

EPPO

**NEW General Principles for the
development and registration of co-
formulated mixtures of Plant
Protection Products**

Specific Scope:

- guidance for the efficacy justification for using co-formulated mixtures, their potential advantages and disadvantages
- appropriateness of such mixture products in terms of resistance management
- decision making process in considering the approval of such mixtures.
- guidance for trial design and the type of data required

Mixtures may be developed for a variety of reasons:

- synergistic effects
- resistance management
- broader spectrum of pest control
- flexibility of application

indicate what benefits the mixture may deliver in comparison to a solo active product, to ensure there is no unnecessary over use of an active substance

This Standard provide a decision making framework, both for applicants in identifying appropriate uses and generating an appropriate data package, and regulatory authorities in the regulatory decision making process for approval

Justification for use of mixtures with respect to effectiveness

Potential advantages (compared to solo active products):

- Combining active substances with different properties
- enhance the overall target spectra
- more effective and control than if applied singly in sequence
- using active substances in combination, whether against a single pest or a pest complex, lower rates may sometimes be used compared to using products containing single active substances
- The mixture may provide higher and/or more consistent levels of control against the same species.
- Co-formulated mixtures may offer an advantage over tank mixtures where risks to beneficials have been evaluated and deemed acceptable.

Justification for use of mixtures with respect to effectiveness

Potential disadvantages (compared to solo active products):

- The presence of two pests at threshold levels controlled by different active substances of a mixture may coincide. Difficult that will happen = overuse or unnecessary use of plant protection product
- If the mixture is targeting different pests, the timing may not be optimal for all, resulting in reduced effectiveness.
- The use of mixtures may prevent subsequent use of one of the single active components

Justification of mixtures of plant protection products with respect to resistance risk and management strategies

- The use of mixtures is recognized as a potential modifier in a resistance management strategy for any pesticide.
- for resistance management purposes it is important that each active component should provide sufficient control of sensitive populations of the target pest(s) when used alone at the dose rate applied in the mixture.
- Mixtures where there is no benefit over the use of single active substances would not be authorized
- Mixtures of the same MOA whilst potentially offering improved effectiveness would not be considered as an anti-resistance strategy and would normally be treated as a solo active substance for resistance management
- mixtures containing greatly reduced doses of active substances are not considered appropriate for resistance manage

Evidence required to support effectiveness of a mixture

- A minimum requirement for the mixture is to demonstrate the absence of antagonism across the main target pests and to demonstrate crop safety.
- Field trials or any other supporting evidence should primarily focus on the justification for the mixture
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- Where there is an overlap in the activity of the constituent active substances field trials would normally be required to justify the need for both active substances and would be expected to include a comparison of the proposed new mixture product with the solo active substances.

General principles to be considered for the justification of mixtures for resistance management

Mixtures where there is no benefit over the use of single active substances would not be authorized

Principles to consider when justifying the mixture	Key issues to consider
Effectiveness	<p>A clear benefit <u>should</u> be identified and supported by a strong reasoned case or new trials.</p> <p>Possible justification may include, but is not restricted to, one or more of the following reasons:</p> <ul style="list-style-type: none"> i) improved control of individual pests ii) control of different life cycle stages iii) an extended range of pests (that exceed damage thresholds or need treatment at the same time) iv) more consistent control v) greater persistence of control vi) allows use of lower doses to achieve comparable control ??????
Ratio of active substances in mixture products	<p>May be based on the rates of the solo products (where no overlap in activity against target pests exists) or preliminary tests/small number of trials (where some overlap of activity exists).</p>
Resistance	<p>Implications for resistance management (RM) <u>should</u> be considered.</p> <p>If resistance management is a major part of the justification for the mixture, this should be explained and supported.</p> <p>Mixtures may compromise existing RM strategies for either of the component actives.</p> <p>Consider resistance status of all active substances present in the mixture and the possibility/occurrence of cross-resistance.</p> <p>Mixing of two different MOAs may not always be an acceptable RM strategy.</p> <p>Consider impact on resistance management strategies of mixtures with greatly reduced applied doses of the active substances.</p>

Principles to consider when justifying the mixture	Key issues to consider
Need for effectiveness data with the mixture	<p>As a minimum requirement, data should be provided to demonstrate a lack of antagonism.</p> <p>Minimum Effective Dose may be extrapolated from solo products in cases where there is no overlap in activity and the applied active substance dose and formulations are comparable.</p> <p>A full data set is required where the applied dose of the active substances in the mixture are greatly reduced compared with the solo products.</p> <p>A full data set is required where new claims (not present on either solo active) are proposed.</p> <p>A full data set is required to support claims of improved effectiveness relative to the solo active substances.</p> <p>A bridging approach may be possible where the applied doses of the active substances are comparable to the solo products and no claims for improved control are being made.</p>
Relevant comparisons	<p>Trials should include solo actives at the authorized dose where available.</p> <p>In addition, where the mixture applies reduced doses of the active substances, those solo active substances may also be included at the same dose.</p> <p>It is not necessary for regulatory purpose to include the corresponding tank mixture.</p> <p>An additional reference product should be included if additional claims are made (not present on either solo active).</p>
Need for crop safety/taint/transformation succeeding/adjacent crops data with the mixture product	<p>Data should be provided to demonstrate crop safety.</p> <p>Consider whether extrapolation can be based on similarity of formulation types of the mixture and solo products and the relative doses of the active substances.</p>