

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

Potential future discussion items – horizon scanning

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 (FSA) and Public Health England (PHE).
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. Members have 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 at <http://cot.food.gov.uk/cotmtgs/futurecotmeetings/>

Agenda items for 2015

4. There are a number of ongoing items, either on the current agenda or scheduled for further discussion at a future meeting:
 - COT input into the Scientific Advisory Committee on Nutrition (SACN) review of complementary and young child feeding focussing on infants up to 12 months of age, including topics related to a number of classes of polybrominated flame retardants.
 - Potassium salt replacers in vulnerable groups
 - Assessment of the adequacy of the 10-fold uncertainty factor to allow for interspecies variation in developmental toxicity
 - Effects of soya phytoestrogens on thyroid function
 - COT input into the SACN review of complementary and young child feeding focussing on children age 1 to 5 years.
 - Assessment of new formulations for incapacitant sprays

5. Requests for COT advice are frequently received at short notice.
6. The FSA has a substantial programme of surveys to monitor the safety and quality of food. Details of these are available on the FSA 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.

COT review of risk arising from the infant diet and the development of atopic and autoimmune disease

8. The COT have been asked by SACN to provide advice on risks arising from the diet that are related to the development of atopic and autoimmune disease, in support of a review SACN are undertaking on UK Government recommendations on complementary and young child feeding practices.
9. Four separate systematic reviews of the available, published, scientific literature have been commissioned by the FSA:
 - Systematic review A will explore the evidence relating to milk feeding and the child's future risk of developing atopic or autoimmune disease
 - Systematic review B will explore the evidence concerning the timing of introduction of allergenic foods into the infant diet during the first year of life
 - Systematic review C will explore the evidence concerning the avoidance or exposure to specific dietary patterns, food groups or nutrients during infancy, pregnancy and lactation
 - Systematic review D will explore the evidence concerning infant formulae containing protein hydrolysates and risk of developing atopic or autoimmune disease
10. Work on the reviews is progressing well. The FSA is expecting delivery of the draft final report for review A in April 2015 and the draft final reports for reviews C and D in May 2015. Work on review B is being extended in order to incorporate the results from two randomised controlled trials, these being the Learning Early About Peanuts (LEAP) study (due to report in March 2015) and the Enquiring About Tolerance (EAT) study (due to report in August 2015). The FSA is expecting delivery of the draft final report for review B in November 2015.
11. The FSA proposes that the findings of review A are discussed by the COT in May 2015, the findings of review D are discussed in June 2015, that review C is discussed in September 2015 and that review B is discussed in December 2015.

12. **Members are invited to comment on the proposed timelines/approach?**

Potential discussion topics

Consultations of the European Food Safety Authority (EFSA)

13. EFSA frequently consults on draft documents on issues of generic relevance across its remit, or that are particularly high profile. When these have been of particular importance to the Food Standards Agency, the COT has been invited to respond to the consultation (e.g. aspartame, bisphenol A, acrylamide, and caffeine is on the current agenda). Similarly, EFSA documents on toxicological risk assessment approaches with potential relevance to the working practice of the COT have also been discussed (e.g. default values to be used in risk assessment in the absence of actual measured data). It is anticipated that further relevant EFSA documents will be presented to COT during 2015.

Items carried forward from the 2014 horizon scanning

Update on Tox21 and ToxCast

14. A brief overview of recent developments in these American initiatives was presented. Members were asked for their thoughts on the topics, which they had considered in previous years. The Committee noted the major challenges faced by the Tox21 project. In particular, there had been poor progress in the integration of metabolism with *in vitro* assays.

15. The Committee supported the objective of ToxCast to prioritise substances for *in vivo* testing, which otherwise would not be tested. The Committee indicated that it would welcome a presentation on progress in this area in due course, although it was not considered a priority in the short term. It was noted that PHE would be interested in presenting detailed results of the ToxCast project to the Committee in the future.

16. ToxCast is the contribution of the US Environmental Protection Agency to the Tox21 program. ToxCast is environmental chemicals but the whole Tox21 program includes pharmaceuticals in addition to the ToxCast chemicals. These toxicity data are high throughput robotically generated in cell lines that lack most capability for metabolic conversion; a recognised limitation of the program. Assays conducted are any that can be adapted to a high throughput approach such as cell viability by measuring lactate dehydrogenase (LDH) or ATP, mitochondrial toxicity using fluorescent molecules sensitive to mitochondrial membrane potential and receptor/chemical interactions utilising receptor constructs linked to fluorescent reporters. Similar methods can be used for gene damage using gene damage sensitive genes such as GADD445 linked to fluorescent reporters.

17. One method for presenting the data from these assays has been through the use of the ToxPi¹ where the sizes or the individual slices represent the hazard potential of the molecule.

18. Do Members have any comments on ToxCast, and would they like a presentation on the results in the coming year?

Modelling kinetics

19. Recent publications stemming from European-wide cooperation in the areas of physiologically-based toxicokinetic modelling were presented. These covered: available (including freely-available) models; the generation of supporting data for such models; and the use of such models to aid the incorporation of *in vitro* data into risk assessment.

20. Members had not had experience with the freely-available models but speculated that they may be rather complex for inexperienced users. The Committee agreed that a presentation on developments in the field would be interesting, and that it would be useful if such a presentation provided examples of different methods with their pros and cons. However, this was not viewed as a high priority.

21. Has the priority for a presentation on this topic increased?

The FSA's New Recipes Database

22. In response to a question about possible FSA research to improve future COT risk assessments in the 2014 horizon scanning discussion, a member had suggested improvements to the food databases used in exposure assessments. The Committee was informed that a project to update the compositional data for recipes was underway and a paper for information would be prepared for a future meeting.

23. The FSA commissioned a project in April 2013 for a Recipes Database to help ensure that foods consumed as ingredients of other foods are accounted for more fully in dietary exposure assessments. The new Database will ensure that the recipes are up to date, and that any assumptions made are consistent and documented. The database is currently undergoing peer review. The Recipes Database will be tested in some exposure assessments, prior to finalising its implementation into the Agency's dietary exposure assessment tool by April 2015. The Database will be published, in line with the FSA's policy on openness. National Dietary and Nutrition Survey data are already in the public domain and it is anticipated that the Recipes Database would complement the use of this data for the purposes of dietary risk assessment.

¹ http://epa.gov/ncct/download_files/factsheets/Tox_Pi_Technical_Fact_Sheet_9-22-2010.pdf

24. The Committee will be presented with an information paper on the Recipes Database and its use in dietary exposure assessment later in 2015.

New potential discussion items

Human Biomonitoring in the UK and Europe

25. Over the last ten years there has been an increased interest in the application of human biomonitoring (HBM) to the assessment of human exposure to chemicals in food, consumer products and the environment.

2004-2013

26. The [European Environment and Health Action plan \(2004\)](#)² built on the SCALE initiative which proposed a more integrated approach to environment and health with closer cooperation between health, environment and research areas. Acton 3 within the action plan (To develop a coherent approach to biomonitoring in Europe) led to a call for consortia to develop such an approach on a European Scale.

27. One of the objectives was to develop inventories of HBM initiatives within countries in order to develop a Member State Networks or hubs. In 2006 a scoping study was carried out to document projects in the UK where human biomonitoring data were being gathered. Reply to a questionnaire was purely voluntary and many projects did not respond. Thus this was far from a comprehensive listing but shows that there were a number of projects which covered a range of analytes and age groups. Tables 1 and 2 summarises the findings. Such a scoping exercise is required again and is part of proposed future work.

Table 1: Summary of Projects Reported and the Funding Body

	<i>Title</i>	<i>Funding Body</i>
1	Study of Eczema and Asthma to Observe the effect of nutrition (SEATON)	UK National Asthma Campaign
2	Human Cellular Radiosensitivity	Department of Health
3	A study of organohalogen chemicals in human blood from around the United Kingdom	Co-operative Bank
4	Chlorinated paraffins in human milk-fat from London and Lancaster	Eurochlor
5	Chlorinated paraffins in human milk-fat from London, Lancaster & Wirral	Eurochlor
6	Lead Body burden in children: A pilot study	Department of Health
7	A normative study of levels of uranium in the urine of British Forces personnel	Ministry of Defence
8	Assessment of cadmium dose and early kidney damage in a population sample: Pilot Study	Department of Health
9	Assessment of cadmium dose and early kidney damage in a population sample: Pilot Study	Environment Agency
10	Asthma UK Growth Charts for Lung Function in Young	Asthma UK

² <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52004DC0416>

11	Children The contribution of age and genotype to sensitivity to environmental genotoxins	Department of Health
12	1) WWF UK pilot study 2) WWF-UK report "Contamination"	WWF UK
13	3) WWF-UK biomonitoring of "celebrities" 1) WWF-UK Chemicals and Health campaign - "Contamination, the Next Generation" 2) WWF-DETOX EU campaign "Generations-X"	WWF
14	1) "Chemical Check Up" An analysis of chemicals in the blood of MEPs 2) "Bad Blood" - A survey of chemicals in the blood of European ministers	WWF
15	Susceptibility to effects of organophosphate exposure	DEFRA
16	Investigation into Gastrointestinal Effects of OP Residues on Young Children	DEFRA
17	Background Incidence of Key Biomarkers of Chemical Exposure within the General UK Population	The European Chemical Industry Council (CEFIC)

Table 2: Breakdown of the Biomarkers and Age Groups Studied.

<i>Biomarker</i>	<i>No. of Projects</i>	<i>Age 0 to 1</i>	<i>2 to 6</i>	<i>7 to 19</i>	<i>20 to 60</i>	<i>61+</i>
Acetylcholinesterase	1				1	
alpha-1-microglobulin	1			1	1	1
Aromatic Amines	1				1	1
artificial musks	3			1	1	1
Asthma/Eczema	1	1	1			
Benzene	1					
Bisphenol-A	1			1	1	1
Cadmium	2			1	1	1
carbamate pesticides	2		2			
Chlordane	4			1	4	2
Chlorinated hydrocarbons	1					
Chlorinated paraffins	2				2	
DDE	3			1	3	1
DDT and metabolites	4			1	4	2
DECA - Poly brominated flame retardants	1				1	1
Dithiocarbamates	1					
DNA Damage	1				1	
Endocrine disruptors	1				1	1
Flame retardants HBCD and TBBP	1				1	
Genotyping	1				1	1
HCB	4			1	4	2
HCHs	4			1	4	2
Heavy Metals	1				1	1
Lead	2		2			
Lung function	2	1	2			
Mercury	1					
N-acetyl-beta-D-glucosaminidase	1			1	1	1
Naphthalene	1					
Nicotine	1					
Organochlorines	4			1	4	2
organophosphate metabolites	2		2			
PBDEs	4			1	4	2
PCBs	4			1	4	2

PFCs (incl PFOS and PFOA)	3			1	3	1
Phthalates	1					
Phthalates (incl DEHP)	3			1	3	1
Pyrethroids	1					
Radiation Response	1				1	
Retinol Binding Protein	1			1	1	1
Selenium	1	1	1			
Skin prick	2	2	2			
Triclosan	1			1	1	1
Uranium	1				1	
Xylene	1					
Total		5	12	17	56	29

28. PHE (formerly HPA) lead the UK component of Consortium to Perform Human Biomonitoring on a European Scale ([COPHES](#))³ was funded through DG Environment FP7 in 2008.

29. The main objective of COPHES was to build a coherent and sustainable framework for HBM surveys in Europe and increase the comparability of data across countries. A key step in such a framework is the elaboration and testing of common guidelines for setting up international surveys. One of the objectives was to develop inventories of HBM initiatives within countries in order to develop a Member State Networks or hubs. A sister demonstration project ([DEMOCOPHES](#)⁴ funded by the LIFE+ Programme) applied the protocols developed by COPHES. (Refer to the web site for further details).

30. The first [results](#)⁵ of the pilot study were presented at a joint COPHES/DEMOCOPHES final conference organised under the Cypriot Presidency of the EU Council on 23-24th October 2012 in Larnaca, Cyprus.

2013 -2014

31. Following the success of COPHES/DEMOCOPHES DG Research and Innovation established an expert working group to build on the networks and protocols. Two working group meeting have been held. Twenty two member states have expressed their willingness to support such an initiative and many with government backing.

32. In addition to the European level activities, PHE has a number of research projects (see Table 3).

Table 3: Recent projects within PHE/HPA which include HBM.

Title	Status	Matrix and analyte
COPHES/DEMOCOPHES	Complete in 2012	Urine – cadmium, cotinine, phthalates Hair – mercury

³ <http://www.eu-hbm.info/cophes>

⁴ <http://www.eu-hbm.info/democophes>

⁵ <http://www.eu-hbm.info/euresult>

PHE Tracking – Arsenic in private drinking water supplies	Incomplete – to be published In collaboration with Manchester University and British Geological Survey	Urine – As (speciated) plus other heavy metals Hair – and Toenails – arsenic
Saliva as an alternative HBM matrix	Complete in 2013 Collaboration with Health and Safety laboratory	Blood and saliva - Lead
Human Biomonitoring	Complete Newcastle University, Sponsored by HPA	Blood – whole and plasma. Range of heavy metals, pesticides and some organic compounds.
Brominated flame retardants – indoor air	On-going project in collaboration with Birmingham University	Blood – BFRs and PFOS & PFOA Urine – metabolites Hair – BFRs
Exposure related to living in the vicinity of municipal waste incinerators	Ongoing research – Imperial project	Breast milk - ??
Blood Spot utilisation for toxicology monitoring	Project in its early stages in collaboration with John Radcliff Hospital in Oxford, funded by the National Institute for Health Research (NIHR)	Neonatal blood spots – heavy metals, organic pollutants
Heavy metal body burden and health in the Newcastle Thousand Families birth cohort	Proposal in collaboration with Imperial and Health and Safety Laboratories	Heavy metals mainly

33. There is a need to make efficient use of data gathered across the UK within large scale surveys (E.g. UK BIOBANK, Understanding Society, and the Health Survey for England) and research projects which focus on human health and environmental exposures and establish links with other groups and institutions. This will be one of the aims of future work.

2015 -2016

34. This work has led the European Commission to propose a science-policy HBM initiative which will be launched in 2016. The purpose of this European HBM Initiative (EHBMI) is to improve our understanding of human population exposure to chemicals and potential health effects in order to establish evidence-based policy-making at EU level.

35. This is a huge step forward. EC DG Research and Innovation has asked for nominations to represent each member state. PHE will take the lead as the main focus is human health. PHE (Ovnair Sepai) has been nominated by the Foreign and Commonwealth Office and the permanent representative in Brussels to represent the UK on the steering group.

36. Tasks ahead:

- Develop a UK (England and Wales) Government steering group (could use the Interdepartmental Group on Health Risks of Chemicals [IGHRC] as a starting point).
- Establish a UK working group
- Stakeholder engagement and involvement
- Need strong networks across the many initiatives which produce relevant and useful data.

37. Members are asked to advise on additional UK human biomonitoring studies that they are aware of, and whether they would like a more complete review of this topic in order to advise on priorities.

Histamine in cheese

Background

38. Histamine (scombrototoxin) poisoning is a well-established phenomenon arising from consumption of foods, most notably scombroid fish, such as fresh tuna and anchovies and fermented fish products, which have become contaminated with high levels of the biogenic amine histamine as a result of bacterial spoilage. Although the concerns about histamine toxicity initially related to fish, biogenic amines such as histamine also occur in fermented products such as cheese or sausage with reports of excess levels of histamine in cheese becoming increasingly common.

39. The symptoms of scombrototoxin (histamine) poisoning include flushing, headache, nausea, itching, rash, palpitations and altered blood pressure.

40. The histamine levels in scombroid fish and fermented fish products are controlled by legislation which specifies the maximum concentration(s) of histamine that can occur in batches of fish. However, the histamine levels in other foods are not covered by any specific legislation.

41. The FSA gives advice on histamine incidents on a pragmatic basis. In the absence of specific legislation, a number of factors are taken into account, these include the regulatory levels for scombroid fish which have been used as a benchmark to assess the effects of histamine in cheese since intakes of, for example, fresh tuna are comparable to those of cheese (145 g high level acute consumption for cheese and 140 g for fresh tuna) (Bates, 2012). In addition, the results of volunteer studies which suggest that mild symptoms can occur at histamine intakes of 75-90 mg are also relevant, although many individuals can tolerate much higher levels without adverse effects occurring. In 2011, EFSA set a reference dose of 50 mg/meal for biogenic amines; this has also been incorporated into the FSA advice.

42. A concentration of 1000 mg/kg histamine in food is considered to be a “toxic” level where adverse effects would be expected following consumption. Below this level, the likelihood of adverse effects occurring would depend on the amount consumed and the sensitivity of the consumer. Histamine levels tend to be higher in cheeses made from unpasteurised milk and in cheeses which have a long maturation

period. Levels are also affected by the starter culture used and may be affected by the salt content. Biogenic amines are not destroyed by heating or cooking and incidents have occurred through the consumption of, for example, lasagne.

43. The FSA is increasingly being asked for advice regarding the monitoring of histamine in cheese and this is addressed by setting out various consumption scenarios and how these compare with the reference dose. The nature of the cheese and the quantity that might be consumed are also taken into account as are the likely consumers and in particular whether children may consume it since data from our incidents suggest that children may be more sensitive.

COT advice

44. It is proposed that the COT are asked for their comments on the EFSA opinion and the current FSA advice on histamine in cheese. A paper will be provided setting out data from the available volunteer studies and from incidents and discussing some of the complicating factors such as hot spots and potentiation from other biogenic amines. The exposure scenarios used would also be included.

45. Members are asked whether this topic would be of interest and, if so, to comment on what type of information would be of use.

References

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The microbiome

46. The microbiome is defined as the collective genomes of the microbes (bacteria, bacteriophage, fungi, protozoa and viruses) that live inside and on the human body. These microbial communities digest food, prevent disease-causing bacteria from invading the body, and synthesise essential nutrients and vitamins. The total number of genes associated with the human microbiome exceeds the total number of human genes by a factor of 100-to-one.

47. There is a recognition that the human microbiome has a role to play in xenobiotic metabolism and that diversity in the human microbiome can influence individual susceptibility to exposure. Until recently methods have not been available to assess the diversity of the human microbiome and thus its role in xenobiotic susceptibility. This has changed though with the development of high throughput

sequencing methods that allow rapid assessment of the diversity of the 16S genome region that can identify bacterial content without the bias associated with culture methods. This technology has opened up possibilities for exploring the interaction between chemical and drug exposure, the microbiome and outcomes and furthermore how this affects risk and susceptibility.

48. Professor Tim Gant of PHE is currently exploiting the emerging toxicity issue of the effect of individual microbiomes on chemical toxicity on behalf of the Health and Environmental Sciences Institute. He will be attending the International Microbiome consortium meeting in March and will be happy to provide a summary paper for COT following the meeting.

49. Do Members have any comments on the toxicological relevance of the microbiome, and would they like a paper on this issue in the coming year?

Synthetic Biology and the implications of the discipline for the work of COT in its toxicological assessments.

50. Synthetic Biology (SynBio) is emerging as a new biological discipline, although the term first appeared just over a century ago [1, 2, 3, 4, 5]. However, both SynBio's definition and scope are heavily disputed; in part because it extensively overlaps with technologies used for genetic engineering (or modification) [1, 3, 4, 6]. Thirty-five definitions were collated by a 2014 European Commission (EC) [3] opinion paper, which deemed that none were operational due to the lack of 'quantifiable and measurable criteria'. It has been argued that much of SynBio is a rebranding of (or a milestone in) genetic engineering; an approach to avoid the controversy associated with genetic engineering and to source new funding [5, 7]. The EC opinion paper proposed the following operational definition: "*SynBio is the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms*". They [3] caution that this definition is subject to change as the understanding of SynBio evolves.

51. Indeed, the authors of an FSA commissioned report [4] found it challenging to distinguish between products or applications using genetically modified (GM) and SynBio routes within the food and feed sectors. The report [4] identified five potential SynBio products (and/ applications) within the food and feed sector. However, the organisms assessed in each case seemed to meet the EU legal definition of a GM organism (GMO) or GMM (genetically modified micro-organism) and thus, are covered by current regulations [4]. Whilst these SynBio case studies appear to fall under GM regulations, there is concern that the existing regulatory framework is not flexible enough to cope with the potential technological advancements of SynBio [3, 8]. It is important to note that many chemicals currently produced by GMM's (referred to as, fermentation products) do not fall under the scope of the GM regulations as long as the GMM cannot be detected in the final product. This would probably also apply to common food chemicals produced by a SynBio route (e.g. using SynBio microbes). Novel food chemicals produced by a SynBio route should be detectable because of their unique characteristics [4].

52. The FSA funded report [4] indicated that flavours and fragrances subsector of the food and feed sector would probably be among the first SynBio products/ applications to appear on the UK market. The production of artificial vanillin via GM yeast was identified as closest to commercialisation. Flavourings are regulated by the flavourings directive. The authors [4] believe that SynBio food and feed products and applications thought are likely to be in the market in 5-10 years. The report [4] did not extend to the toxicity of chemicals in food or feed produced by the SynBio route.

53. From the information provided, or other knowledge of the topic, do Members consider there is a remit for COT in considering synthetic biology applications/products? If so, would a more detailed review of the topic be a priority for the 2015 workprogramme?

References

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http://ec.europa.eu/health/scientific_committees/emerging/docs/scenih_r_o_044.pdf

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http://www.easac.eu/fileadmin/Reports/Planting_the_Future/EASAC_Planting_the_Future_FULL_REPORT.pdf

Balance of expertise on the Committee

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

Analytical techniques	Biochemistry
Bioinformatics	Cell biology
Clinical practice	Dietary exposure assessment
Endocrinology	Environmental exposure assessment
Epidemiology	Human toxicology
Immunology	Mathematical Modelling
Mechanistic toxicology	Molecular biology
Neurotoxicology	Nutrition
Paediatrics	Pharmacokinetics
Pharmacology	Probabilistic modelling
Reproductive toxicology	Respiratory toxicology
Risk assessment	Statistical aspects of experimental design
Statistics	Systems biology
Toxicogenomics	Toxicological pathology
Xenobiotic metabolism	

55. 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 are also invited to attend meetings for specific topics to supplement missing knowledge.

56. Members are invited to comment on whether this list is still appropriate and if there are important gaps amongst the current membership, bearing in mind that the current COT chair will step down at the end of March 2015.

Questions on which the views of the Committee are sought

57. Members are invited to comment on each of the above areas and the questions in paragraphs 12, 18, 21, 32, 36, 44, 48, 52 and 55, 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.
- Do Members have proposals for research that FSA should fund in order to improve future COT risk assessments?

ii) Which are the highest priority proposals?

58. Members are reminded that they may draw particular issues to the attention of the Secretariat at any time.

**Secretariat
January 2015**

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