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 2016

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 children age 1 to 5.
- COT review of risk arising from the infant diet and the development of atopic and autoimmune disease
- Histamine in cheese
- Potassium replacements for sodium chloride and sodium-based additives
- Results of FSA-funded research on toxicokinetics of persistent organic pollutants in obese individuals.

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.

Potential discussion topics

Consultations of the European Food Safety Authority (EFSA)

8. 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). 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, and draft guidance on uncertainty). It is anticipated that further relevant EFSA documents will be presented to COT during 2016.

Items carried forward from the 2015 horizon scanning

Tox21 and ToxCast

9. In 2015, the Committee received a brief overview of recent developments in these American initiatives. Members were asked for their thoughts on the work, 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 data on metabolism with *in vitro* assays.

10. The Committee supported the objective of ToxCast to prioritise substances for *in vivo* testing, so that resources could be used more effectively. The Committee indicated that it would welcome a presentation on progress in this area in due course.

11. Do Members have any comments on developments in Tox21 and ToxCast, of which they have become aware, and would they like a presentation on the results in the coming year?

Modelling kinetics

12. The Committee agreed that it would be useful to keep abreast of developments in the area of physiologically-based toxicokinetic (PBTK) modelling, particularly as it might be asked in the future to advise on risk assessments using such models. This issue was also discussed in the context of the COT symposium on

the implications of obesity on the kinetics of persistent organic pollutants held in March 2015.

13. Insufficient data had been presented at the COT symposium to consider building PBTK models. It was considered that compared to pharmaceutical drugs, for environmental chemicals there was usually a lack of good PBTK data which can be used in modelling. The US had made a heavy investment into the replacement, reduction and refinement of animals in research (the 3Rs) and had started to take a bottom-up in vitro and in silico approach, in which toxicokinetic extrapolation plays a key role. It was noted that the COT should keep a watching brief on this topic.

14. As noted at paragraph 4 above, the results of the FSA-funded research on toxicokinetics of persistent organic pollutants in obese individuals will be presented to the COT at a meeting during 2016.

15. Members are invited to comment on whether they are aware of further developments in this area that should be followed up during 2016?

Analysis of the evidence gap for postulated human health effects of Endocrine Disrupting Chemicals.

Background

16. Following a meeting at Downing St chaired by Professor Mark Walport (CSO) in May 2014 Professor Godfray (Jesus College Oxford) was commissioned to produce an evidence restatement about the environmental (non-human) effects of Endocrine Disrupting Chemicals (EDCs). PHE Centre for Radiation, Chemicals and Environmental Hazards (CRCE) has been made aware from DEFRA that there was further discussion at the meeting about consideration for a full systematic meta-analysis/review of the human health effects of EDCs. One of the non-governmental organisations (NGOs) with an interest in the human health effects of EDCs has championed the contracting of this meta-analysis with DEFRA. Cabinet Office and DEFRA have discussed taking this work forwards and involved the Chief Medical Officer (CMO) who has asked CRCE for comment via the PHE Director of Health Protect and Medical Services. CRCE Toxicology department have replied that there is no further need for another systematic meta-analysis or review because of on-going work in the OECD and other recent reviews and reports such as those from WHO and EFSA. However a number of proposals were made, short of a full meta-analysis or systematic review. One of these was to bring this item for a COT opinion and response via the horizon scan and that is the purpose of this item.

Previous work encompassing aspects of EDCs from COT and others

17. COT has previously reviewed aspects of health effects of Endocrine Disrupting Chemicals on a number of occasions including:

- Male reproductive system (2004[1], 2006[2])
- Bisphenol A and bisphenols in canned foods (1997[3] [4], 2001[5])
- COT statement on the health hazards of polychlorinated biphenyls (1997[6])
- COT statement on the tolerable daily intake for dioxins and dioxin-like polychlorinated biphenyls (2001[7])
- COT work on phytoestrogens (2003[8], 2012[9], 2013[10])
- Mixed halogenated dioxins and biphenyls in UK food (2010[11]) and other related reports on the same chemicals and other chemicals such as tetrabromobisphenol A (2004[12])
- COT commented on a draft EFSA opinion on the risks to public health related to the presence of bisphenol A in foodstuffs (2014[13]).

18. Members will also be aware of other work in the field which includes EU - State of the Art assessment of endocrine disruptors 'Kortenkamp' report 2012, EC JRC report 2013, EFSA opinion 2013; WHO State of the science report 2012; OECD - improving testing and assessment of EDCs 2012 and the New Endocrine endpoints Thyroid scoping document 2014).

19. In development CRCE are aware of: Sweden is leading a detailed review paper for OECD (www.nanotec.or.th/.../HH_OECD-EDTA-WG-Paris-Oct-2015_Final-revi.) on the Retinoid System and Development for which DG Environment will be providing consultant funding and in which the UK is participating. An OECD Non-genotoxic carcinogen assay scoping document that includes EDC modes of action (2016).

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1 http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2004/cotstatements2004malerepro

2 http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2006/371075

3 http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements1997/bisphena

4 http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements1997/402216

5 http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2001/bisphenol

6 http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements1997/polybip

7 http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2001/dioxinsstate

8 http://cot.food.gov.uk/cotreports/cotwgreports/phytoestrogensandhealthcot

9 http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2012/cot201201

10 http://www.food.gov.uk/sites/default/files/cot/cotstaphytos.pdf

11 http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2010/cot201002

12 http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2004/cotstatements2004tbbpa

13 http://cot.food.gov.uk/sites/default/files/cot/tox201415.pdf

20. A search of the US National Library of Medicine and Google Scholar with the search term

(endocrine disrupt* OR EDC) AND review AND health AND human

yields a substantive literature though there are few single reviews of the with the scope of all possible human health effects. The closest maybe a recent book from Academic Press 'Endocrine Disruption and Human Health' edited by Philippa Darbre ISBN 978-0-12-801139-3 published in 2015. At the time of writing PHE has not had the opportunity to review this book.

21. **Questions for members**

a. Would a systematic review of the human health effects of EDCs contribute to understanding and reduce uncertainly in the field?

b. Would a systematic meta-analysis of the data relating to the human health effects of EDCs contribute to understanding and reduce uncertainty in the field?

c. Would a paper to identify the evidence gaps in the understanding of the human health effects of EDC's be a worthwhile contribution to the field and assist in the targeting of any available funding?

Possible human health effects of E-cigarettes

Background

22. E-cigarettes are widely regarded as safer than tobacco-based cigarettes and with a recent PHE report stating e-cigarettes are 95% safer than cigarettes (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/457102/Ecigarettes_an_evidence_update_A_report_commissioned_by_Public_Health_England_FINAL.pdf) . This number was not based on a systematic review of the literature PHE state in their report that '…..*given the short timeframe for this report, a systematic review of the literature was not possible*'.

23. Perceptions of safety vary and the different ingredients used, particularly flavourings that are tested for oral but not inhalational safety, could render altered safety profiles in different products. Different products also have the potential to release additional chemicals formed from the heating of the e-cigarette liquid depending on the physical characteristics of the unit. Additional concerns have been tabled in respect of second hand exposure from E-cigarette vapour.

24. Until recently there were no licenced e-cigarette products. This has recently changed with MHRA licensing one product (BAT e-Voke) for prescription. MHRA now

has responsibility for the licensing of non tobacco containing nicotine products. Non licensed products are widely available however but cannot be marketed as smoking cessation devices.

25. There is a considerable diversity of opinions amongst Public Health experts about the actual safety of e-cigarette products with some publications stating they are no safer than conventional cigarettes. This is likely contributing to differing public perceptions of the actual safety of these products.

Previous and ongoing work from COT and others

- COT has not undertaken any other work on these products.
- PHE is involved with a research project under the Horizon 2020 programme 'Multidisciplinary tools for improving the efficacy of public prevention measures against smoking'. This project has an overall objective to examine the effectiveness of smoking aids in cessation but contains a workpackage that will examine the potential health consequences of nicotine and derived compounds such as nitrosoamines in which PHE is involved.
- Other work is on-going in academia and government and would be evaluated as part of any COT review.

26. Questions for members

a. Is a systematic review of the health effects of e-cigarettes necessary?

b. If yes – what should be the scope of the review?

c. Would a smaller piece of work be desirable for example looking just at flavourings?

d. What other on-going work are members aware of?

Update on the COT 2008 Trans and multigenerational toxicity statement

Background

27. The 2008 statement from COT[14] was the output from a workshop on transgenerational epigenetics. The conclusions in paragraphs 46-50 state that in brief there was reasonable evidence that epigenetic changes associated with environmental exposures during development can result in adverse effects, which

[14] http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2008/cot200803

might be detected in F1 and F2 generations in standard regulatory testing but that effects in F3 generations would be beyond the detection levels of current testing. The science was not yet developed and was not mature enough to be included in regulatory risk assessment. It was unclear if the effects seen in animals would occur in humans. Paragraph 50 called for several new research activities including the possibility of work in human populations. Since the publication of this statement there has been a considerable further contribution to the literature, and a number of workshops have taken place on various aspects of trans- and multi-generational toxicity. While effects have been reported in animal models some of these have proven difficult to replicate in subsequent studies. Epidemiological studies have given some indication of phenotypic effects to the second and third generation associated with maternal nutrition in females and smoking behaviour in males.

28. The purpose of this suggested work would be to update the 2008 statement taking into account the latest literature and including the views of PHE, reviewing and changing or re-iterating as necessary the conclusions in the 2008 statement.

Previous and on-going work

- COT has a statement from 2008 that is the basis for this horizon scan
- PHE has completed a semi-systematic review 'Environmentally-Induced Epigenetic Toxicity: Potential Public Health Concerns' that is currently submitted for publication.
- There is on-going work involving PHE (CRCE Toxicology Department) on testing methods with a related publication in ALTEX (Greally JM, Jacobs MN In vitro and in vivo testing methods of epigenomic endpoints for evaluating endocrine disruptors ALTEX. 2013;30(4):445-71 (PMID:24173168). Work is continuing under the auspices of the OECD.
- ECETOC are developing a report on the basis of a meeting that took place in November 2015 'The Role of Epigenetics in Reproductive Toxicity'.

29. Questions for members

a) Is there a need to review and update the 2008 statement?

b) If yes; should chemicals reported as having epigenetic effect be considered separately?

c) If yes; should testing methods be included in the review or not?

Role of chemicals in altering the microbiome and potential human health effects

Background

30. The microbiome is the community of microorganisms that are resident on, or in our bodies. This can be bacteria, viruses or fungi. Collectively these are symbionts and fall into three categories:

1) Mutualists – benefit themselves and the host
2) Commensals – benefit themselves but on the host (but do not harm the host)
3) Pathogens – benefitting themselves by harming the host.

31. The total diversity of the microbiome is probably about 100 trillion organisms of which we know about 1% or less. The gene pool far exceeds that of the host.

32. The microbiome occurs on all areas of the body that have contact with the environment and sites of particular importance are the alimentary canal, skin, vagina and lung. Additionally there is at the environmental microbiome - the community of microorganisms in the environment to which humans may be exposed.

33. The microbiome is established after birth with the first 'seeding' coming from our route of birth. Vaginally delivered babies establish and initial microbiota resembling that of that of their mothers vagina dominated by *Lactobacillus sp*, *Prevotella sp* and *Snethia sp*. In contrast babies born by caesarean section inherit a microbiota resembling the skin surface communities of their mother dominated by *Staphlococcus sp*, *Corynebacterium sp* and *Propionibacterium sp*.

34. This differential community is then further affected by environmental factors including diet, antibiotic use and chemical exposure starting immediately after birth can continuing throughout life.

35. Understanding of the microbiome is developing rapidly building on improved 16S ribosomal sequencing that has provided the ability to rapidly survey the genus and species of bacteria, fungi and viruses. Factors such as diet are known to affect the microbiome as well as xenobiotics such as antibiotics, which due to their mechanism of action have a specific effect on the microbiome. Studies have indicated that the diversity of the microbiome can be affected for many years after exposure to such agents. It can be hypothesised that environmental chemicals such as glyphosate that have a similar selective toxicity for bacterial species could exert an effect on the microbiome. Changes in the microbiome result from, and give rise to, human health effects. In a similar manner microbiome alterations can lead to differential susceptibility to xenobiotic toxicity.

Previous and ongoing work

36. The primary literature is increasing rapidly with a substantial number of published reviews. A great many of these have a focus on the diet rather than xenobiotics. A cursory search using the term

systematic AND review AND microbiome AND chemical AND environment did not yield any publications

37. Questions for members

a. Is there a need now to (systematically) review the effects of xenobiotics on the microbiome and potential for human health consequence?

b. If yes should there be a focus on any particular xenobiotics or microbiomes?

c. If yes should the review be focused on dietary exposure or include all exposure including air? And if so should other expert committees be included such as COMEAP be involved?

Balance of expertise on the Committee

38. 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	

39. 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.

40. 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

41. Members are invited to comment on each of the above areas and the questions in paragraphs 11, 15, 21, 26, 29, 37 and 40, 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?

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

Secretariat
January 2016