Event report

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# Workshop on read-across: role and guidance in chemical risk assessment

European Food Safety Authority (EFSA)

## Abstract

The workshop on read-across, held on 27–28 March 2025 in Brussels, Belgium, brought together experts from various organisations to explore the application of read-across in chemical risk assessments. The event aimed to strengthen the use of read-across in chemical risk assessments across organisations, with a focus on regulatory approaches, the technical aspects and EFSA's draft guidance. It provided a platform to share experiences and insights on the role of read-across in chemical risk assessment, its importance in screening, classification and hazard assessment, and the challenges and opportunities associated with its implementation. The insights gained from this meeting will be taken into consideration during finalisation of draft guidance before possible adoption by EFSA's Scientific Committee, as well as to inform the needs and content of post-publication activities.



**Keywords:** read-across, hazard and risk assessment, chemicals, food and feed

**Question number:** EFSA-Q-2020-00416[1]

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[1] https://open.efsa.europa.eu/questions/EFSA-Q-2020-00416

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# Table of contents

# Introduction

Read-across is an approach used in chemical risk assessment for the screening, classification, prioritisation and hazard assessment of substances, based on toxicological data of similar chemicals. It is meant to complement and inform the risk assessment, e.g. to provide supporting evidence that must be seen as part of the overall weight of evidence (WoE). The process includes the use of known information from one or more (data-rich) source substances to predict the same property for a (data-poor) target substance, and it is one of the most common alternatives to animal testing for filling data gaps.

The read-across approaches outlined in the Organisation for Economic Co-operation and Development's (OECD) guidance documents (OECD 2007, 2014[2]), as well as the European Chemicals Agency's (ECHA) guidance and framework (ECHA 2008, 2017) developed in the context of information requirements under the REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) regulation[3], have been applied and amended for use in various other domains. In this regard, ECHA is currently working on a practical guide for the application of grouping and read-across for use in the classification, labelling and packaging (CLP) of chemical substances and mixtures[4].

In this context, EFSA's Scientific Committee identified a need within its remit and has developed guidance[5] (EFSA SC, 2025) on the use of read-across to be applied in food and feed risk assessment.

## Objectives

The first objective of the workshop was to examine the regulatory approaches on read-across that have already been developed and implemented by different organisations to support the alignment of methodologies applied in chemical risk assessment across different regulatory frameworks.

The second objective was to discuss and clarify the technical aspects of read-across methodology, and to receive feedback on EFSA's draft guidance.

Overall, the workshop aimed to contribute to strengthening a robust, scientifically sound and transparent application of read-across in chemical risk assessment across organisations.

[2] Under revision.
[3] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. OJ L 396, 30.12.2006, p. 1–849.
[4] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1–1355.
[5] The draft guidance was available for public consultation from 10 March to 21 April 2025. Available online: https://connect.efsa.europa.eu/RM/s/consultations/publicconsultation2/a0lTk000003ufZp/pc1359

## Workshop summary and outcome

The workshop[6] was attended by over 60 people in person and more than 300 followers online. The event attracted a diverse group of stakeholders from various affiliation categories and countries. Of all registrants, the private sector had the highest representation, followed by universities and public research institutes. Other significant groups included EU national authorities, international organisations and both EU and non-EU national authorities. EFSA and EFSA scientific panels were also well-represented. Several non-governmental organisations (NGOs) also registered for the event (Figure 1).

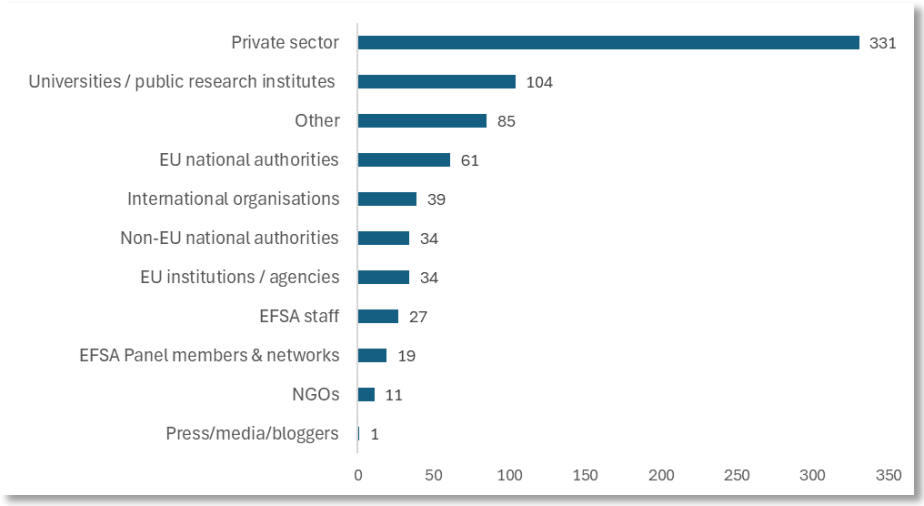


Figure 1: Affiliation category of the registrants for the workshop (the data reflect the registrants and not the actual attendance)

The workshop accommodated two sessions: one addressed the regulatory application of the read-across approach to chemical risk assessment across sectors and the other was for users of the guidance (Figure 2).

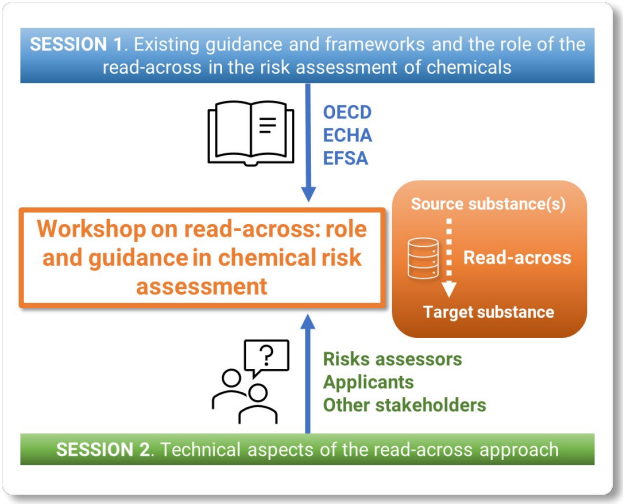


Figure 2: Structure of the workshop

[6] https://www.efsa.europa.eu/en/events/workshop-read-across-role-and-guidance-chemical-risk-assessment

## Session 1 – Existing guidance and frameworks, and the role of read-across in chemical risk assessments

The event's welcome was delivered by Daniela Maurici (EFSA Scientific Committee Team Leader) with opening remarks on the cross-cutting guidance development work performed by the Methodology and Scientific Support Unit. The first session (Chaired by Susanne Hougaard Bennekou, EFSA Scientific Committee Chairperson) was dedicated to a general introduction to the read-across approach, followed by presentations on the relevant guidance documents from the OECD and ECHA, as well as the proposed EFSA guidance. These were followed by a discussion on the role of read-across in the risk assessment process and as part of a WoE approach. The discussion supported the implementation of read-across, identifying challenges, similarities and possible divergences between approaches, e.g. due to use in different contexts or under different frameworks. The session also allowed participants to further clarify aspects related to the context of use and degree of obligation for the guidance documents of the various organisations.

### Presentation summaries

**Introduction to the read-across approach**, Mark Cronin, Liverpool John Moores University, United Kingdom

Read-across is an approach used in chemical risk assessment to fill gaps in the data. There are numerous applications of read-across; however, for regulatory purposes these focus on screening, classification, prioritisation and hazard assessment of substances. Read-across has been widely and successfully applied in many contexts to predict toxicological outcomes when experimental data are lacking. This presentation focused on the background and fundamentals of the read-across approach. The underlying premise of read-across is to identify data-rich compounds that are similar to those for which data are lacking, such that the toxicological information may be utilised for the data-poor compound. A standard workflow is often utilised to apply read-across. While there is some variation in the workflow among applications and legislative regimes, there are usually a number of common steps. These include, but are not limited to: problem formulation; characterisation of the target (data-poor) substance; identification and evaluation of source (data-rich) substances – often termed the analogues; filling the data gaps; and the assessment of uncertainties inherent in the read-across process and the data utilised. The crucial aspect of the process is the definition, characterisation and justification of the similarity between the target and source substances. Structural similarity can be considered in terms of structural analogues alone, although the arguments are frequently strengthened by the inclusion of other data such as physicochemical properties along with mechanistic and other biological information. An assessment of uncertainty in the read-across is commonly performed for every aspect of the process. The intention here is to determine whether the uncertainty is acceptable for a particular purpose, as stated in the problem formulation. The read-across can also be supplemented by data from new approach methodologies (NAMs). These include in silico models or in vitro assays that may provide data to support the toxicodynamic and toxicokinetic aspects of the similarity assessment. NAMs may also be applied, where necessary, to reduce the overall uncertainty in the read-across.

**Read-across application for food or feed ingredients**, Sylvia Escher, Fraunhofer Institute for Toxicology and Experimental Medicine, Germany

Read-across is an approach frequently used to assess the hazards of compounds occurring unintentionally in food and feed products, such as contaminants. In such cases, substance-specific toxicological data can usually not be generated because the test material is unavailable, and the time available to assess such compounds is limited. One challenge of the read-across

process is the selection of relevant source compounds (SCs). As recommended by ECHA's read-across assessment framework (RAAF), an initial list of SCs is often defined based on the physicochemical properties of the data-poor target compound. These SCs are then restricted to the most relevant ones, which also exhibit similar toxicokinetic and dynamic properties.

A study by Irwan et al. (2024) examined how existing data on biological responses or metabolites could help within SC identification. Structural information presented in simplified molecular-input line-entry system (SMILES) notation, biological data sourced from the ToxCast inventory and metabolite information observed in in vivo legacy studies or predicted by in silico tools were combined in a modular way to explore the most specific approach for substance selection. As an example, 27 triazoles were used as the reference group, of which propiconazole was designated as the hypothetical target compound.

Information on similar occurring metabolites produced initial SC lists with high specificity. Both observed and predicted metabolites yielded comparable results in this study. A stepwise combination of first structural and then biological similarity for propiconazole successfully identified most of the reference group compounds. Biological similarity was further improved by restricting the analysis to more relevant assay outcomes. Starting from the biological similarity, an overwhelmingly high number of SC candidates emerged, indicating that generic readouts are activated by numerous compounds.

The study highlights the value of similar metabolites in the identification of relevant SCs. An improved SC identification workflow was proposed, which is complementary to the recently published EU-ToxRisk read-across workflow.

**OECD's guidance on grouping of chemicals, with a focus on the read-across**, Ester Carregal Romero, OECD

The OECD Guidance on Grouping of Chemicals (OECD, 2014) provides guidance for assessing the hazards of chemicals by read-across, thereby gaining efficiencies and reducing the need for animal test data. The approach considers closely related chemicals as a group or category, rather than as individual chemicals. Not every chemical in a group needs to be tested for every endpoint, and data from tested chemicals can be used to predict properties of untested chemicals. Chemical groups may be based on similarity in structure, physicochemical properties, modes of action and biology. A third edition of the OECD guidance was updated by a steering group of international experts representing national regulatory authorities, academia, NGOs and industry, co-chaired by experts from the United States Environmental Protection Agency and ECHA. This edition provides expanded guidance on uncertainty and new approaches to quantifying read-across performance based on advances in science as well as experience garnered from the OECD Integrated Approaches to Testing and Assessment (IATA) case studies programme. This presentation highlighted updates to the document on the use of omics technologies, phenotypic profiling, quantitative structure–activity relationships (QSARs), adverse outcome pathways (AOPs) and high-throughput and high-content screening data to support grouping and read-across. Updates also clarify grouping approaches in the context of IATA and defined approaches for specific endpoints and introduce new guidance on grouping nanomaterials.

While grouping approaches can dramatically increase the number of chemicals for which hazards can be assessed, the associated uncertainty must be considered if using such approaches for regulatory decision-making. The uncertainty in chemical grouping and read-across focuses primarily on the quantity, quality and relevance of the data for analogues/category members, as well as the rationale underlying the groups. In addition, uncertainties may be considered at

various levels, from individual data sources, steps in data interpretation and data integration to read-across predictions. Many organisations have recommendations for how to evaluate uncertainty, though the information is often fragmented and usually specific to a jurisdiction or sector. The updated OECD document provides guidance for the international harmonisation of grouping approaches that can contribute to safety assessments of chemicals without the use of animals.

**ECHA's activities and guidance related to grouping and read-across**, George Cartlidge, ECHA

Grouping to apply read-across is a long-used technique to predict the properties of a (target) substance using data available from similar (source) substances in a regulatory context. Correctly applied, it has the potential to reduce animal testing and costs and to speed up chemical risk assessments. An analysis of read-across applied in REACH dossiers was presented.

Frameworks outlining the steps to develop grouping and read-across are generally based on common scientific principles. A crucial step is to formulate the problem, which sets out the purpose of the read-across (e.g. the property under investigation) and the applicable conditions for applying read-across (e.g. legislative requirements). Hence, the scientific assessment of a read-across must be seen through the lens of regulatory requirements. Examples under REACH and CLP were presented.

A small difference in the structures of target and source substances may lead to different properties due to toxicokinetic or toxicodynamic differences. Under REACH, there needs to be an explanation (hypothesis) of how the properties of one substance can be predicted from the others. This hypothesis must be based on a relationship between structural similarity and the predicted property, e.g. why the results of a repeat-dose toxicity test on one source can be extrapolated to the target substance. This usually requires supporting information, e.g. bridging data to demonstrate toxicodynamic similarity or other absorption, distribution, metabolism and excretion data to show toxicokinetic similarity.

ECHA developed the RAAF to help experts assess read-across under REACH. The scientific principles of assessing read-across included in the RAAF may have wider applicability. Examples of findings from RAAF were presented.

NAMs, in vitro and in silico tools can support read-across by generating data on the toxicokinetic and toxicodynamic profile of the substances which are candidates for read-across and defining category boundaries. However, further development and objective criteria for regulatory acceptance are needed. There are many initiatives to further develop NAMs and regulatory acceptance (e.g. under the Partnership for Assessment of Risk from Chemicals). To support such activities, ECHA has published its Key Areas of Regulatory challenge highlighting its research needs for a range of endpoints and for read-across.

**EFSA's draft guidance on the use of read-across in food and feed safety assessments**, Lucian Farcal, EFSA

EFSA's Scientific Committee has developed guidance on the use of read-across for chemical safety assessments in the food and feed chain. Within a structured workflow, it supports the harmonisation and justification of the read-across approach, minimising uncertainty and ensuring regulatory alignment.

The guidance lays out the terms of reference, identifies the target audience and explains its intended use and degree of obligation. It introduces the concept of read-across, highlighting its significance as an alternative to animal testing for addressing data gaps in chemical safety

assessments. The document reviews the existing frameworks and methodologies used as references for the proposed methodology. Further, the document presents the read-across context and requirements at EFSA, discussing the utility of the read-across approach in regulatory risk assessments for food and feed.

The core guidance includes a detailed description of the read-across workflow, providing practical guidance on performing read-across. This includes problem formulation, target substance characterisation, source substance identification and evaluation, filling the data gaps, assessing uncertainty, drawing conclusions and reporting them.

Additionally, the guidance covers aspects related to the applicability domain and characterisation of the boundaries for read-across, supported by practical examples. The document is complemented with appendices that provide detailed information on the processes related to the read-across workflow. These include a list of available in vitro methods, a template for uncertainty assessment in read-across, examples of case studies and a glossary of relevant terminology and definitions.

Overall, the guidance equips risk assessors and applicants with a framework for transparently and systematically carrying out read-across. It emphasises the need for comprehensive documentation, scientific justification and critical evaluation of uncertainties to support the conclusions of read-across assessments in a regulatory context.

### Discussion and main questions on the presentations

The event's presentations focused on the opportunities and challenges associated with implementing the read-across approach, particularly in a regulatory context. A key theme was the issue of uncertainty; specifically, how to define tolerable levels of uncertainty and the role of context and expert opinion in making these determinations. Another major focus was the integration of in vitro and in silico predictions into the read-across workflow. Presentations and discussions also explored the evolving regulatory landscape, including the adaptation of existing frameworks, guidance documents and harmonised reporting templates to incorporate NAMs. Questions addressed the protection and use of data in regulatory submissions, highlighting the balance between data accessibility and proprietary rights. Additionally, the session revisited the challenge of defining the applicability domain, emphasising the need for a responsible, thoughtful and expert approach to establishing the boundaries of read-across applications.

Overall, the presentations underscored the ongoing development of toxicological assessment frameworks, emphasising the critical roles of uncertainty management, data integration and regulatory adaptation in advancing read-across as a viable alternative to animal testing.

### Panel discussion and Q&A

Panellists: Ester Carregal Romero (OECD), George Cartlidge (ECHA), Juan Manuel Parra Morte (EFSA), Mark Cronin (Liverpool John Moores University, UK) and Emilio Benfenati (Mario Negri Institute for Pharmacological Research, Italy).

In this activity, experts and participants explored the integration and consistency of regulatory documents related to read-across methodologies in chemical risk assessment, noting the similarities and differences among approaches.

In support of this session, a set of three questions was asked via the Slido tool[7], in order to gather feedback from the online and in-person audiences.

[7] https://www.slido.com

**Q1. What is the role of the read-across approach in the risk assessment process?** (55 responses)

The feedback from participants covered the following themes:

- **Data gap filling**: a significant number of responses highlighted the primary role of read-across as a tool for filling data gaps in chemical risk assessment. By leveraging existing data, read-across helps to address missing information, particularly for data-poor substances, enabling more comprehensive hazard assessments.
- **Reduction of animal testing**: the responses emphasise read-across as a means to reduce the reliance on animal testing. By utilising existing data to fill gaps, the approach supports animal welfare initiatives and reduces the number of animals needed for experimental purposes.
- **Hazard assessment and safety evaluation**: read-across plays a crucial role in hazard identification and assessment, providing supportive data to evaluate the potential harm of new or existing substances. Within a WoE approach it can enhance the accuracy and reliability of risk assessments.
- **Prioritisation and efficiency**: the approach is noted for its utility in prioritising substances for further study and speeding up the grouping and evaluation processes. By increasing the efficiency of risk assessments, read-across minimises the need for additional studies and helps streamline decision-making.
- **Support for assessments**: read-across is recognised as a valuable tool in the assessment of emerging contaminants and pesticide metabolites. It facilitates the evaluation of substances with limited data, thereby supporting timely and informed risk management decisions.
- **Cost reduction**: by leveraging existing information, read-across helps to reduce the expenses associated with generating new data. This cost-effective approach benefits regulatory bodies and industries by minimising the need for extensive testing.

**Q2. Rank the importance of the major improvements that read-across can bring to the risk assessment process** (79 votes)

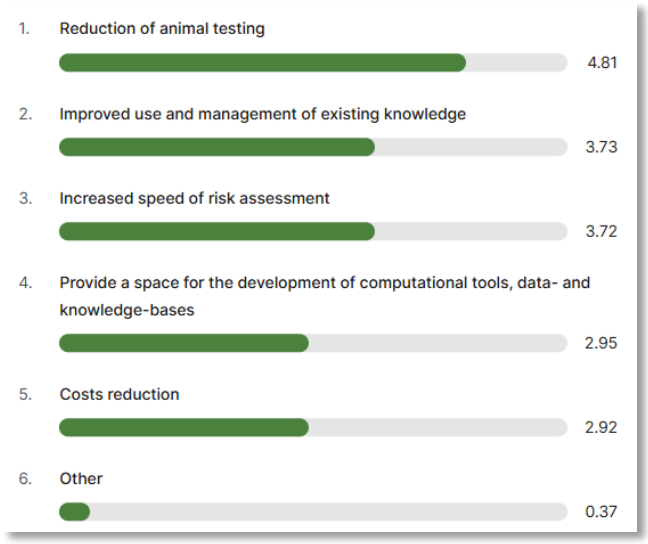


Figure 3: Results of Question 2

**Q3. What additional support is needed to implement read-across in chemical risk assessments (e.g. sectoral guidance, data repositories)?** (48 responses)

The feedback from participants covered the following themes:

- **Tools and databases**: to enhance the read-across process in chemical risk assessment, there is a strong need for advanced tools. This includes user-friendly computer programs and dashboards to gather and process information, reliable databases and in silico tools. Integrating artificial intelligence and machine learning tools can further streamline data processing. Accessibility to robust databases and open-source data and tools is crucial, along with the development of a uniform digital interface that supports tiered and iterative approaches.
- **Guidance and frameworks**: there is a call for standardised and consistent guidance to ensure reliable and transparent application of read-across. This involves defining acceptable levels of uncertainty and creating harmonised frameworks that align with regulatory criteria.
- **Training and education**: training and educational initiatives are essential for all stakeholders involved in chemical risk assessment, including risk assessors, applicants and regulators. As such, workshops and training can help to expand the understanding and application of read-across methods. These should focus on innovative approaches and include specific programmes for different categories of user.
- **Case studies and practical examples**: there is a demand for more case studies and practical examples to illustrate successful read-across applications. Transparent case studies, especially those accepted by authorities, can provide valuable insights and learning opportunities. Sharing these examples can help to clarify acceptable practices and provide guidance on addressing uncertainty.
- **Regulatory support and policy development**: to foster the adoption of read-across, there needs to be increased regulatory support and policy development. This includes encouraging bilateral dialogue between registrants and regulators, offering feedback on accepted methodologies. Improved interagency communication and harmonisation of criteria can facilitate broader acceptance and implementation.
- **Integration with NAMs and other scientific approaches**: integrating read-across with other strategies, like QSAR models and systems biology, is recommended. This broader integration can leverage general chemical descriptors and binding affinities, supporting a more comprehensive approach to risk assessment. The evolving landscape of scientific methods, including NAMs, should also be reflected in the developed methodologies.
- **Customisation and flexibility**: the attendees emphasised the importance of flexibility and customisable methodologies that can be adapted on a case-by-case basis, rather than relying on a single tool or approach. This adaptability ensures that the read-across process remains relevant and effective across diverse scenarios and chemical assessments.

During the panel discussion, various key topics were explored focusing on improving consistency among regulatory documents from organisations such as OECD, ECHA and EFSA, and considering alignment with the 'one substance, one assessment' (1S1A) framework. One important question referred to the key differences and common aspects among the three guidance documents presented during the workshop. The discussion emphasised that while the scientific principles of the read-across approach are similar among the different guidance documents, key differences are related to their context of development and use. These differences require adaptations of the methodology to the specific sectoral requirements under which they are applied (i.e. OECD's guidance covers the broader area of 'grouping of chemicals', has a general applicability to

chemical risk assessment, and offers comprehensive strategies and workflows; ECHA's guidance and framework were developed in the context of REACH data requirements, supporting flexible application with high standards for documentation; EFSA's draft guidance was developed in the context of food/feed assessments, being also relevant to general chemical risk assessments). As such, the context is an overarching consideration for the implementation of read-across, from regulatory remit to determination of tolerable uncertainty.

The discussion also covered the role of read-across in risk assessments, integration with existing validation guidelines (e.g. the OECD guidance document on validation and international acceptance of new or updated test methods for hazard assessment (OECD, 2005)), and the significant role of expert judgement in the process.

Additional questions received from the participants via the Q&A session in Slido covered various aspects of read-across and chemical similarity, including the assessment of negative outcomes, the importance of case studies, reducing uncertainties, transparent justification documents, minimum data requirements, balancing the similarity threshold and sensitivity, and criteria/legal requirements for wider acceptance and a standardised WoE approach.

## Session 2 – Technical aspects of the read-across approach, including a discussion of case studies

This session (Chaired by George Cartlidge, ECHA) unpacked the technical aspects of, and clarified, the steps of the read-across approach, with a special focus on EFSA's draft guidance. During the session, members of EFSA's working group on read-across as well as the EFSA staff involved in risk assessment explained details of the read-across steps along with representative examples and responded to questions from participants.

During the session, several key questions were addressed, focusing on the understanding and application of the read-across approach. Participants were asked whether their comprehension of this approach had improved following the workshop and if the potential opportunities for its application were adequately explored. Additionally, they were asked to evaluate the helpfulness of the guidance and identify areas for potential improvement.

In the break-out group activity, participants were introduced to EFSA's draft guidance steps through a brief presentation by the moderator. Following this, specific cases were shown, where the read-across approach had been applied in assessments conducted at EFSA before the development of the draft guidance. The purpose of the session was to discuss the characteristics of these cases, address the practical aspects of the stepwise read-across approach, and identify areas for future development. It concluded with an engaging debrief summarising the case study applications of the read-across approach, allowing participants to explore its practical implementation and address any questions or concerns.

### Group 1 (case studies A and B)

Moderator: Emilio Benfenati (Mario Negri Institute for Pharmacological Research, Italy)

Presenter: Paola Manini and Hans Steinkellner (EFSA)

Rapporteur: Mark Cronin (Liverpool John Moores University, UK)

Support: Lucian Farcal (EFSA)

Group 1 was presented with two case studies relying on known modes of action for selected source chemicals. These were addressed by careful expert evaluation, applying well-known strategies for dealing with uncertainty in the presence of toxicological information from human, animal and in vitro studies. The question of whether the assessment considered sufficient data was deliberated in both cases, which triggered the production of in silico prediction data in one example but also the agreement on the potential for greater use of NAMs to support these instances of read-across.

**Case Study A: Application of read-across for the assessment of the sesquiterpenes cis-thujopsene, α-cedrene, β-cedrene and the oxygenated derivative (+)-cedrol as major components of cedarwood Texas oil when used as a feed additive**

The aim of the case study was to evaluate the possibility of filling the data gaps (i.e. the lack of reference points to be used in the safety assessment of target animal species) for the major components of cedarwood Texas oil, cis-thujopsene, (+)-cedrol, α-cedrene and β-cedrene (the target substances) by applying read-across from β-caryophyllene (the source substance). The example presented was based on published scientific opinions (EFSA CEF Panel 2015; EFSA FEEDAP Panel 2016, 2024).

**Case Study B: Application of read-across from perchlorate to chlorate for setting a tolerable daily intake (TDI) based on human evidence using potency factors derived from a comparison of rat studies**

The aim of the case study was to evaluate the application of read-across from human data on the source substance (perchlorate) in the absence of appropriate (human) data on the target substance (chlorate) and refine it with comparative data on the toxic potency of the source substance (perchlorate) and the target substance (chlorate), for the assessment of chronic health risks. The example presented was based on published scientific opinions (EFSA CONTAM Panel, 2014, 2015).

### Group 2 (case study C)

Moderator: Qasim Chaudhry (University of Chester, UK)

Presenter: Carla Martino (EFSA) and Manuela Pavan (Innovatune srl, Italy)

Rapporteur: Alicia Paini and Juan Parra Morte (EFSA)

Support: Ana Diges and Daniela Maurici (EFSA)

Group 2 was presented with a case study on the evaluation of smoke flavourings that are regulated products consisting of complex mixtures. A component-based approach was used to assess the genotoxicity of the identified components of the smoke flavourings; the identified components were assessed individually for their genotoxic potential, using experimental data if available and *in silico* information including (Q)SAR and read-across analysis where experimental data were not available. As such, read-across was used as part of a WoE strategy to assess the genotoxic potential of identified components of the smoke flavourings. Read-across was applied following the key principles and best practices established by the relevant regulatory guidance documents available at the time of evaluation (ECHA and OECD guidance), particularly in the evaluation of the quality of the source substance data and the establishment of an acceptable

level of dissimilarity. It was agreed that fit-for-purpose guidance on reporting could have facilitated an appropriate documentation of read-across within the EFSA opinions.

**Case Study C: Application of read-across to assess the genotoxic potential of identified components in smoke flavouring primary products**

The aim of this case study was to illustrate how the read-across was applied by EFSA as part of the risk assessment of complex mixtures, such as smoke flavouring primary products, to assess the genotoxic potential of several identified components for which no genotoxicity data were available from either experimental studies or the literature. The examples presented were based on published scientific opinions (EFSA FAF Panel, 2023a–h).

### General discussion

In summary, the case studies illustrated instances of the application of read-across in food and feed, revealing the future advantages of having sector-specific guidance while maintaining alignment with the existing ECHA and OECD frameworks. The examples explored the use of in silico tools, the critical role of data appraisal and expert judgement in selecting the source substance. Both break-out groups concluded that further sector-specific development of the guidance was needed, especially on assessing the uncertainty, establishing the level of tolerable uncertainty, adaptation to the regulatory context for greater acceptability, and integration of NAM data in the approach. Notably, the EFSA draft guidance was considered to complement the ECHA and OECD frameworks well in many respects, including the goal to replace and reduce animal testing. The ongoing importance of maintaining dialogue and ensuring mutual understanding between industry and regulators was emphasised as essential for advancing these goals and improving acceptability.

## Conclusions

The workshop covered the theoretical and practical aspects of the read-across approach. The sessions included presentations on the read-across principles, the existing guidance or frameworks and their applications, and real case studies where the approach had been used.

The first session emphasised the role of read-across in regulatory chemical risk assessment as part of a WoE approach, principally in screening, classification and hazard assessment. As such, it was underscored that read-across is not a substitute for risk assessment but provides a useful line of evidence for the hazard assessment. The approach is more acceptable when presented as part of a WoE method alongside other lines of evidence. Moreover, the importance of careful scientific documentation and justification in conducting the read-across was highlighted.

The case studies covering the areas of feed additives, food contaminants and flavourings were valuable and helped the participants to clarify several technical aspects. They were considered illustrative, as they presented examples of the assessments that had been conducted before the development of EFSA guidance and therefore did not strictly follow all the steps as outlined in the draft guidance. The usefulness of the guidance will be determined by future regulatory use and acceptance.

Overall, it was agreed that the guidance is generally useful and sets high standards, thereby facilitating regulatory approval and promoting the approach to meet future demands to reduce animal testing by better use of existing data. It provides a broad framework for building and justifying a read-across, while highlighting the need for harmonisation and flexibility in reporting.

It was acknowledged to be an indicator towards best practice, particularly in terms of documentation, and a very helpful guide for the assessors and applicants.

The discussions emphasised the importance of the context of use, noting that the problem formulation step guides the subsequent generation and use of information, as well as setting of the tolerance levels of uncertainty. Participants learned that the read-across approach is both integrative and iterative, requiring careful tracking and reporting to enable independent assessment.

Finally, several areas for improvement were identified and discussed, e.g. the need for tools and databases, training, additional examples or case studies from various other sectors to complement the generic guidance, and clearer criteria for the use of NAM data.

The working group of EFSA's Scientific Committee considered the workshop discussion feedback as well as the parallel public consultation comments in their finalisation of the draft guidance.

# References

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# Abbreviations

| | |
|---|---|
| 1S1A | one substance, one assessment |
| AOP | adverse outcome pathway |
| CEF | EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids |
| CLP | classification, labelling and packaging |
| CONTAM | EFSA Panel on Contaminants in the Food Chain |
| ECHA | European Chemicals Agency |
| FAF | EFSA Panel on Food Additives and Flavourings |
| EFSA | European Food Safety Authority |
| EU | European Union |
| IATA | Integrated Approaches to Testing and Assessment |
| NAM | new approach methodology |
| NGO | non-governmental organisation |
| OECD | Organisation for Economic Co-operation and Development |
| QSAR | quantitative structure–activity relationship |
| RAAF | read-across assessment framework |
| REACH | registration, evaluation, authorisation and restriction of chemicals |
| SC | source compound |
| TDI | tolerable daily intake |
| WoE | weight of evidence |

# Appendix A Workshop agenda

## Day 1 | Thursday, 27 March 2025

| | | |
|---|---|---|
| 13:00-13:30 | **Registration** | |
| **SESSION 1 \| EXISTING GUIDANCE AND FRAMEWORKS, AND THE ROLE OF READ-ACROSS IN CHEMICAL RISK ASSESSMENTS**<br>**Chair: Susanne Hougaard Bennekou, EFSA Scientific Committee Chairperson** | | |
| 13:30-13:40 | **Welcome and introduction to the event** | **Daniela Maurici**<br>European Food Safety Authority (EFSA)<br>**Susanne Hougaard Bennekou**<br>EFSA Scientific Committee Chairperson |
| 13:40-14:00 | **Presentation 1. Introduction to read-across approach** | **Mark Cronin**<br>Liverpool John Moores University (UK) |
| 14:00-14:30 | **Presentation 2. Read-across application for food or feed ingredients** | **Sylvia ESCHER**<br>Fraunhofer Institute for Toxicology and Experimental Medicine (Germany) |
| 14:30-15:00 | **Presentation 3. OECD's guidance on grouping of chemicals, with a focus on the read-across** | **Ester Carregal Romero**<br>Organisation for Economic Cooperation and Development (OECD) |
| 15:00-15:30 | **Presentation 4. ECHA's activities and guidance related to grouping and read-across** | **George Cartlidge**<br>European Chemicals Agency (ECHA) |
| 15:30-16:00 | **Coffee/tea break** | |
| 16:00-16:30 | **Presentation 5. EFSA's draft guidance on the use of read-across in food and feed safety assessment** (document opened for public consultation) | **Lucian Farcal**<br>EFSA |
| 16:30-17:20 | **Panel discussion and questions from participants** | **Chair of Session 1 and panellists** |
| 17:20-17:30 | **Concluding remarks for Session 1** | **Susanne Hougaard Bennekou** |
| 17:30-18:30 | **Networking cocktails** | |

## Day 2 | Friday, 28 March 2025

| | | |
|---|---|---|
| **SESSION 2 \| TECHNICAL ASPECTS OF THE READ-ACROSS APPROACH**<br>**Chairperson: George Cartlidge, European Chemicals Agency (ECHA)** | | |
| 09:00-09:15 | **Introduction to the second session of the workshop** | **George Cartlidge**<br>ECHA |
| 09:15-10:45 | **Break-out groups** (including introduction to EFSA's guidance steps, read-across cases or examples, discussion of technical aspects on the application of read-across approach) | **Group moderators** |
| 10:45-11:15 | **Coffee/tea break** | |
| 11:15-12:00 | **Break-out groups (continuation)** | |
| 12:00-12:45 | **Summary of the break-out group discussions and lessons learned** | **Group rapporteurs** |
| 12:45-13:00 | **Concluding remarks and wrap-up of the workshop** | **George Cartlidge**<br>and<br>**Susanne Hougaard Bennekou** |