Meeting

Draft Minutes of the 3rd September 2024 COT Meeting

Meeting of the Committee at 10:00 on 3rd September 2024 on Microsoft Teams

Present

Chair:	Professor Alan Boobis

Professor Gary Hutchison

Professor Thorhallur Halldórsson (To item 7)

Dr Sarah Judge

Dr Michael Routledge

Dr Natalie Thatcher

Dr Simon Wilkinson

Professor Mireille Toledano

Professor Philipe Wilson

Ms Jane Case

Professor Gunter Kuhnle

Professor Shirley Price

Dr Cheryl Scudamore

Dr Stella Cochrane

COT Members: Professor James Coulson

Dr David Lovell (From item 4)

Professor Peter Barlow

Dr Steven Enoch

Dr Mac Provan

Professors Maged Younes

Professor Philippe Wilson

Dr Steven Enoch

Professor Peter Barlow

Dr Chris Morris

Dr Meera Cush (To item 7)

Mr Gordon Burton (To item 7)

Dr Andreas Kolb

	Ms Cath Mulholland - FSA Scientific Secretary
	Dr Alex Cooper
	Mr Barry Maycock
	Ms Claire Potter
	Dr Barbara Doerr
	Dr Olivia Osborne
	Ms Sabrina Thomas
	Dr Gail Drummond
	Ms Cleanncy Hoppie
	Ms Jocelyn Frimpong-Manso
	Ms Sophy Orphanos
Food Standards	Dr Gaetana Spedalieri
Agency (FSA)	Mr Thomas Hornsby
Secretariat:	Dr Emily Hudson
	Dr Aaron Bradshaw
	Dr Lorcan Browne
	Ms Natasha Adams
	Dr Katie Schulz
	Ms Katie Wetherall
	Mr Barry Maycock
	Ms Frederique Uy
	Dr Rachel Kerr
	Mr James Metcalfe
	Ms Yoana Petrova
	Ms Polly Bevan
	Ms Alba Urena Rusillo

UK HSA Secretariat:	Ms Britta Gadeberg - UK HSA Scientific Secretary Ms Sanyukta Pallavi - UK HSA Scientific Secretary Ms Sanyukta Pallavi
Assessors:	Ms Poornima Paramasivan - HSE - Health and Safety Executive Ms Frances Hill - Office for Product Safety and Standards, part of the Department for Business and Trade Ms Susannah Brown - Office for Health Improvement and Disparities (OHID), Department of Health and Social Care (DHSC) Ms Rachel Elsom - OHID
FSA and other Officials:	Ms Lucy Reid - Food Standards Northern Ireland (FSA NI) Ms Krystle Boss - FSS – Food Standards Scotland Ms Lauren Adams - FSA Nive Raja - UKHSA

Contents

2	Draft minutes of March meeting – TOX/MIN/2024/04	4 – 6
3	Matters arising: • JEG updates • ORO and ABB decisions • Publications • Microbiome workshop • Subgroups and working groups • SAC recruitment	7 – 21
4	RP1245 Steviol glycosides (reserved)	22 – 25
5	Application to authorise Iron enriched yeast (reserved)	26 – 29
6	COT Ways of Working-2	30-43
7	New Approach Methodologies (NAMs) in regulatory decisions for chemical safety Review	44-54
8	Update on the work of other FSA Scientific Advisory Committees	55
9	Any other business	56

Announcements

1. The Chair welcomed Members and other attendees.

2. Dr Letizia Carramusa, Dr Rosalinda Gioa and Dr Emma Miller of the Yordas Group would be present as observers.

Interests

3. The Chair reminded those attending the meeting to declare any commercial or other interests they might have in any of the agenda Items.

Item 1: Apologies for absence

4. Apologies were received from COT Members Dr Mac Provan, Dr Michael Routledge, Professor Mireille B. Toledano, Dr Silvia Gratz, and Dr Alison Yates.

Item 2: Draft minutes and reserved minutes of the 9th July 2024 meeting (TOX/MIN/2024/04).

5. The Committee reviewed the draft minutes and the reserved minutes of the 9th of July 2024 meeting (TOX/MIN/2024/04). It was noted that there was repeated text in paragraph 73, which would be deleted.

6. The minutes and reserved minutes were accepted as an accurate record.

Item 3: Matters arising

Joint Expert Group (JEG) updates

AEJEG

7. The full AEJEG last met on the 18th of July 2024. In that meeting they discussed a request for clarification provided by the Applicant for RP733. This application was an assessment for the authorisation of soy legume haemoglobin for use as a flavouring precursor in plant-based meat alternatives.

8. The AEJEG also considered the Draft Committee Advice Document for application RP1245, which requested a modification to the Specifications of steviol glycosides to include a new manufacturing process of rebaudioside D. The AEJEG also considered an updated paper for application RP40 after receiving a response to a request for information.

9. The AEJEG Smoke Flavourings Working group (SFWG) met on the 25th of July 2024. In that meeting a forward look at Phase 3 meetings was discussed followed by a question-and-answer session. The SFWG also discussed a weight of evidence update paper and discussed minutes of their previous Phase 2

meetings. The next full AEJEG meeting will take place on 11th of September and the next SFWG meeting will take place on the 18th of September 2024.

FCMJEG

10. The last meeting of the FCMJEG was on the 28th of August, where Members reviewed the updated CAD for a plastic additive (RP1702) following COT review. Members looked at additional information on a plastic additive (RP2147-chopped carbon fibre), and following their discussions, an additional RFI will be issued.

11. There have been no new applications under the remit of the FCMJEG. The most recently received application, RP2229 Poly(2-ethyl-2-oxazoline), has undergone suitability checks and a request for information (RFI) has been issued.

12. There are currently three applications at the RFI stage (RP1898, RP262 and RP2147), two applications that have been concluded and are at the Committee Advice Document (CAD) stage for COT review in due course (RP1741 and RP1862), and two applications "on hold" (RP1415 and RP1642).

ORO and ABB decisions

13. At the January/February meetings of the FSA Scientific Advisory Committees (SACs) and Joint Expert Groups (JEGs) that support the regulated products service, a ways-of-working paper (as TOX-2024-10 for COT) was presented to Members. This explained two additional ways in which the FSA would be assessing regulated products. These updated ways of working were 1) the use of other regulator's opinions by the FSA (ORO) and 2) the use of an 'abbreviated process' (ABB) for safety assessments. These processes involve internal assurance via an FSA decision panel that is chaired by a senior leader from the Risk Assessment Unit with regular oversight from the FSA Chief Scientific Advisor. Applications progressing through these assessment routes would not routinely be considered by SACs, but a summary of the applications would be periodically presented to the COT for information.

14. A table setting out these decisions has been uploaded to the Members' area folder for information, along with the original ways of working document as an *aide memoire*. These documents should be treated as confidential.

Publications

15. The Executive Summary of the COT review of titanium dioxide was published on the 22nd of August 2024. The full review, along with the reviews by the Committee on the Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM), would be published at the end of September 2024.

16. The statements on raspberry leaf in the maternal diet, green tea catechins and turmeric have been finalised and will be published together with lay summaries in the near future.

COT 2024 Workshop in the microbiome

17. The COT workshop on the microbiome will take place on Tuesday 22nd October 2024. Members were updated on the agenda and invited to comment and to contribute any final questions for the round table discussions.

Subgroups and working groups

ACNFP/COT working group on CBD

18. The next meeting will take place on the 11th of September.

PFAS working group

19. The PFAS Working Group met on the 24th of July and discussed liver and thyroid endpoints. A date has not yet been set for the 4th meeting of the group.

Joint SACN-COT working group on plant-based drinks

20. The draft working group report on plant-based drinks was published for peer review in July 2024. The Secretariat will be reviewing the responses in mid-September. A working group meeting will follow later in the year.

SAC recruitment

21. The FSA SAC recruitment campaign had opened and would remain open until early October. Members are asked to share the details with their networks. Members were asked to inform the Secretariat of any potential individuals or organisations who could be approached regarding recruitment. Thanks were extended to Members who have already made some highly useful suggestions.

Item 4: RP1245 Steviol glycosides (reserved) (TOX/2024/31)

22. A personal interest was declared by Professor Maged Younes stating that he had previously reviewed steviol glycoside applications whilst on European Food Safety Authority (EFSA) Panels. This was deemed to be a personal, non-specific interest and did not preclude him taking part in the discussion. No other interests were declared.

23. A confidential AEJEG Committee Advice Document on the safety of a proposed change to modify the specification of steviol glycosides provided by enzymatic conversion (E960c) to include the production of rebaudioside D via enzymatic conversion of stevia leaf extract was presented to the COT.

24. The item is currently being treated as reserved whilst policy is developed. The minutes will be published once confidentiality agreements have been finalised.

25. Members reviewed and commented on the paper.

Item 5: Application to authorise Iron enriched yeast (reserved) (TOX/2024/32)

26. No interests were declared.

27. The Department of Health and Social Care (DHSC) have asked the COT to review an application for the authorisation of iron-enriched yeast as a permitted form of iron, which can be voluntarily used in food fortification, food supplements and foods for specific groups in Great Britain.

28. This item is currently being treated as reserved, as the application contains commercially sensitive and confidential data.

29. Members reviewed and commented on the paper.

Item 6: COT Ways of Working-2 (TOX/2024/33)

30. No interests were declared.

31. Following on from the discussions at the May COT meeting Final Minutes of the 21st May 2024 COT Meeting | Committee on Toxicity (food.gov.uk) where the Committee discussed their ways of working with a view to reduce the workload of the Chair, the Secretariat thought that it would be timely to review some other areas of the COT's activities including the best use of discussion papers, the development of technical guidance and horizon scanning.

32. The aim of the discussion was to ensure that the Committee had a range of outputs that were appropriate for the work that it is undertaking, including the planned updating of the COT guidance but also, to promote the Committee's work more widely.

33. Members were asked whether it would be appropriate to remove the current "Do not cite" heading from discussion papers where appropriate and, if so, what wording might be suitable? The aim of the marking was to ensure that the Committee's final views were not inferred from the discussion papers, which should be taken from the agreed minutes, the Annual Report or the final statements. However, it was considered that there was much useful information in the discussion papers not otherwise citeable, so it would be useful if they could be more widely cited. But, potentially, inaccuracies will be present, so there could be reputational damage to the Committee, despite any caveats given about the standing of the paper. Similarly, there could be potential harm to the integrity of the Committee if there are interpretations of data that do not reflect the considered views of the COT.

34. It was suggested that a watermark could be used so that it was clear the papers were unverified and not peer reviewed or otherwise assured. The papers could also be marked "first draft" or "preliminary" and subsequently linked to the relevant minutes.

35. It was noted that the equivalent EFSA papers were published only once they were finalised, this included technical reports and background documents, which fed into the work of the EFSA panels but were not themselves published. In contrast, the COT discussion papers, draft statements and other preliminary papers, were all available on the website if they did not contain commercially or other confidential information.

36. For topics and discussion papers that did not have a statement produced, it was suggested that they could have a paragraph added that provides a hyperlink to the COT minutes, which would provide the considered views of the Committee.

37. Overall, it was considered that the current approach to discussion papers worked but it should remain under review. However, Members agreed that reformatting some of the discussion papers as technical guidance documents or state of the science reports would be useful and the Committee would review a more developed version of a potential template for this purpose in due course.

38. Members then discussed horizon scanning; it was agreed that while they would be interested in information on different horizon scanning techniques, it was important in considering these to determine what exactly the Committee needed to get out of the process.

39. It was asked whether horizon scanning could be automated. It was noted that one possibility was that Artificial Intelligence (AI) could be used to generate word clouds, for example from media stories or social media posts.

40. It was noted that other Advisory Committees and Regulatory Agencies covering chemicals undertook horizon scanning and it might be useful to learn what they were doing, noting that, for example, the United States Environmental Protection Agency (EPA) or the German Federal Institute for Risk Assessment (BfR) might be a nearer equivalent than the COC or the COM, whose interests were more focused. The results of horizon scanning should be a living document.

41. Members made a number of suggestions as to how the profile of the Committee could be raised, included working with the British Toxicology Society on a dedicated congress session, possibly built around a particular topic, or a COT sponsored lectureship.

42. The Secretariat highlighted that some, but not all, COT statements currently have a DOI number; Members were advised that these would routinely be applied going forward.

Item 7: New Approach Methodologies (NAMs) in regulatory decisions for chemical safety Review (TOX/2024/34)

43. No interests were declared

44. FSA has funded a literature review on New Approach Methodologies (NAMs) to Support Regulatory Decisions for Chemical Safety | Published in FSA Research and Evidence (food.gov.uk). Dr Letizia Carramusa from the Yordas

Group, which carried out the review, presented the results of their findings.

45. The 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.

46. The literature search and methodology were explained. 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.

47. 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.

48. Members complimented the Yordas Group for a comprehensive, interesting and thorough review. The Members thanked Dr Letizia Carramusa for an excellent presentation.

49. 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).

50. The Committee discussed the report with respect to recommendations related to qualification and validation. They emphasized the need for mechanisms to qualify, validate, and generate confidence in the suitability of novel approaches

(NAMs) and the challenges in securing funding for this purpose. They highlighted that this, and previous, reports have noted funding in the area of NAMs predominantly supports innovation rather than translation of research. Members discussed the lack of funding avenues for translation through UK Research and Innovation (UKRI) and stressed the need for alternative funding solutions. Members raised the distinction between scientific validation and qualification for regulatory application, urging more focus on the latter. It was pointed out that there was ongoing work in the USA and Asia, and recommended collaboration within the Organisation for Economic Co- operation and Development (OECD) framework.

51. Members raised concerns about the unavoidable bias in retrospective evaluations of the adequacy of conventional animal toxicity studies, particularly in pharmaceuticals. They highlighted that the drugs evaluated in human studies were a selective subset as many did not make it through development, and NAMs were likely used as part of that process. As an example, 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.

52. One member noted the lack of discussion on genetic toxicology, emphasizing its importance in both *in vivo* and *in vitro* work and suggested that the report could benefit from more insight into how genetic toxicology methodologies integrate with other modelling approaches. The Secretariat clarified that methods such as the Ames test had been deemed “Out of Scope” prior to the report being written, as they had been developed over a decade ago and were now well established.

53. Members also emphasized the importance of understanding adverse outcome pathways (AOPs) to make more informed safety assessments, despite the inherent uncertainties. They highlighted the importance of strengthening AOPs for meaningful risk assessment and suggested focusing on working within the OECD framework.

54. Finally, the Committee suggested that they themselves and other similar 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.

Item 8: Update on the work of other FSA Scientific Advisory Committees (TOX/2024/35)

55. This paper was circulated for information, but Members should contact the Secretariat if they have any questions.

Item 9: Any other business

56. There was no other business.

Date of next meeting

The next meeting of the Committee will be at 11:00 on the 21st of October at Broadway House, London and via Microsoft Teams.