Background

1. The Committee Terms of Reference specify “To advise at the request of” (……government departments). Therefore the work of the Committee is primarily reactive and the agendas are set by the Secretariat based upon the need for advice from government departments and agencies particularly, but not exclusively, the Food Standards Agency and the Health Protection Agency.

2. The Code of Practice for Scientific Advisory Committees (Office of Science and Technology, December 2001), specifies that “committees should ensure that they have mechanisms in place that allow them to consider on a regular basis whether new issues in their particular areas of responsibility are likely to emerge for which scientific advice or research might be needed”.

3. In 2001, Members agreed that it would be useful to have an annual agenda item to discuss potential future topics. The list of topics is displayed on the Committee’s website.

Agenda items for 2012

4. There are a number of ongoing items, either on the current agenda or scheduled for further discussion at a future meeting:

   • Use of toxicogenomics data in risk assessment

   • COT input into the SACN review of complementary and young child feeding. This item is expected to cover a number of papers and topics over several meetings – see paper TOX/2012/03 of the current agenda

   • FSA-funded research on phytoestrogens

   • Results of FSA-funded research on effect of soy phytoestrogen supplementation on thyroid status and cardiovascular risk

   • SACN review of vitamin D

5. Requests for COT advice are frequently received at short notice. Future items of which the Secretariat is currently aware are as follows:
Food survey results

6. The Food Standards Agency has a substantial programme of surveys to monitor the safety and quality of food. Details of these are available on the Agency’s website at http://food.gov.uk/science/surveillance/foodsurvprog.

7. Where appropriate, the Committee’s advice will be sought on the health implications of the results.

Interaction of caffeine and ethanol (carried forward from 2011)

Issue

8. Concerns have been expressed that an interaction between the caffeine in energy drinks and alcohol could result in adverse behavioural or toxic effects, in particular, a phenomenon described as “wide awake drunk” where the stimulatory effect of caffeine prevents the consumer from realising how intoxicated they are, with the potential for increased toxicological damage and adverse behavioural effects occurring. In general, energy drinks contain levels of caffeine consistent with those in coffee. For example a mug of filter coffee contains approximately 140 mg caffeine whereas a standard can of energy drink contains 80 mg caffeine. New “shot” products have also become available where the same amount of caffeine is present but in a smaller volume (e.g., 80 mg in a 60 ml rather than 250 ml volume). However, energy drinks are frequently mixed with alcohol by consumers and some alcoholic drinks already contain significant quantities of caffeine (notably Buckfast tonic wine which contains 375 or 550 mg/L).

9. The possibility of an interaction between caffeine and alcohol was considered by the SCF in 2003 who concluded that the data supported the generally held belief that caffeine antagonised the depressant effects of alcohol but that the effects was generally seen at lower levels on simpler tasks. The effects are dose dependent and caffeine does not affect blood alcohol levels, however other data suggest that caffeine may not antagonise the psychomotor effects of alcohol and may enhance the effects especially in the early stages of drinking. Overall the SCF concluded that the majority of studies suggested that caffeine would not exacerbate the adverse effects of alcohol and at lower blood alcohol levels might improve performance. The SCF noted a number of case reports but was unable to draw conclusions from them.

10. However, in light of the continuing concerns about this issue, the FSA are requesting that the available data be reviewed by COT to establish whether there is evidence for a specific interaction and whether risk management action might be necessary.

Background

11. Caffeine is readily able to cross the blood brain barrier, where it acts as a non-selective adenosine antagonist (competitive inhibition); by counter-acting adenosine, caffeine reduces resting cerebral blood flow and has a generally disinhibitory effect
on neural activity. It is not completely clear how these effects result in the increased alertness and arousal associated with caffeine.

12. Adenosine is involved in a number of fundamental processes such as ATP related energy metabolism and RNA synthesis but is also released in response to metabolic stress and acts to protect the brain by suppressing neural activity and increasing blood flow through adenosine receptors A2A and A2B in vascular smooth muscle. A2A receptors are largely concentrated in the basal ganglia region and may be involved in the dopamine system (which is involved in reward and arousal). Adenosine may also be involved in the sleep wake cycle.

13. Caffeine has secondary effects which may not be related to adenosine, since caffeine is also a competitive non-selective phosphodiesterase inhibitor, allowing the build up of cyclic AMP in the cells. Caffeine metabolites such as paraxanthine have additional pharmacological effects.

14. Ethanol is a central nervous system (CNS) depressant, producing impaired sensory and motor function, slowed cognition, stupefaction, unconsciousness and possible death as dosage increases. More specifically, ethanol acts in the CNS by binding the GABA–A receptor.

New information

15. Since 2003 a number of new studies on the association between caffeine and alcohol have been published. These consist of epidemiology studies reporting a link between energy drink consumption and subsequent problems such as alcohol dependence, volunteer studies investigating the effects of energy drinks on the symptoms of alcohol intoxication, or on parameters such as locomotor activity or reaction time in human volunteers. Some animal data exploring similar aspects of this potential interaction are also available.

16. Two experts in psychopharmacology have been identified to assist the COT discussions. It is anticipated that a discussion paper will be brought to the March meeting of the COT.

Consideration of whether the 10-fold uncertainty factor for interspecies extrapolation is sufficient for developmental toxicity (carried forward from 2011)

17. The adequacy of the default uncertainty factors used in risk assessment was considered in the COT’s 2007 report on Variability and Uncertainty in Toxicology of Chemicals in Food, Consumer Products and the Environment. Regarding interspecies extrapolation, the report concluded that “Data from the available research in which compounds have been studied in both animals and man suggest that the default uncertainty factor of 10 allows adequately for interspecies differences.” However, some data, which were not discussed in the report, appear to indicate that the 10-fold factor may not be sufficient for some developmental toxicants for which human data are available, e.g. thalidomide, when considering
data from the two commonly used laboratory species for food chemicals - rats and rabbits – but excluding data from non-human primates.

18. Early work by Brown and Fabro (1983) compared the lowest reported teratogenic doses in the most sensitive animal species tested for 8 substances with the lowest reported teratogenic doses in humans. The ratios ranged from 1.8-50. The animal data taken into account were from a wide range of species, including cats and monkeys.

19. More recently, Newman et al. (1993) conducted a similar assessment for four pharmaceutical substances (valproic acid, isotretinoin, thalidomide and methotrexate). The authors divided the no observed adverse effect level (NOAEL) for the most sensitive laboratory species tested by 100 to estimate a “safe dose” for humans, and compared this to the lowest dose level reported to be teratogenic in humans. The lowest dose reported to be teratogenic in humans was in each case >10 times higher than the estimated safe dose, and the authors therefore concluded that the standard 100-fold uncertainty factor applied to laboratory animal data was adequate to protect against teratogenicity. However, this took into account data from monkeys, which were the most sensitive animal species for three of the four substances, and primate data are not required or usually available for food chemicals. Using the NOAEL for the most sensitive of the rat or rabbit to estimate a “safe” dose, the lowest reported teratogenic doses in humans would be 3.33, 13.3, 4.17 and 16.7 above the estimated “safe” doses for valproic acid, isotretinoin, thalidomide and methotrexate, respectively.

20. Schardein and Keller (1989) reviewed the developmental toxicity data for 28 substances identified as developmental toxicants in humans. They did not restrict the assessment to teratogenicity, but instead considered all the endpoints of growth retardation, death-abortion, malformation and functional alteration. They compared overall lowest observed adverse effect levels (LOAELs) for developmental toxicity in the most sensitive animal species tested with the estimated LOAEL in humans. The ratios ranged 1.2 to 200. The authors concluded that “The human is remarkably sensitive to those agents characterized here as human developmental toxicants.”

21. If the analysis is limited to chemicals assessed for developmental toxicity in both the rat and rabbit, and to data for these species (excluding data from mice and monkeys for some substances) then there are 7 substances, for which the ratios range 1.5-50. A 10-fold UF for extrapolating from the more sensitive of the two species to humans would appear to not be sufficient for thalidomide (ratio = 50), lithium (ratio = 25) or isotretinoin (ratio = 50). Including the data from mice does not affect the results.

22. It appears that possible differences in the incidences of effects at the LOAELs in laboratory animals compared to those estimated in humans are not able to explain the differences in the LOAELs being greater than 10. For example, the LOAEL for thalidomide in rabbits (the most sensitive laboratory species excluding primates) was 25 mg/kg bw/day, and the NOAEL in the same study was 12.5 mg/kg bw, which is still 25 times higher than a teratogenic dose in humans. It has been reported elsewhere that at the 12.5 mg/kg bw/day dose there was a very low incidence of minor skeletal anomalies (Newman et al., 1993). However, even taking this dose
level as a LOAEL it is likely that a NOAEL in rabbits would be in the order of 10 times higher than a teratogenic dose in humans. The human LOAEL estimate was based on the lowest dose taken by humans with reasonably good evidence of teratogenicity being 25 mg/day taken for 2 or 3 days, and the assumption of 50 kg bodyweight (Newman et al., 1993). The human LOAEL would be lower than 0.5 mg/kg bw/day if a bodyweight greater than 50 kg is assumed, and the calculated ratios greater.

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

24. Do members have further suggestions for the approach to be taken on this issue?

References


Potential discussion topics

Vitamin E

25. In 2009, the COT discussed two vitamin E supplementation trials in which there were indications of adverse effects of vitamin E in pregnancy (Boskovic et al. 2005 Reproductive Toxicology, 20, 85-88; Poston et al., 2006, The Lancet, 367, 1143-1154). Although COT members considered that the two studies did not indicate significant concern they requested additional information which was provided at a subsequent meeting. 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.

26. 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. 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 (see COT 2009 Annual Report ¹).

27. Members will wish to be aware that a paper will 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.

28. A metanalysis of 13 randomised controlled trials on vitamin E supplementation in the prevention of stroke was published in 2011 (Bin et al., Thromb Haemost. 2011 Apr;105(4):579-85). This found neither decreased nor increased risk of stroke with vitamin E supplementation, with confidence intervals evenly distributed around 1.0. The Secretariat will continue to monitor the literature in this area and update the Committee if significant research is published showing adverse effects of vitamin E within the COT remit.

Obesogens

29. Over the last two decades, the incidence of obesity and associated metabolic syndrome diseases has risen dramatically. Increased caloric intake and decreased physical activity are believed to represent the root causes of this dramatic rise. However, more recently some researchers have suggested the possible involvement of environmental obesogens, xenobiotic chemicals that can disrupt the normal developmental and homeostatic controls over adipogenesis and energy balance. The environmental obesogen hypothesis predicts that inappropriate receptor activation by certain chemicals will lead directly to adipocyte differentiation and a predisposition to obesity and/or will sensitize exposed individuals to obesity and related metabolic disorders under the influence of the typical high-calorie, high-fat Western diet. Obesogenic chemicals could act in different ways to disrupt adipose tissue biology. Three main mechanisms of action have been proposed;

- alterations in the action of metabolic sensors in which obesogens mimic metabolic ligands acting to either block or upregulate hormone receptors;

- dysregulation of sex steroid synthesis, in which they alter the ratio of sex hormones leading to changes in their control of lipid balance; and,

- changes in the central integration of energy balance including the regulation of appetite and satiety in the brain and the reprogramming of metabolic setpoints.

30. The obesogen theory has been around for several years but as yet there appears to be limited data nor a clear hypothesis. Further research to investigate the obesogen theory is on-going internationally. There was an NTP meeting in the US in January 2011 to look at ways of investigating the theory but the monograph has not yet been published. Once this monograph is published it may provide an opportunity to evaluate the current evidence for the theory and the proposed research strategies.

31. Do members consider it would be appropriate to monitor progress in the NTP work and, if resources are available, produce a brief overview of the obesogen theory and the research proposals?

**Balance of expertise on the Committee**

32. It has previously been agreed that the following types of specialist expertise are required by the Committee for some or all of its evaluations:

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<td>Cell biology</td>
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<td>Endocrinology</td>
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33. It would not be necessary to have an individual member for each listed expertise as some people would have a combination of the required skills. Additional key experts could also be invited to attend meetings for specific topics to supplement missing knowledge.

34. Members are invited to comment on whether this list is still appropriate and if there are important gaps amongst the current membership. An expert in environmental exposure assessment has been invited to join the COT with effect from April 2012.

**Questions on which the views of the Committee are sought**

35. Members are invited to comment on each of the above areas and the questions in paragraphs 24 and 31, and also to consider the following questions:

i) Do Members have additional suggestions for future topics for:

- Specific issues to be included as routine agenda items
- Focussed topics for one-day open meetings
- Generic issues requiring establishment of a Working Group.
36. Members are reminded that they may draw particular issues to the attention of the Secretariat at any time.

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

Potential Future Discussion Items – Horizon Scanning

Role of Environmental Exposures in the Development of Obesity, Type 2 Diabetes, and Metabolic Syndrome

1. Since the early 2000s, NIEHS has been working to stimulate this field, including various talks, publications, a listserv, and a section on environmental obesogens in the White House Obesity report, culminating in the January 2011 NTP conference, Role of Environmental Chemicals in the Development of Diabetes and Obesity (http://ntp.niehs.nih.gov/?objectid=49E4B077-C108-8BBA-25B2F05DE614C9C4). An NTP Monograph was intended to be published in summer 2011 but is not yet available. However a brief report in the form of a Concept discussion was presented to the National Advisory Environmental Health Sciences Council in February 2011 and is summarised below (http://www.niehs.nih.gov/about/assets/docs/february_2011_minutes.pdf).

2. There has been a huge increase in obesity in the US and around the world, in both adults and children, which constitutes a major public health problem. A major research program at NIEHS, Developmental Origins of Disease, explores the concept that developmental exposures lead to disease throughout life, often long after the exposure has taken place. Disease areas that have been shown in animal models to be stimulated by developmental exposures include reproductive/endocrine (diabetes, metabolic syndrome, and obesity), immune/autoimmune, pulmonocardiovascular, and brain and nervous system disorders. The obesogen hypothesis posits that the increase in obesity and diabetes is due, in part, to environmental exposures during development, modifying adipose tissue development, food intake and metabolism, thereby altering the programming of the obesity and diabetes setpoint (or sensitivity) for developing obesity later in life. An obesogen is defined as a chemical that can alter any of the affected systems. The hypothesis states that while food intake and metabolism are important, the sensitivity of the system is programmed during development, and that EDCs can alter that programming. The hypothesis changes the focus from genetics to exposure to environmental chemicals during development, which have effects that last a lifetime. Although the importance of food intake and exercise is recognized, environmental chemicals can alter the setpoint for gaining weight, affecting how much food it takes to put on weight, and how much exercise is needed to reduce weight.

3. As an example, data from a study by Retha Newbold and colleagues at NIEHS that showed that exposure of mice to DES in early development led to pronounced obesity later in the animals lives. Along with affecting weight gain, researchers are also seeing altered glucose tolerance and insulin sensitivity, and increased lipids, blood pressure and cardiovascular disease, with overlaps among the various chemicals involved.
4. The 2011 workshop sought:
   - To evaluate the science associating exposure to certain chemicals or chemical classes with development of diabetes or obesity in humans
   - To provide input to NTP and NIEHS for development of a research agenda
   - To bring together diverse expertise, including toxicologists, epidemiologists, bio-informaticists, and experts in the pathobiology of disease

5. The overall goals of the workshop were to:
   - Evaluate strength/weaknesses, consistency, and biological plausibility of findings reported in humans and experimental animals for certain environmental chemicals including arsenic and cadmium, PCBs, DDT/DDE, other organohalogens, bisphenol A, phthalates, and organotins.
   - Identify the most useful and relevant endpoints in experimental animals and *in vitro* models.
   - Identify relevant pathways and biological targets for assays for the Toxicology Testing in the 21st Century high throughput screening initiative (“Tox21”).
   - Identify data gaps and areas for future evaluation/research.

6. Workshop participants were asked to evaluate existing findings, identify the most useful and relevant experimental endpoints, identify data gaps, and consider targets and pathways for assays for inclusion in the Tox21 high-throughput screening initiative.

7. Some points of general agreement had emerged from the workshop:
   - Maternal smoking during pregnancy is associated with lower birth weight and later excess weight gains in children (providing support for the plausibility of the obesogen hypothesis)
   - Evidence linking high arsenic exposure (>150 ppb) with diabetes in humans is limited-to-sufficient
   - Evidence is sufficient for an association between diabetes and pesticides/POPs exposures based on collected analyses of cross-sectional, prospective/retrospective, and occupational exposure studies
   - Human studies are insufficient (in the case of phthalates) or non-existent (organotins) for evaluating an association with diabetes or obesity

8. In conclusion, there had been general support at the workshop for:
   - Plausibility of the obesogen hypothesis
   - Linkage of type 2 diabetes to certain chemical exposures
   - Common mechanistic basis for certain chemical classes
• Utilization of Tox21 approaches to identify substances of potential interest
• Refinement of endpoints examined using high throughput screening (HTS) approaches

Secretariat
January 2012