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

Annual Report 2012

Contents

ABOUT THE COMMITTEES 3

***COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT* 4**

PREFACE 5

COT EVALUATIONS 6

Caffeine and alcohol: combined effects on health and behaviour 6
Default values to be used in risk assessment in the absence of actual measured data 6
Dioxins - reanalysis by EPA 9
Expression of uncertainty 11
Phytoestrogens Research Programme 12
Risks of chemical toxicity and allergic disease in relation to infant diet 13
Toxicogenomics data in risk assessment 15

COMMITTEE PROCEDURES 17

Horizon Scanning 17

WORKING GROUPS 18

Bystander Risk Assessment Working Group (BRAWG) 18
Working Group on the review of epidemiological literature on organophosphates and health outcomes relating to the nervous system 19
Lowermoor Subgroup 19

ONGOING WORK 21

Risks arising from the infant diet and the development of atopic and autoimmune disease 21
SACN review of dietary guidelines for vitamin D 21
Toxicity of chemicals in the infant diet 22

2012 MEMBERSHIP OF THE COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT 24

DECLARATION OF COT MEMBERS' INTERESTS DURING (2012) THE PERIOD OF THIS REPORT 27

About the Committees

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

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

In common with other independent advisory committees, Committee members are required to follow a Code of Conduct which also gives guidance on how commercial interests should be declared. Members are required to declare any commercial interests on appointment and, again during meetings if a topic arises in which they have an interest. If a member declares a specific interest in a topic under discussion, he or she is normally excluded from the discussion. In exceptional circumstances, and at the Chairman's discretion, the member may be allowed to contribute to the discussion (e.g to answer specific questions), but not to decision-making. Annex 1 contains the terms of reference under which the Committees were set up. The Code of Conduct is at Annex 2 and Annex 3 describes the Committees' policy on openness. Annex 4 has the Good Practice Agreement for Scientific Advisory Committees. Annex 5 contains a glossary of technical terms used in the text. Annex 6 is an alphabetical index to subjects and substances considered in previous reports. Previous publications of the Committees are located at Annex 7.

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

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

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

This report contains summaries of the discussions and includes the Committees' published statements in full in order to fulfil the obligation to publish statements both electronically and in hard copy.

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

Preface

I am pleased to present this report, which summarises the work of the Committee on Toxicity (COT) during 2012. 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 2012, the Committee published four statements covering: possible toxic interactions of caffeine and alcohol; an evaluation of FSA's research programme on phytoestrogens; developments in toxicogenomics and their potential relevance to toxicological risk assessment; and risks of chemical toxicity and allergic disease in relation to infant diet. The last of these presented initial conclusions from an ongoing programme of work that is being undertaken in collaboration with the Scientific Advisory Committee on Nutrition (SACN), which will determine whether any changes are warranted to the Government's current dietary advice for infants and young children.

Work was also completed on two major reports compiled by working groups of the Committee. The first, which was produced jointly with the Advisory Committee on Pesticides (ACP), addressed methods of regulatory risk assessment for exposures to pesticides in bystanders and residents living near to treated crops. The second concerned possible long-term toxicity following an incident in 1988, in which water supplies in Camelford, North Cornwall, were contaminated by aluminium sulphate. This was a detailed and thorough investigation, and I am extremely grateful to Professor Frank Woods, a former Chairman of COT, who chaired the working group.

Other activities included consideration of proposed default values for parameters such as body weight, to be used in chemical risk assessment when empirical data are not available, and review of the toxicological reference dose for dioxins.

The Committee's work has wide-ranging impacts. An example in 2012 was guidance that the Food Standards Agency issued, in particular to people in the bodybuilding community, not to use "fat-burner" products containing the chemical 2,4-dinitrophenol (DNP). This action, which followed two deaths in people believed to have taken such substances, was underpinned by advice that had been given by COT in 2003.

Sadly, in 2012, the Committee lost the services of two long-standing members, Professor Alan Boobis and Dr John Foster, whose valuable expertise is much missed. I thank them for all of the work that they did on behalf of the Committee, and also the secretariat, who as ever, have given us tremendous support.

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

COT evaluations

Caffeine and alcohol: combined effects on health and behaviour

1.1 The Committee on Toxicity (COT) was asked by the Food Standards Agency to comment on concerns that caffeine in energy drinks may interact with alcoholic beverages in causing adverse behavioural or toxic effects.

1.2 Since 2004, energy drinks have been the fastest growing sector of the drinks market in the UK. The popularity of consuming energy drinks mixed with alcoholic beverages has also increased. Moreover, individuals who consume high quantities of both energy drinks and alcohol are perceived to engage in a greater degree of risk-taking. This has raised concerns about the health effects of caffeine and alcohol in combination. In particular, a phenomenon described as “wide awake drunk” has been suggested, in which the stimulatory effect of caffeine prevents consumers of alcohol from realising how intoxicated they are, thereby increasing the potential for toxic damage to the body and adverse behavioural effects. Most energy drinks contain levels of caffeine approximately equivalent to those found in a cup of coffee (approximately 80mg caffeine per 250ml can).

1.3 Currently beverages containing more than 150 mg/l caffeine (other than those based on coffee or tea) must carry the statement ‘High caffeine content’. Under new Regulations, which come into effect on the 13 December 2014, these beverages must carry the statement ‘High caffeine content. Not recommended for children or pregnant or breast feeding women’ in the same field of vision as the name of the beverage, followed by a reference in brackets to the caffeine content expressed in mg per 100ml. There are currently no legal restrictions on the amount of caffeine that may be present in a food or drink product.

1.4 Caffeine acts primarily as a stimulant, increasing arousal and vigilance, reducing fatigue, and decreasing reaction times in some tasks. At higher doses, it can induce insomnia, anxiety, tremors, and seizures. Susceptibility to the effects of caffeine varies between individuals as people develop tolerance with repeated exposure.

1.5 Alcohol is widely consumed in the UK with at least one alcoholic drink being reported as consumed in the week before interview by 68% of men and 54% of women in the 2009 General Lifestyle Survey carried out by the Office for National Statistics. It depresses brain function, and outward signs of intoxication include impaired sensory perception and control of movements, slowed cognition, and stupor. How exactly it causes these effects has not been fully elucidated.

1.6 Accurate estimates of the extent to which alcohol and caffeine are consumed together are not available. One of the reasons for this is that drinks containing alcohol and caffeine are often sold separately and mixed by the consumer rather than being formulated in a single product – for example rum with cola or energy drinks with vodka.

1.7 Various studies were identified which provided relevant information. These included studies of the association between consumption of energy drinks and alcohol, and whether this is influenced by genetic constitution; of risk-taking behaviour, adverse alcohol-related incidents and use of illicit drugs in people who consume alcohol with energy drinks; and of brain function following experimental dosing with caffeine and alcohol in combination. In addition a number of published reports described cases of illness or death following consumption of caffeine with alcohol.

1.8 The balance of evidence suggests that higher intake of caffeine is associated not only with higher alcohol intakes but also with use of other psychoactive substances. There is limited evidence that the relationship may be determined, at least in part, by an individual's genetic make-up. It appears that, at least in some population groups, there is a correlation between high consumption of alcohol and of energy drinks specifically. However, it is unclear whether this is because consumption of energy drinks causes people to drink more alcohol, or because people who are inclined to more risky behaviour tend generally to consume larger quantities of psychoactive substances, including caffeine and alcohol.

1.9 A number of studies have suggested that caffeine can reduce the outward effects of alcohol, especially on reaction times, but other investigations have failed to support this. The evidence that perceptions of alcohol intoxication are modified by caffeine is conflicting. Overall, the range of methods used in reported studies prevents firm conclusions on whether caffeine counteracts the short-term effects of alcohol on brain function.

1.10 Published case reports of illness or death following consumption of caffeine and alcohol in combination do not allow firm conclusions about the contribution of either substance, or on whether caffeine increases the toxicity of alcohol.

1.11 Overall, the COT concludes that the current balance of evidence does not support a harmful toxicological or behavioural interaction between caffeine and alcohol. However, because of limitations in the available data, there is substantial uncertainty, and if important new evidence emerges in the future, then this conclusion should be reviewed.

1.12 The full COT statement can be found at: http://cot.food.gov.uk/pdfs/cotstatementcaffalco201204.pdf

Default values to be used in risk assessment in the absence of actual measured data

1.13 The COT considered guidance published by the European Food Safety Authority (EFSA) Scientific Committee on default values to be used in the absence of empirical data. These values were for bodyweights of different age groups, chronic daily total liquid intake for adults, factors for converting concentrations of substances in the feed or drinking water of laboratory rats and mice to intakes, and uncertainty factors. In addition the guidance advised on the rounding of figures when deriving health-based guidance values. The EFSA guidance is available at: http://www.efsa.europa.eu/en/efsajournal/doc/2579.pdf. The proposed default

values do not need to be used in all cases; alternative values can be used, provided that justification is given.

1.14 Dietary exposure assessments used by the COT generally use empirical data on people's bodyweight within the relevant dietary surveys. Therefore the COT would not usually need to use default bodyweights. However, the COT considered the suggested EFSA defaults of 70 kg for adults, 12 kg for children aged 1-3 years, and 5 kg for infants to be reasonable.

1.15 Similarly, the COT would usually use empirical data on liquid consumption. However, the proposed default of 2 L/day was considered reasonable.

1.16 Some of the factors for converting concentrations of chemicals in the feed of rats and mice to intakes were the same as previously published by the World Health Organization. However, these had been checked and extended. The COT agreed with the proposed factors, which are replicated below. However, the factors should not be used inappropriately; for example, palatability problems can reduce food or water consumption and therefore chemical intake.

1.17 Factors for converting concentrations in feed to daily dose (ppm in diet x factor = mg/kg bw intake)

Study duration	Rat	Mouse
Subacute	0.12	0.2
Subchronic	0.09	0.2
Chronic	0.05	0.15

1.18 Factors for converting concentrations in drinking water to daily dose (ppm in water x factor = mg/kg bw intake)

Study duration	Rat	Mouse
Subacute	0.12	0.18
Subchronic	0.09	0.15
Chronic	0.05	0.09

1.19 The proposed subdivision of the default 100-fold uncertainty factor into sub-factors of 4.0 and 2.5 for inter- species variation in toxicokinetics and toxicodynamics, respectively, and 3.16 each for inter-individual variation in toxicokinetics and toxicodynamics, was consistent with the existing view of the COT as expressed in the 2007 report on Variation and Uncertainty in Toxicology (available at: http://cot.food.gov.uk/pdfs/vutreportmarch2007.pdf). However, the COT cautioned that removing individual sub-factors or replacing them with data-derived values might reduce the reassurance of safety provided by the total composite uncertainty factor. This is because when the default composite uncertainty factor of 100 is used, if one of the individual sub-factors is not adequate for a particular chemical, there will be compensation if one or more of the other sub-factors is larger than necessary for that particular chemical. This potential to compensate for inadequacy

of an individual sub-factor might be reduced if some sub-factors were removed or replaced by data-derived values, and the latter needs to be justified on a case-by-case basis.

1.20 The COT agreed with the proposed approach to rounding of expressing health-based guidance values to one significant figure unless the rounded figure varies by more than 10% from the unrounded figure, in which case the value should be expressed to two significant figures. Rounding should only be at the very end of the process.

Dioxins - reanalysis by EPA

1.21 The COT considered a risk assessment of non-cancer end points for dioxins; Volume 1 of the United States of America Environmental Protection Agency's (US EPA) Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments, accompanied by a second volume of appendices[1] . A subsequent US EPA assessment (Volume 2) yet to be published would cover the cancer end points.

1.22 The EPA reanalysis established a reference dose (RfD) of 0.7 pg/kg bw/day, which is about 3 times lower than the tolerable daily intake (TDI) established by the COT (2 pg/kg bw/day). A number of topics were discussed, such as: the inclusion and exclusion criteria for studies; the use of human data relating to the accident in Seveso in 1976 to establish the RfD; end points addressed in the studies; and the physiologically based pharmacokinetic (PBPK) model and uncertainty factors applied in deriving the RfD. The Committee commented on the US EPA approach in deriving the RfD in comparison with that used by the COT to establish the TDI.

1.23 The US EPA had identified four epidemiological studies and 78 animal bioassays as presenting potentially useful results. After further evaluation, one epidemiology study and 30 animal bioassays had been excluded. The RfD had been derived on the basis of two epidemiological studies related to the Seveso accident, which were considered to provide robust data (Mocarelli et al., 2008[2]; Baccarelli et al., 2008[3]). The modified Emond PBPK model together with the epidemiology studies had been used to derive the point of departure (POD). The EPA comments on the animal data with regard to the National Toxicology Programme (NTP) and FSA-funded studies of Bell et al., 2007, previously reviewed by the COT[3] had also been taken into consideration.

1.24 The COT noted that the Seveso cohort had experienced very high peak exposures to 2,3,7,8-tetrachloro-p-dioxin (TCDD) as a consequence of an industrial accident, and that it might not be appropriate to extrapolate from a POD based on such exposures to populations continuously exposed to much lower background levels of dioxins. An increased level of thyroid-stimulating hormone (TSH), presumed to be

[1] available at: http://www.epa.gov/iris/supdocs/1024index.html and http://www.epa.gov/iris/supdocs/dioxinv1sup_apps.pdf

[2] Mocarelli, P. et al (2008). Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality. Environ Health Perspect116: 70-77.

[3] Baccarelli, A. et al (2008). Neonatal thyroid function in Seveso 25 years after maternal exposure to dioxin.PLoS Med 5: e161.

secondary to other effects, suggested increased clearance of the thyroid hormone, thyroxine (T4). There was a question of whether effects on TSH resulting from increased activity of hepatic liver enzymes, such as the UDP-glucuronosyltransferases (UGTs), were a consequence of current body burden or a lasting effect of the peak exposure in 1976. Other factors such as medications and iodine deficiency could also influence thyroid activity.

1.25 The COT concluded that the Seveso data represented an atypical exposure scenario which could not necessarily be equated with body burdens resulting from lower chronic exposures, and that it was uncertain whether reported health outcomes resulted from an acute or continuous exposure.

1.26 The COT agreed that the assumption of a constant half-life value for the clearance of TCDD from long-term or chronic exposure was not well-supported biologically. TCDD measurements shown in Table 3-14 of the EPA report indicated that the elimination of TCDD may depend on age, protein binding, induction of CYP1A2 and fat content, and that individuals displayed different trends. Although there was some evidence of non-linearity at high doses of TCDD, perhaps due to protein binding, whether there were similar changes at low doses was still unknown. Induction of CYP1A2 in animals was not a good reflection of what happened in humans.

1.27 The COT agreed that use of a PBPK model was preferable to emphasis on half-life, and that a one compartment model was not appropriate. The sensitivity analysis indicated that the PBPK model was influenced by the Hill coefficient. However, this did not appear consistent with known data on organ blood flow.

1.28 The COT agreed with the US EPA approach of excluding studies with higher exposure levels than those providing a basis for deriving a RfD. The US EPA RfD had been based on two epidemiological studies that associated TCDD exposures with adverse health effects. Mocarelli et al. (2008) reported decreased sperm concentration and sperm motility in men who were exposed to TCDD during childhood as a consequence of the Seveso accident in 1976. The POD for derivation of a candidate RfD had been calculated by estimating dose as the mean (across persons) of the peak exposure following the accident. The study by Baccarelli et al. (2008) analysed developmental effects and increased TSH levels in neonates. The POD was then calculated from estimates of maternal exposure during pregnancy. The COT considered that the Baccarelli study appeared to be more reliable as the effects reported in the Mocarelli study could be due to acute exposure. Furthermore, the differential effects according to age at the time of the acute exposure could have been influenced by the choice of age cut-points in the analysis.

1.29 The US EPA report had applied the TSH benchmark level of 5 µU/mL, established by the World Health Organization as an indicator of possible iodine deficiency, in evaluating the equivalent effect size (for chemically-induced hypothyroidism) related to TCDD exposure. The COT agreed that this was acceptable. Elevated TSH was described as an indirect indicator of increased clearance of thyroid hormones, which could be due to induction of UGTs. Changes in T4 levels could affect brain development, and Members found it unusual that only levels of TSH were reported,

since circulating T4 levels are biologically more important. It was asked whether T4 levels would have been measured but not reported in the publication if they were not altered. It was also asked whether chronic stimulation of TSH would maintain T4 at normal levels. Deficiency of iodine or exposure to compounds inhibiting T4 synthesis would be more potent causes of hypothyroidism than compounds stimulating the UGTs, and would be expected to show a steeper dose response relationship.

1.30 The COT commented that the changes in sperm parameters observed in the Moccarelli study were not functionally significant, although the power to detect a functional change could have been limited by the small number of participants. The uncertainty in exposure estimation also needed to be considered. It was noted that some changes in sperm quality were within the normal range. It was also possible that there was a time-window of sensitivity which could have resulted in an acute effect leading to long-term compromise of reproductive function. Nevertheless the observed abnormalities were undesirable, even if not strictly adverse, and could be employed as the basis of a conservative approach.

1.31 The COT discussed the logic of using the animal data as support for the RfD derived from the human data and whether the epidemiology data would support the protective nature of a TDI derived from the animal data given the differences in exposure scenarios. The animal studies at the lower end of the candidate RfD distribution were dominated by mouse studies. The US EPA had been less confident in these models due to the lack of key mouse-specific data and the use of large toxicokinetic interspecies extrapolation factors. It was mentioned that human AhR receptors are less responsive than those in certain mouse strains. The COT had higher confidence in the rat data, and these were not contradicted by the human data. The Committee concluded that the animal data would have been a preferable basis for establishing the RfD, with human data supporting the animal data and providing reassurance and a reality check.

1.32 Although the US EPA had used the human data as the basis for its RfD, and COT had used animal data in setting its TDI, the difference in the values obtained was driven by the different uncertainty factors applied in extrapolation from a lowest observed adverse effect level (LOAEL) to a no observed adverse effect level (NOAEL). COT had applied an uncertainty factor of 3 and US EPA had selected a factor of 10. There were two points to consider in selecting an appropriate factor: the steepness of the dose response relationship (and the position of the LOAEL on the curve), and the severity of the effect. Changes in TSH and sperm counts were indicators of toxicity, but not viewed as severe effects. However, information on the shape of the dose-response relationship was lacking.

1.33 On balance, the COT concluded that its TDI of 2 pg/kg bw/day did not need to be reviewed, and that the new epidemiological data described in the US EPA report provided additional support for the value previously set.

Expression of uncertainty

1.34 Following publication of the COT report on Variability and Uncertainty in Toxicology of Chemicals in Food, Consumer Products and the Environment in 2007[4], the FSA had 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[5]. It was decided that it would be helpful to develop a scale of terms describing different levels of uncertainty, with input from the FSA Social Science Research Committee (SSRC). The FSA had subsequently commissioned research to assess the COT's draft uncertainty framework from a social science perspective and in 2011 the COT was presented with the report of the social science research. Following discussion of this report, the SSRC had issued a paper giving a social science perspective on the expression of uncertainty in risk assessment[6].

1.35 The key messages of the paper were:

- *Even the best communication strategies will not work for everyone.*
- *Numerical and verbal quantifiers of risk and uncertainty are subject to highly variable interpretations and qualifications based on varied social contexts.*
- *It is therefore vital to understand how risk and uncertainty are understood by experts and non-experts before a communication strategy is devised.*
- *This understanding should inform not only the communication of risk and uncertainty but the entire assessment and management process. It should form part of a codified Risk Assessment Policy.*

1.36 The COT agreed with the SSRC's advice that standardised terminology was unlikely to be helpful in communication of uncertainty, particularly to the general public. Rather, the wording needed to be tailored to the particular circumstances of each risk assessment. However, it was important to describe the major sources of uncertainty in the assessment, and the direction and potential magnitude of their impact. For estimates of quantitative parameters (e.g. dietary intake of a chemical), it was considered helpful to express uncertainty as a range of plausible numerical values. In contrast, qualitative questions (e.g. on whether or not a chemical was teratogenic), could be answered on the balance of available evidence, with an indication of how robust that evidence was (i.e. how likely it was that the conclusion might be overturned by future research). A checklist of sources of uncertainty, which had been proposed in the earlier report by Dr Andrew Hart[7], had been tried out by the Secretariat. So far it had not proved to be very helpful, but the COT agreed that it could be revisited at a later stage.

1.37 The Interdepartmental Group on Health Risks from Chemicals (IGHRC) held a workshop on uncertainty which had been attended by officials of different Government Departments and Agencies. The Secretariat of the COT provided the COT's conclusions on this subject at the meeting.

Phytoestrogens Research Programme

[4] http://cot.food.gov.uk/cotreports/cotwgreports/cotwgvut
[5] http://www.food.gov.uk/science/research/foodcomponentsresearch/riskassessment/t01programme/t01projlist/t01056/
[6] TOX 2012/12; available at http://cot.food.gov.uk/pdfs/tox201212.pdf
[7] http://www.foodbase.org.uk/results.php?f_category_id=&f_report_id=676

1.38 Phytoestrogens are naturally occurring compounds found in some plant-based foods, notably soya. These compounds, as their name suggests, have structural similarities to the female sex hormone, oestradiol. This has prompted concern that consuming phytoestrogens might have oestrogenic, anti-oestrogenic and/or other effects in humans. These effects could be either adverse or beneficial and might differ in particular subgroups of the population.

1.39 The Phytoestrogen Research Programme (T05/T06) was established to improve assessment of the risks and benefits from dietary phytoestrogens and the scientific evidence base underpinning advice to consumers. In 2011 the COT was asked to review briefly the final projects on-going at the time of an earlier 2007 review, and to consider the overall contribution of the Phytoestrogen Research Programme to risk assessment for phytoestrogens.

1.40 The COT noted that the three on-going studies were based on a recommendation that the programme concentrate on human studies. However, while well designed and conducted, their results were not sufficiently strong to support definitive conclusions. The COT noted that the research programme had earlier made a significant contribution to a COT report on phytoestrogens published in 2003. A significant strength of the programme had been the development of analytical standards for a wide range of phytoestrogens.

1.41 Overall the COT considered that the T05 programme had met its original remit and had delivered work of at least satisfactory scientific quality and in some cases of very high quality. The work had delivered value for money in all cases and in some cases exceptional value for money. The programme had covered areas not addressed elsewhere and helped to reduce uncertainties in the understanding of phytoestrogen effects and exposures. In doing so the programme had assisted in delivering the FSA's policy requirements.

1.42 The COT Statement is available at: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2012/cot201201

Risks of chemical toxicity and allergic disease in relation to infant diet

1.43 The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that bears on the Government's dietary recommendations for infants and young children. The review will identify new evidence that has emerged since the Government's current recommendations were formulated, and will appraise that evidence to determine whether the advice should be revised. SACN is examining the nutritional basis for the advice, and asked the COT to advise on risks of toxicity that might need to be taken into account. In addition to other adverse effects, this includes the influence of the diet on development of allergic and autoimmune disease.

1.44 The first phase of the review focuses on the diet of infants (0-12 months old), and will be followed by consideration of dietary recommendations for young children (1-5 years old). For the first phase, the COT selected a number of chemicals to be evaluated on the basis of their known or suspected adverse effects and the

potential for dietary exposure of infants through breastfeeding, infant formula and weaning foods.

1.45 In 2012, a statement was published, setting out the COT's conclusions regarding a subset of the chemicals selected for evaluation:

- Caffeine: Available information does not provide a basis for refining the current advice that breastfeeding mothers should avoid drinking too much strong tea or coffee (only occasionally rather than every day).

- Alcohol: Evidence supports the current recommendations that breastfeeding mothers should consume no more than 1 or 2 units of alcohol once or twice a week.

- Methylmercury: The exposure of infants to methylmercury from breast milk, infant formula and weaning foods does not exceed the current safety guideline. The toxicity of methylmercury is at present being reviewed by the European Food Safety Agency (EFSA) and there may be a need for further evaluation by COT depending on the EFSA conclusions.

- Dioxins and dioxin-like compounds: Dietary exposures of infants may briefly exceed the safety guideline, but because the exceedence would only be for a short time, it would not be expected to produce a build-up in the body to levels that would be harmful. Furthermore, there is clear evidence from multiple studies that exposures are decreasing over time.

- Phthalates: In the UK, the exposures of infants to phthalates from breast milk, infant formula and weaning foods are unlikely to exceed the safety guidelines.

- Bisphenol A: The exposures of infants to bisphenol A from breast milk, infant formula and weaning foods are well below the safety guideline. Moreover, exposures are likely to be even lower in the future as a result of decreased use of the chemical in plastic bottles used for infant feeding. The COT will review its conclusions following completion of an ongoing EFSA re-evaluation of BPA.

- Legacy pesticides: These are a group of pesticides that were banned during the 1980s and 1990s, but which, because of their persistence in the environment, can still be detected in the food chain. The few studies that are available indicate that levels in breast milk are declining, and do not point to a concern for the health of UK infants

1.46 The COT is currently evaluating the other chemicals that have been selected for consideration (vitamin A, soy phytoestrogens, aluminium, lead, brominated flame retardants and persistent organic pollutants), and will publish statements on these in the near future.

1.47 Scientific evidence concerning the influence of infant diet on risks of allergic and autoimmune disease will also be addressed in a separate review.

1.48 The full COT statement can be found at:
http://cot.food.gov.uk/pdfs/cotstatementoverarch201203.pdf

Toxicogenomics data in risk assessment

1.49 The term “toxicogenomics” refers to the production of large quantities of biological information about the regulation of genes, proteins and metabolism in cells, in a way that can be applied in toxicology. It is an area of science that has been developing rapidly. As part of the COT’s remit to advise on new scientific advances that bear on the understanding of toxic risks from chemicals, a statement was compiled, reviewing important developments in toxicogenomics since the last COT statement on the topic in 2009, and considering the aspects of risk assessment to which toxicogenomics might contribute.

1.50 In recent years, there has been major expansion in the use of laboratory techniques that produce large quantities of information about the function of cells and organisms. These techniques have been used to investigate a large number of different diseases and the biological consequences of chemical exposures. In parallel with this, there has been improvement in the availability and quality of analytical software that can be used to discern meaningful patterns in such data. The ways in which toxicogenomic findings are interpreted have also changed to take a greater consideration of how different genes and metabolic pathways relate to one another.

1.51 Most progress within the field of toxicogenomics has been made where it has been applied to measuring changes in gene activity. As a result, the conclusions of the COT on the use of toxicogenomics in risk assessment were largely based on such studies. In the future, those conclusions may be applicable to toxicogenomic studies applied to other material such as proteins and metabolites.

1.52 Possible uses of toxicogenomics in risk assessment for chemicals include:

- To help characterise the biochemical processes by which a substance produces toxic effects
- To provide information on differences between species in their response to chemical exposures, enabling better assessment of the implications for human health of toxicological findings in laboratory animals
- To help develop reliable ways of assessing aspects of chemical toxicity that avoid the use of laboratory animals
- To identify and understand the effects of chemicals at doses below those which produce overt toxicity, which may be relevant for assessing the risk of human exposure to low levels of a chemical
- To improve understanding of when toxicological findings for one substance are likely to apply to another with similar chemical structure
- To identify chemicals in body fluids that can be measured as markers of exposure to a chemical or of its effects on the body (known as “biomarkers”)

1.53 As yet, there are few examples of toxicogenomics being applied for such purposes, most published data having been generated for other reasons, and not to answer specific questions in risk assessment. However, the potential is there, provided that findings are sufficiently reproducible within and between laboratories, and can

be linked with required confidence to specific biochemical pathways that are relevant to toxic effects.

1.54 The COT will continue to monitor developments in this rapidly evolving field.

1.55 The full COT statement can be found at: http://cot.food.gov.uk/pdfs/cotstatementtgxinra201202.pdf

Committee procedures

Horizon Scanning

1.56 At the February 2012 meeting, the COT were invited to consider emerging or developing topics of importance within the COT remit, which might be included in future agendas for detailed discussion. They also received a presentation from Mr Terry Donohoe (Chemical Safety Division of the FSA) who described the activities of the FSA and the European Food Safety Authority EFSA on emerging risks.

1.57 Possible topics for future discussion included:

Vitamin E

1.58 COT had agreed in 2009 that a full review of vitamin E in pregnancy was not necessary at that time, but that the topic should remain under review. A paper would be presented to the Committee on Carcinogenicity of Chemicals in Food Consumer Products and the Environment (COC) in 2012, discussing evidence for an association of vitamin E supplementation with risk of prostate cancer. The Secretariat would continue to monitor the literature in this area and update the Committee if significant research was published indicating adverse effects of vitamin E within the COT's remit

Obesogens

1.59 Some researchers had suggested a possible role of xenobiotic chemicals that could disrupt the normal developmental and homeostatic controls over adipogenesis and energy balance, in the increasing prevalence of obesity. The environmental obesogen hypothesis proposed that obesogens could predispose individuals to obesity and/or related metabolic disorders under the influence of the typical high-calorie, high-fat Western diet. The COT agreed that it would be useful to examine this area as some of the reported effects were observed at very low doses in some animal studies. It was also agreed that since obesity was a huge and complex area, it was important to define clearly what question would be addressed - namely, the strength of evidence for a direct contribution of chemicals to obesity. It was noted that a mother's diet and lifestyle before and during pregnancy could have long-term effects on the metabolism of her children, and would therefore need to be considered as possible confounders in human studies.

Consideration of whether the 10-fold uncertainty factor for interspecies extrapolation is sufficient for developmental toxicity

1.60 In 2011, the COT had agreed that it would be useful to investigate this topic and that relevant new data should be reviewed. It was noted that human and primate data would be limited, and that comparisons of sensitivity between rodent species could also be considered. It was anticipated that a discussion paper would be brought to the COT in the autumn.

Other possible topics

- *Plant micro RNAs* - these were known to survive in the gut and therefore it would be interesting to know whether they can be taken up into the body.

- *Immunotoxic effects of environmental chemicals* – a question was raised about the validity of methods for detecting effects on the immune system that had been used in some recent epidemiological studies.

1.61 It was agreed that there was a good balance of expertise on the Committee, especially with the addition of the two new Members who would be appointed shortly. It was suggested that some additional expertise in paediatrics (perhaps from a member of SACN) was needed for the discussions related to complementary and young child feeding. Toxicogenomics should be added to the template of requirements in order to ensure that expertise in this area was maintained in the future.

1.62 Members were invited to make suggestions for future topics and were reminded that they may draw particular issues to the attention of the Secretariat at any time.

Working Groups

Bystander Risk Assessment Working Group (BRAWG)

1.63 The BRAWG was 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 were:

- To agree definitions 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 risks arising from these exposures in the light of current knowledge

1.64 The BRAWG considered an opinion on pesticide exposure assessment for regulatory risk assessment that was published in 2010 by the Panel on Plant Protection Products and their Residues (PPR) of the European Food Safety Authority (EFSA), and research funded by the Department for Environment, Food and Rural Affairs (Defra), which was aimed at better assessment of the factors influencing exposures of bystanders and residents to pesticides. The Group prepared a draft report through a series of meetings, and revised it after consultation and comments at an open public meeting in 2011.

1.65 The draft report was then considered by the full COT and ACP committees in March 2012. Further revisions were made to the report, which was then endorsed

by the COT and ACP at meetings in October and November 2012, respectively. The final report is available at http://cot.food.gov.uk/pdfs/brawgreport.pdf.

Working Group on the review of epidemiological literature on organophosphates and health outcomes relating to the nervous system

1.66 In 1999, the COT published a report entitled 'Organophosphates,' which considered whether 'single, prolonged or repeated exposure to low doses of organophosphates cause long-term adverse health effects'. Low doses were defined as 'those which do not produce overt acute toxicity accompanied by recognised clinical symptoms or signs of acute toxicity'. The focus was on five neurological health outcomes: neuropsychological abnormalities; electroencephalographic (EEG) abnormalities; peripheral neuropathy and neuromuscular dysfunction; psychiatric illness; and effects on the autonomic nervous system.

1.67 In addition to drawing conclusions, the report made recommendations for further research to establish whether the risk of more severe neurological and neuropsychiatric disease was increased by low-level exposure to organophosphates. To address these recommendations, research was subsequently funded jointly by a number of Government departments, and findings were reviewed by the COT at its meetings in September 2007, and September and December 2009. On those occasions the COT reached a number of conclusions about the results reported, but noted that the data needed to be considered in the context of a wider review of epidemiological studies published since 1999. Also, in December 2007, the COT was informed of a request from the Advisory Committee on Pesticides (ACP) for an updated review of the published literature on organophosphates, to include neuropsychological and neuropsychiatric effects. The COT agreed that systematic review procedures should be applied and that it was important to continue to liaise with the ACP and the Medical and Scientific Panel of the Veterinary Products Committee.

1.68 The COT considered a draft review of the epidemiological literature on organophosphates and health outcomes related to the nervous system at its September 2012 meeting. This had been undertaken by the HPA COT Secretariat and the HPA Toxicology Unit, Imperial College London. The Committee agreed to establish a Working Group to consider the review in detail. External experts with expertise on epidemiology, psychiatry, epidemiological psychiatry, neurophysiology and neurology were recruited to participate in the Working Group, in addition to COT members with expertise in epidemiology. The first meeting of the Working Group would be held in February 2013.

Lowermoor Subgroup

1.69 The COT Lowermoor Subgroup (LSG) had been established in 2001 to advise Health and Environment ministers on possible long-term health effects arising from a 1988 water pollution incident in North Cornwall, and on the adequacy of existing monitoring and research programmes. The water pollution incident had occurred on 6 July 1988 at the Lowermoor water treatment works near Camelford, North

Cornwall. A contractor's relief tanker had put 20 tonnes of aluminium sulphate into the water supply at the works. Water supplies to an estimated 20,000 people had been polluted with aluminium, sulphate and metals dissolved from pipework and plumbing materials (copper, lead and zinc). Flushing of the distribution system to remove the contaminated water had resulted in the disturbance of old sediments in the water mains, mainly deposits of iron and manganese oxides, leading to raised levels of these metals in the water.

1.70 The LSG had produced a comprehensive report on the incident which the COT had discussed previously as a draft in 2005 and 2007. Due to a case of congophilic angiopathy in an individual from the area who had died at an unusually young age, a Coroner's inquest had been opened and, following correspondence with the Coroner and receipt of legal advice, publication of the report was delayed until the Coroner's proceedings were completed. The inquest had concluded in March 2012, and given the time that had elapsed, it was considered appropriate for the report to be updated and for the COT to review the final version before publication.

1.71 The COT considered that the updated report provided an extremely thorough assessment of the relevant science, taking into account some major gaps in the available data. There had been potential for a high spike of aluminium exposure from water over the few days immediately after the incident, in addition to lower level background exposures, but there were no animal studies simulating this pattern of exposure, and the exposures that actually occurred were uncertain. Members endorsed the work that had been carried out in relation to the Coroner's inquest.

1.72 In the light of the report's findings, Members had a number of additional recommendations for the handling of future incidents involving significant environmental contamination. Depending on the scale of exposure and potential adverse impact on health, and also on likely levels of public concern, consideration should be given to:

- Environmental sampling at an early stage to inform and validate models of the contamination
- Replication of environmental sampling and measurements by independent laboratories
- Sensitivity analyses to characterise uncertainties in modelled exposures (and possibly modelling of exposures by more than one independent group)
- Collection of biological samples and/or measurement of biomarkers at an early stage to assess individual exposures and/or their effects
- A population register of those exposed, drawn up at the earliest opportunity, with early planning of follow-up
- Health studies based on exposure (or good proxies for exposure) and not limited only to those reporting symptoms or illness
- Early, targeted literature review to establish which health outcomes might be expected at the estimated exposure levels, and rapid collation of any reports of unexpected effects, so that they can be taken into account in the design of follow-up studies and healthcare responses.
- Prompt investigation of associated reports of ill-health in animals, including examination of tissue or blood samples

- 'In vivo' animal experiments in appropriate model systems, especially if unexpected health outcomes or syndromes are reported

1.73 The final report is published at: (FP to supply info once publication agreed)

Ongoing work

Risks arising from the infant diet and the development of atopic and autoimmune disease

1.74 As part of the SACN review of the UK Government recommendations on complementary and young child feeding, the COT were asked to provide advice on risks arising from the infant diet related to the development of atopic and autoimmune disease.

1.75 To assist in the development of this advice, the FSA prepared an external research call to identify an external contractor to undertake a detailed review of the published literature. When completed, this will be presented to the COT so that the evidence can be discussed and any conclusions shared with SACN. The COT discussed in detail the scope and the approach that the literature review should take, allowing the research call to be refined; it was noted that the FSA would work with the appointed contractors to ensure that the review met the COT specifications.

1.76 The literature review is unlikely to be completed before the autumn of 2013.

SACN review of dietary guidelines for vitamin D

1.77 The SACN are undertaking a review of their recommendations on appropriate levels of vitamin D intake. As part of this process, COT were asked to provide SACN with advice on the effects of high levels of vitamin D intake. The SACN review began in 2011, will be completed in 2014, and will include a public consultation.

1.78 The COT are continuing to review the potential toxicity of vitamin D exposure. The Committee have considered introductory papers on the scope of the review, an overview of the adverse effects of vitamin D, including data from epidemiology studies, human supplementation studies and animal studies and a discussion paper on serum calcium measurement.

1.79 Elevated levels of vitamin D are associated with the occurrence of hypercalcaemia and hypercalciuria. This occurs because vitamin D promotes the absorption of calcium and resorption of calcium from bone; the resulting high blood calcium levels result in calcium deposition in soft tissues, diffuse dimineralisation of bones and irreversible renal and cardiovascular toxicity.

1.80 It is anticipated that the COT review will be submitted to SACN by the spring of 2013 with further updates as required.

Toxicity of chemicals in the infant diet

1.81 The COT has been asked to consider aspects of the toxicity of chemicals in the infant diet, in support of the SACN review of Government recommendations on complementary and young child feeding. The COT reviews aim to identify whether current advice is appropriate in relation to potential toxicity, or whether there is a need for new or revised advice. In addition to the overarching statement on risks of chemical toxicity and allergic disease in relation to infant diet (see paragraphs 1.43 to 1.48), more detailed reviews commenced in 2012, and statements will be published in 2013:

Potential risks from high levels of aluminium in the infant diet

1.82 The aim of this statement is to provide an overview of the potential risks from high levels of aluminium in the infant diet. The total aluminium content of food includes naturally present aluminium, aluminium as a contaminant, food additives and aluminium from food contact materials. Additional exposure can come from drinking water used in food preparation, including reconstitution of infant formula, as well as water that is directly consumed. Infant exposures to aluminium in the UK have been calculated and form the basis of the risk characterisation.

Potential risks from high levels of lead in the infant diet

1.83 The aim of this statement is to provide an overview of the potential risks from high levels of lead in the infant diet. There are currently no Government recommendations on complementary and young child feeding that relate to lead. The general population is exposed to lead via food, water, air, soil and dust. Infants may also be exposed to lead from breast milk and for small children and infants ingestion of soil and dust can be an important contributor. Infant exposures to lead in the UK have been calculated and form the basis of the risk characterisation.

Potential risks from high levels of vitamin A in the infant diet

1.84 The aim of this statement is to provide an overview of the potential risks from high levels of vitamin A in the infant diet. Vitamin A is an essential micronutrient , but very large intakes may lead to hypervitaminosis A, resulting in toxicity. The COT awaits the results of the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) to support improved assessment of vitamin A intake in infants.

Potential risks from high levels of soy phytoestrogens in the infant diet

1.85 The aim of this statement is to provide an overview of the potential risks associated with high levels of soy isoflavones, genistein, daidzein and glycitein in infant diet. Infants can be exposed to isoflavones through breast milk and cows' milk, with the highest exposure estimated for infants consuming soy-based weaning diet and exclusively fed soy-based infant formulas.

2012 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

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Mrs J Shroff BA (Hons)	Administrative Secretary
Mr J Battershill BSc MSc	Scientific – HPA (until September 2012)
Ms Frances Pollitt MA DipRCPath	Scientific – HPA (from September 2012)
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Mr T Chandler BSc (Hons)	
Mr B Maycock BSc (Hons) MSc	
Dr D Parker BSc (Hons) MSc PhD	

Declaration of COT members' interests during (2012) the period of this report
(a up-to-date version can be found on the COT website) TO BE UPDATED

Professor David Coggon OBE		
Personal Interest		**Non Personal Interest**
Shareholder Halifax/Lloyds Standard Life		**Trustee** Colt Foundation
Mr Derek Bodey		
Personal Interest		**Non Personal Interest**
None		None
Professor Alan Boobis (ceased 31 March 2012**)**		
Personal Interest		**Non Personal Interest**
Consultancy Endura Fine Chemicals Proctor & Gamble Sumitomo Chemical (UK) Plc		**Member** ECETOC Task Force on Guidance for Classification of Carcinogens under GHS EFSA Chemical Contaminants in the Food Chain Panel EFSA Plant Protection Products and their Residues Panel EFSA Scientific Committee Working Group on Risk-Benefit Assessment EFSA Scientific Committee Working Group on the Benchmark Dose ILSI HESI, ILSI Europe and ILSI Research Foundation Working groups on Generic Risk Assessment Issues JECFA (vet drugs) JMPR
Shareholder Banco Santander SA Barclays BG Group BT Group Centrica Plc HBOS Iberdrola SA Lloyds Bank National Grid Scottish Power		**Editor-in-Chief** Elsevier - Food and Chemical Toxicology **Research Contract** Department of Health Commission of the EU (FP6) Food Standards Agency Medical Research Council **Misc** GlaxoSmithKline - Support by Industry ILSI HESI - unpaid Chair of Board of

		Trustees ESRC - PhD Studentship

Dr Roger Brimblecombe

Personal Interest		Non Personal Interest
Shareholder Vertex Pharmaceuticals, Inc		**Member** British Pharmacological Society British Toxicology Society Society for Medicines Research
Advisor MVM Life Sciences Partnership LLP		
Member Home Office Advisory Council on the Misuse of Drugs National Trust – Nominations Committee		
Misc 2gether NHS Foundation Trust - Non-Exec, Director & Mental Health Act Manager Drug Discovery World - Consultant Editor		

Professor Janet Cade

Personal Interest		Non Personal Interest
None		Kellogg - PhD student

Dr Rebecca Dearman

Personal Interest		Non Personal Interest
Consultancy European Chemical Plasticizers Industry (ECPI) Research Institute for Fragrance Materials (RIFM) The European Chemical Industry Council (CEFIC)		**Research Grant** American Chemical Council AstraZeneca BASF ECPI Novartis Proctor & Gamble RIFM Syngenta Syntaxin Unilever
Employee University of Manchester		
Shareholder AstraZeneca Syngenta CTL		

Dr John Foster (ceased 1 September 2012**)**		
Personal Interest		**Non Personal Interest**
Shareholder and Employee AstraZeneca		**Misc** British Toxicology Society – Member of Executive Committee Society of Toxicologic Pathology - Member and Editor in Chief of journal *Toxicologic Pathology*
Dr Mark Graham		
Personal Interest		**Non Personal Interest**
Employee AstraZeneca		None
Dr Anna Hansell		
Personal Interest		**Non Personal Interest**
Employee Department of Epidemiology & Public Health Imperial College, London (includes Small Area Health Statistics Unit)		**Research Grant** AstraZeneca **Misc** ESRC - PhD Studentship
Shareholder Halifax		
Supporter (non-active) Greenpeace		
Professor David Harrison		
Personal Interest		**Non Personal Interest**
Consultant University of Canberra University of Florida Quintiles		**Trustee** Medical Research Scotland Melville Trust
Shareholder Avipero		**Research collaboration** Myriad Genetics Cytosystems Genentech Somalogic Destina Ltd Antoxis Ltd Biopta Ltd

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

Professor Roy Harrison (joined 1 April 2012)

Personal Interest		**Non Personal Interest**
Consultant		**Trustee**
Shareholder		**Research collaboration**
		Misc

Professor Brian Houston

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

Professor Justin Konje

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

Professor Brian Lake		
Personal Interest		**Non Personal Interest**
Employee Leatherhead Food Research(LFR)		**Member** British Toxicology Society Society of Toxicology
		Member of the editorial board Food and Chemical Toxicology Xenobiotica
		Misc Various pharmaceutical and other companies - Contract research at LFR and consultancy
Professor Ian Morris		
Personal Interest		**Non Personal Interest**
Consultancy Takada Pharmaceuticals		**Member** Department of Health, Yorkshire and Humber Research for Patient Benefit Research Committee
Membership British Society for Toxicology Society for Endocrinology Society for Medicines Research Society for study of Fertility		**Misc** Son is a student fellow of the British Heart Foundation
Dr Nicholas Plant		
Personal Interest		**Non Personal Interest**
Employee University of Surrey		**Research Funding** AstraZeneca - GlaxoSmithKline Pfizer
		Member International Society for the Study of Xenobiotics (ISSX) MHRA Pharmacovigilance Expert Advisory Group

		Misc Xenobiotica - Associate Editor Frontiers in Predictive Toxicology – Editorial Board British Toxicology Society – Secretary of Education sub-committee
Professor Robert Smith		
Personal Interest		**Non Personal Interest**
Membership Rodenticide Resistance Action Group		**Misc** Support by Industry - Research costs for a student monitoring rodenticide resistance
Dr John Thompson		
Personal Interest		**Non Personal Interest**
None		None
Professor Faith Williams (joined 1 April 2012**)**		
Personal Interest		**Non Personal Interest**
Shareholding Rio Tinto National Grid Vodaphone BP SSE Aviva		**Member** Commission on Human Medicines (currently invited expert) EMA Ad Hoc Group 3Rs ILSI Expert Working Group **Current and recent research funding** Astra Zeneca Syngenta HPA Department of health BBSRC Pfizer