European Crop Protection

POSITION PAPER
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ECPA View: EFSA guidance document on Establishment of Residue Definition for Dietary Risk Assessment in the EU

Key Recommendations

ECPA believe the current EFSA guidance document for establishing the Residue Definition for Dietary Risk Assessment will increase complexity of the evaluation process for deriving a residue definition, and that the scheme leads to an inconsistency with other national and international systems, therefore impacting global harmonisation of residue definitions and respective MRLs, import tolerances and trade.

ECPA emphasises the cumbersome and complex nature of the evaluation scheme, and in particular stress that additional elements (*e.g. QSAR tools and databases*) are required for the workable implementation of the guidance document; proceeding without such tools will lead to additional toxicological testing including unnecessary vertebrate testing.

The prospect of deriving crop and use pattern specific residue definitions creates problems in extrapolating residue definitions to other crops and will lead to increased complexity of the risk assessments. In addition it will lead to challenges when registering new uses at a national level.

The proposed concept for deriving a residue definition is based solely on residue levels in metabolism studies and does not consider actual dietary exposure. This leads to complex residue definitions without necessarily increasing consumer protection.

The establishment of such complex residue definitions will lead to low acceptance of Codex MRLs in Europe due to the differing residue definitions.

The challenges of increased numbers of metabolites in the residue definition and the complexity of the analytical methods to facilitate the associated data generation will make it difficult not only for industry but also for other key stakeholders e.g. minor use associations.

Therefore the content of the guidance document for regulatory purposes should be further reviewed before it can be considered suitable for implementation. In addition time is needed for appropriate training of all stakeholders to learn and understand the GD requirements and what it means in practice.

ECPA view: Detailed Considerations

Provision of a scientific toolkit

- A scientific toolkit comprising suitable and reliable QSAR tools and databases is necessary to facilitate the implementation of the GD, including the relevant training and development of expertise; without this in place it is expected that there will be the need to perform extensive genotoxicity testing (*in-vitro and in-vivo*) of metabolites.
- The ongoing EFSA projects to develop a genotoxicity metabolite database and the subsequent assessment of the domain coverage and utility of existing QSARs should be completed and reported prior to any introduction of the guidance.
- The QSAR toolkit should be considered as a living source and updated as more data are made available
- In cases where toxicology data are sourced from the scientific literature or public domain repositories in support of read-across, these may not have been generated to any prevailing test guideline (e.g. OECD). However, subject to satisfactory assessment (e.g. Klimisch assessment) the use of such data should be encouraged to reduce the potential need for further (in vivo) testing.

Metabolite assessments and evaluations

- The grouping of metabolites and identification of a representative metabolite to focus the testing may be different in terms of genotoxicity and general toxicity, and is considered subjective leading to a diverging range of interpretations.
- The subjective grouping approach and the interpretation of what is considered a similar dataset metabolite vs parent is leading to huge uncertainties and bears the risk of being assessed as having an incomplete data package.
- The TTC approach for assessment of single compounds or to subgroups is considered scientifically acceptable, from a human health assessment perspective. However within the GD the application of the TTC concept for single metabolites/distinct groups is not foreseen, but only a TTC assessment against all uncharacterized metabolites, which does not prevent further testing. This increases the need for animal testing (e.g. a *28 day study, or other studies depending on the parent*).
- Testing of additional metabolites will require increased efforts and costs for synthesis and analytical method development; in some cases the required synthesis of the metabolites to perform the toxicity tests and to develop and validate the residue analytical methods for use in residue studies may not be achievable.
- The complexity of the evaluation scheme and the application of the toxicological burden approach requires in-depth training and development of expertise at Member State level and across Industry, so that some level of consistency in approach can be achieved.
- The toxicological burden approach uses only the relative quantities of metabolites as a tool for deriving the residue definition, and disregards the impact on the actual dietary exposure, leading to complex residue definitions that may not significantly enhance consumer safety. ECPA propose to include indicative exposure assessments as a tool for refining the residue definition.

- A multiple residue definition approach can lead to increased complexity of risk assessments without necessarily increasing consumer safety. It is proposed to adhere to the OECD principle and to derive **one common residue definition for plants**, if the metabolism is qualitatively similar across 3 crop groups, and considering the actual dietary contribution of major metabolites from all covered crop groups.
- Crop specific residue definitions may trigger reconsideration of the residue definition in the frame of further use registrations at national level following active substance approval/renewal. ECPA consider this as not desirable since it enhances workload for Member States and uncertainty for notifiers.
- A lack of consistency with other national and international review systems is noted along with the impact on global harmonisation of RDs, MRLs, ITs and trade

ECPA recommendations prior to Implementation

- Given the significant refinements proposed in the guidance document, a testing phase (amongst EFSA/MSs/industry) is required to understand the GD requirements and what it means in practice. Based on the testing phase, improvements to the GD should be considered before full implementation.

- The guidance document needs to ensure consistency with national and international review systems, and should not negatively impact the acceptance of CODEX MRLs and the general global harmonisation of RDs, MRLs, ITs and trade. We would request a detailed consultation of international partners to promote global consistency.

- Efforts are required to ensure that the guidance does not unnecessarily lead to increased animal testing. ECPA would support a review of the guidance to ensure that relevant approaches are included in the guidance to reduce the need for additional testing

- Applicable QSAR toolkit must be made available before implementation of the GD, to deliver reliable and robust results.

- The provision of a sufficient transition period is critical before full implementation, including time to allow training of experts in Member States and industry.