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 2019

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. This is now nearing completion and will hopefully be finalised in mid-2019.
- Electronic nicotine (and non-nicotine) delivery systems (E(N)NDS) – e-cigarettes
- Phosphate-based flame retardants
- Irritant sprays
- Review of Risk Assessment Unit approaches
- SAC structure – future developments to take account of EU exit
- Developing Methods for Potency Estimation research project

- PBPK modelling project for PFOA
- Microplastics
- Dioxins?

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. nanomaterials, dioxins and cyanogenic glycosides in foods other than raw apricot kernels, in 2018). Similarly, EFSA documents on toxicological risk assessment approaches with potential relevance to the working practice of the COT have also been discussed (e.g. guidance on harmonised methodology for human health, animal health and ecological assessment to combined exposure to multiple chemicals and guidance on the threshold of toxicological concern (TTC) approach in 2018). It is anticipated that further relevant EFSA documents will be presented to COT during 2019. This includes the public consultation on the phthalates opinion at this meeting.

Items carried forward from the 2018 horizon scanning

Endocrine active Chemicals

9. Previously Members had agreed that a systematic review of the health effects of Endocrine Disrupting Chemicals (EDCs) would be useful but recognised that this would be a major task. A similar task had been conducted by the WHO but more focussed questions would have been helpful. Without a coordinated systematic review to understand the evidence base (possibly an "umbrella" review of reviews to obviate author selection bias) the impact of EDCs was uncertain. In the first instance, a paper on the evidence gaps should be prepared by PHE but other priorities have meant that this item has not been progressed. This is likely to continue to be the case in 2017.

10. This has been on the horizon scan for a while, but recent discussions have suggested a slightly different direction.

11. Following recent discussions concerning the implications of the possible presence of low levels of potent endocrine active compounds in food, the Committee noted that there were divergent views between different committees. For example, the VPC had concluded that thresholds do exist, but may vary according to age, gender and organ/tissue, while the SCVPH had concluded that no threshold doses could be established. The Committee noted the arguments that had led to a hazard-based approach being taken to pesticides and biocides that are endocrine disruptors in the EU. However, there was a need for a risk-based approach which involved consideration of potency of individual compounds and sensitive time periods. The Committee noted that none of the currently proposed approaches to endocrine active substances incorporated these aspects and that there may be an opportunity to develop a new UK approach.

12. It was recognised that sensitivity may depend on the life-stage and hormonal system, with some systems having thresholds and others not at some life-stages. The Committee decided that they needed to review endocrine-mediated effects more broadly and come to a view on these before considering the risks from specific endocrine active substances further.

13. The Committee suggested the first stage would be a review on endocrine active substances, divided into the different endocrine systems. This would be followed by identification of the key themes and issues and their synthesis into a proposal for a risk based evaluation of endocrine active substances.

14. The Secretariat recognises that such an approach would require a substantial amount of work, require additional expertise and would be of widespread interest across government. As such it was unlikely to be feasible to undertake the work during COT meetings and considers that this might be a suitable topic for a focussed working group. The Secretariat suggests that initially a scoping paper should be produced setting out the range of interested parties including Committees dealing with regulated products and an outline of the proposed scope and terms of reference for the working group. It is envisaged that this would include both the state of the science and the needs of the regulators together with identification of the supplementary skills needed. Whilst this work would be focussed on the human health risks of endocrine active substances, it might be useful to explore whether other advisory committees providing advice on environmental risks such as HSAC would have an interest and whether a more integrated approach might be beneficial.

Update on the COT 2008 Trans and multigenerational toxicity statement

15. In 2017, a joint symposium of COT, COM and COC was held during which epigenetics was discussed. A statement on this joint discussion has recently been approved by the Chairs of the COT, COC and COM and will be published in due course.

Role of chemicals altering the microbiome and potential human health effects

16. The Committee agreed that since the importance of the microbiome in many areas of health and disease was becoming increasingly apparent, the effects of xenobiotics on the microbiota and of the microbiota on xenobiotics should be

considered in a short discussion paper. Both the makeup of the microbiological population, i.e. the species of bacteria and other microorganisms present, and its functional makeup, i.e. the biochemical pathways contributed by the total mass of microorganisms, would be taken into account, along with other potential interactions, for example between air pollution, microorganisms in the respiratory tract and the development of asthma. Progress was not possible during 2016 and 2017 due to other Committee priorities. A joint symposium with the Interdepartmental Group on Hazards and Risks from Chemicals (IGHRC) was intended in 2018 but postponed. It would be useful to identify any particular aspects the Committee considers should be taken forward on this.

Modelling kinetics

17. 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.

18. 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.

19. The Secretariat is considering links between modelling kinetics, uncertainty in risk assessment and approaches on these by global regulatory agencies and may scope this in a separate paper in due course.

20. Members are invited to comment on whether they are aware of further developments in this area that should be followed up during 2019?

Priorities from the joint COC, COM and COT Horizon Scanning meeting in October 2017

21. A Joint Committee Horizon Scanning took place in October 2017 and a number of items were discussed which could be discussed at future COT meetings. These were detailed in the 2018 Horizon Scanning paper (TOX/2018/11)[1]. The key topics to be focussed on are outlined below:

22. In terms of priorities for joint Committee consideration, it was suggested one important area was how to evaluate the biological or toxicological relevance of a reported response or perturbation, especially where this may be an atypical endpoint and how statistics can, and should, be used to help determine this. The COT may wish to be aware of an ECHA workshop in 2016 on new approach methodologies

[1] https://cot.food.gov.uk/sites/default/files/tox2018-11.pdf

and use in regulatory science[2]. This should encompass how the Committees could judge whether the statistics used were appropriate. Consideration of sufficient levels of health protection and dealing with uncertainty could also be useful, for example, the degree of confidence over a non-significant result in relation to health protection. Another area of importance was how to deal with different sources of evidence considered by the Committees (e.g. predatory journals and poor quality non-standard tests). One question that has been raised is how to deal with published studies of poor quality. Members noted that such studies could cause difficulties for various expert Committees, where poor studies were used to question Committee opinions in some cases. It was noted that EFSA currently required scoring of individual papers and used a weight of evidence approach in its evaluations using its PROMETHEUS approach. The secretariat have considered these items could be considered in the context of the proposed subgroup to review the synthesis of epidemiological and toxicological evidence.

New suggestions for topics

23. The Secretariat would welcome Members views on whether the current structure of three separate Committees remains appropriate and sustainable in light of future challenges or whether they should explore other possibilities in consultation with the Secretariats of COC and COM and departmental sponsors.

Synthesis of epidemiological and toxicological evidence

24. The Committees on Toxicity and Carcinogenicity (COT and COC) have recently published a joint report on synthesising epidemiological evidence[3]. During their meetings the subgroup also discussed the possibility of quantitative synthesis of epidemiological and toxicological evidence. Guidance on this, following evaluation of the literature, would most likely be the work of another joint subgroup who would aim to deliver a report within 2-3 years from initiation.

25. Current approaches usually consider epidemiological evidence separately from toxicological evidence, and then combine information at the end, because a common dose response is often difficult to establish. There are a number of methods available for quantitative synthesis of epidemiological studies, which were reviewed in the SEES report. However, there are very few methods for combining epidemiological and toxicological studies, or for toxicological studies alone. Those that have been published should be reviewed. There is some work underway at the International level at providing guidance on how to integrate toxicological and

[2] https://echa.europa.eu/documents/10162/22816069/scientific_ws_proceedings_en.pdf

[3] Report of the Synthesising Epidemiological Evidence Subgroup (SEES) of the Committee on Toxicity and the Committee on Carcinogenicity. Available at: https://cot.food.gov.uk/cotreports/cotjointreps/synthesising-epidemiology-evidence-subgroup-sees-report

epidemiological evidence and was briefly mentioned in the SEES report[4,5]. A brief search has shown that not a great deal has been published since the SEES report.

26. Members of the PHE secretariat have recently had a meeting with Dr Eva Negri from Milan at which the Epid-Tox framework[6] was raised as a useful tool which they have used for PFOA and PFOS[7].

27. There are a number of International bodies that have considered the weight of evidence approach and issued guidance, including EFSA[8], who have also issued guidance on biological relevance[9]. However, within these documents there seems to be a lack of clear guidance for how to perform weight of evidence evaluation or systematic review.

28. It would be useful for the Committees to have clear and sufficient guidance on how to integrate epidemiological and toxicological data, for use by the secretariats and Members. There is also interest in this combined approach from the PHE Air Quality and Public Health team, who oversee COMEAP and could provide useful discussion/representation.

Workshop to scope out the potency estimation project

29. When responding to Incidents we regularly have chemicals, particularly novel foods and sports/dietary supplements where certain ingredients have very little or no toxicological information. For certain novel ingredients, a lot of which tend to be from plants and have a history of medical use in certain parts of the World, again there is very little toxicological information and sometimes it is not possible to give any risk advice to our Policy colleagues. For some novel ingredients there may be efficacy studies and the safety of the chemical is assessed by the longest tolerated dose in an efficacy study in humans. However, generally these studies will not be looking for toxicological endpoints and it is not an ideal approach. Alternatively, the possible toxicological values for the chemical can be estimated by read across from chemicals with a similar structure or in the same group. However, in this case the same potency would be estimated and this could be a significant over- or under-estimation of the true potency of the chemical. For example, we have had Incidents over the last year for DMHA, an amphetamine like stimulant, similar in structure to DMAA. DMAA is a drug which was withdrawn from the market. It has since been banned from use in sports supplements where it was used as a stimulant, as it has

[4] https://ehjournal.biomedcentral.com/articles/10.1186/s12940-016-0156-6
[5] http://www.wcrf.org/int/research-we-fund/continuous-update-project-cup/mechanisms-research
[6] Toxicological Sciences 122(2), 223-234 (2011). Available at: https://academic.oup.com/toxsci/article/122/2/223/1676944
[7] Critcal Reviews in Toxicology 47(), 489-515 (2017). Available at: https://www.tandfonline.com/doi/full/10.1080/10408444.2016.1271972
[8] Guidance on the use of the weight of evidence approach in scientific assessments. Available at: https://www.efsa.europa.eu/en/efsajournal/pub/4971
[9] Guidance on the assessment of the biological relevance of data in scientific assessments. Available at: https://www.efsa.europa.eu/en/efsajournal/pub/4970

caused deaths. Currently, due to lack of information we assume that the effects of DMHA are equal to those of DMAA. A method or approach which could provide a means of estimating the potency of these chemicals could improve the accuracy of the information and confidence in the risk assessment.

30. The same approaches would also be extremely useful for selective androgen receptor modulators (SARMs). We have had a couple of incidents involving a number of SARMs (Annex C) which are intended to have similar effects to androgenic drugs like anabolic steroids but be much more selective in their action to avoid undesirable side effects. Tissues that are the target of SARM therapy will respond as they would to testosterone. Again, there are very few data for some of these, and although others may be undergoing clinical trials the data aren't in the public domain yet.

31. These approaches could also be used for other chemical groups such as brominated flame retardants (BFRs) or mycotoxins. For these groups of chemicals there may be toxicity data, but only for a handful of these. For naturally occurring toxins, such as mycotoxins, especially, there are generally no full toxicity packages, as there would be for drugs or pesticides. Therefore, risk assessments are carried out using toxicity information read across from the chemicals for which toxicity testing has been performed, if the chemical structure is very similar. Otherwise, there is little or no toxicity information to inform the risk assessment.

32. Relative potencies or toxic equivalency factors (TEFs) would enable more informed risk assessments to be undertaken where the potential toxicity can be more accurately estimated from the difference from the chemical for which there are toxicity data. This will be more accurate than assuming equal potency and would provide more confidence in the level of safety defined by the risk assessment.

33. The Secretariat have recently revised the outline for a project to determine potencies of chemicals through calculation of relative potencies or TEFs. Having assessed tender applications it was suggested that it would be prudent to hold a COT workshop to determine the best strategy for how to deal with new chemicals. A strategic approach would probably be a more realistic option than a generic approach. Pre-engagement should be considered by inviting external groups and possible partnership with the NC3R's CrackIT system[10]. This could be a really useful way to come up with a specification that could be responded to by a number of applicants. It would be useful to provide some examples of some of the chemicals that have come in and that the specification could be based on. It would be good to be able to have some measure of relative potency. The outcome of the project should be to help Policy teams be able to make a decision to either recall or withdraw products as appropriate.

Joint Committee Horizon Scanning

34. It may be of use to consider a Joint Committee Horizon Scanning towards the end of 2019 to monitor any changes brought about by the EU Exit. This could also

[10] https://www.nc3rs.org.uk/crack-it

include members from the Joint Expert Groups. Members may consider it more pertinent to have a joint training/awareness day.

35. At this time the Secretariat do not have any further items for 2019. Do Members have any ideas/suggestions that they would lie discussed at the meeting?

Balance of expertise on the Committee

36. 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	

37. 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.

38. Members are invited to comment on whether this list is still appropriate and if there are important gaps amongst the current membership or in light of possible future developments.

Questions on which the views of the Committee are sought

39. Members are invited to comment on each of the above areas and the question in paragraphs 20 and 38 and also to consider the following questions:

a. 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.

40. Do Members have proposals for research that FSA should fund in order to improve future COT risk assessments?

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

Secretariat

March 2019