Other Committee Activities: Joint Expert Groups, Presentations and Workshop 2024

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Postdoctoral Fellow presentation

1.126 The FSA and COT have been reviewing New Approach Methodologies (NAMs) to scope the best scientific methodologies available to be used in the risk assessment of chemicals in foods and the environment, and to understand how these can be incorporated and accepted in a regulatory context. NAMs include but are not limited to, high throughput screening and other in vitro assays, omics and in silico computer modelling strategies (e.g. Artificial Intelligence (AI) and machine learning) for the evaluation of hazard and exposure in risk assessment

1.127 In 2021, the FSA started funding a 4-year computational toxicology postdoctoral fellow at the University of Birmingham and a PhD Student (London Interdisciplinary Doctoral Program-LIDo) at King's College London on the use of artificial intelligence in chemical risk assessment.

1.128 The fellow and PhD student have been working alongside other government departments to understand how NAMs will improve indicative levels of safety in chemical risk assessment.

1.129 In addition, these new partnerships have helped with networking, research collaboration, training opportunities and other activities in this area. The Fellowship and studentship also compliment the work set out in the COT FSA UK Roadmap towards using NAMs in chemical risk assessment.

1.130 The Postdoctoral Fellow prepared a yearly review and gave a presentation to the Committee on progress of the two case studies that have been conducted, to date.

1.131 The first case study focused on the plasticiser di-2-ethylhexyl terephthalate (DEHTP) and the main objective was to derive a health-based guidance value HBGV. Concentration-response data obtained from ToxCast, via the Chemicals Dashboard (US EPA), was used.

1.132 The second case study was to establish HBGV for a perfluorinated substance, perfluorooctanoic acid (PFOA) using a workflow utilising multiple NAM approaches. The NAMs used included: NAMs in relation to the type of testing platform using *in vitro* hepatic microtissues; NAMs in relation to the type of data/read-outs using transcriptomics data, which provide an untargeted measurement of extensive gene expression; NAMs in relation to data analysis using Physiologically Based Pharmacokinetic (PBPK) modelling.

1.133 The Fellow also presented some preliminary work on the third case study, which is on tropane alkaloids.

1.134 The COT Members were impressed with the progress to date and gave feedback to the Fellow.

Marine biotoxins – Presentation on occurrence and exposure to pinnatoxin (data reserved)

1.135 The FSA is considering the current advice and monitoring programme for marine biotoxins and whether there is a need to update or change existing legislative standards.

1.136 As pinnatoxins (PnTX) are not currently regulated in England or Wales, the views of the COT were sought on whether PnTX would pose a risk to UK consumers. Therefore, in July 2023, the information and data on the risks associated with PnTX in shellfish was discussed. At the meeting the Committee concluded that due to the lack of toxicological and occurrence data it was currently not possible to determine the extent of any public health risk Occurrence data on PnTX would be useful to help fill some data gaps, including whether the UK population would be exposed to PnTX from shellfish consumption.

1.137 The recent availability of new analytical standards has allowed PnTX to be monitored in UK shellfish. Liquid chromatography–mass spectrometry (LCMS) monitoring data for PnTX-G were available to the FSA by the Agri-Food and Biosciences Institute (AFBI) in Northern Ireland and by Food Standards Scotland (FSS) and these data were discussed by the Committee in May 2024. The data are currently confidential as they are awaiting publication by the respective institutes.

1.138 The available occurrence data also allowed for some preliminary PnTX exposure estimates to be carried out for UK consumers, using EFSA’s estimated shellfish portion size of 400 g (excluding shells). The Committee noted that the exposures estimated by EFSA using this portion size assumed that a consumer would eat 400 g of a single shellfish type and questioned how likely this would be for some shellfish species. It was noted that cultural differences could also lead to variation in the amounts and types of shellfish consumed. Data from the National Diet and Nutrition Survey (NDNS) showed that in the UK shellfish is consumed in lower quantities than EFSA’s estimated 400 g. Therefore, some of the exposure estimates presented may be overestimations of UK exposures.

1.139 The Committee questioned whether PnTX-G was known to co-occur with other marine biotoxins, however, there did not appear to be any reports of regular co- occurrence. It was noted that the different feeding habits of shellfish could potentially influence toxin levels.

1.140 With respect to reducing the levels of PnTXs in shellfish, there were no data available on the efficacy of depuration tanks and as PnTXs are lipophilic biotoxins this would make extraction into clean water less likely. The toxins are relatively heat stable but processes such as cooking or dehydration of the meat during

steaming and canning could lead to different levels of PnTX in the final product compared to the raw shellfish.

1.141 Overall, the Committee thought the information presented was useful but reiterated that there were significant data gaps on PnTX, especially regarding its toxicity.

New Approach Methodologies (NAMs) in regulatory decisions for chemical safety presentation and review

1.142 Dr Letizia Carramusa from the Yordas Group presented the results of a FSA funded a literature review on New Approach Methodologies (NAMs) to Support Regulatory Decisions for Chemical Safety to the Committee.

1.143 It was explained that the he objectives of the project were: to collate, review and categorise the most up-to-date scientific literature for the UK's own evaluation of NAMs in the field of chemical risk assessment; to assess the regulatory readiness of NAMs and the degree to which these technologies have been successfully integrated into regulatory frameworks; to gather and summarise expert opinions on the gaps that hinder the further adoption of New Approach Methodologies (NAMs) in the regulatory process.

1.144 The literature search and methodology were outlined. Publications were retrieved from 2014 onwards to prioritise the most recent literature and ensure the relevance of the studies. NAMs published more than a decade ago were excluded from the literature review as they were considered to be either well-established within the regulatory framework or have been superseded by improved methods, meaning that research into them had halted.

1.145 Global stakeholder interviews were then undertaken. Topics and key findings from the interviews included: views on the term "NAM"; research investment focus; how NAMs integrate with traditional hazard assessment and when they will become the primary approach, either to supplement existing approaches, or to completely replace animal testing; regulatory application, especially for food; how are NAMs best used for regulatory activities and how food regulations integrate NAMs; the barriers to integration of NAMs and how they can be overcome; and the types of substance or material where NAMs can play a role in the near future. It was concluded that no single NAM can replace animal studies entirely and the FSA should explore the adoption of concepts like

"endorsement" or "qualification" used in the US for tier-one decisions.

1.146 Members complimented the Yordas Group for a comprehensive, interesting and thorough review.

1.147 The Committee noted that physiologically based pharmacokinetic (PBPK) modelling was more commonly used than described in the report. Specifically, JECFA reports on contaminants regularly utilized PBPK modelling, emphasizing its critical role in determining Tolerable Daily Intakes (TDIs).

1.148 The Committee discussed the report with respect to recommendations related to qualification and validation of NAMs. There is a need for mechanisms to qualify, validate, and generate confidence in the suitability of the novel approaches and there are challenges in securing funding for this purpose. This, and previous, reports have noted funding in the area of NAMs predominantly supports innovation rather than translation of research. The lack of funding avenues for translation through UK Research and Innovation (UKRI) was noted and the need for alternative funding solutions stressed. The distinction between scientific validation and qualification for regulatory application was noted, with more focus on the latter being noted. There is ongoing work in the USA and Asia on this area, and collaboration within the Organisation for Economic Co-operation and Development (OECD) framework is recommended.

1.149 Members noted unavoidable bias in retrospective evaluations of the adequacy of conventional animal toxicity studies, particularly in pharmaceuticals since the drugs evaluated in human studies were a selective subset as many did not make it through the pre-clinical development process, and NAMs were likely used as part of that process. As an example of this, pre-clinical testing was very effective in identifying direct hepatotoxins before market release, and those drugs that were withdrawn for liver toxicity post-marketing almost always involved idiosyncratic reactions, which were not detectable in animal studies or even clinical trials.

1.150 It was noted that genetic toxicology, methods such as the Ames test had been deemed “Out of Scope” prior to the report being written, as they were already well established.

1.151 The importance of understanding adverse outcome pathways (AOPs) in making more informed safety assessments was noted, despite their inherent uncertainties. It was important to strengthen AOPs to allow meaningful risk assessment, and there should be focus on working within the OECD framework.

1.152 The Committee suggested that they along with other advisory groups should highlight gaps in evidence, particularly where additional data from the use of NAMs could improve confidence in decision-making. Furthermore, the Committee highlighted the need to champion the use of the best science in regulatory risk assessment, including the use of NAMs as appropriate, which would require stimulating engagement from developers, especially in the context of limited funding.

FSA Research Programme Presentation

1.153 A presentation was given to Members to update them on the updated structure of the FSA research programme and provide a brief overview on the roles and responsibilities of individuals and groups involved in the commissioning and delivery of the research programme.

1.154 The Research Evidence Programme (REP) most closely aligned to the work of the COT is the Chemical, Radiological and Food Hypersensitivity REP. The external research projects currently being delivered within this programme and of interest to the Committee are:

- Advancing in silico Methods of Assessing Toxicological Risk (Fellowship).
- TOX-AI: Digitalising Toxicological Databases using artificial intelligence and in silico tools for food safety (Studentship).
- Multi-allergen analysis using multiplex PCR, include case study for mustard allergen detection (L&S).
- Projects due to be commissioned in early 2025 are: Determination of the bioavailability of cyanogenic glycosides on consumption.
- Literature review of nitrates and nitrites as food additives.

1.155 Updates on the status of the Chemical, Radiological and Hypersensitivity REP will be provided to the Committee periodically and the outputs from some projects may be brought to the Committee for peer review.

Evolving Our Assessment & Future Guiding Principles Workshop Report

1.156 The COT held a workshop in May 2023 to start work on updating their guidance on toxicity testing and its supporting principles. The overall objective of the workshop was to discuss how the Committee moves forward in a new era of risk assessment.

1.157 The workshop aimed to identify areas where guidance needed to evolve and included reviewing fundamental risk assessment principles, current guidance on risk assessment and what can be learned from it, integration of new approach methodologies (NAMs), exploring hazard vs risk and weight of evidence. The four sessions were: Where are we at; What we need to improve; How to achieve; and Looking to the future - moving forward.

1.158 Members discussed the output of the workshop, considering “must, could and should” priorities to be taken forward. The most important aim was to have applicable guidance to ensure public safety.

1.159 The workshop report is now available: (DOI: https://doi.org/10.46756/sci.fsa.qpo647)

Gut reactions: xenobiotics and the microbiome workshop

1.160 The COT held a workshop in October 2024 in London, United Kingdom on xenobiotics and the microbiome. The workshop included themed sessions consisting of short flash presentations followed by roundtable discussions. There was attendance from multiple stakeholders including academia, government and industry.

1.161 The workshop set out to explore the complex current state of the science of the microbiome pathophysiology and the possible impact of xenobiotics on host-microbiome interactions and vice versa, including possible mechanisms and health implications, with a particular emphasis on the gut microbiome and dietary exposure.

1.162 In addition, the aim was to enable new insights, review the science, initiate discussions to determine where the data gaps are in research, what effects are of concern, and how might xenobiotics be evaluated practically for such effects in the future.

1.163 The four sessions were: Interactions of the host microbiome system; Gut microbiome and xenobiotics; Assessing the impact on the microbiome; Possible ways to evaluate in the short to medium term and microbiome interventions for maintaining health and treating disease and Future Directions.

1.164 The finalised report will be published in due course.

Hazardous Substances Advisory Committee (HSAC) discussion on the effects of flame retardants on human health: developing a work programme

1.165 The COT was invited by Defra to comment, along with the Hazardous Substances Advisory Committee (HSAC), on developing a work programme on flame retardants and using information on human risk to aid prioritising the compounds or groups of compounds for review.

1.166 The COT provided a number of comments with respect to availability of evidence on effectiveness, toxicity and exposure data to allow comparisons across different flame retardants. Grouping and read-across were suggested as a means to aid prioritisation. A number of aspects related to sources and routes of chemical exposure were noted for consider.

1.167 Defra thanked the COT for its input which it would take forward with the Secretariat and other partners.

Horizon Scanning

1.168 The COT undertake horizon scanning at their February meeting, where they review the work anticipated for the coming year; this includes ongoing topics, the annual workshop, current or planned working groups and the skills balance of the Committee. However, Members are also encouraged to suggest topics for discussion throughout the year.

1.169 The COT terms of reference include advising, at the request of many different government departments, on a wide variety of chemicals and routes of exposure, making them very broad, and potentially overlapping with those of a number of other Scientific Advisory Committees. Thus, while the Committee's work is mostly reactive, the terms of reference also include advising on important general principles and scientific discoveries in relation to toxic risks, which was more proactive. The Committee is constrained by a heavy workload, but it is important that it is proactive where it can be, taking a lead on advances in the application of novel science in the risk assessment of chemicals. The continuing work on new approach methodologies is an example of this.

1.170 A number of topics were suggested for potential consideration as either individual papers or as a future COT workshop; these included potential regulatory changes to chemicals in the environment, the microbiome (including the effects of chemicals other than antimicrobials), the presence of novel contaminants in the oceans that could enter the food chain, vegan/vegetarian foods and their ultra- processed replacements (where these were in the COT remit), non-EATS (estrogen, androgen, thyroid and steroidogenesis) mechanisms for endocrine disruption, and obesogens.

1.71 Horizon scanning techniques were discussed more generally, with a view to considering what would be the most useful approach for the Committee to take and it was agreed to review this at a future date.