

Developing COT guidance

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Introduction

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1. The COT has agreed to update its guidance on toxicity testing and its supporting principles. The previous COT guidelines date from 1982 but were superseded by guidance from the former Scientific Committee on Food (SCF) and the European Food Safety Authority (EFSA), and so have not been updated since then. To start this work, the COT held a workshop in May 2023. The workshop aimed to focus on identifying the principles that would underpin the development of the guidance. It was considered that the COT should identify existing frameworks and guidance and use or adapt these as necessary, and that it should integrate new approach methodologies, using the best science available.

2. The purpose of this paper is to start the work developing new COT guidance, and seek the Committee's agreement on the way forward, including whether establishing a working group would be the most appropriate approach.

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COT workshop: Evolving Our Assessment & Future Guiding Principles

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3. In May 2023, the COT held a workshop to start the work on new COT guidance. The workshop report is at Annex A. It was noted that the starting point for the process should be existing frameworks and guidance, but with the aim of including innovative improvements, where possible. The workshop aimed to identify the key areas that need to be considered in developing the guidance, and these 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 versus risk, and weight of evidence. The overall objective of the workshop was to discuss how the Committee moves forward in a new era of risk assessment.

4. Topics discussed at the workshop included models and tools, assessment methods, data sources and quality, uncertainty, NAMs, training and skills, validation, regulatory interfaces, and the role of scientific advisory committees.

5. The workshop’s recommendations, priorities and proposed improvements to guidance are shown in Table 1.

Table 1. Recommendations, priorities, and proposed improvements to the COT guidance from the “Evolving our assessment and future guiding principles” workshop.

Recommendations	Priorities	Improvement
Transparency	Resourcing and capturing institutional wisdom	Clear distinction between who is responsible for what
Build relationships with other agencies and harmonization internationally	Weight of Evidence	Strengthen links between Scientific Advisory Committees across government agencies
Explore uncertainty and validation	Tiered Testing	Integrated (systematic) reviews in risk assessment
Explore risk benefit and comparative risk	Enhancing public health	Codify what we have

Table 1 sets out the recommendations and priorities for improvement identified in the COT workshop "Evolving our assessment and future guiding principles." The table is shown in black line and text. It has 3 columns and 5 rows.

6. Following the workshop, the COT reviewed the draft workshop report at its October 2023 meeting, and identified the most important “must,” “could” and “should” points. These are shown below.

Must: Identify and adapt existing frameworks, guidance, and assessments to enhance public safety.
Should: Integrate new approach methodologies by using the best available science.
Could: Explore risk benefit and comparative risk.

This box follows on from Table 1 separating the recommendations into must, should and could. The image shows a table in black line and text.

7. The Committee noted that assessment of benefits was not within the terms of reference of the COT and thought should be given as to how COT advice could be best aligned for this to be undertaken when needed or appropriate.

8. The Committee noted that to take the guidance forward, establishing an initial framework would be important. This could then be expanded and linked to

other guidance as necessary. There were considered to be two parts to the work, to codify what the Committee currently do, and then to provide guidance on areas where the approach was not yet codified such as benchmark dose modelling.

9. The Committee agreed that it would be important to work with the policy colleagues from the relevant Government departments and not re-invent the risk analysis process. In particular, the required levels of protection needed for consumers should be considered.

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10. EFSA's Scientific Committee and panels have produced a large number of guidance documents. These include cross-cutting areas of guidance as well as sector specific guidance. These are listed in Annex B. The cross-cutting areas of guidance address a wide range of topics of relevance to the COT, including benchmark dose modelling, risk assessment of mixtures, weight of evidence, biological relevance and risk-benefit assessment, amongst others. The COT responded to public consultations by EFSA on the draft versions of many of the cross-cutting areas of guidance. Consideration of sector-specific guidance by EFSA, e.g. on food additives and consumer risk assessment of feed additives, may

be of value in developing the overarching approach. In general, the guidance documents for food additives, feed additives and food contact materials take tiered approaches to the data requirements, but there are differences between them.

11. Also listed in Annex B are relevant guidance documents published by the United States (US) Food and Drug Administration (FDA) and Environmental Protection Agency (EPA).

12. EHC 240, the International Programme on Chemical Safety's "Principles and methods for the risk assessment of chemicals in food" was developed and published in 2009, and chapters and sections on genotoxicity, dose-response assessment and derivation of health-based guidance values, dietary exposure assessment and enzymes were updated in 2020. This is available with the updated chapters at [Principles and methods for the risk assessment of chemicals in food](#).

13. Other guidance which the COT may wish to consider includes the REACH guidance on chemical safety assessment ([Guidance on Information Requirements and Chemical Safety Assessment - ECHA](#)) and VICH guidelines for veterinary medicines ([Guidelines](#)).

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Proposal on the potential structure of COT guidance

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14. Based on the COT's discussions to date it is proposed that the guidance take the form of a main guidance document, which contains the overarching principles, and then separate guidance documents on specific topics which link to this. The starting point for the guidance would be existing guidance. It is suggested that the guidance should:

- Take a tiered approach.
- Be flexible.
- Take into account the 3/6 Rs (replacement, reduction and refinement of animal testing, but also recently extended to include the reproducibility, relevance and regulatory acceptance of alternatives).
- Specify the information needed rather than the specific studies.
- Be futureproof.
- Include NAMs and how they can be used in risk assessment or to support risk assessment.
- Include the integration of evidence.

15. Aspects that have been noted that may need to be taken into account include:

- Regulatory requirements / sector specific risk assessment needs.
- General chemical risk assessment versus assessment of applications for regulated products.
- The roles of COC and COM, how to interlink with or cross-reference their guidance and possible areas of joint working.
- The joint COT/COC reports on synthesising epidemiological evidence (SEES) and synthesising and integrating epidemiological and toxicological evidence (SETE) reports.
- The four nations of the UK and divergence, e.g. between Great Britain and Northern Ireland.

16. Views of the COT are sought, but areas where UK-specific guidance may be helpful may include:

- Risk assessment of mixtures.
- Integrated approaches to testing and assessment (IATA).

- Benchmark dose modelling.
- Exposure assessment.
- Novel forms of, for example, supplements ingredients.
- The use of artificial intelligence (IA).
- Risk-benefit approaches.
- Biological and statistical significance.
- Biomonitoring.
- Systematic reviews and literature techniques.
- Risks to infants <12 weeks of age.

17. Members are asked to consider where UK-specific guidance is required as it would be helpful to not diverge significantly from EFSA guidance where this is not necessary.

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Discussion and Questions

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Discussion

18. Members are asked to consider how they would wish to proceed with this work, for example, if they agree with establishing a working group, initially to develop the main guidance document. It would also be useful to consider where

existing guidance could be used or signposted in the main COT guidance document. Members are also asked to consider what topics require UK-specific guidance.

19. It would also be helpful for Members to consider whether they would wish to develop sector-specific guidance or whether this should be considered by the JEGs once the main COT guidance document is finalised.

Questions on which the views of the Committee are sought

20. Members are asked to consider the following questions:

- i. Are Members content with the proposal on the format of the guidance?
- ii. Are there any other factors that need to be taken into account?
- iii. On what topics should COT guidance be developed, and on what can existing guidance be endorsed or signposted?
- iv. Does the Committee agree with establishing a working group to develop the main guidance document containing the general principles?
- v. What is the priority order in establishing stand-alone guidance pieces?
- vi. Would the COT wish to develop sector-specific guidance, or should this be considered by the JEGs once the main COT guidance document giving the general principles is finalised?

21. If the Committee agrees to establishing a working group, volunteers are sought to participate in this working group. It is anticipated that four meetings of the working group would be held in 2025, the first by March 2025.

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November 2024

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BMD benchmark dose

BMDL benchmark dose lower confidence limit

COC Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

COM Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment

COT Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

EFSA European Food Safety Authority

EPA Environmental Protection Agency

FDA Food and Drug Administration

NAMs New approach methodologies

REACH Registration, Evaluation, Authorisation and Restriction of Chemicals

VICH Veterinary International Conference on Harmonisation

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Annex A

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Evolving Our Assessment & Future Guiding Principles Workshop Report (2023)
DOI: <https://doi.org/10.46756/sci.fsa.qpo647> the report can also be found at the web address: [Evolving Our Assessment & Future Guiding Principles Workshop Report \(2023\) | Committee on Toxicity](#).

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Lists of guidance documents by EFSA, the US FDA and US EPA

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EFSA Guidance

Cross-cutting guidance

[Guidance on the use of the **benchmark dose approach** in risk assessment](#)

[Guidance on **aneugenicity** assessment.](#)

[Guidance on risk assessment of **nanomaterials** to be applied in the food and feed chain: human and animal health.](#)

[Guidance on technical requirements for regulated food and feed product applications to establish the presence of small particles including **nanoparticles**.](#)

[Guidance on the use of the **Threshold of Toxicological Concern** approach in food safety assessment.](#)

Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of **combined exposure** to multiple chemicals.

Genotoxicity assessment of chemical **mixtures**.

Clarification of some aspects related to **genotoxicity** assessment.

Guidance on **uncertainty analysis** in scientific assessments.

Guidance on the risk assessment of substances present in food intended for **infants below 16 weeks** of age.

Guidance on the use of the **weight of evidence approach** in scientific assessments.

Guidance on the assessment of the **biological relevance** of data in scientific assessments.

Guidance on **statistical reporting**.

Guidance on **Expert Knowledge Elicitation** in Food and Feed Safety Risk Assessment.

Statement on the applicability of the **Margin of Exposure approach for the safety assessment of impurities** which are both genotoxic and carcinogenic in substances added to food/feed.

Guidance on selected **default values** to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data.

Scientific opinion on **genotoxicity testing strategies** applicable to food and feed safety assessment.

Guidance on **risk-benefit assessment** of foods.

Application of **systematic review methodology** to food and feed safety assessments to support decision making.

Transparency in risk assessment carried out by EFSA: Guidance Document on procedural aspects.

Guidance of the Scientific Committee on **transparency** in the scientific aspects of risk assessments carried out by EFSA. Part 2: General Principles.

Opinion of the Scientific Committee related to **uncertainties in dietary exposure assessment**.

Opinion of the Scientific Committee on a request from EFSA related to a harmonised approach for **risk assessment of substances which are both genotoxic and carcinogenic**.

Scientific Committee guidance on **appraising and integrating evidence from epidemiological studies** for use in EFSA's scientific assessments.

Sector-specific guidance

Guidance for submission for **food additive** evaluations.

Scientific Guidance for the submission of dossiers on **food enzymes**.

Scientific Guidance for the preparation of applications on **smoke flavouring primary products**.

Scientific Guidance on the data required for the risk assessment of **flavourings** to be used in or on foods.

Guidance on the scientific requirements for an application for authorisation of a **novel food** in the context of Regulation (EU) 2015/2283.

Guidance on the scientific requirements for a notification and application for authorisation of **traditional foods** from third countries in the context of Regulation (EU) 2015/2283.

Guidance on the renewal of the authorisation of **feed additives**.

Update: methodological principles and scientific methods to be taken into account when establishing Reference Points for Action (RPAs) for **non-allowed pharmacologically active substances** present in food of animal origin.

Guidance on the assessment of the safety of **feed additives** for the consumer.

Guidance on the assessment of the safety of **feed additives** for the target species.

General approach to assess the safety for the target species of botanical preparations which contain compounds that are genotoxic and/or carcinogenic when used as **feed additives**.

Guidance for establishing and applying tolerable upper intake levels for **vitamins and essential minerals**.

Note for guidance for the preparation of an application for the safety assessment of a substance to be used in **plastic food contact materials**.

Guidelines on submission of a dossier for safety evaluation by the EFSA of a recycling process to produce **recycled plastics intended to be used for manufacture of materials and articles in contact with food**.

Scientific Guidance on the criteria for the evaluation and on the preparation of applications for the safety assessment of **post-consumer mechanical PET recycling processes** intended to be used for manufacture of materials and articles in contact with food.

Guidelines on submission of a dossier for safety evaluation by the EFSA of active or intelligent substances present in **active and intelligent materials and articles intended to come into contact with food**.

Guidance on conducting repeated-dose 90-day oral toxicity study in rodents on **whole food/feed**.

Explanatory statement for the applicability of the Guidance of the EFSA Scientific Committee on conducting repeated-dose 90-day oral toxicity study in rodents on whole food/feed for **GMO** risk assessment.

Scientific Opinion on a Qualified Presumption of Safety (QPS) approach for the safety assessment of **botanicals and botanical preparations**.

Guidance on safety assessment of **botanicals and botanical preparations** intended for use as ingredients in food supplements.

Introduction of a Qualified Presumption of Safety (QPS) approach for assessment of selected **microorganisms** referred to EFSA.

Guidance for **establishing and applying tolerable upper intake levels** for vitamins and essential minerals.

Guidance on scientific principles and data requirements for the **safety and relative bioavailability assessment of new micronutrient sources**.

FDA toxicology guidance documents for food ingredients

[Preparation of **food contact substance** notifications \(toxicology recommendations\).](#)

[Toxicological principles for the safety assessment of **food ingredients**: Redbook 2000.](#)

[Toxicological principles for the safety assessment of direct **food additives and color additives**: 1993 Draft Redbook II. Sections of Draft Redbook II not yet finalized in Redbook 2000 are available.](#)

[Summary table of recommended toxicological testing for **additives** used in food.](#)

EPA toxicology guidance

[**Framework** for human health risk assessment to inform decision making.](#)

[Guidance for applying quantitative data to develop **data-derived extrapolation factors** for interspecies and intraspecies extrapolation.](#)

[**Benchmark dose** technical guidance.](#)

[Recommended **use of body weight**^{3/4} as the default method in derivation of the oral reference dose](#)

[Framework for **metals** risk assessment.](#)

[Guidelines for **carcinogen** risk assessment.](#)

[Supplemental guidance for assessing susceptibility from **early-life exposure to carcinogens**.](#)

[Guidelines for **neurotoxicity** risk assessment.](#)

[Guidance on **cumulative risk assessment**: part 1. planning and scoping.](#)

[Guiding principles for **Monte Carlo analysis**.](#)

[Guidelines for **reproductive toxicity** risk assessment.](#)

[Guidelines for **developmental toxicity** risk assessment.](#)

[Guidelines for **mutagenicity** risk assessment.](#)

[Guidelines for the health risk assessment of chemical **mixtures**.](#)

Note: only clear guidance documents (not other scientific opinions, reviews, case studies or white papers) that are relevant to the remit of the COT have been listed here.

Guidance related to the regulatory risk assessment of pesticides has not been listed, though some relates to combined exposures and may be of relevance to the COT's work. These are:

[Guidance on **cumulative risk assessment** of pesticide chemicals that have a common mechanism of toxicity.](#)

[Guidance for identifying pesticide chemicals and other substances that have a **common mechanism of toxicity**.](#)

[Risk Assessment Guidance | US EPA.](#)