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 including the Regulatory Authorities, and are published as statements on the Internet. Details of membership, agendas and minutes are also published on the Internet.

During 2009, the Committee agreed six statements, five relating to specific chemicals or exposures (glucosamine, methylglyoxal, perfluorooctanoic acid, chloroparaffins and polychlorinated naphthalenes), and one on the more generic topic of 21st century toxicology. The last followed a workshop in which international experts were invited to present perspectives on ways in which methods for assessing the toxicity of chemicals were likely to evolve. While exciting advances in molecular biology and computational methods offer a long-term prospect of more efficient evaluation of chemical toxicity, with reduced use of experimental animals, the Committee concluded that conventional approaches are unlikely to be superseded in the short to medium term.

At the end of the year, there was a vigorous public debate about the role of scientific advisory committees, and how they should relate to Government. I am pleased to report that, at least during the terms of office of current members, the COT's sponsoring Departments (the Food Standards Agency and the Department of Health) have at all times respected our independence, and have never attempted to influence or modify our conclusions. Dialogue with our sponsors has always been constructive, helping to ensure that the value of our advice to policy-makers is maximised.

I would like to thank Joy Hinson, Peter Jackson and David Bell, who left the Committee during 2009 after valuable service, and also the administrative and scientific secretariats, who as always, have given us excellent support.

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COT evaluations

Arsenic in food, opinion of the European Food Safety Authority

1.1 The European Food Safety Authority (EFSA) scientific opinion on arsenic in food was adopted on 12 October 2009[a], concluding that the Joint FAO/WHO Expert Committee on Food Additives (JECFA) provisional tolerable weekly intake (PTWI) of 15 µg/kg body weight for inorganic arsenic was no longer appropriate; and that dietary exposure to inorganic arsenic should be reduced. This conclusion is in line with previous COT opinions. In order to refine the risk assessment of inorganic arsenic, EFSA noted that there is a need to produce speciation data for different food commodities to support dietary exposure assessment and dose-response data, for the possible health effects.

Bystander/resident exposure to pesticides

1.2 The COT initially considered this issue in April, when its advice was sought in relation to the conclusions of a judicial review concerning the current consideration of risk to bystanders and residents in the pesticide approval process. The COT subsequently considered further information provided by the Health and Safety Executive (HSE) Chemicals Regulation Directorate (CRD) at its September meeting.

1.3 "Bystander" is taken to mean people exposed to a pesticide at the time of application, whereas "residents" may be exposed later and over a longer timescale. Three exposure scenarios are considered in the UK regulatory assessments. The first is a bystander who stands upright, wearing no clothing, 8 m from the nearest part of the sprayer, during one close pass of the sprayer per day. The amounts of pesticide which might land on the skin or be inhaled are estimated. The model uses data from spraying trials that used food dyes as marker substances, in which the wind speed was higher than the maximum recommended for spraying. From this, the mean data point is used. The second scenario relates to residents who are exposed to a pesticide in the air for 24 hours per day. Worst-case data are used from Californian monitoring of about 26 active substances. The maximum application rates in the studies tended to be higher than those used in the UK. Air monitoring had been for 72 hours and the highest 24-hour value was used. For example, in the case of chlorpyrifos used on a 60 acre orchard, there had been some spraying on 2 consecutive days and the highest exposure was on the second day. The

[a] http://www.efsa.europa.eu/en/scdocs/scdoc/1351.htm

third scenario is a small child playing on a lawn, with dermal, hand-to-mouth and object-to-mouth exposures. For this scenario, a US Environmental Protection Agency model of the exposures of children from lawn treatments is used.

1.4 All pesticide inhaled is assumed to be retained in the body, none being exhaled. Empirical dermal absorption data are used where available, but otherwise 100% absorption is assumed. The data are used to estimate a systemic dose, which is compared to the Acceptable Operator Exposure Level (AOEL). In practice, for the arable situation, estimates of potential exposure are up to approximately 10% of the AOEL, and often are <1% of the AOEL. For orchard applications, drift is greater and estimates of potential exposure can be up to around one third of the AOEL. Where potential exposure is estimated to exceed the AOEL a pesticide would not be authorised unless further data (e.g. on dermal absorption) allowed a refined exposure assessment.

1.5 The COT heard that a 3½ year research project had been funded to generate better data to underpin risk assessment for bystanders and residents. This was due to report in January 2010. The Committee saw data from biomonitoring studies conducted in different parts of the world and a comparison with predicted exposures based on UK regulatory exposure assessment models. Studies of US farm families included paraoccupational exposures and bystander exposures which were not directly applicable to the UK. However, the data indicated that bystander or resident exposures might be higher than predicted, but are lower than exposures measured in operators, which are lower than exposures predicted in operators. HSE (CRD) and the Health and Safety Laboratory (HSL) were due to initiate a research project in the near future to investigate biomonitoring of rural residents living within 100 m of agricultural land.

1.6 The AOEL is a health-based reference value, analogous to other reference values such as the Acceptable Daily Intake (ADI), but expressed as systemic exposure. The AOEL is usually based on toxicity studies of 90-days duration or less in rats or a one-year dog study. The Committee questioned whether the AOEL was appropriate for use in risk assessment of residents, since exposure might be chronic and low level. This differed from exposure to bystanders which may be acute and perhaps high. It was noted that, while the AOEL was usually based on subchronic toxicity data, anecdotal evidence was of chronic effects such as multiple chemical sensitivity and chronic fatigue syndrome. Moreover, there were no animal models for these effects.

1.7 The COT was provided with data on the ratios of AOELs to ADIs for pesticides after correction for oral absorption. It observed that the ratios were not all in the same direction. In a few cases AOELs were lower than ADIs, or in one instance greater than the Acute Reference Dose (ARfD), after correction for oral absorption. It was noted that it would be unusual for AOELs to be lower than ADIs. In most cases the AOEL was similar to or higher than the ADI after correcting for oral absorption. In order to consider the appropriateness of an AOEL that was higher than the corresponding ADI, more information was needed on the usage pattern of the pesticide. The Committee requested information additional to that provided by CRD on usage pattern (including number of applications and seasonality) for all pesticides where the ratio of the AOEL to ADI was ≥ 5 after adjustment for oral dosing. If the Committee found that the usage patterns for these pesticides did not justify large differences between AOELs and ADIs then it might be appropriate to recommend changes to the process of setting AOELs in some instances. The Committee asked CRD to provide an explanation for the one example (dimoxystrobin) where the ARfD was lower than the AOEL.

1.8 The COT was concerned that the database used to estimate bystander exposure from a close pass of a spray boom was not large and there would have been considerable variation between exposures of individuals. Thus the exposure of a bystander on a single day could be underestimated, which might be of concern for an acutely toxic pesticide. A separate acute reference value (to the standard AOEL) may therefore be required for acute risk assessment of bystander exposure. However, unusually high exposure on a single day was not a concern in relation to the risk assessment for longer term exposures of residents.

1.9 The COT considered information from the Pesticides Incidents Appraisal Panel (PIAP) on “confirmed” cases for 1998-2008, which were defined as cases in which there were clinical symptoms that might be expected from exposure to the cited pesticide formulation, combined with either corroborating medical and (where appropriate) biochemical evidence or evidence of pesticide exposure. PIAP had been instituted to help HSE inspectors in enforcement duties. It uses a standardised approach to assess whether exposure occurred, whether any adverse effects occurred, and whether adverse effects could be related to exposure. The available information tended to be poor, as often either no consent was received from the individual to investigate, or the available medical information was limited. Most incidents were the result of occupational exposure to pesticides. Members observed that two incidents which did not involve occupational exposure involved irritant reactions to exposure. These particular incidents may have been associated with exposure to

dilute mixtures of pesticide formulations, and could possibly have been due to co-formulants rather than active ingredients. Members noted that exposure to sulphuric acid used on potato crops could result in irritant reactions. Notifications of use had now to be posted when using sulphuric acid as a desiccant on potato tops. It was observed that only a limited number of pesticides were implicated in the "confirmed" cases. However, the Health and Safety Executive advised that <5% of possible cases reviewed by PIAP were "confirmed". It was suggested that all "confirmed" and "likely" cases over a year or several years could be examined to gain a better picture of patterns of exposure. It was noted that other sources of information on pesticide incidents were the National Poisons Unit TOXBASE and the Health Episodes Statistics database which recorded hospital admissions in England.

1.10 The COT viewed a DVD submitted by a member of the public presenting evidence of ill health in bystanders and residents. The Committee agreed that these did not provide any evidence of toxic causation. It was pointed out that individuals can have ill health which appears to be linked to exposure, but when the tools are available to investigate further, there is not necessarily any link. Members agreed that some of the exposures reported must have been unpleasant, with, for example, strong smells and/or a greasy film on windows, and that there was no choice about the exposure and often no information on when spraying would take place. The COT agreed that it would be easy for an individual to make an association between their ill health and pesticide exposure on this basis, but this did not prove toxicity.

1.11 The assessment of local effects was considered. There can be local effects on skin, eyes or upper respiratory tract. These arise through irritation or sensitisation. Very rarely, an AOEL is set on the basis of acute inhalation effects using data from toxicity studies with inhalation exposure. More usually, the AOEL is set on the basis of systemic effects only, and there is a separate assessment of irritation and sensitisation. Both active substances and formulated products are tested for their potential to cause irritation and sensitisation. If a product contains a sensitiser at lessthan 5% concentration, then it does not need to be tested for sensitisation or classified as a sensitiser. If a product is classified as a sensitiser or irritant the risk to operators is managed through label warnings, including recommendations for the use of personal protective equipment. When the dilution of pesticide products is considered, even if a product were classified as an irritant or sensitiser, it would not normally meet the criteria to be so classified after dilution. The exception is aerial applications, where the dilution can be up to 20%. However, a product for aerial application would not be approved unless it was not a sensitiser.

1.12 The COT suggested that the scientific literature be examined for information on the effects of dilution of chemicals on irritancy and sensitisation in order to assess whether a hazard was demonstrable when chemicals classified as irritants or sensitisers were diluted 100-fold. If there were no data available, then further research might be needed.

1.13 The Advisory Committee on Pesticides (ACP) had proposed the establishment of a subgroup of COT and ACP members to undertake a detailed review of risk assessment for bystander and residential exposure to pesticides. The Committee agreed that this would be a useful way forward. As part of its work, the subgroup could follow up the COT's requests for further information. The subgroup is expected to start in early 2010. Four COT Members, including a public interest representative, volunteered to join the subgroup.

Cadmium in the 2006 Total Diet Study

1.14 In 2008 the Committee had evaluated the results of analyses for metals and other elements in the Food Standards Agency (FSA) 2006 Total Diet Study and published a statement (COT statement 2008/08). Cadmium was one of the elements surveyed and the Committee had reached the following conclusion: '*The current dietary exposures to cadmium are not of toxicological concern. This conclusion might need to be reviewed after the current risk assessment by the European Food Safety Authority (EFSA) is published.*'

1.15 The EFSA scientific opinion on cadmium in food[b] was adopted in January 2009, establishing a revised Tolerable Weekly Intake (TWI) for cadmium of 2.5 µg/kg bw (equivalent to 0.36 µg/kg bw per day). The opinion noted that the average dietary exposure for adults across Europe is close to or slightly exceeds the revised TWI; and that subgroups of the population may exceed the TWI by 2-fold. EFSA concluded that although adverse effects on kidney function are unlikely to occur at exposures 2-fold greater than the TWI, exposure to cadmium at the population level should be reduced.

1.16 The estimates of dietary exposure to cadmium from the 2006 Total Diet Study for pre-school children aged 1.5-4.5 years (mean and high-level intakes) and for high-level intakes in young people (aged 4-18 years) exceeded the new TWI by up to 2-fold. For other age groups, estimated

[b] http://www.efsa.europa.eu/en/scdocs/scdoc/980.htm

dietary exposures, even for people with high-level dietary intakes, were below the new TWI.

1.17 Members were asked to comment on the revised TWI and to consider whether they wished to revise their previous conclusions. The Committee made the following conclusions:

The approach used by EFSA to derive the TWI was appropriate, although conservative.

Given the conservative manner in which the TWI was derived, and that exceedances from dietary exposure are modest (generally less than 2-fold) and only for a limited part of the lifespan, they do not indicate a major concern. Nevertheless, in view of the uncertainties, it would be prudent to reduce dietary exposures to cadmium at the population level where this is reasonably practical.

Chlorinated paraffins in food

1.18 The COT was asked for advice on possible risks associated with the levels of chlorinated paraffins (CPs) in foodstuffs that had been found in an FSA investigation.

1.19 CPs are a large group of several thousand individual chemicals. They are chlorinated linear hydrocarbons with between 10 and 30 carbon atoms and varying numbers of chlorine atoms, with a maximum of one chlorine atom per carbon atom. Depending on the length of the carbon skeleton, CPs are classified as short (SCCPs: C10-13), medium (MCCPs: C14-17) and long chain (LCCPs: C18-26).

1.20 The industrial applications of CPs vary depending on the chain length, and include use as industrial lubricants in metal manufacturing and as additives in plastics, paints and sealants. In addition, a common current use is as flame retardants. CPs have the potential to contaminate the food chain following their release during product use or through improper disposal. The FSA investigation was carried out as there were no UK data on their occurrence in food and samples were assessed for SCCPs and MCCPs.

1.21 The Committee assessed the available data and established a Tolerable Daily Intake (TDI) of 30 µg/kg b.w. for SCCPs and 4 µg/kg b.w. for MCCPs. Using these TDIs and highly conservative assumptions about dietary exposure, the Committee concluded that the results of the FSA

investigation of occurrence of SCCPs and MCCPs in food do not give rise to concern for human health

1.22 The COT statement can be found at:. http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2009/cot200905

Developmental neurotoxicity

1.23 The COT report on Variability and Uncertainty in Toxicology (VUT) identified developmental neurotoxicity assessment as an area of recent interest and emphasised the need to keep abreast with methods for assessing developmental neurotoxicity. This recommendation coincided with the anticipated adoption of a new OECD guideline 426 on developmental neurotoxicity, which was adopted in October 2007. The guideline addresses the need to incorporate endpoints of relevance to neurotoxicity in studies of developmental toxicity used for risk assessment. Based on the US EPA developmental neurotoxicity guideline (EPA, 1998) it was drafted to meet a gap in existing OECD guidelines for reproductive and developmental toxicity using a test protocol in laboratory animals.

1.24 A number of chemicals are known to produce developmental neurotoxic effects in humans and other species. Developmental neurotoxicity studies are designed to provide data, including dose-response characterisations, on the potential functional and morphological effects on the developing nervous system of the offspring that may arise from exposure *in utero* and during early life.

1.25 The relevance of extrapolation from animal to human and the issue of whether behavioural tests in rodents are sufficiently sensitive to detect certain more subtle effects was raised in the VUT report and in other papers. The topic has been under consideration by an expert panel assembled by the International Life Sciences Institute (ILSI) whose remit was the “Evaluation and Interpretation of Neurodevelopmental Endpoints for Human Health Risk Assessment”. The ILSI report was comprised of a series of five review papers and a short summary paper all of which were published in Neurotoxicology and Teratology.

1.26 The COT considered that the ILSI papers identified important issues in the interpretation of developmental neurotoxicity studies, and proposed a suitable strategy for assessing such studies. The COT noted that substantial information was required on a study for its thorough evaluation. This level of detail might be available in reports of regulatory

developmental neurotoxicity studies as it could be required by regulatory authorities and in guidelines but was unlikely to be available for published studies due to editorial constraints on space. This would be reflected in the discussion of uncertainties and might influence the weight given to findings.

1.27 Although well established neurotoxicants had not necessarily been tested under the precise conditions used in regulatory studies, it was likely based on a review of available studies that they would produce positive results under such conditions. A number of unpublished case studies on established neurotoxicants had been prepared for the ILSI discussions but were not incorporated in the published paper. The authors were approached through ILSI and agreed that the COT could have access to their unpublished manuscripts. These reviews summarised a great deal of information on the four best characterised agents known to produce developmental effects in humans and allowed conclusions on the predictability of animal developmental neurotoxicity studies for such effects in humans. Essentially the case studies showed that there were developmental effects in animals at about the same exposure level as is damaging in humans.

Glucosamine and hepatotoxicity

1.28 Glucosamine is a popular food supplement taken alone or in combination with chondroitin sulphate usually by sufferers of osteoarthritis. In view of a small number of case reports linking glucosamine and hepatitis, including one that became the subject of a Scottish Fatal Accident Inquiry, the COT was asked to consider whether a causal association was plausible.

1.29 The COT concluded that current evidence does not suggest that glucosamine is likely to be a cause of hepatitis although a causal link cannot be completely excluded. It should be noted, however, that the likelihood of an individual user of glucosamine experiencing adverse effects is, at most, very low.

1.30 The COT statement can be found at: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2009/cot200901

Methylglyoxal

1.31 As part of its annual horizon scanning discussion in February 2009, the Committee was provided with information on occurrence of methylglyoxal (MG) in food, possibly as an intermediate in the formation of acrylamide, and on the association between endogenously formed MG with a number of diseases. The Committee expressed an interest in a more thorough review of methylglyoxal including, if possible, a comparison between dietary exposure to MG and endogenous production. A discussion was held at the June meeting and a statement drafted for the October meeting.

1.32 MG is a reactive dicarbonyl compound that is produced endogenously in the body, primarily through anaerobic glycolysis. MG and other products of glycolysis have been shown to produce adducts in both DNA and proteins. Elevated MG levels and associated MG-protein adducts in the kidney, lens and blood have been associated with complications commonly found in patients with diabetes mellitus. Elevated levels of protein adducts have been associated also with aging, renal failure and Alzheimer's disease and of DNA adducts with cancer.

1.33 As MG is ubiquitous in living cells, it will be found in food products of both animal and plant origin and therefore exogenous exposure occurs through consumption of all foods. Particularly high levels have been reported in manuka honey and some soft drinks. MG can be present as a free molecule in the diet and can be found bound to biological material, such as proteins, as AGEs, which are poorly absorbed.

1.34 The COT concluded that the database on toxicity of MG is poor, and inadequate for characterisation of dose-response relationships. In order to support an evaluation of the risks associated with MG, it was suggested that a study to investigate the kinetics of MG would be the first priority, followed by a 90-day study to assess the toxicity of MG and an *in vivo* genotoxicity study.

1.35 The COT statement can found at: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2009/cot200904

Multi-strain assays

1.36 During discussions of the COT Working Group on Variability and Uncertainty in Toxicology about strain differences in xenobiotic metabolism, Dr Michael Festing submitted a number of papers and correspondence.

1.37 Dr Festing's proposal was to use multiple genetically well-characterised inbred strains of laboratory animals in toxicity testing (a multi-strain assay; MSA) in place of an equal number of animals from one or two outbred strains. Dr Festing submitted further correspondence to the COT and the Committee invited him to the February meeting to discuss his views.

1.38 In the light of discussions at this meeting and the meeting in April 2009, members felt that there was value in looking at the theoretical advantages of Dr Festing's proposals, but at that time there was little evidence that utilisation of MSAs would improve on the current risk assessment paradigm. If regulatory frameworks were to change to request MSAs in place of one or more inbred or outbred species then the benefits would need to significantly outweigh the disadvantages of the change. The Committee returned to this topic at their June and September meetings in 2009 to discuss correspondences with Dr Festing. A number of further issues had been identified and it was agreed that no further discussion of this topic was required.

1.39 Minutes of these discussions at the February, April, June and September meetings can be found on the COT's website: http://cot.food.gov.uk/cotmtgs/cotmeets/

National Diet and Nutrition Survey

1.40 The COT was provided with a paper on the National Diet and Nutrition Survey (NDNS) programme and was requested to comment on its utility and importance, particularly with respect to informing UK consumer exposure assessments for chemicals in food. The COT comments were used to inform the review of the FSA's nutrition research and survey portfolio.

1.41 The NDNS programme gathers detailed information on food consumption (by dietary record); nutrient intake (by combining food consumption data with data on the nutrient content of foods); nutritional status (by measurement of blood and urine analytes); physical measurements (for example, height, weight and blood pressure); and socio-economic, demographic and lifestyle characteristics. One of the key benefits of the NDNS programme is the provision of this information in the same individuals; this allows the analysis of links between these parameters.

1.42 In April 2008, a new rolling programme was set up to collect data continuously. The core NDNS rolling programme examines a UK representative cross-sectional sample of 1000 individuals aged 1.5 years

and upwards per year (excluding pregnant and lactating women and people in institutions). The rolling programme provides more frequent dietary data for better tracking of trends over time and allows greater flexibility to respond to changing policy needs, for example, to collect additional data for a specific population group where a need has been identified.

1.43 The NDNS programme provides evidence about the dietary habits and nutritional status of the UK population and is the main source of dietary data used by the FSA for conducting exposure assessments for chemicals in food.

1.44 The Committee unanimously agreed that the NDNS programme is an important resource and supported the move to the rolling programme for continuous rather than periodic data collection. It was noted that the NDNS programme has a wide usage, which supports academic research in addition to informing policy.

Organophosphates and human health: outstanding Government-funded research

1.45 In 1999 the COT published a report entitled “Organophosphates,” which considered whether chronic low level exposure to organophosphates, or acute exposures to levels insufficient to cause overt toxicity, can cause long term adverse health effects. The COT report made recommendations for research in five different areas, expressed in the form of questions to be addressed. Research to address the recommendations was funded jointly by a number of Government Departments. In 2007 the Committee considered a review of the research reports available at that time. At its September 2009 meeting the Committee considered three additional research reports, and the final one was considered in December 2009.

Research project 1: report on SHAPE: Survey of Health and Pesticide Exposure

1.46 This project was a clinical investigation of selected farmers who has reported symptoms of peripheral neuropathy in phase 1 of the SHAPE study. The study design involved unblended examination of patients without a control group and thus could not be used to draw conclusions regarding the association of exposure with findings on clinical investigations, or with signs or symptoms of peripheral neuropathy.

1.47 The Committee received expert advice on the neurophysiological testing. The sample size was considered small and the neurophysiological testing very limited. There were no control subjects or background data on the expected range of values for neurophysiological tests undertaken by the study investigators. Only one upper limb nerve (median in the hand) had been studied and the authors had not controlled for carpal tunnel syndrome. The deep peroneal nerve had been investigated in the lower limb. The extent of electrodiagnostic investigations was considered inadequate to clinically investigate nerve conduction. The researchers had stated the F-response to be a monosynaptic reflex response, which is incorrect; and no data on F-response were presented. The investigators had not attempted to correlate the results of clinical assessments of individuals for signs (e.g. loss or abnormal sensations in extremities) symptoms (e.g. muscle weakness), electrodiagnostic status, and quantitative sensory testing. There was no mention of having controlled for skin temperature. Muscle weakness was poorly defined in the questionnaire, and when assessed clinically only a small number of patients had muscle weakness. It was noted that nerve conduction velocity was more affected in the upper limbs of patients than the lower limbs which would be contrary to expectations from the dying-back neuropathy suggested by the researchers. There was discussion of autonomic dysfunction in patients, but this was not objectively studied.

1.48 The researchers referred to electromyography (EMG) results but no data were presented and there was no quantitative analysis, which would have been informative. The investigation of reflexes was too limited to draw conclusions. It was observed that it was difficult to assess ankle jerks consistently; thus ankle jerks needed to be investigated by a single trained assessor. Quantitative sensory tests for peripheral neuropathy were considered particularly difficult to undertake and had not been adequately performed in this study. Unexposed controls would be needed with assessors blind to exposure status. It is also possible that findings are incidental, if not enough nerves are studied. Testing at least three nerves in the upper limbs and three in the lower limbs would be recommended. Overall, there were many contradictions and the findings neither proved nor disproved clinical neuropathy.

1.49 The situation was different when diagnosing individual patients than in investigation of a group of exposed individuals, but the minimum number of nerves tested would be more than in this study, and on both sides of the body if necessary. Each department should have its own normative data. Each person conducting the testing should have their own normative data. Diagnosis would typically be dependent on findings being below the limit

of the normal range. It was not clear how the normative standards reported by the study investigators had been derived.

1.50 The Committee considered the lack of adequate control data to be a major weakness. There was insufficient information on many aspects of neurophysiological investigations which would have been important for a full assessment of the data, including, for example, on autonomic function and the results of EMG investigations. However, the Committee also considered it important that the researchers should have an opportunity to respond. To summarise, in a selected sample, the researchers had found unusual patterns of neurophysiological responses, but the tests undertaken were technique- and observer- dependent and the Committee could not conclude that genuine abnormalities had been identified.

Research report 2: report on disabling neuropsychiatric disease in famers exposed to organophosphates

1.51 There were major problems with the interpretation of the data from this study, arising from the lack of blinding of exposure and outcome measurements, the low response rate, and limited assessment of confounding. The Committee commented that the study should be considered as a cross sectional investigation, that the methods for investigation of clinical outcomes (in particular peripheral neuropathy and symptoms of Parkinson's disease) were limited, and that the exposures evaluated were to sheep dipping rather than to specific organophosphate pesticides. The low response rate in the phase 2 investigation further limited the value of the study, as had been acknowledged by the study investigators. It was suggested the authors should undertake logistic regression analyses to further investigate the impact of confounding. There was no association with depression and a link with Parkinson's disease appeared unlikely. The findings on peripheral neuropathy suggested an association with sheep dipping, but they were liable to recall bias and no definite conclusions could be reached.

1.52 The Committee considered that the study report had been drafted to a high standard and the investigators had been aware of the inevitable limitations of the study design. The Committee concluded that little reassurance could be drawn from the absence of positive associations for some health outcomes. Nor could conclusions be reached regarding causality from the positive associations that were observed.

Research report 3: Neuropsychological and psychiatric functioning in sheep farmers exposed to organophosphate pesticides

1.53 The interpretation of results was hampered by various aspects of the analyses undertaken, including amalgamation of data on different tasks into a single average score, limited attempt to explore the locus of cognitive functions that might be impaired, and the analysis of continuous performance measures as binary variables (normal/impaired function). There were also some inconsistencies in the findings (e.g. verbal ability was negatively associated with exposure in additional analyses but there were no group differences in the main analysis). Overall, whilst there appeared to be evidence for impairment, the precise nature of this remained to be elucidated, and given the influence of verbal abilities on memory and other cognitive functions, there remained a question of whether associations would remain after appropriate control for this, and whether the impaired motor skills in simple tasks would translate into the observed impairments of speed in cognitively more demanding tasks. These additional analyses could be explored using the available data set.

1.54 Recruitment had been based on self-reported exposure. Neuropsychological testing had been performed by investigators who knew the subjects' occupational status (farmer (exposed) or police officer (control)) but without detailed knowledge of their exposure. Selection was based on reported low level exposure to organophosphates with exclusion of farmers who reported evidence of acute toxicity to organophosphates. It was noted that the response rate had been very low and that recruitment had been partly via campaign groups. Controls were excluded if they had experienced psychiatric problems at any time in the past, but farmers were not excluded if they had suffered psychiatric problems only after they were first exposed to organophosphates (which typically was many years earlier). Some participants had been excluded to improve matching, and it was not clear how these participants were selected, although this was unlikely to make a large difference to the results. The authors had also included comparisons of test data from exposed study subjects with published test norms derived from a cross section of healthy adults in the general population.

1.55 There was a correlation of cognitive function with duration of exposure, but it was not clear if adjustments had been made for age. The Committee was aware that there is a high rate of early retirement due to ill health in police officers.

1.56 It was reported that no association was found between genotype and paraoxonase (PON1) activity measured under non-physiological

conditions. Such assay conditions are not predictive of inter-genotype differences in PON1 activity towards diazinon *in vivo.* No difference was reported in farmers according to work status in either genotype or phenotype. The Committee was unable to reach any conclusions regarding a possible association between PON1 phenotype and neuropsychological outcome on the basis of the information provided.

1.57 The Committee received expert advice on the neuropsychological testing undertaken. The Committee was informed that performance could be impaired by deficits anywhere along a chain of functions that were assessed by a particular test, including, but not limited to, cognition. Therefore the results of tests should be analysed for specific patterns of impairment, not just overall deficits, which had not been done. The statistical approach was considered acceptable in the assessment of clinical status of individuals but less so for group analysis. ANOVA had been used to assess the results of ranges of tests, but the analysis conducted would not tease out the precise nature of any impairment in the exposed group. Thus some of the reported deficits thought to be due to cognitive deficits could be simply due to motor impairment.

1.58 Differences in performance of tasks could be expected between rural farmers and rural police officers. The population norms used were not specified to be from the UK, and results of neuropsychological tests can vary geographically. Test results are also age-dependent, but there appeared to be no separate evaluation of adjustment for age. There would be differences in absolute performance between different geographical population groups but differences in relative performance would not be expected. Further analysis of the datasets would be possible. Adjustment for mood could be included in any further analyses of test data if it were a confounding factor for the specific tasks under analysis. The Committee observed that there were no differences between farmers who had retired through ill health and those currently working, contrary to a prior hypothesis of the researchers.

1.59 In summary, there was some evidence of poorer performance in farmers, but although a large number of tests had been performed, the analysis was not focused, so it was not clear what was causing the poorer performance. Additionally, there was still a need to identify appropriate UK control data, and to adjust for age where it was a potential confounder. It was possible that many of the cognitive differences reported might disappear after adjustment for motor performance. The Committee concluded that no definite conclusions could be drawn from this study report but the data could be subject to further analysis.

1.60 The Committee discussed the extent to which these three research projects addressed the research recommendations made by the COT in 1999. The Committee concluded that the studies reviewed needed to be considered in the context of the review of Government funded research carried out by COT in 2007 and the ongoing review of the peer-reviewed scientific literature on organophosphates. No clear conclusions could be reached from the reports reviewed at this meeting. One Member commented that a particular challenge in the epidemiological investigation of low-level exposure to organophosphates was the difficulty in ascertaining exposure to organophosphates specifically, rather than to pesticides in general, and in excluding confounding effects of other factors associated with farming.

1.61 The Committee discussed the extent to which these three research projects addressed the research recommendations made by the COT in 1999. The Committee concluded that the studies reviewed needed to be considered in the context of the review of Government funded research carried out by COT in 2007 and the ongoing review of the peer-reviewed scientific literature on organophosphates. No clear conclusions could be reached from the reports reviewed at this meeting. A particular challenge in the epidemiological investigation of low-level exposure to organophosphates was observed to be the difficulty in ascertaining exposure to organophosphates specifically, rather than to pesticides in general, and in excluding confounding effects of other factors associated with farming.

Research report 4: Prospective cohort study of sheep dip exposure and 'dipper's' flu'

1.62 In 2007, the COT saw an interim report of this research project. The final report of the project was now available, and the Committee was asked to consider the final report and advise on the significance of the results.

1.63 The study showed that sheep dipping as an activity was associated with subjective reporting of ill health effects. However, the study did not show an association of health effects with objective measures of exposure to organophosphates or pyrethroids. The pattern of health effects did not indicate dipper's flu as it had been previously described. It was surprising that there did not appear to have been an association between pyrethroid dip use and dermal paraesthesiae. The Committee agreed that re-analysis of the data to determine whether dermal paraesthesiae was associated with repeated pyrethroid use or pyrethroid metabolites in urine would be useful to explore a potential exposure-symptom link.

1.64 The Committee expected there to be considerable physical activity involved in sheep dipping which might explain effects such as musculoskeletal pain or fatigue in the following days; there was no control for this.

1.65 Farmers had used organophosphate dips, pyrethroid dips, pour-ons containing pyrethroids or other substances, and/or avermectin injections to treat sheep ectoparasites. Some farmers would have used a combination of products. The results were not broken down by type of application though this would be reflected by the type of active ingredient involved (organophosphates were not injected).

1.66 The COT considered the subject selection, observing that approximately 8700 people were approached to take part, one half did not respond, and ultimately 9.3% of those approached were interviewed. Not all of the interviewed farmers completed symptom diaries and only 5% completed the study. There might be an over-representation of farmers with ill health since they could be more motivated to take part. However, farmers were not included if they were not actively involved in sheep dipping between May 2005 and July 2006, so the study would miss farmers who had retired early due to ill health. Bias may have occurred as farmers who considered they had suffered 'dippers' flu in the past may have been more willing to take part in the study. The prevalence of previous dipper's flu in participants was observed to be more than 20%. Overall it was concluded that there were some difficulties in extrapolating the results to sheep farmers in general, but that the sample was probably a reasonable representation of the community overall.

1.67 Butyrylcholinesterase activity, used to assess exposure to organophosphates, decreased in some farmers following treatment of sheep, and increased in others. Since no farmer had a decrease of more than 20.8%, the Committee considered that the decreases could be consistent with normal variation and it was not possible to conclude that there was evidence of significant exposure to cholinesterase inhibiting agent(s). Changes in butyrylcholinesterase activity (at any level) are not considered to indicate an adverse effect in the absence of an effect on acetylcholinesterase activity measured in erythrocytes.

1.68 Other observations made by the Committee were that:

- Farmers with a certificate of competence for handling pesticides were less likely to report symptoms, which could indicate that other exposures were responsible for reported symptoms.

- The incidence of health effects was highest during the first two days following treatment, but was not associated with indices of organophosphate exposure.
- There was no association between health effects and endotoxin concentration in sheep dip at the end of dipping, but exposure to endotoxins might be more related to the activity of the farmer than the concentration of endotoxins in the dip.
- Only three farmers were reported to have temperatures above 38.2°C after dipping, and this was not related to indices of exposure.
- The presentation of confidence intervals rather than statistical significance would have aided interpretation of results, and there was multiple testing.
- Some of the adjustments made might not be appropriate – for example, having a history of dipper's flu might be an effect modifier rather than a confounder.
- The incidence of dipper's flu in the study varied greatly depending on how many symptoms were included.
- It would be useful to see if there were differences in clinical biochemical parameters between visits one and two.

1.69 The Committee wondered whether exposure to organophosphates from sheep dip use would have decreased since the 1990s and whether there was any evidence that reports of dipper's flu had decreased.

1.70 Approximately 30% of total immunoglobulin E (IgE) blood levels were outside the reference laboratory range on visit two (i.e. following treatment). It was not clear whether there had been any analysis of IgE prior to treatment. More than 30% of farmers reported having various allergies. The Committee wondered whether the time of year of treatment might be important. For example, dipping in the hay fever season might cause the increase in Ig E levels and not chemical exposure.

1.71 Overall, the COT concluded that the study did not provide evidence for acute toxic effects of organophosphates in sheep dippers, though the exposure was low. The negative results could be due to: a) exposure to organophosphates in sheep dippers now being lower than previously; b) limitation of adverse effects to a small number of susceptible individuals, who were not represented in this study; or c) illness described as dipper's flu not being a consequence of exposure to organophosphates. This particular study did not provide information on chronic effects.

1.72 With regard to research recommendation ii) from the Committee's 1999 report "Organophosphates" (how common is 'dipper's flu' and what causes

it?), the Committee agreed that the study provided information on the frequency symptoms of 'dippers flu' after sheep dipping, and indicated that they are not specific effects of organophosphate compounds. With regard to research recommendation iii), the study did not provide evidence of adverse effects due to low level exposure to organophosphate compounds, and did not identify a subset of susceptible individuals.

Pathway Analysis Software for the interpretation of complex datasets

1.73 At its April 2009 meeting whilst discussing the workshop on 21st century toxicology, the Committee noted:

In order to aid the interpretation of toxicological results obtained in vitro and in silico, such results will need to be incorporated into the physiologically-based pharmacokinetic models and pathway analysis strategies that underpin systems biology. It was noted that in vivo research in fields outside toxicology may provide good examples of practical applications. Correspondingly it was felt that a review of pathway analysis strategies could be useful.

1.74 In the past decade there has been an explosion of high-content and high-throughput data associated with a large number of disease states, chemical exposures and biological species. To fully interpret this information it has become necessary to develop a range of software tools that will identify the potentially biologically important patterns within a given set of data, and present it in a context that is both understandable to non specialists and searchable so that the data underlying the constructed networks can be viewed and assessed. To this end a number of analysis tools have been developed. The Committee were provided with an overview of the most commonly used software suites that are available for the interpretation of complex datasets.

1.75 The three major concepts (literature mining, over-representation analysis, and gene ontology) and the commonly used databases that are relied upon for network analysis were highlighted. There are two levels of analysis, namely, pathway identification and pathway visualisation, and the limitations of such analysis software were discussed.

1.76 The Committee agreed that analysis tools are useful for complex datasets, providing a plausible pathway for further identification, rather than an endpoint. The Committee noted that they needed to be aware of such approaches to analysing data because it would be likely that the

Committee would be reviewing increasingly more information from high throughput screening.

Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS)

1.77 Levels of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) were measured in the 2004 Total Diet Study and the Committee had previously been invited to assess the toxicity of these contaminants. It had published statements in 2006 which recommended TDIs of 3 and 0.3 µg/kg bw per day, respectively. At that time the Committee had stated that the TDIs should be reviewed if new information became available.

1.78 Recent publications by EFSA[c] in 2008 and the Office of Water of the US Environmental Protection Agency[d] in 2009 had proposed lower health-based guidance levels for PFOA and PFOS than those recommended by the COT. The US EPA had subsequently proposed limits for these substances in drinking water which were far lower than those used in the UK.

1.79 Members were asked to review their previous advice in the light of the new evaluations by the EFSA and the US EPA. The difference in the assessments was not in the toxicological endpoints used to derive the TDIs, but in the uncertainty factors applied and the reasoning behind them. The EFSA had used an additional factor of 2 to compensate for uncertainties relating to the internal dose kinetics, whereas the US EPA had developed data-derived extrapolation factors for toxicokinetics, concluding that measures of internal exposure should be used for interspecies extrapolation.

1.80 Regarding PFOA, Members were able to follow the reasoning of the EFSA approach, which they considered justifiable. The COT concluded that the US EPA approach was unsatisfactory because it made too many assumptions that were not supported by data and the uncertainty factor of 81 for interspecies toxicokinetics, as opposed to 4 and 8 applied by COT and EFSA respectively, was excessive. The Committee concluded that some additional allowance for interspecies toxicokinetic differences (such as that used by the EFSA) was appropriate. The COT therefore adopted the TDI derived by the EFSA for PFOA (1.5 µg/kg bw per day).

[c] http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902012410.htm.
[d] http://www.epa.gov/waterscience/criteria/drinking/pha-PFOA_PFOS.pdf.

1.81 Regarding PFOS, Members noted that similar concerns regarding the US EPA methodology applied to PFOS. They agreed there was no need to account for uncertainty due to the short duration of the critical study in primates because an extensive database in rodents supported the primate NOAEL. They concluded that the larger uncertainty factor used by the EFSA and the US EPA to allow for differences in interspecies toxicokinetics was not necessary. Members therefore re-confirmed their previous evaluation of PFOS and the TDI of 0.3 µg/kg bw per day.

1.82 An updated statement on the TDI for PFOA can be found at: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2009/cot200902

Polychlorinated naphthalenes in Food

1.83 The Committee was asked for advice on possible risks associated with the levels of polychlorinated naphthalenes (PCNs) in foodstuffs that had been found in an FSA investigation.

1.84 PCNs are a group of 75 congeners, with structures similar to those of polychlorinated dibenzo-p-dioxins and -furans (PCDDs and PCDFs). The PCN congeners contain between one and eight chlorine atoms bound to the naphthalene structure.

1.85 PCNs were formerly manufactured extensively, and they possess high chemical and thermal stability, good weather resistance, good electrical insulating properties and low flammability properties. Their usage is now banned in most countries, including the UK. PCNs can also be produced as combustion products during waste incineration and may also be released when products containing PCNs are disposed of to landfill.

1.86 PCNs have been detected in fish and human milk in other countries. The FSA investigation was carried out as there were currently no UK data on PCNs in food.

1.87 The COT concluded that because some PCNs exhibit dioxin-like activity, protection of public health requires a cumulative approach to risk assessment for this aspect of their toxicity. The currently available data were inadequate to establish TEFs for PCNs, but in the absence of other data, relative potencies compared to TCDD from in vitro studies could be used as a highly conservative approach to indicate if dioxin-like activity of PCNs in food presents a risk to the consumer. It was considered unlikely

that all the toxic effects of PCNs occur through interactions similar to those of dioxins, but the available studies on PCNs were not considered sufficient to permit a full hazard characterisation. Although the data were insufficient for a robust risk assessment, the results of the FSA investigation did not suggest specific toxicological concerns.

1.88 The COT statement can be found at: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2009/cot200905

Toxicological aspects of the SACN report on Iron

Introduction

1.89 In their 1998 report, *Nutritional Aspects of the Development of Cancer*, the Committee on Medical Aspects of Food Policy (COMA) highlighted the possible links between red and processed meat and colorectal cancer and recommended that "*higher consumers should consider a reduction*" in consumption. However, it was also noted that as this could compromise iron status, the possible adverse implications of this advice should be the subject of review. To assess this, the Scientific Advisory Committee on Nutrition (SACN), the expert committee succeeding COMA, established a working group to consider iron and health. In their review, the SACN Working Group considered both the beneficial and adverse effects of increased and decreased iron intakes.

1.90 The draft report of the SACN working group was published for consultation in June 2009 and the COT was asked to comment on the sections of the report that considered the possible adverse effects of excess iron and, in particular, the potential adverse effects on iron supplementation on growth in iron-replete children and on the incidence and morbidity of infectious disease.

Negative effects on the growth of iron replete infants

1.91 Several studies are available that suggest iron supplementation could reduce weight and length gain in iron-replete infants (Idjradinata *et al*, 1994; Dewey *et al*, 2002: Majumdar *et al*, 2003; Lind *et al*, 2008) compared to placebo, although this effects was not reported in a small study by Ziegler *et al* (2009). The COT agreed with the draft SACN conclusion that *"Limited evidence suggests that iron supplementation may have detrimental effects on the physical growth of iron replete infants and children*" but noted that it was uncertain whether the effect would occur in older children, since the children in the studies were aged between 4 and

24 months. It was also recognised that the doses of iron used in the supplementation studies were significantly higher than both iron intakes from food and the Reference Nutrient Intake for iron. It was agreed that any advice would need careful targeting, so that children who needed iron supplementation for medical reasons, would not be deterred from taking them.

Effect of iron supplementation on infectious disease incidence and morbidity

1.92 The COT considered the section of the draft report discussing the effects of excess iron on the incidence and morbidity of infectious disease and the draft conclusion that "*On balance, there is no evidence to suggest that improving iron status in the UK would have any impact on infectious disease incidence or morbidity. Some evidence suggests that iron supplementation to improve iron status may have adverse effects in some subgroups of the population, e.g. those with HIV and children at risk of diarrhoea*". The COT agreed with this conclusion and added that there were a number of studies suggesting that occupational inhalation of metal fumes was associated with an increase in respiratory disease such as lobar pneumonia which might be of relevance to this section of the report. The Committee noted that the effect of iron on emerging diseases such as H1N1 influenza should also be considered.

Other aspects of high iron intake considered in the draft report

1.93 Members had no comments on other effects associated with iron excess and did not wish to consider any topic in more detail. It was noted that the COC would be providing comments with respect to the associations between iron and red meat intake and carcinogenicity.

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Vitamin E in pregnancy

Introduction

1.94 Vitamin E is a generic description of a group of eight lipid soluble chemicals which prevent lipid oxidation and maintain membrane integrity throughout the body. As a result of vitamin E's anti-oxidant function, it has been investigated for potential beneficial effects in women at risk of pre-eclampsia.

1.95 In a large randomised placebo-controlled trial by Poston *et al.* (2006) women were given 1000 mg vitamin C and 400 IU vitamin E or placebo. More low birth weight babies were born to women in the treatment group (28%) compared to the controls (24%). The mean birth weights of the babies in the treatment and placebo groups were 2901 and 2967 g respectively. Additionally, in a small prospective observational study by Boskovic *et al* (2005) it was suggested that birth weights were significantly reduced (3173 $\pm$ 467 g) in the babies of women who had taken more that 400 IU vitamin E per day during pregnancy, compared to the babies of women in the control group (3417 $\pm$ 56 g). The authors themselves noted that the finding could be due to chance.

1.96 As part of their horizon scanning exercise, the COT considered whether the papers raised concerns about the potential effects of vitamin E in pregnancy, and whether there was sufficient information available to make a full review of vitamin E in pregnancy worthwhile. The Committee initially considered the study by Poston *et al* (2006) noting that, although this was a large and randomised trial, the different characteristics of the two groups, as described in the paper, indicated that the association could be due to chance. They concluded that the finding was of interest but did not indicate significant concern. Members then considered that the investigation by Boskovic *et al* (2005) noting that this was a small study

with a strong potential for selection bias and the results could be due to chance. It was considered that there was no likely or plausible mechanism for the reported effect at the doses of vitamin E present in supplements. There were few animal studies investigating the effects of vitamin E alone but, where these were available, there was no indication of any adverse effects. It was noted that both the UK Expert Group on Vitamins and Minerals and the EU Scientific Committee on Food had undertaken full reviews of vitamin E to establish safe upper levels and had not identified any concerns.

Additional information

1.97 Although COT members considered that the two studies did not indicate significant concern they requested additional information on a number of areas: whether there were any intervention studies currently in progress; the status of any relevant Cochrane reviews; details of the relevant animal data as considered by EVM and SCF; and, effects associated with vitamin C. This was provided at a subsequent meeting.

1.98 There were three relevant Cochrane systematic reviews: vitamin E supplementation in pregnancy (Rumbold and Crowther, 2005a), anti-oxidants for preventing pre-eclampsia (Rumbold and Crowther, 2008) and vitamin C supplementation in pregnancy (Rumbold and Crowther, 2005b). No evidence of any effects on birth weights was noted in the reviews but the number of studies considered was very small. In addition to the Poston *et al* (2006) study, two additional studies were considered in the Cochrane reviews, these reported that anti-oxidant treatment (1g vitamin C and 400 IU E) was associated with a non-significant decrease (Beazley *et al*, 2005) and a non-significant increase (Rumbold *et al,* 2006) in birth weights respectively. As most of the studies were examining the effects of anti-oxidants on pre-eclampsia, the anti-oxidant treatment was given late in pregnancy, usually in the second trimester, making it difficult to draw conclusions.

1.99 It was noted that there were several large intervention studies of the effects of anti-oxidants in pregnancy currently in progress, but it was unclear when any publications were expected.

1.100 The COT agreed that the available animal data, while limited, did not suggest any concerns with regard to vitamin E since doses up to 1500 mg/kg bw had not resulted in any adverse effects. There were also no data suggesting that vitamin C was associated with adverse reproductive effects.

Conclusion

1.101 Overall, COT members agreed that a full review of vitamin E in pregnancy was not necessary at the current time, but that it should remain under review.

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Committee procedures

Horizon Scanning

1.102 At the February 2009 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.

1.103 A Member alerted the Committee to the use of over-the-counter antacids by pregnant mothers and evidence of increased asthma in their children. This was agreed by another Member who noted that there were some animal data confirming this association.

1.104 Members also discussed the balance of expertise on the Committee and agreed that ‘dietary exposure assessment’ and ‘systems biology’ should be added to the list of specialist expertise required by the Committee.

Working Groups and Workshops

Lowermoor Subgroup

1.105 Members were previously informed that the deaths of two individuals who had lived in the area which received contaminated water following the 1988 Lowermoor Water Pollution Incident had been referred to the West Somerset coroner. The two individuals both had a neurodegenerative disease and had been reported to have higher than usual levels of aluminium in the brain. Information on brain neuropathology and aluminium concentrations was available for one of the individuals but not the other.

1.106 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 had been postponed to November 2010 and therefore the final Subgroup report will not be published until 2011.

Workshop on 21st Century Toxicology

1.107 In February 2009 the Committee held a one-day workshop on 21st Century toxicology where invited experts gave presentations on recent advances in toxicology. Insights into uses for toxicogenomics, computational toxicology, metabonomics and batteries of high-throughput screens were described with an emphasis on moving towards obtaining greater mechanistic understanding.

1.108 Such understanding informs risk assessment and can provide a basis for developing predictive toxicology. Members participated in discussions along with other delegates at the meeting and subsequently while producing a statement containing the speakers' abstracts and summarised discussions.

1.109 The COT statement can found at: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2009/cot200903

Ongoing work

Chemical exposure resulting from landfill sites

1.110 In 2001, the Committee published a statement on a major study of health outcomes in populations living around landfill site. The Committee was largely reassured by the findings but considered that the small raised risk for all congenital anomalies for people living around special waste landfill sites merited further investigation. At the time, the Committee was informed that a programme of research and reviews was underway on congenital anomalies and landfill sites. This included a project 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).

1.111 The Committee reviewed the results of these studies from 2007 to 2009. A statement is under preparation and will be published in 2010.

Idiopathic Environmental Intolerance: Evidence for a toxicological mechanism

1.112 In their conclusions on the Royal Commission on Environmental Pollution (RCEP) report on crop spraying and health of residents and bystanders, the Committee had recommended that a further review of Idiopathic Environmental Intolerance (IEI, also described as Multiple Chemical Sensitivity) be undertaken.

1.113 The COT have considered a draft discussion paper on the evidence for toxicological mechanisms for IEI. The COT requested further consideration of psychological aspects of IEI in consultation with experts in psychology. Further discussions will take place during 2010 after which a statement will be drafted.

Para-occupational exposure to pesticides and health outcomes

1.114 In September 2009 the COT considered a review of para-occupational exposure to pesticides and health effects in people in a para-occupational setting. An example of para-occupational exposure to pesticide is someone who co-habits with a farm employee, who has the potential to experience greater exposures to pesticides than a neighbour who does not. The COT will complete its evaluation after the COC has provided its opinion on the studies relating to cancer.

Waste and Resources Action Programme (WRAP)

1.115 Waste And Resources Action Programme (WRAP) Confidence in Compost Programme's had produced three peer-reviewed risk assessments looking at biological and chemical risks associated with the use of composts from different source segregated feedstocks across a range of agricultural sectors. The FSA intends to seek advice on the microbiological aspects from the Advisory Committee on the Microbiological Safety of Food (ACMSF) and on chemical aspects from COT early in 2010. The COT discussed an initial paper on the background to the work, its context and the methodology used for the assessment of risks.

2009 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

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Declaration of COT members' interests during 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	Halifax Standard Life	Shareholder	Colt Foundation British Occupational Health Research Foundation Faculty of Occupational Medicine Public Health Commission	Trustee Trustee President and Trustee Member
Dr D Bell	Alliance & Leicester BAA BG Centrica HBOS Plc International Power National Grid RT Group Rolls Royce Scottish Power Thus Transco United Utilities University of Nottingham	Shareholder Employee	Food Standards Agency Central Science Laboratory Dow Aptuit Inc EFSA CEF Panel British Toxicology Society	Research Contract Part funded PhD studentship Research Grant Consultancy Member (with renumeration) Member of executive committee

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) 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
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	NONE	NONE	Schering AG Yamanouchi	Research Grant

Dr C Elcombe	CXR Biosciences Ltd	Salaried Director Shareholder	Various Pharmaceutical and chemical companies	Contract Research at CXR
Dr J Foster	AstraZeneca	Shareholder	NONE	NONE
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	The Forensic Institute, University of Edinburgh Lothian NHS Response Genetics University of Florida University of Canberra	Shareholder Consultant (no fee payable) Consultant Consultant	EMMS Nazareth Melville Trust Medical Research Scotland Alma Diagnostics Yorkshire Cancer Research DoH GTAC HPA Committee on Carcingenicity CRUK Science Strategy Advisory Group Biomedical & Therapeutics Res Comm. (Scotland)	Trustee Trustee Trustee Research Collaboration Scientific advisory committee Vice chair Member Member Member
Dr J Hinson (to 31st March 2009)	GlaxoSmithKline	Shareholder	Society for Endocrinology Journal of Endocrinology Current Opinions in Endocrinology and Diabetes	Council member and Education Advisor Member of the editorial board

Dr P Jackson (to 11th February 2009)	Carillion Computacenter Ecofin Friends Provident Hochschild Mining Plc Informa Legal General Mapeley Melrose Senior St Ives St James Place Capital TT Electronics Venture Production	Shareholder	Bayer	Departmental Research Funding
Professor J Konje				
Professor B Lake (from 1st April 2009)	LFI/BIBRA	Consultancy	British Toxicology Society Society of Toxicology	Member Member
Dr G McNeill	Smith & Nephew Diageo Café Direct BHP Billiton	Shareholder	World 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	NONE	Xenobiotica British Toxicology Society Pfizer GlaxoSmithKline AstraZeneca	Associate Editor Member of Education sub-committee Research Funding

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Miss A Ward	NONE	NONE	Farm Animal Welfare Council	Member
Mrs A Williams	NONE	NONE	NONE	NONE