(Q)SAR and Read Across Analyses in Regulatory Assessment of Pesticide Metabolites and Impurities in the Light of Current Insights and Demands

Termeer de Amanqui S. C.[1], Harder V.[1]
[1]SCC – Scientific Consulting Company GmbH, Bad Kreuznach, Germany

Introduction

Consumers can be exposed to pesticide residues potentially containing active substances (a.s.) and concomitantly to impurities and residue metabolites. As these substances may have properties of concern for human health, they need to be evaluated. In contrast to the comprehensive toxicological data set of an a.s., toxicological information on pesticide a.s. metabolites and impurities of plant protection products is generally scarce or non-existent. Based on legislation there is the possibility to apply New Approach Methodologies to assess the toxicological relevance of a.s. metabolites and impurities.

In this poster an approach is presented which enables a rapid and feasible hazard assessment of a.s. metabolites and impurities combining (quantitative) structure activity relationship ((Q)SAR) and read across (RA) analyses. This approach considers current guidance documents as well as on-going scientific discussions.

Requirements assessing a.s. metabolites

Metabolites found as residues in crops and/or in livestock are evaluated according to the EFSA (2016) proposal including assessment of genotoxic potential and general toxicity, as well as evaluation of toxophores, structural similarities and organic functional groups for grouping.

EFSA (2020) further proposes a reporting template for assessing (Q)SAR analysis as well as overview tables for summarizing and integrating the evidence in overview tables.

The forthcoming OECD Guidance on residue definition (2023) is expected to consider current scientific approaches and tools (grouping of metabolites, read-across, threshold of toxicological concern (TTC)) and available information concerning the draft Guidance is taken into account.

Requirements assessing pesticide impurities

To assess **relevance of impurities**, *e.g.,* genotoxic potential, the Guidance on assessment of equivalence (2012) is followed.

(Q)SAR analyses are conducted for all new/increased levels of impurities and alert patterns of impurities are being compared to those of the a.s. to establish if the potential concern is addressed by studies on the a.s..

In accordance with EFSA (2016) and EFSA (2018), details of the analysis including applicability domain and reliability of the results is being assessed and reported.

General workflow

Data gathering
- Evaluation of available experimental data
- Identification of data gaps
- Establishment of a strategy

Robust (Q)SAR predictions
- Genotoxicity and other toxicity endpoints
- Valid, applicable and adequate tools
- Evaluation of the applicability domain and the reliability of the prediction

Read across by the OECD QSAR Toolbox
- Toxicity screening
- Assessment of similarity
- Grouping and selection of analogues

Expert weight of evidence analysis
- Establishment of a case with a rational and if needed with a testing proposal
- Exposure based waiving (TTC*)
- State-of-the-art reporting

* TTC – threshold of toxicological concern

Key elements for (Q)SAR applications

(Q)SAR results should be generated by scientifically **valid** (relevant and reliable) models according to the agreed OECD Principles (OECD, 2007):

1. A defined endpoint;
2. An unambiguous algorithm;
3. A defined domain of applicability;
4. Appropriate measures of goodness-of-fit, robustness and predictivity;
5. 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) (ECHA, 2008).

Finally, the information needs to be **well documented** (EFSA 2018).

Key elements for RA applications

- Well defined endpoint,
- Identity and characterization of the substances,
- Quality of the available experimental data,
- Similarity of substances and justification of hypothesis,
- Related Uncertainties (EFSA, 2018)

Set of typical *in silico* tools

Complementary **expert-rule-** and **statistical-based software tools**

1. VEGA,
2. Toxtree,
3. Derek Nexus,
4. OCED QSAR Toolbox

SCC's experience in the field of pesticides (last 5 years)

Conducted *in silico* toxicity assessments:

Substance(s)	Type	Number
Metabolites	(Q)SAR & RA	16
Impurities	(Q)SAR & RA	10
Pesticide a.s.	(Q)SAR RA	14 3

Discussion and Conclusion

Computer modelling of biological effects has been investigated for many years. Different valid software tools are available with respective strengths and weaknesses. It is current best practice to use complementary software tools and to assess the data with expert knowledge in a weight of evidence approach. Thus, it is crucial to have knowledge of the chemical and of the chemistry/ biology regarding the endpoint for evaluation.

The impact of *in silico* analyses is expected to increase in the forthcoming years and the field of (Q)SAR modelling is likely to expand due to advances in scientific knowledge, the 3R principles as well as political and societal pressure.

In summary, *in silico* methods are an efficient and accepted tool in the assessment of the toxicological relevance of pesticide metabolites and impurities. (Q)SAR and RA analyses enable rapid and reliable hazard assessments supporting the conclusion for dietary risk assessment of pesticide a.s. metabolites and for the evaluation of the relevance of impurities.

References

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