European Crop Protection

POSITION PAPER
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ECPA's position Stereoisomers

Proposal for Tiered Approach to Risk Assessment

Introduction

ECPA fully supports the development of guidance for the hazard and risk evaluation of the constituent stereoisomers (diastereomers and enantiomers)i within an active substance. Due to the complexity of the subject, ECPA also supports the need for consistent terminology based on clear definitions and nomenclature.

ECPA proposes a science-based tiered approach to hazard and risk evaluation that could form the principles of the guidance currently in development and which:

- minimises, as far as is reasonably possible, the need for additional animal testing with stereoisomers, whilst ensuring that products are safe for users, consumers and the environment.
- recognises that, in most cases, the component stereoisomers of an active substance have already been tested in safety studies, and therefore any significant toxicological or environmental alerts would already have been identified in the study package (although the actual exposure levels need to be considered).
- minimises the impediment to innovation that significantly limiting stereochemistry from crop protection chemistry in the EU would entail; ca. 30% of existing crop protection chemistry is chiral and has been evaluated to be safe for users, consumers and the environment in the absence of any evidence to the contrary
- ensures the economic competitiveness of EU crop protection chemistry by limiting as far as is reasonable the commensurate cost implications of requiring large-scale production of individual stereoisomers (due to the need for costly chiral synthesis and/or purifications).

Tiered Approach

The proposal for a tiered approach is based on five steps, described below and presented in Figure 1. If any of these steps indicate that there is no impact on the risk assessment of the plant protection product, then no further testing will be necessary.

Step 1: Initial Chemical Evaluation

Based on the chemical structure and known chemical properties of the active substance, provide a science-based case considering the feasibility of any interconversion between the constituent stereoisomers under physiologically or environmentally relevant conditions. In addition, based on the proposed use pattern, consider whether stereo-selective metabolism is a relevant mechanism. If a scientific case can be presented that no interconversion or stereo-selective metabolism will be possible, then no further testing is needed. If a convincing scientific case cannot be presented, then Step 2 is applied.

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Step 2: - Human and Environmental Risk Evaluation

Conduct a conservative risk evaluation using the following worst-case assumptions:

- all the toxicity resides with a single stereoisomer[1]
- the measured exposure in residue studies is entirely due to the same individual stereoisomer

This combination of worst-case assumptions provides a highly conservative risk assessment of the potential risks of the individual stereoisomer. If the substance passes this assessment, it can be concluded, with a high level of certainty, that it presents low risk.

Step 3: Exposure Profile

Determine the stereoisomeric ratio to which humans and non-target species will be exposed. This may be determined using samples from metabolism or residue studies and compared with the stereoisomeric ratio of the starting material. Where no significant change in stereoisomer ratio is observed, relative to that in the active substance dosed in toxicology or ecotoxicological studies, the risk evaluation can be considered to be consistent and the data for the active substance can be used for risk assessments.

Step 4: Hazard Evaluation

Conduct toxicology and ecotoxicology hazard testing to evaluate if any differences exist between the stereoisomers. The objective is to evaluate if the stereoisomers contribute equally to the hazard. Where no significant qualitative or quantitative differences are observed, then risk assessments based on total exposure to all stereoisomers are appropriate.

Step 4a: Targeted Testing

These tests would be targeted at testing appropriate species and for specific endpoints; the exact tests would be guided by the hazard profile of the active substance. Where no significant differences are observed, it can be concluded that all stereoisomers contribute equally to the hazard and therefore risk assessments based on total exposure to all stereoisomers are appropriate.

Step 4b: - Hazard Testing

If step 4a shows significant differences in endpoints or potency it may be necessary to conduct more detailed toxicology and ecotoxicology hazard testing of most relevant endpoints to determine the impact of any qualitative or quantitative (i.e. potency) differences between the stereoisomers. Where significant differences are observed, a risk assessment with the specific endpoints for the individual stereoisomers is considered appropriate.

[1] European For a racemic mixture (i.e. an enantiomeric pair) and assuming the toxicity resides in a single enantiomer then a factor of two is applied. A larger factor may be applied in the case of compounds with more than one chiral centre.

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Figure 1: Diagrammatic approach to tiered risk and hazard evaluation for stereoisomers

Step 1 – Initial Chemical Evaluation		
Is there a robust scientific rationale that interconversion or stereoselective metabolism is not possible?	YES	No further testing
NO		
Step 2 – Human and Environmental Risk Assessment		
Using worst-case assumptions, is the risk assessment still acceptable?	YES	No further testing
NO		
Step 3 – Exposure Profile		
Does analysis of metabolism, residue and product chemistry samples indicate significant change in stereoisomeric ratio?	NO	No further testing
YES		
Step 4a – Targeted Hazard Testing		
Tests targeted at testing in appropriate species and for specific endpoints. Do all stereoisomers contribute equally to the hazard ?	YES	No further testing
NO		
Step 4b – Hazard Assessment		
If there are significant qualitative or quantitative (i.e. potency) differences between the stereoisomers for relevant endpoints, then risk assessments for the individual stereoisomers may be considered appropriate.		

Definitions

Steroisomer: compounds containing same number and type of atoms and same arrangement of bonds but different 3D arrangement in space

Diastereomer: arises when more than one chiral centre is present in the molecule. Exists as a pair of enantiomers (unless a meso compound)

Enantiomer: one of two stereoisomers that are non superimposable mirror images of each other

Enantiomer: an equimolar mixture of an enantiomeric pair