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Abstract #295

Pesticide residues: Concept of Grouping, Read-across and Prioritisation for Hazard and Risk Assessments of Active Substance Metabolites

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Introduction

Plant protection product use in agriculture can lead to findings of their active substance (a.s.) metabolites in food, feed and drinking water. Consumers are exposed to these a.s. metabolites through dietary intake and drinking water, raising potential public health concern that requires thorough assessment.

Guidance documents outline methodologies for identifying and characterising hazards of these residues of a.s. metabolites. The forthcoming update of the OECD guidance will incorporate current scientific approaches and tools, including grouping and read-across. Additionally, EFSA has launched a public consultation on its draft guidance for applying read-across in chemical safety assessments for food and feed.

Residue metabolites may differ from their parent a.s. in terms of toxicokinetics, toxicodynamics and overall toxicity profiles. Since some metabolites occur at low levels or not at all *in vivo*, their intrinsic hazards may not be fully covered by toxicity studies on the parental a.s. In the absence of experimental data on such a.s. metabolites, their toxicological relevance can be assessed by (Q)SAR and read-across analyses, providing a rapid and practical alternative to toxicity testing.

In line with current guidance, we present two excerpts of hazard assessments using (Q)SAR, grouping and read-across for relevant metabolites drawing on our extensive experience as consultants in this area. In a first simplest scenario data from the parent a.s. are used for predicting metabolite toxicity considering them as a group and the parent a.s. as the most suitable analogue. If metabolites are found to be dissimilar to the source substance(s), further assessment would be conducted by identifying suitable external analogues. When prioritising testing, especially in cases where toxicity concerns have been identified for the parent a.s., a ranking can be established based on grouping considerations. This ranking assumes that the likelihood of bearing the same toxicological property diminishes with “distance” of the metabolites to the parent a.s. and is presented in a second scenario.

Lines of evidence are integrated and evaluated based on a weight of evidence approach, assessing structural similarity to determine the accuracy of the read-across. Based on all available information, a case is established incorporating common assessment elements and if necessary, a testing proposal is provided (presented hazard assessment is an excerpt only).

Reporting

We generate state-of-the-art reports according to actual requests using the templates provided by EFSA (2020) and following the RAAF, ECHA (2017) and EFSA (2025).

- EFSA (European Food Safety Authority), 2020. Technical report on the outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology. EFSA supporting publication 2020:EN-1837. 26 pp. doi:10.2903/sp.efsa.2020.EN-1837. ISSN: 2397-8325
- ECHA (European Chemicals Agency), 2017. Read-Across Assessment Framework (RAAF). ECHA-17-R-01-EN. ISBN: 978-92-9495-758-0
- EFSA (European Food Safety Authority), 2025 Guidance on the use of read-across for chemical safety assessment in food and feed. EFSA Journal. 2025;23:e9586. doi: 10.2903/j.efsa.2025.9586

Conclusion

In summary, (Q)SAR and read-across analyses enable fast and efficient hazard assessments and are an accepted approach elucidating the toxicological relevance of pesticide a.s. metabolites.

Two exemplary schematic concepts for standard analyses at Ramboll-SCC

Case I: Justification to use parent active substance (a.s.) health-based reference values (HBRV)

1. Key Question	2. Goals	3. Data Gathering	4. Results
Can the reference values of the parent a.s. be used for the risk assessments of its metabolites?	• Analyse similarities to reduce further testing, e.g., *in vivo* • Grouping and a risk-based sequence of testing should reduce testing to a minimum, where unavoidable	• Analysis of existing toxicological data • Literature search • (Q)SAR analyses • Read-across • Grouping proposal • WoE analysis • Uncertainty analysis	✓ Risk assessments with parent HBRV ✓ Risk assessments after derivation of metabolite specific HBRV

Case II: Justification that a CRM hazard of parent a.s. does not apply to metabolites

1. Key Question	2. Goals	3. Data Gathering	4. Results
Do metabolites share a CRM hazard of the parent a.s.?	• Analyse dissimilarities to reduce further testing, e.g., *in vivo* • Grouping and a risk-based sequence of testing should reduce testing to a minimum, where unavoidable	• Analysis of existing toxicological data • Literature search • (Q)SAR analyses • Read-across • Grouping proposal • WoE analysis • Uncertainty analysis	✓ Rationale why CRM hazard can be excluded for metabolites ✓ Establishment of a testing proposal based on proposed ranking

Figure 1. Two examples for standard metabolite analyses. a.s.: active substance. CRM: carcinogenic, toxic to reproduction, or mutagenic. HBRV: health-based reference values. (Q)SAR: (Quantitative) Structure Activity Relationship. WoE: weight of evidence.

Further details on data gathering methodology at Ramboll-SCC

1. Toxicological data

Includes analyses of:

- Data gaps (parent and metabolites)
- Metabolite ADME (detected at >10% *in vivo* in the rat?)
- Metabolite specific hazards e.g., recent regulatory developments: ED/DNT

2. (Q)SAR

Depending on regulatory background:

- Robust predictions for genotoxicity and/or other toxicity endpoints
- Valid, applicable and adequate complementary expert-rule- and statistical-based tools
- Evaluation of the applicability domain & the reliability of the prediction

3. Read-across

- Toxicity screening via profiling
- Assessment of (dis)similarity
- Grouping and selection of analogues
- Establishment of a ranking (“distance” to parent a.s.: likelihood of bearing the same toxicological property)
- Read-across from suitable analogues

4. Expert weight of evidence analysis

Establishment of a rationale and if needed with a testing proposal

- Exposure based waiving (threshold of tox. concern)
- State-of-the-art reporting
- Optional: Proposal and defence towards authorities

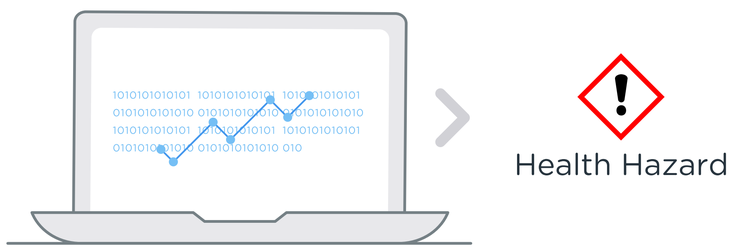
Figure 2. Further details on data gathering strategy. ADME: absorption, distribution, metabolism, and excretion. DNT: developmental neurotoxicity. ED: endocrine disruption.

Key elements for (Q)SAR predictions

(Q)SAR results should be generated by scientifically valid (relevant and reliable) models (OECD Principles):

- A defined endpoint;
- An unambiguous algorithm;
- A defined domain of applicability;
- Appropriate measures of goodness-of-fit, robustness and predictivity;
- A mechanistic interpretation, if possible.

The (Q)SAR model should be applicable to the query chemical (applicability domain) and the model endpoint should be adequate (relevant for the regulatory purpose).



Key elements for read-across approaches

The following is needed for data gap filling with a read-across approach using information from source substance(s):

- Well defined endpoint;
- Identity and characterisation of the substances;
- Quality of the available experimental data;
- Similarity of substances and justification of hypothesis;
- Related uncertainties.

Read-across approaches use two types of chemical grouping: Analogue or category approaches and contribute to the overall weight of evidence reducing uncertainty in risk assessment.

Contact

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