointment

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

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

25. The COC/COM/COT Chair must also be available for a number of other activities including: attending, with the FSA Chief Scientist, the FSA Board's annual discussion of the Agency's science; engaging with the media on any high-profile relating to the Committee's work, and discussion with the Agency Chief Scientist and GACS Secretariat in planning and developing the Committee's work (including

discussing and agreeing with the Agency's Chief Scientist a framework for providing assurance on the work of the Scientific Advisory Committees in providing advice to the Agency). It is expected that these additional activities might require 5-10 days input per year.

Feedback on performance

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

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

ANNEX 4 – Good Practice Agreement for Scientific Advisory Committees

Introduction

1. *Guidelines 2000: Scientific Advice and Policy Making*[12] set out the basic principles which government departments should follow in assembling and using scientific advice, thus:

   - think ahead, identifying the issues where scientific advice is needed at an early stage;
   - get a wide range of advice from the best sources, particularly where there is scientific uncertainty; and
   - publish the scientific advice they receive and all the relevant papers.

2. The *Code of Practice for Scientific Advisory Committees*[13] (revised in December 2007) provided more detailed guidance specifically focused on the operation of scientific advisory committees (SACs). The Agency subsequently commissioned a *Report on the Review of Scientific Committees*[14] to ensure that the operation of its various advisory committees was consistent with the remit and values of the Agency, as well as the Code of Practice.

3. The Food Standards Agency's Board has adopted a **Science Checklist** to make explicit the points to be considered in the preparation of papers dealing with science-based issues which are either assembled by the Executive or which draw on advice from the Scientific Advisory Committees.

4. Scientists who serve on a scientific advisory committee which advises the Agency are expected to comply with the **Universal Ethical Code** for Scientist, launched by the Government's Chief Scientific Adviser in March 2007.

5. The Board welcomed a proposal from the Chairs of the independent SACs to draw up Good Practice Guidelines based on, and complementing, the Science Checklist.

6. These Guidelines have been developed by nine advisory committees:

Advisory Committee on Animal Feedingstuffs[15]
Advisory Committee on Microbiological Safety of Foods
Advisory Committee on Novel Foods and Processes
Advisory Committee on Research (disbanded in 2007)
Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment[16]

[12] Guidelines on Scientific Analysis in Policy Making, OST, October 2005. Guidelines 2000: Scientific advice and policy-making. OST July 2000
[13] Code of Practice for Scientific Advisory Committees, OST December 2001
[14] Report on the Review of Scientific Committees, FSA, March 2002
[15] Joint FSA/Defra Secretariat, FSA lead

Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment[17]
Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment[18]
Scientific Advisory Committee on Nutrition[19]
Spongiform Encephalopathy Advisory Committee[20]

7. These committees share important characteristics. They:
   - are independent;
   - work in an open and transparent way; and
   - are concerned with risk assessment not risk management.

8. The Guidelines relate primarily to the risk assessment process since this is the committees' purpose. However, the Agency may wish on occasion to ask the independent scientific advisory committees whether a particular risk management option is consistent with their risk assessment.

9. Twenty seven 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.

10. This list of principles will be reconsidered by each committee annually as part of the preparation of its Annual report, and will be attached as an Annex to it.

Principles

Defining the issue

1. The FSA will ensure that the issue to be addressed is clearly defined and takes account of stakeholder expectations. The committee Chair will refer back to the Agency if discussion suggests that a re-definition is necessary.

Seeking input

2. The Secretariat will ensure that stakeholders are consulted at appropriate points in the committee's considerations and, wherever possible, SAC discussions should be held in public.

3. The scope of literature searches made on behalf of the committee will be clearly set out.

[16] Joint FSA/HPA Secretariat, HPA lead
[17] Joint FSA/HPA Secretariat, HPA lead
[18] Joint FSA/HPA, FSA lead
[19] Joint FSA/DH Secretariat
[20] Joint Defra/FSA/DH Secretariat

4. 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.

5. Data from stakeholders will be considered and weighted according to quality by the committee.

6. Consideration by the secretariat and the Chair will be given to whether expertise in other disciplines will be needed.

7. Consideration will be given by the Secretariat or by the committee to whether other scientific advisory committees need to be consulted.

Validation

8. Study design, methods of measurement and the way that analysis of data has been carried out will be assessed by the committee.

9. If qualitative data have been used, they will be assessed by the committee in accordance with the principles of good practice, e.g. set out in guidance from the Government's Chief Social Researcher[21].

10. Formal statistical analyses will be included wherever possible. To support this, each committee will have access to advice on quantitative analysis and modelling as needed.

11. 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.

12. The list of references will make it clear which references have either not been subject to peer review or where evaluation by the committee itself has conducted the peer review.

Uncertainty

13. When reporting outcomes, committees 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.

14. Any assumptions made by the committee will be clearly spelled out, and, in reviews, previous assumptions will be challenged.

[21] There is of guidance issued under the auspices of the Government's Social Research Unit and the Chief Social Researcher's Office (Quality in Qualitative Evaluation: A Framework for assessing research evidence. August 2003. www.strategy.gov.uk/downloads/su/qual/downloads/qqe-rep.pdf and The Magenta Book. www.gsr.gov.uk/professional_guidance/magenta_book/guidance.asp).

15. Data gaps will be identified and their impact on uncertainty assessed by the committee.

16. An indication will be given by the committee about whether the database is changing or static.

Drawing conclusions

17. The committee will be broad-minded, acknowledging where conflicting views exist and considering whether alternative hypotheses fit the same evidence.

18. Where both risks and benefits have been considered, the committee will address each with the same rigour.

19. Committee 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.

20. The committee'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.

21. Committees will make recommendations about general issues that may have relevance for other committees.

Communicating committees' conclusions

22. Conclusions will be expressed by the committee in clear, simple terms and use the minimum caveats consistent with accuracy.

23. It will be made clear by the committee where assessments have been based on the work of other bodies and where the committee has started afresh, and there will be a clear statement of how the current conclusions compare with previous assessments.

24. The conclusions will be supported by a statement about their robustness and the extent to which judgement has had to be used.

25. As standard practice, the committee secretariat will publish a full set of references (including the data used as the basis for risk assessment and other committee 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.

26. The amount of material withheld by the committee 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.

27. Where proposals or papers being considered by the Board rest on scientific evidence, the Chair of the relevant scientific advisory committee (or a nominated expert member) will be invited to the table at Open Board meetings to provide this assurance and to answer Members' questions on the science. To maintain appropriate separation of risk assessment and risk management processes, the role of the Chairs will be limited to providing an independent view on how their committee's advice has been reflected in the relevant policy proposals. 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.

Universal Ethical Code for Scientists

The Universal Ethical Code for Scientists, developed by the Government Chief Scientific Adviser, is a public statement of the values and responsibilities of scientists. The term 'scientists' means anyone whose work uses scientific methods, including social, natural, medical and veterinary sciences, engineering and mathematics.

Rigour, respect and responsibility: A universal ethical code for scientists

Rigour, honesty and integrity

- Act with skill and care in all scientific work. Maintain up to date skills and assist their development in others.
- Take steps to prevent corrupt practices and professional misconduct. Declare conflicts of interest.
- Be alert to the ways in which research derives from and affects the work of other people, and respect the rights and reputations of others.

Respect for life, the law and the public good

- Ensure that your work is lawful and justified.
- Minimise and justify any adverse effect your work may have on people, animals and the natural environment.

Responsible communication: listening and informing

- Seek to discuss the issues that science raises for society. Listen to the aspirations and concerns of others.
- Do not knowingly mislead, or allow others to be misled, about scientific matters. Present and review scientific evidence, theory or interpretation honestly and accurately.

You can read the full version of the Code at:
http://www.food.gov.uk/science/researchpolicy/commswork/ethcode

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 dose-response 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 *non-genotoxic* carcinogens which act through other mechanisms. The activity of genotoxic carcinogens can often be predicted from their chemical structure - either of the parent compound or of active metabolites (qv). Most chemical carcinogens exert their effects after prolonged exposure, show a dose-response relationship and tend to act on a limited range of susceptible target tissues. Carcinogens are sometimes species or sex-specific and the term should be qualified by the appropriate descriptive adjectives to aid clarity. Several different chemical and other carcinogens may interact, and constitutional factors (genetic susceptibility, hormonal status) may also contribute, emphasising the multifactorial nature of the carcinogenic process.

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

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

Cell transformation: The process by which a normal cell acquires the capacity for neoplastic growth. Complete transformation occurs in several stages both *in vitro* and *in vivo*. One step which has been identified *in vitro* is 'immortalisation' by which a cell acquires the ability to divide indefinitely in culture. Such cells do not have the capacity to form tumours in animals, but can be induced to do so by extended passage *in vitro*, by treatment with chemicals, or by transfection with oncogene DNA. The transformed phenotype so generated is usually, but not always, associated with the ability of the cells to grow in soft agar and to form tumours when transplanted into animals. It should be noted that each of these stages of transformation can involve multiple events which may or may not be genetic. The order in which these events take place, if they occur at all, *in vivo* is not known.

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

Chromosome: In simple prokaryotic organisms, such as bacteria and most viruses, the chromosome consists of a single circular molecule of DNA containing the entire genetic material of the cell. In eukaryotic cells, the chromosomes are thread-like

structures, composed mainly of DNA and protein, which are present within the nuclei of every cell. They occur in pairs, the numbers varying from one to more than 100 per nucleus in different species. Normal somatic cells in humans have 23 pairs of chromosomes, each consisting of linear sequences of DNA which are known as genes (qv).

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

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

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

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

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

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

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

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

Cohort study: (Synonyms - follow-up, longitudinal study) The study of a group of people defined at a particular point in time (the cohort), who have particular characteristics in common, such as a particular exposure. They are then observed over a period of time for the occurrence of disease. The rate at which the disease develops in the cohort is compared with the rate in a comparison population, in which the characteristics (e.g. exposure) are absent.

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

Confounding variable: (synonym - confounder) An extraneous variable that satisfies BOTH of 2 conditions: (1) it is a risk factor for the disease under study (2) it is associated with the study exposure but is not a consequence of exposure. For example cigarette smoking is a confounding variable with respect to an association

between alcohol consumption and heart disease. Failure to adjust for a confounding variable results in distortion of the apparent magnitude of the effect of the exposure under study. (In the example, smoking is a risk factor for heart disease and is associated with alcohol consumption but is not a consequence of alcohol consumption.)

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

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

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

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

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

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

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

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

Dominant lethal assay: See Dominant Lethal mutation.

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

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

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

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

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

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

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

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

Erythrocyte: Red blood cell.

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

Exogenous: Arising outside the body.

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

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

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

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

Forestomach: (See glandular stomach).

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

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

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

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

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.

LC_{50}: The theoretical lethal concentration for 50% of a group of organisms

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

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

Ligand: A molecule which binds to a receptor.

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

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

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

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

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

Malignancy: See 'tumour'.

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

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

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

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

Metabolic activation system: A cell-free preparation (e.g. from the livers of rats pre-treated 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 proto-oncogene).

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).

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 sub-units 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 self-destruction if too much DNA damage has occurred.

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

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

TDI: See 'Tolerable Daily Intake'.

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

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

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

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

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

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

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

Toxicogenic: producing or capable of producing a toxin.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Xenobiotic: A chemical foreign to the biologic system.

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

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ANNEX 7 – Previous Publications

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

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

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

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

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

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

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

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

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

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

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

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

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[++]

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)[+]

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

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Available on the COT archive at http://archive.food.gov.uk/dept_health/archive/cot.htm

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Available on the COC website at
http://www.iacoc.org.uk/index.htm

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

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