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

CHAIRMAN

Professor David Coggon OBE MA PhD DM FRCP FFOM FFPH FmedSci
Professor of Occupational & Environmental Medicine, University of Southampton

MEMBERS

Mr Derek Bodey MA
Public Interest Representative

Professor Alan Boobis OBE BSc PhD CBiol FIBiol
Professor of Biochemical Pharmacology, Imperial College, London.

Dr Roger Brimblecombe BSc MSc PhD DSc FRCPath FSB CBiol
Consultant

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

Dr Rebecca Dearman BSc (Hons) PhD
Faculty of Life Sciences, University of Manchester

Dr John Foster BSc PhD FRCPath
Senior Principal Pathologist, AstraZeneca Pharmaceuticals
Chair of Panel of Examiners for the Toxicology Specialty, Royal College of Pathologists

Dr Mark Graham BSc PhD
Senior Principal Scientist, AstraZeneca Pharmaceuticals

Dr Anna Hansell MSc MB BCh MRCP MFPH PhD
Senior Lecturer and Assistant Director of the Small Area Health Statistics Unit, MRC-HPA Centre for Environment and Health, Imperial College London

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

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

Professor Justin Konje MBBS MD MRCOG
Head of Clinical Division of Obstetrics and Gynaecology, Leicester Royal Infirmary

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

Professor Ian Morris BPharm PhD DSc
Associate Dean for Research and Professor of Pharmacology and Physiology
Hull York Medical School

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

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

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

SECRETARIAT

Dr D Benford BSc(Hons) PhD	Scientific Secretary
Mrs J Shroff BA(Hons)	Administrative Secretary
Mr J Battershill BSc MSc	Scientific – HPA
Dr D Gott BSc(Hons) PhD	
Ms C A Mulholland BSc(Hons)	
Dr C Baskaran BSc MSc PhD	
Dr E Cemeli BSc PhD	*(from 3 October 2011)*
Ms C Potter BSc MSc	*(from 28 November 2011)*
Dr M Kurzawa-Zegota MSc(Hons) PhD	*(from 12 December 2011)*
Mrs F Hill BSc	
Dr N Thatcher BSc(Hons) PhD	*(up to 12 April 2011)*
Mr T Chandler BSc(Hons) MSc	
Mr B Maycock BSc(Hons) MSc	
Dr D Parker BSc(Hons) MSc PhD	
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

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

		Misc Various pharmaceutical and other companies - Contract research at LFR and consultancy
Professor Ian Morris		
Personal Interest		**Non Personal Interest**
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