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

Preface

The Committee on Toxicity (COT) evaluates 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.

During 2010, the Committee agreed statements on possible health risks associated with exposure to chemicals emitted from landfill sites, and on mixed halogenated (chlorinated and brominated) dibenzo-p-dioxins (PXDDs), dibenzofurans (PXDFs) and biphenyls (PXBs) in fish, shellfish, meat and eggs. In addition, various other topics were discussed, without publication of a formal statement. These included phthalate esters, endocrine disrupting chemicals and mixtures toxicity. We also had a detailed discussion on methods of analysis for shellfish toxins, and the scope to replace use of the mouse bioassay in the UK monitoring programme for these toxins by alternative approaches that do not require testing in live animals. Many of the matters considered by COT require discussion at more than one meeting, and several items of business were still in progress at the end of 2010. Work on these was due to be completed early in 2011, and formal statements will be included in the 2011 Annual Report.

I would like to thank Dr David Tuthill, Professor Corinne De Vries, Ms Alison Ward, Ms Alma Williams and Dr Cliff Elcombe, who left the Committee during 2010 after valuable service. As always the administrative and scientific secretariats have given us excellent support.

Finally I would like pay tribute to Dr David Ray. Sadly David died in November 2010 after suffering from pneumoblastoma. David was an internationally renowned expert in neurotoxicology, and had been a member of COT from 2003 until he resigned in April 2010 because of his illness. He was a valued and much-liked member of the Committee, who contributed a wealth of knowledge on his specialism, and on the broader aspects of our discussions. His death is a sad loss to the COT and to the Scientific Community more widely.

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COT evaluations

Danish Environmental Protection Agency (EPA) report on health assessment of the exposure of 2 year-olds to chemical substances in consumer products'

1.1 As part of its consideration of mixtures of endocrine disrupting chemicals, in February 2010 the COT considered a summary of the Danish Environmental Protection Agency (EPA) report *'Survey and Health Assessment of the exposure of 2 year-olds to chemical substances in Consumer Products'*.

1.2 The COT subsequently discussed in more detail sections of the report relating to the calculation of the exposure estimates for each compound, and to the endpoints used as the basis for the no effect level (DNEL) for each compound. The DNEL is derived from No Observed Adverse Effect Levels (NOAELs) or Lowest Observed Adverse Effect Levels (LOAELs) by application of assessment factors to account for possible inter and intra-species differences in susceptibility to toxic effects. In addition, the COT requested information on time trends in exposure to a selection of the compounds investigated, since whilst some compounds had been withdrawn from use in certain applications, the use of others was growing, such trends might reduce or increase concerns about the risks of adverse effects.

Exposure assessment

1.3 The COT welcomed the approach taken in the EPA report of studying total exposures from a range of different scenarios, noting that 2-year old children are exposed to phthalates from a variety of sources, in and out of the home, through the diet, and through contact with clothes, consumer products and toys. The reported exposure calculations assumed high exposure to high concentrations of the chemicals by each route, and thus represented an extreme worst case. For some compounds the total calculated exposures were above the DNEL reference value. However, as assessment factors were used in deriving these reference values, the margins between exposures and the minimum effect levels in critical studies were likely to be substantial.

Endpoints used to derive DNELs

1.4 Since the report focused on substances with endocrine disrupting effects, the risk assessments were based on NOAELs and LOAELs from animal experiments that had shown such effects. Thus, the selected NOAELs and LOAELs did not necessarily relate to the critical adverse effects (normally those seen at the lowest concentrations or doses) of the compounds, which would generally be used in risk assessments. In many cases, the

NOAELs/LOAELs came from studies in which the effects were observed following *in utero* exposure to the substances, which the COT considered were likely to over-estimate risks in children.

1.5 The COT was presented with data from Scandinavia on exposure to dibutylphthalate (DBP) from rubber clogs, indicating that exposure would be above the DNEL. Members noted that it was unclear how relevant these data would be to the UK, and uncertain exactly how the exposure had been calculated. In addition Members questioned the basis for the DNEL derived by the Danish EPA, which was a study by Lee *et al*. (Toxicology 203, 221-238, 2004), and agreed to consider this study further as part of other items to be discussed during 2010 (see paragraphs 1.9-1.15).

Time trends

1.6 Phthalates were selected for closer consideration of time trends in exposure, as this was a group of endocrine disrupting chemicals for which the Danish EPA had estimated that exposures were higher than the DNELs.

1.7 A number of studies were identified which provided information on phthalate exposure through routes such as food, dust, indoor air, toys, consumer products, and medical devices/medications. These studies did not address changes in phthalate exposure over time. Some biomonitoring data were available which suggested both increases and decreases in exposure to different phthalates over time. However, 2003 was the last year for which there were time trend data, and Members concluded that it would be helpful to know current levels of usage, as these were likely to have changed. Ideally the validity of the modelled exposure levels would be assessed by comparison with biomonitoring data, but no UK biomonitoring data were available.

1.8 Members agreed that, before deciding whether more detailed consideration was required for other substances covered in the Danish EPA report, it would be best to wait for the results of studies being conducted under the European Union (EU) Framework Programme and a report on mixtures of endocrine disrupting chemicals being prepared for the European Commission (see paragraphs 1.33-1.37).

Dibutylphthalate (DBP) in clogs

1.9 In considering the report by the Danish EPA (see paragraphs 1.1 – 1.8), Members asked for further information on possible exposure to DBP from rubber clogs and on the basis of the DNEL for the compound that had been derived by the Danish EPA.

1.10 Subsequently, the COT considered in detail the interpretation of the critical toxicity study (Lee *et al*., Toxicology 203, 221-238, 2004) used to set the DNEL for DBP, taking into acount advice from additional experts in reproductive toxicity. Members agreed that a review should be undertaken of studies cited in a 2005 opinion of the European Food Safety Authority (EFSA) on DBP[a], and of other relevant studies on the compound, including toxicological, biomonitoring and epidemiological investigations, published since 2005. In addition, information on dermal absorption and exposure estimation was considered.

1.11 EFSA used the study by Lee *et al*. (Toxicology, 203, 221-238, 2004) as a basis for establishing a Tolerable Daily Intake (TDI) for DBP. In this study, maternal rats were fed DBP in the diet during the period from late gestation to the end of lactation. The LOAEL was 2 mg/kg bw/day, which was much lower than the NOAELs (in the region of 50 mg/kg bw/day) that had been observed in other studies. The COT noted that the study measured a lot of endpoints, not all of which were considered to be relevant, in rather small groups of animals. Effects at 2 mg/kg bw/day were on testicular spermatocyte development and mammary gland effects in male offspring. The effects on testicular spermatocyte development were reversible with continued dosing and lacked dose-dependence. The mammary gland effects seemed unlikely to be a manifestation of toxicity since they would be expected to be associated with an androgenic substance and not with the anti-androgenic mode of action of DBP. However the biological activity and some of the reported effects were plausible, and therefore the findings could not be discounted. Further work would be needed to confirm those effects at low doses, but meanwhile, the COT considered that the TDI proposed by EFSA was reasonable.

1.12 The COT agreed that, from the available dermal absorption studies, it was appropriate to assume a 2% absorption rate in humans, although it was noted that further empirical evidence on this would be helpful. Since the key study used to establish the TDI, involved exposure to DBP *in utero* and from lactation, it was not directly relevant to exposure of children to DBP from clogs. It was acknowledged that the worst-case risk characterisation ratio that had been proposed by the Danish EPA was likely to be an over-estimate, due to the conservative nature of the LOAEL and the long duration (10 hours) assumed for wearing clogs. Direct measurements of systemic uptake of DBP from clogs would be useful, together with information on the prevalence of DBP in the environment and on how commonly it occurs in clogs.

[a] http://www.efsa.europa.eu/en/efsajournal/pub/242.htm

1.13 COT noted that measurements of phthalates in urine samples taken as part of the US National Health and Nutrition Examination Survey (NHANES) project reflected exposures from a variety of sources. Some of the intakes estimated from such biomonitoring studies exceeded the EFSA TDI, but there was no information on whether and how levels were changing over time. The COT advised that the implications of exposures above the TDI and the potential contribution from wearing rubber clogs should be taken into account when considering different risk management options.

1.14 Epidemiological studies investigating the relationship of mono-butyl phthalate (MBP; the monoester of DBP) to cryptorchidism suggested possible hormonal effects. Similarly epidemiological studies investigating anogenital distance provided some evidence of endocrine disruption by DBP in humans.

1.15 The COT agreed that whilst small children were the critical population subgroup with regard to possible risks from DBP in rubber clogs, there was a need for biomonitoring studies in the UK with particular focus on women of childbearing age. This programme of work should explore the main sources of DBP exposure, and should investigate trends over time as well as patterns and determinants of exposure at baseline. Members agreed that an assumption of dose additivity would be appropriate when assessing the combined effects of phthalate esters.

Endocrine disrupting chemicals – definition for regulatory purposes

1.16 The classification of substances as endocrine disrupters has become important in a number of regulatory contexts. An example is the introduction into the new European Plant Protection Products (PPP) Regulations (1107/2009) of a requirement that an active substance, safener and synergist with endocrine disrupting properties that may cause adverse effects in humans cannot be approved for marketing and use unless the exposure of humans under realistic proposed conditions of use is negligible.

1.17 The COT was asked to comment on a paper that proposed a definition and method for determining whether a substance is an endocrine disrupter, which could be applied in the context of legislation relating to plant protection products, biocides, and the Registration, Evaluation, Authorisation and Restriction of Chemical substances (REACH). The COT's views would be used by the Health and Safety Executive to feed into and inform European Union discussions. It was noted that the discussions and recommendations from the meeting could have implications with respect to environmental chemicals more widely.

1.18 In European Union legislation, endocrine disruption, along with carcinogenicity, mutagenicity and teratogenicity, had been singled out as hazard triggers of special concern. However, the scientific basis for treating endocrine disruption differently from other toxic modes of action was debatable. In the view of the COT current evidence did not indicate special features of endocrine disruption that warranted a different approach from that for most other toxic modes of action. For example, there was strong evidence of monotonic dose/concentration-response relationships *in vitro* and *in vivo*, and non-monotonic effects seemed unlikely. Moreover, additivity at the estrogen receptor was in essence no different from that for other receptor-mediated effects. However, as COT has noted previously[b], there is stronger evidence from environmental studies that endocrine disrupters can adversely affect reproductive growth rates in populations of wild animals.

1.19 A number of definitions for endocrine disrupters have been proposed, some of which are ambiguous and, for regulatory purposes, are overly inclusive, in that they fail to discriminate between alterations of the endocrine system which fall within the physiological balance/homeostatic capabilities of the body, and adverse effects that disturb an organism's endocrine system to an extent beyond that compatible with normal function. This has led to the development of more restrictive definitions that account for the fact that many alterations of the endocrine system can be regarded as adaptive, falling within a range for which compensation can occur readily, and which pose no threat to the normal functioning of the organism.

1.20 The widely accepted scientific definition of an endocrine disrupter proposed by the World Health Organisation International Programme on Chemical Safety (WHO/IPCS) was considered as a starting point for the COT discussion: *"An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub)populations."*

1.21 The COT suggested it might be considered to be too much of a "catch-all", and that it should capture concepts of potential to alter function based on mode of action and dose. Incorporating "*the potential* to alter function(s)" would allow for use of results of predictive systems or read across. However "potential" might be too broad a definition for regulatory purposes. The words "*, or (sub)populations*" were considered unnecessary.

1.22 The COT proposed the following revised definition for an endocrine disrupter: "*an exogenous substance or mixture that has the potential to alter function(s) of the endocrine system and consequently cause adverse effects in an intact organism, or its progeny*"

[b] http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2006/371075

1.23 The COT also considered the qualifying criteria that had been proposed by the WHO/IPCS. It was agreed that the use of the following four criteria would make it possible to confirm that a substance was an endocrine disrupter for regulatory purposes:

i. *"adverse effects to have been seen in one or more standard toxicity studies in which the substance was administered by a route relevant for human exposure"* More detailed information might need to be taken into account – for example the quality of the studies, the form of the substance and its stability

ii. *"the adverse effect(s) believed to be related to endocrine disruption to have been produced at a dose at or below the relevant guidance value for the application of Category 2 "Specific Target Organ Toxicity-Repeated Exposure, STOT-RE" classification & labelling"*

iii. *"a mode-of-action link between the toxic effects of concern and endocrine disruption to have been established*". In practice data gaps would need to be taken into account.

iv. *"the effects seen in experimental animals to be judged to be of potential relevance to human health"*

1.24 Members noted that the evidence required to conclude that a substance was not an endocrine disrupter would ultimately depend on the degree of certainty that risk managers required.

Landfill sites

1.25 In 2001, the COT published a statement on a major study of health outcomes in populations living around landfill sites[c]. The COT was largely reassured by the findings but considered that a small elevation of risk for all congenital anomalies in people living around special waste landfill sites merited further investigation. At that time, the COT had been informed that a programme of research and reviews was underway on congenital anomalies and landfill sites. This included a project by the Environment Agency (EA) to measure emissions of chemicals, common air pollutants and biohazards from landfill sites, and further epidemiological studies by the Small Area Health Statistics Unit (SAHSU).

1.26 The results of these studies were reviewed from 2007 to 2009. The COT welcomed the monitoring work by the EA and found no cause for concern for the health of families with infants, or for couples who live in the vicinity of landfill sites and who are considering having a baby. Based on the results of

[c] http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2001/sahsulandfill

the monitoring, conclusions and recommendations were made in relation to specific chemicals and to future monitoring and research.

1.27 The COT statement can be found at: http://cot.food.gov.uk/pdfs/cotstatementlandfill201001.pdf

Mixed halogenated dioxins

1.28 The COT considered a recently completed Food Standards Agency (FSA) study that analysed 19 mixed halogenated (chlorinated and brominated) dibenzo-p-dioxins (PXDDs), dibenzofurans (PXDFs) and biphenyls (PXBs) in samples of fish, shellfish, meat and eggs consumed in the UK.

1.29 PXDDs, PXDFs and PXBs contain mixed bromine and chlorine substitutions in the hydrocarbon rings rather than exclusively chlorine or exclusively bromine substitutions. Theoretically 4600 individual PXDDs and PXDFs and 9180 PXBs are possible. Except for some PXBs produced for research purposes, mixed halogenated dioxins, furans and biphenyls have never been produced commercially.

1.30 The TEFs[d] developed for the polychlorinated dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs) and dioxin-like biphenyls (PCBs) were used as an indication of the dioxin-like activity of the corresponding PXDDs, PXDFs and dioxin-like PXBs congeners. This was the greatest source of uncertainty in assessing potential health risk for mixed halogenated dioxins, but the approach is conservative as available evidence overall suggests that PCDDs, PCDFs and dioxin-like PCBs have higher relative potencies and lower rates of clearance from the body than other structurally analogous compounds.

1.31 Based on the levels estimated per portion of the foods surveyed, the PCDDs, PCDFs and dioxin-like PCBs were likely to be the major contributors to the total TEQ. Assuming that the measured congeners were representative, PXDDs, PXDFs and dioxin-like PXBs were considered likely to be only a minor contributor to the total TEQ, and the measured levels were judged not to be a health concern.

[d] Toxicity Equivalency Factors (TEFs) allow concentrations of the less toxic dioxin-like compounds (16 PCDDs/PCDFs and 12 PCBs) to be expressed as a concentration equivalent to the most toxic dioxin 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). These toxicity-weighted concentrations are then summed to give a single value, which is expressed as a Toxic Equivalent (TEQ). The system of TEFs used in the UK and a number of other countries is that set by the World Health Organisation (WHO), and the resulting overall concentrations are referred to as WHO-TEQs.

1.32 The COT statement can be found at:
http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2010/cot201002

Mixtures – an appraisal of a report on "State of the Art on Mixture Toxicity"

1.33 In September 2010, the COT appraised a report entitled State of the Art Report on Mixture Toxicity by Professor Kortenkamp and colleagues[e]. The report summarised the output of a project commissioned by the European Commission (EC) Directorate General for the Environment. The COT was asked for comments in order to inform the UK's representatives in later discussions of mixture toxicity within the EU.

1.34 Members were not aware of any important literature on the concepts, frameworks and experimental strategies that had not been considered in the report, or of any omissions in the literature cited that could influence the conclusions drawn.

1.35 It was agreed that the report provided a reasonable representation of the literature describing the combined effects of chemicals on specific mammalian toxicity endpoints. However, Members considered that the literature did not support a concern about response addition at human exposure levels or the authors' claim that a default uncertainty factor of 100 was insufficient.

1.36 The COT approach to the risk assessment of mixtures of chemicals had evolved over time. The current default position for mixtures of chemicals that have a common target is as follows:

a. Where there is clear evidence that compounds act by different mechanisms, and on different biological pathways, independent action is assumed.

b. Where there is clear evidence that compounds act by the same mechanism, dose addition should be assumed.

c. Where there is clear evidence that compounds act on different elements of the same pathway, or where there is inadequate evidence on mechanism of action, dose addition should be assumed. Members elaborated that this may be highly conservative.

1.37 The European Food Safety Authority was expected to be producing a statement on mixtures during 2011, which Members felt they should also

[e] http://ec.europa.eu/environment/chemicals/pdf/report_Mixture%20toxicity.pdf

review. The published[f] minutes of the discussion set out the conclusions of the COT.

Mixtures – consideration of FSA-funded research on joint endocrine effects of multi-component mixtures of food contaminants and additives

1.38 The COT discussed pre-publication results of this FSA-funded research (T01045). Members considered it to be a well designed, executed and reported *in vitro* study into mixture effects of food additives and contaminants with endocrine effects. The results suggested that any deviation of the mixture effect from the prediction of dose additivity would be negative, and therefore, the COT's recommended approach of assuming dose additivity would be adequately protective of public health.

1.39 Members noted that as this work had been carried out *in vitro*, there were limitations, including the fact that the cells have limited homeostasis, the possibility that conformation of the receptor was altered by reporter attachment, and failure to include negative controls. In addition the assays were not thought to be predictive of the human hazard or the *in vivo* potency of the compounds.

1.40 Limitations in extrapolating the results to the *in vivo* situation included the involvement of the brain in feedback control of hormone levels, the presence of receptors in various tissues which have different responses to receptor activation, and the possibility of combined effects resulting from interactions at different sites. The COT advised that, due to these limitations, there would be limited value in pursuing further *in vitro* work.

National Health And Nutrition Examination Survey (NHANES)

1.41 The NHANES is a major program of the National Center for Health Statistics (NCHS). NCHS is a part of the Centers for Disease Control and Prevention (CDC) which has responsibility for producing vital and health statistics for the United States of America.

1.42 During the 2010 horizon-scanning session, a Member suggested that the outputs of the NHANES would be of interest to the COT. Members were provided with a paper giving information about the NHANES. At the May 2010 meeting and at the September 2010 meeting, a further paper was presented describing uses of NHANES data (with particular reference to

[f] http://cot.food.gov.uk/pdfs/cotmins14sept2010.pdf

endocrine disrupters considered in the 2010 Danish EPA report, see paragraphs 1.1-1.8).

1.43 Members commented that the outputs from the NHANES could provide a useful resource for epidemiologists and that the biomarker data were a particular strength. However, the data were largely cross-sectional, which limited their value in the investigation of causal relationships.

1.44 It was noted that NCHS go to great lengths to ensure that the survey reflects the demographics of the national population, with oversampling of specific sub-populations where appropriate. However, Members commented that no economically feasible survey could be fully representative.

1.45 Due to the nature and scope of the surveys it was inevitable that some associations would emerge by chance. Thus it was important to interpret reports that used NHANES data in the context of relevant scientific evidence from other sources.

1.46 It had been suggested that the NHANES data might be used to identify chemicals that were a priority for cumulative risk assessment due to evidence of simultaneous internal exposure. However, no published papers were identified that had taken this approach.

1.47 A literature search was undertaken to assess the uptake and use of NHANES genetic data. Forty two papers were identified as being of possible interest but only nine proved relevant. These were reviewed by the COT. Members noted that, given the data available, relatively few papers had been published that made use of the NHANES genetic datasets, and suggested this might be due to the need for much larger sample sizes than could be provided by the NHANES.

1.48 Members also observed that NHANES data appeared to have had limited impact on public health decisions; although it was noted that blood lead data had been instrumental in developing policy to reduce exposures.

1.49 In considering whether NHANES could be used to inform future COT risk assessments, Members noted that the data could provide a “reality check” when carrying out a mixture assessment. NHANES data could provide evidence as to which substances should be included in a combined risk assessment and could be used to demonstrate co-exposure. However, it would not be possible to confirm whether the exposure had been dietary. It was also noted that the distribution of biomarker levels and ethnic make-up would be specific to the US population, and there might be uncertainties in extrapolating to the UK population. A similar database covering the UK population would therefore be more useful for UK risk assessments. It was

noted that a biomarker study on exposure to 30 chemicals in a UK blood donor population was being conducted by the University of Newcastle.

1.50 Members agreed that the information provided on NHANES data did not indicate a need for full COT evaluation of any of the chemicals investigated.

Paralytic Shellfish Poisoning biotoxins

1.51 A number of marine phytoplankton produce biotoxins that can bioconcentrate in shellfish. Consumption of contaminated shellfish with sufficiently high levels of these toxins can result in human illness.

1.52 Paralytic Shellfish Poisoning (PSP) is a neurotoxic syndrome with symptoms that include tingling and numbness of extremities, respiratory distress and muscular paralysis leading to death by asphyxiation. The predominant toxin responsible for PSP is saxitoxin (STX), but at least 20 other related compounds have also been identified. The COT previously considered a risk assessment and monitoring of marine biotoxins associated with PSP towards the end of 2005, and published a statement in 2006. At that time the COT had concluded that High Performance Liquid Chromatography (HPLC) should be used for quantification of PSP toxins, subject to appropriate quality control measures and method validation.

1.53 At the March 2010 meeting Members were presented with a report of work commissioned by the FSA and carried out by the Centre for Environment, Fisheries & Aquaculture Science (Cefas) to validate of the HPLC methods for detection of PSP toxins in mussels, cockles, Pacific and native oysters, and king and queen scallops

1.54 Progress had already been made with replacement of a mouse bioassay (MBA) by HPLC in monitoring for PSP biotoxins in mussels. However the advice of the COT was sought on the public health implications of replacing the MBA with the HPLC method for monitoring of cockles, Pacific and native oysters, razor and hard clams, and king and queen scallops. Members noted that due to the major economic impacts on harvesting of closing shellfish beds, a robust scientific basis was needed for any method used to underpin decisions about closures.

1.55 It was recognised that whilst it was the current reference method, the MBA, had limitations with respect to limits of quantification and other performance characteristics. The best way of determining accuracy of any method was to carry out the analysis with a certified reference material comprising the shellfish matrix of interest with known concentrations of a range of toxins. If

certified reference material was not available, a well characterised material was the preferred option.

1.56 For mussels a well characterised material was available from Canada, and was used as part of the validation of the method. This material had been well characterised using HPLC and liquid chromatography with mass spectrometry (LC-MS). Accuracy was ensured through use of different quantitation methods as well as different extraction methods.

1.57 Neither certified reference material nor well characterised material was available for the other shellfish matrices under consideration. In the absence of these, samples spiked with known concentrations of toxins were used; however, these do not reflect the manner in which shellfish naturally accumulate PSP toxins, and thus provide an indication of recovery rather than accuracy. The homogenates used as a starting point for spiking were considered to be PSP-free as they were collected at a time of year when PSP toxins are not prevalent, and repeated analyses had shown these to be toxin-free.

1.58 Limits of detection (LoD) and quantitation (LoQ) were determined by Cefas for each toxin by establishing the amounts of toxins giving a signal to noise ratio on the chromatograms of 3:1 and 10:1 respectively. The LoDs and LoQs were determined for the whole method using the spiked homogenates rather than just representing instrument sensitivities by analysing extracts. Noise in the chromatograms was assessed from the results obtained by application of appropriate algorithms.

1.59 Cefas sought to ensure that the HPLC method for the detection of PSP toxins was precise, repeatable and reproducible. Members were informed that in assessment of the method, precision reflected short term variability in instrument performance, for example in retention time and peak size. Repeatability in the short term reflected the within batch replication of recovery variables by assessment of triplicate spiked homogenates. In the medium term, repeatability reflected the variation in concentrations measured over a longer period (2-3 weeks) and was influenced by a number of variables (e.g. change in operator, batch of reagents, etc). Reproducibility, while normally an assessment of the variability in performance between laboratories, applied in this single laboratory validation exercise to the long term repeatability (over time periods greater than 6 months) of the whole method. This was considered to provide a thorough assessment of how the method varied from day to day, taking into account factors such as different analysts performing the method, use of different instruments and carrying out the analysis on different days.

1.60 Recovery was an assessment of how much toxin was measured at the end of the analysis of a known amount of toxin present in the homogenate. Selectivity was the ability of the method to distinguish toxins, and an assessment of the effects of matrix interference. Linearity was a measure of how toxin concentration related to the detector measurement, the aim being a linear relationship.

1.61 The overall uncertainty of the total STX equivalent concentration had not been presented in the report as it would vary depending on the toxin profile of each sample. Not all the constituent uncertainties would necessarily operate in the same direction and therefore they could not be summed to obtain an overall value. Members suggested that the researchers could assess a number of samples in which the total STX equivalent concentration was close to the regulatory limit, to derive a distribution of overall uncertainties. These could then be compared with the uncertainty associated with the mouse bioassay method.

1.62 The report on cockles, Pacific oysters and native oysters showed the method to perform well, results comparing satisfactorily with those obtained in validation of the method in mussels. The recovery of the PSP bioxtoxin known as dcGTX2,3 was low in cockles but this had also been found in other laboratories, and it was noted that dcGTX2,3 does not appear to be frequently detected in United Kingdom shellfish samples, The low recovery was therefore considered to be of limited concern. Performance data for the HPLC method compared favourably with those of the mouse bioassay.

1.63 The HPLC results obtained for PSP-contaminated cockles, prepared by feeding cockles with toxic *Alexandrium* algae in the laboratory, showed good correlation with those obtained by the mouse bioassay, the measured levels by the HPLC method being 30-40% higher. This difference was thought to be due to use of the higher toxic equivalency factors (TEFs) where toxin epimer pairs are present. However, as HPLC resulted in a higher estimation of the toxin content than the mouse bioassay, there were no false negatives in the analysis and there would be no increased risks from its use. It was noted that, due to shortage of contaminated material, only a limited set of 19 cockle samples had been compared using the two methods.

1.64 HPLC results for contaminated Pacific and native oyster samples, most of which, like cockles, had been prepared in the laboratory, were 2-3 fold higher than those determined by the mouse bioassay. While up to 30% of this variation could be attributed to use of higher TEFs for toxin empimer pairs, no explanation had yet been found for the remaining variation. Members noted that whilst there would be no increased risks to public health, from using the HPLC method, there could be adverse implications for the shellfish industry.

1.65 The performance characteristics and standardised uncertainties determined for the method in razors and hard clams were reasonable and similar to those obtained for cockles and oysters. Analysis of contaminated samples showed that the HPLC and mouse bioassay methods compared well, but again only a small number of samples (8 razors and 8 hard clams) had been assessed.

1.66 The performance of the HPLC method for king and queen scallops was poor for N-hydroxylated toxins such as GTX1,4, NEO and dcNEO due to a lack of effectiveness at the periodate oxidation stage of the assay. The data for queen scallops indicated that the limit of detection for GTX1,4 in queen scallops was close to the regulatory limit.

1.67 No further work had been undertaken to validate the methodology for queen scallops due to the need for further optimisation to make it fit for purpose. As a result, Members considered the HPLC method was not appropriate, even as a qualitative screen for queen scallops, and in the monitoring programme all samples of queen scallops should continue to be assessed using the mouse bioassay. For king scallops however, it would be acceptable to use the HPLC method as a qualitative screen from which any positive results would be further assessed by the mouse bioassay. Poor recovery (less than 30%) for some of the toxins suggested that further work would be required on this method. Members noted that a number of N-hydroxylated toxins are prevalent in the United Kingdom, and therefore the potential for their underestimation was undesirable.

1.68 Despite poor performance characteristics, analysis of contaminated whole king scallops (some of which had been prepared in the laboratory), processed king scallops and Atlantic scallops showed good correlations between HPLC and the mouse bioassay. However, only a small number of samples of each were assessed. For queen scallops HPLC results showed concentrations approximately half of those seen by mouse bioassay, but it was emphasised that this was based on two samples only, so the results might be unrepresentative.

1.69 The COT noted that the work on validation had been performed in only one laboratory and on only a limited number of samples, and that these were sources of uncertainty. However, it was understood that other laboratories were also working on validation of the HPLC method, with some samples being analysed at more than one site to enable the assessment of between-laboratory variation.

1.70 Members questioned whether variations in storage conditions were likely to affect the results of the HPLC method. While work to evaluate this had been carried out, it was not considered relevant to the validation of the use of the

HPLC method in the monitoring programme because shellfish samples would all be processed within one day of receipt.

1.71 Members also discussed other available methods for analysis of PSP toxins in shellfish matrices for monitoring purposes. These included an HPLC method involving post-column oxidation which was currently being validated (the HPLC method undertaken by Cefas used pre-column oxidation), and LC-MS approaches that were in development.

1.72 The COT considered that use of the HPLC method as described in the report by Cefas would offer greater public health protection than the mouse bioassay when used for oysters, though it was noted that there was likely to be an increase in the number of positive results found. For cockles and hard and other clams, similar levels of public health protection would be achieved through use of the HPLC method as from use of the mouse bioassay. For razors, public health protection might be slightly less with the HPLC method as compared with the mouse bioassay. The methodology was not yet considered acceptable for king and queen scallops.

Committee procedures

Horizon Scanning

1.73 At the February 2010 meeting, members were provided with information on planned and possible discussion items for the year, and invited to comment on emerging issues that might also need to be addressed. Items scheduled for future discussion were:

- Risk assessment of bystander/resident exposure to pesticides – joint working group with the Advisory Committee on Pesticides
- Review of epidemiological literature of para-occupational exposure to pesticides and health outcomes in cooperation with the Committee on Carcinogenicity (COC).
- Psychological aspects of Idiopathic Environmental Intolerance.
- Detection of biotoxins responsible for paralytic shellfish poisoning.
- Literature related to tobacco, following discussions at the Committee on Mutagenicity (COM) and the COC.
- A paper reviewing toxicogenomics techniques and applications.

- Review of research commissioned as a result of the COT Report on risk assessment of mixtures of pesticides and similar substances.

1.74 In discussing the balance of expertise on the COT, Members identified a number of areas in which additional expertise would be advantageous: environmental exposure assessment; epidemiology; experimental toxicology, including respiratory toxicology; mathematical modelling of dose-response relationships; dietary exposure assessment. The COT would continue where necessary to invite persons with special expertise on an *ad hoc* basis, to assist with evaluations by supplementing the expertise of Members. The need was recognised also to ensure sufficient overlap of expertise in the future as individual Members came to the end of their terms.

1.75 A Member suggested that the outputs of the NHANES of the United States Centers for Disease Control and Prevention would be of interest to the COT. These data were publicly available[g]. Noting recent publications involving NHANES data, and the potential for data-mining, it was proposed that it would be useful for the COT to receive an overview of NHANES. Such a review would cover publications that had made use of the NHANES data, the sorts of data available online and the kinds of samples that are available to researchers. The COT asked to be involved in setting the scope for a review of the NHANES and that the review focus on the inter-relation of biomarkers and health outcomes.

1.76 COT members expressed an interest in reviewing draft toxicological guidelines such as those prepared by the Organisation for Economic Co-Operation and Development. It was pointed out that comments from the COT would be most effective during the earlier stages of guideline preparation. Relevant draft guidelines are emailed to Members for comment when they become available, and Members were encouraged to respond.

1.77 The Chairman reminded Members that topics of emerging interest relevant to the work of the COT could be suggested at any point throughout the year, to either himself or the Secretariat.

Consultation document for updating the Code of Practice for Scientific Advisory Committees (CoPSAC)

1.78 At the November 2010 meeting, the COT was asked to comment on the contents of the Code of Practice for Scientific Advisory Committees (CoPSAC), produced by the Government Office for Science (GO-Science). COT members had previously discussed consultation drafts of a first version

[g] http://www.cdc.gov/nchs/nhanes.htm

of the CoPSAC in 2000 and 2001 and a revised version in 2007. The 2007 version of the CoPSAC was being reviewed to take into account the Principles on Scientific Advice to Government that were issued in March 2010. Members were invited to comment on the specific consultation questions and on any other aspects of the draft code. Members were reminded that CoPSAC had originally been written in a context in which most scientific advisory committees were Non-Departmental Public Bodies (NDPBs), but the consultation indicated that "all Scientific Advisory Committees – whether or not formal Non-Departmental Public Bodies – are covered by this guidance".

1.79 Members questioned the requirement that a committee's advice should be understandable by lay readers. When reporting, committees needed to communicate with Government and the scientific community, as well as the wider public. Inevitably, the rationale underpinning advice was sometimes quite technical, but it needed to be clearly documented and open to scrutiny. Important nuances could be lost if advice were simplified to make it more understandable by the lay reader. An alternative was to provide a "lay summary" to accompany more detailed technical advice, and Members agreed that 'lay summaries' of the COT's conclusions should be included in its future published statements.

1.80 Consultation question 1 related to "Maintaining strong relationships" A Member questioned whether a change in status from independent scientific advisory committee to departmental committee would result in "unpalatable" advice being retained within departments and not reaching ministers. The Chair emphasised that if a chair or members of a committee had concerns about this in a specific case, they should contact first the relevant Department's Chief Scientist and if necessary, the Government's Chief Scientific Advisor.

1.81 Consultation question 2 related to "Openness and Transparency". Para 106 of the CoPSAC was considered to address adequately the issue of communication with the media. Communication should be the responsibility of the chair, delegating to members if appropriate.

1.82 Consultation question 3 related to "Engaging the Scientific Community and Succession Planning". Members discussed the balance of expertise in committees. It was agreed that this would largely depend on the function of the advisory committee. It was suggested that a reduced incentive for younger scientists to get involved with committee work might lead to a decline in available expertise in some areas of science. In addition, the Chair reported that several chairs of scientific advisory committees and other interested parties had recently produced a report highlighting concerns about an impending generation gap in applied scientific expertise relevant to risk

assessment for chemical and physical hazards. A meeting had been arranged with the Government's Chief Scientific Advisor to discuss the problem.

1.83 Consultation question 4 asked "Is there any other information that could be usefully included in the Code of Practice?". The Committee highlighted a need for further guidance on declarations of interests, particularly regarding interests that would not normally present a conflict (e.g. membership of another independent committee that had discussed a topic under consideration).

1.84 A response was sent to GO-Science.

Working Groups and Workshops

Bystander Risk Assessment Working Group (BRAWG)

1.85 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

1.86 The BRAWG held two meetings during 2010. The Group aims to complete its work and to report back to the COT and the ACP during 2011.

Lowermoor Subgroup

1.87 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.

1.88 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. Therefore the final Subgroup report will not be published until 2011.

Workshop on expression of uncertainty

1.89 In March 2007, the COT published a report on Variability and Uncertainty in Toxicology of Chemicals in Food, Consumer Products and the Environment[h]. The report concluded 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.

1.90 The FSA subsequently 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. As part of this project the COT held a one-day workshop in February 2010, at which COT Members and invited guests participated in discussions exploring the evaluation and expression of uncertainties in risk assessment. Participants considered examples of risk assessments previously published by the COT and used a draft framework to consider whether this could make the steps of the risk assessment process easier and more transparent. The potential utility of the framework for COT work was also considered.

1.91 At a subsequent meeting the COT discussed the draft report of the project and a further draft of the framework, which had been revised following the workshop. Members commented that the challenges for the COT in expressing uncertainty are not easily addressed by a simple mathematical approach, and reiterated the reluctance they had expressed at the Workshop to put numerical values on uncertainties regarding qualitative conclusions, as they might easily be misinterpreted. 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).

1.92 The report, including a revised framework, was finalised by the project team. The agreed draft framework will be tested in the course of COT evaluations and may require further modification before being adopted for use by the COT.

[h] http://cot.food.gov.uk/cotreports/cotwgreports/cotwgvut

Ongoing work

Dietary exposure to phthalates – data from the Total Diet Study

1.93 The COT was presented with the results of a recent FSA-funded study of phthalate diesters, a few phthalate monoesters and phthalic acid in Total Diet Study (TDS) samples from 2007. Members considered recent toxicological studies on phthalates identified in a literature review and concluded that these did not indicate a need to revise TDIs set by EFSA (2005) or WHO CICAD (2003), which should therefore be used in assessing possible risks from dietary exposure to phthalates.

1.94 Estimates of dietary exposure to phthalates have been calculated from the results of the study. The COT concluded that a cumulative risk assessment for phthalates should be undertaken based on an assumption of dose-addition. Furthermore a full risk assessment would require non-dietary exposures also to be taken into account.

1.95 Further discussion will take place in 2011 and the statement will be published.

Gluten - timing of introduction into the infant diet

1.96 In 2010, the Department of Health and Food Standards Agency asked the Scientific Advisory Committee on Nutrition (SACN) and the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (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).

1.97 The COT considered the relevant evidence and provisional conclusions have been forwarded to SACN. Further discussions will take place during 2011 and a joint SACN/COT statement will be published.

Idiopathic Environmental Intolerance: Evidence for a toxicological mechanism

1.98 In 2006, the COT discussed a report of the Royal Commission on Environmental Pollution (RCEP) report on crop spraying and health of residents and bystanders, and recommended that a further review of Idiopathic Environmental Intolerance (IEI, also described as Multiple Chemical Sensitivity) be undertaken[i].

[i] http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2006/cotstatementrcep0605

1.99 In 2010, the COT considered a discussion paper on the evidence for toxicological mechanisms for IEI, and subsequently considered psychological aspects of IEI in consultation with experts in psychology. Further discussions will take place during 2011 and a statement will published.

Methanol - chronic toxicity

1.100 Methanol is produced endogenously and also occurs in a number of foods notably fruit and vegetables and their juices.In addition some people are exposed to methanol vapours occupationally. In humans, acute exposure to very high levels of methanol, for example from illegally distilled or counterfeit spirits, has resulted in well characterised toxic effects including metabolic acidosis and neurotoxicity, particularly in the visual system.

1.101 Less is known about whether chronic exposure to methanol at lower levels can result in adverse effects. In response to consumer concerns that methanol arising from the breakdown of the sweetener aspartame could be harmful, the COT has been conducting a review of possible health effects of chronic oral methanol exposure.

1.102 Various data have been considered by the COT including information on the effects of oral exposure to methanol in the diet and of occupational exposure via inhalation. Further discussion will take place in 2011 and a statement will be produced.

Para-occupational exposure to pesticides and health outcomes - systematic review of epidemiological literature

1.103 ‘Para-occupational exposure’ is the term given to exposures that result from living in the same household as a person who is occupationally exposed to a substance For example the wife of a farm worker might be exposed to pesticide contamination that he brought home from work on his person or clothes. It is different from the scenario in which people live in the vicinity of land where pesticides are applied (residential exposure).

1.104 On the 22nd September 2009 Members discussed a systematic review of epidemiological literature reporting health effects associated with para-occupational exposures to pesticides, herbicides, fungicides and insecticides. The COT requested an assessment of publication bias to assist them with their evaluation of the epidemiological data, and this was considered on 14th September 2010.

1.105 In parallel with this the COC has assessed possible associations of para-occupational and residential exposures to pesticides with the occurrence of cancers. The COT and COC will produce a joint statement on para-occupational exposure to pesticides in 2011.

Toxicogenomics in toxicology – design, analysis and statistical issues

1.106 The term toxicogenomics refers to applications in toxicology of genomics, proteomics and metabonomics. The Committees on Toxicology, Mutagenicity and Carcinogenicity jointly considered toxicogenomic tools in 2002 and 2004, and they were discussed again at 2009 COT Workshop[j,k,l].

1.107 On the 22nd of June 2010 the COT began reviewing further progress in the field, considering aspects of study design, and statistical approaches to this analysis of results. Papers will be presented at future meetings on topics such as applications in risk assessment, and a COT statement will be produced.

Waste And Resources Action Programme (WRAP)

1.108 In February Members discussed the 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 report, 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) were also considering these two risk assessments plus a further one which only dealt with microbiological risks. The ACMSF comments were finalised in the Autumn. WRAP have commissioned revised reports and it is expected that these will be available in 2011.

[j] http://cot.food.gov.uk/pdfs/JointCOT-COM-COCStatement.pdf
[k] http://cot.food.gov.uk/pdfs/cotstatementtoxicogen0410.pdf
[l] http://cot.food.gov.uk/pdfs/cotstatementwkshp200903.pdf

2010 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

CHAIRMAN

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Professor of Occupational & Environmental Medicine, University of Southampton

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Mr Derek Bodey MA (from 1st April 2010)
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Professor Corrine de Vries MA MSc PhD FRSM (up to 31st March 2010)
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Professor Justin Konje MBBS MD MRCOG
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Professor Brian G Lake BSc PhD DSc FBTS
Head of Molecular Sciences Department, Leatherhead Food Research

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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

Dr David Ray BSc PhD (up to April 2010)
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Professor Robert Smith BA MSc PhD (from 1st April 2010)
Public Interest Representative
Emeritus Professor, University of Huddersfield

Dr John Thompson BM BS BMedSc FRCP FBTS (from 1st April 2010)
Senior Lecturer in Clinical Pharmacology, Cardiff University
Director, National Poisons Information Service, Cardiff

Dr David Tuthill MB BCh MRCP MRCPCH (up to 23rd June 2010)
Consultant Paediatrician, Children's Hospital for Wales

Miss Alison Ward BA (up to 31st March 2010)
Public Interest Representative

Mrs Alma Williams OBE BA (Hons) (up to 31st March 2010)
Public Interest Representative

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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	
Mr D Renshaw BSc EurBiol CBiol MIBiol	*(upto 22 October 2010)*
Ms C A Mulholland BSc(Hons)	
Dr C Baskaran BSc MSc PhD	*(from 1 November 2010)*
Dr D Key BSc(Hons) PhD	*(from 1 June 2010)*
Ms B Gadeberg BSc MSc	*(up to 12 April 2010)*
Mrs F Hill BSc	
Ms R Harrison BSc MSc	*(up to 16 July 2010)*
Dr N Thatcher BSc(Hons) PhD	
Mr T Chandler BSc(Hons) MSc	*(from 1July 2010)*
Mr B Maycock BSc(Hons) MSc	
Dr D Parker BSc(Hons) MSc PhD	
Mr G Welsh BSc(Hons)	
Miss T Gray BA(Hons)	
Miss J Murphy BA(Hons)	*(up to 22 October 2010)*

Declaration of COT members' interests during (2010) the period of this report
(an up-to-date version can be found on the COT website)

MEMBER	Personal Interest		Non Personal Interest	
	COMPANY	**INTEREST**	**COMPANY**	**INTEREST**
Professor D Coggon OBE	Halifax Standard Life	Shareholder	Colt Foundation British Occupational Health Research Foundation Faculty of Occupational Medicine Public Health Commission	Trustee Trustee President and Trustee Member
Mr D Bodey (from 1st April 2010)	Centre for Alternative Technology Institute of Physics	Shareholder Membership		
Dr R Brimblecombe (from 1st September 2010)	Vertex Pharmaceuticals, Inc MVM Life Sciences Partnership LLP	Shareholder Advisor		

Professor A Boobis OBE	Banco Santander SA Barclays BG Group BT Group Centrica Plc HBOS Iberdrola SA National Grid Scottish Power Thus Astellas Pharma Sumitomo Chemical (UK) Plc Proctor & Gamble Howrey LLP	Shareholder Consultancy	GlaxoSmithKline Food Standards Agency Department of Health Commission of the EU (FP6) ESRC ILSI HESI Elsevier JMPR JECFA (vet drugs) EFSA PPR Panel (Panel on Plant Protection Products and their Residues) EFSA CONTAM Panel (Panel on chemical contaminants in the food chain) ECETOC Task Force on Guidance for Classification of Carcinogens under GHS EFSA Scientific Committee Working Group on Risk-Benefit Assessment EFSA Scientific Committee Working Group on the Benchmark Dose	Support by Industry Research Contract PhD Studentship Unpaid chair of Board of Trustees Editor-in-Chief; Food and Chemical Toxicology Member
Professor J Cade (from 1st September 2010)			Kellogg	PhD student

Dr R Dearman	Syngenta CTL AstraZeneca Research Institute for Fragrance Materials, (RIFM) European Chemical Plasticizers Industry (ECPI)	Shareholder Consultancy Consultancy	Unilever Syngenta European Chemical Plasticizers Industry (ECPI) American Chemical Council (ECPI) BASF RIFM	Research Grant Research Grant Research Grant Research Grant Research Grant Research Grant
Professor C de Vries (upto 31st March 2010)	NONE	NONE	Schering AG Yamanouchi	Research Grant
Dr C Elcombe (upto 4th November 2010)	CXR Biosciences Ltd	Salaried Director Shareholder	Various Pharmaceutical and chemical companies	Contract Research at CXR
Dr J Foster	AstraZeneca	Shareholder	NONE	
Dr M Graham (from 1st September 2010)	AstraZeneca	Employee		
Dr A Hansell	Dept of Epidemiology & Public Health Imperial College London (includes Small Area Health Statistics Unit) Greenpeace Halifax	Employee Supporter (non-active) Shareholder	GlaxoSmithKline AstraZeneca	Research Grant Research Grant
Professor D Harrison	University of Florida University of Canberra The Forensic Institute Avipero	Consultant Consultant Shareholder Shareholder	Melville Trust Medical Research Scotland Office of the Scottish Charity Regulator Myriad Genetics	Trustee Trustee Board Member Research collaboration
Professor B Houston (from 1st April 2010)	Simcyp Xenotech SK Pfizer ISSX BPS BTS	Consultancies and Direct Employment Membership	GSK Pfizer Lilly Servier	Support by Industry

Professor J Konje				
Professor B Lake	Leatherhead Food Research (LFR)	Employee	British Toxicology Society Society of Toxicology Various Pharmaceutical, agrochemical and other companies	Member Member Contract research and consultancy at LFR
Dr G McNeill (upto 31st March 2010)	Smith & Nephew Diageo Café Direct BHP Biliton	Shareholder	Word Cancer Research Fund	Grant panel member
Professor I Morris	Takada Pharmaceuticals Society for Endocrinology Society for Medicines Research Society for study of fertility British Society for Toxicology	Consultancy Membership		Son is a student fellow of British Heart Foundation
Dr N Plant	NONE		Xenobiotica British Toxicology Society Pfizer GlaxoSmithKline AstraZeneca	Associate Editor Member of Education sub-committee Research Funding
Dr D Ray (upto 31st March 2010)	University of Nottingham ZLB Behring (Switzerland) Astellas pharmaceuticals CEFIC ESAP	Employee Consultancy Consultancy Independent advisor		
Professor R Smith (from 1st April 2010)	Research Programme Advisor (Defra) Rodenticide Resistance Action Group	Consultancy Member	Student monitoring rodenticide resistance	Support by Industry - Research costs

Dr J Thompson (from 1st April 2010)	NONE		NONE	
Dr D Tuthill (upto 23rd June 2010)	Cardiff & Vale NHS Trust SMA Nutricia Milupa	Salary Consultancy	Royal College of Paediatrics and Child Health Welsh Paediatric Society British Society of Paediatric Gastroenterology, Hepatology and Nutrition Paediatric Research Society British Association of Parenteral and Enteral Nutrition Nutrition Society British Society of Clinical Allergy and Immunology	Fellowship
Miss A Ward (upto 31st March 2010)	NONE		Farm Animal Welfare Council	Member
Mrs A Williams (upto 31st March 2010)	NONE		NONE	