

Efficacy Guideline 604

Efficacy Data Required For Tank Mixtures and Sequences of Plant Protection Products (PPPs)

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When and why must data be supplied

For information on whether efficacy data supporting a tank-mixture needs to be supplied or whether a compatibility assurance statement can be submitted instead, read the guidance on tank mix recommendations on product labels at www.hse.gov.uk/pesticides/applicant-guide/tank-mix-recommendations-pesticide-labels.htm.

This guideline does not cover chemical and physical compatibility testing which must be considered for convenience and positive tank-mix recommendations.

Biological incompatibility may be defined as, when two or more PPPs are applied in mixture or sequence an adverse effect is seen, in the form of either reduced performance or crop safety, compared to what would be seen when the pesticides are applied alone.

There are a number of reasons why this can occur:

- One pesticide interferes with the mode of action or the translocation of another therefore decreasing its activity, i.e. causing antagonism.
- Pesticides can interact leading to increases in activity, e.g. one pesticide may interfere with the metabolism of the other in the crop plant, so that unacceptable crop effects can occur.
- High levels of surfactant present when two products are applied together may lead to greater uptake and therefore crop damage caused by one of the pesticides.
- With sequences the treatment applied first might cause adverse effects on the crop, such as reduced leaf wax, so that when the second treatment is applied this causes increased crop effects over those usually seen. In some cases the effect of the first treatment can be subtle and might not be noticeable before applying the second product.
- With sequences the effects as described for mixtures can occur with applications applied some time apart. This can be due to a pesticide, or its metabolites, remaining for some time in a plant and interacting with another pesticide applied some time afterwards. This can happen both with antagonism (e.g. reduced grass weed control with sequential application of grass and broad-leaved herbicides in sugar beet), or decreased crop safety (e.g. in maize where insecticides applied at planting interact with herbicides applied postemergence leading to crop damage).

Biological incompatibility is relatively rare in mixtures that do not involve herbicides or plant growth regulators. With herbicides, particularly some graminicides and sulfonylureas, biological activity interactions with other types of pesticides¹ are somewhat more common.

With fungicides and insecticides there is unlikely to be a direct interaction with activity of another pesticide, except on occasion with a herbicide. However, there is a possibility of increased risk of crop damage due to a higher surfactant load in the spray tank.

For a new active substance, representative mixtures should be examined for biological incompatibility. Which representative mixtures to test should depend, where appropriate, on previous experience with related or similar active substances.

Data required to support a convenience tank-mixture or sequence recommendation

Convenience tank-mixtures of PPPs

Convenience tank-mixtures are where a plant protection product (PPP) is tank mixed with one or more other PPPs or an adjuvant, but where there are no enhanced claims of control associated with the mixture. They are described as 'convenience' because it is practical (and appropriate timing) to spray the products together, saving the user time, money and other resources. Often these are included in a 'Compatibility' section on the product label. This may include specific named products or a general statement to the effect that the product may be mixed with other plant protection products. For example:

- 'For up to date details of compatible tank-mixes contact the manufacturer/distributor'
- 'Product X may be tank-mixed with a variety of plant protection products providing that the application timing is correct for both Product X and the partner(s) in the mixture. For further information on the authorisation status of mixture partners, consult the manufacturer'
- 'Consult manufacturer for details of tank mixes'

Any convenience tank-mix recommendation, whether on the product label, or provided to users by the authorisation holder verbally, or via websites, advertising or other material must be supported by physical and chemical compatibility data, whether specific products are named or not.

¹ Hatzios KK & Penner D (1985) Interactions of Herbicides with other agrochemicals in higher plants, Review of Weed Science **1**, 1-63.

A CAS is required for these tank-mixtures for all products, even those products where authorisation is based on access to data out of protection.

Efficacy data are not required unless this is the first tank mixture recommendation as for a new active substance (see below)

The compatibility section of the label may also advise on tank-mixes which are known to be incompatible or on specific mixing instructions to be used with compatible mixes.

Note that even where product labels recommend tank-mixtures as a resistance management tool then a CAS should be submitted.

Type of testing for first tank mixture recommendation

For the first convenience tank-mixture recommendation initial testing is usually in the form of large-scale plot trials with little or no randomisation. Effectiveness and crop safety are assessed following application of the various tank mixtures. The plots used are large-scale in order to simulate practical use, therefore a farm sprayer or other large-scale plot sprayer should be used to apply the treatments. For herbicides, and other pesticides where adverse crop effects are known to occur, both N and 2N doses should be applied. For herbicides where there are known interactions with different varieties then the mixtures and sequences may also need to be applied across a range of varieties. Where a product is always applied at a lower dose in mixture, this lower dose should be considered as the N dose for testing purposes.

It is preferable for the individual mixture components to be also applied alone in the same trials as the mixtures. Otherwise where any unexpected crop damage or lack of pest control is seen, it would not be known if this is due to adverse environmental conditions or the mixture affecting the performance of one of the components. However, taking into account the number of possible tank mixes it is accepted that in initial tests the candidate product mixtures may have to be compared only with other tank mixtures. However, any candidate mixture appearing to give an unacceptable effect in such a trial should then be dropped from the proposed compatibility statement on the label. Further investigations will be required comparing the mixture with the individual components, possibly in fully replicated trials, normally conducted in the following year.

The trials should examine the margin of crop safety and whether any antagonism occurs when controlling representative target organisms. Crop safety is normally examined by assessing visual symptoms, yield is not usually measured in un-replicated large-scale work. Where follow-up replicated trials are required to investigate any adverse crop effects then yield, or components of yield, would normally be measured. It may sometimes be possible to assess the pesticidal activity of the component products of a mixture on the same site but often it is necessary to select separate sites for evaluation of different pest types, e.g. pest, weed and disease. Where more than two 'pests' are involved, e.g. broad-leaved weeds, grass weeds, and a fungal pathogen, the number of

sites may need to be increased accordingly. When complex sequences of various mixtures are applied, such as in top fruit, it is not possible to look at every possible interaction. In these cases, a general assessment that a certain mixture has been included in such a sequence without obvious reduction of pest control or crop safety should be sufficient.

Extent of testing for first tank mixture recommendation

Once it has been decided that there is a need to examine a particular mixture, if it involves a new herbicide then four trials would normally be required, three trials are normally required if a mixture does not involve a herbicide, as interactions are less common. Trials can be from a single season if they cover a range of conditions and targets. As already stated, if reduced weed control or higher levels of phytotoxicity are seen and it is still wished to recommend the convenience mixture, then a further year's testing would be required with randomised plot work to investigate the problem.

Convenience sequences of PPPs

In general, for a convenience sequence trials work would not be required if a suitable interval is allowed between applications to prevent antagonism or reduced crop safety..

An interval of two weeks or greater is acceptable on large-scale arable crops. If a herbicide has the potential to reduce leaf wax or cause other crop effects then a warning can be placed on the label to prevent application of other herbicides until such time as the crop has recovered. Intervals of less than 14 days require supporting trials evidence, examining both crop safety and antagonism of biological activity.

In some cases it is known that a very strong antagonism occurs between two pesticides, either because of data on related active substances, or because a high level of antagonism is discovered when examining mixtures. In these circumstances, even to support sequences of 14 days or longer, trials work is needed to determine the interval that is required between applications of the two materials in order to ensure that this antagonism does not occur. This interval should appear on the product label.

Data required to support a positive tank-mixture or sequence recommendation

A positive tank-mix or sequence is when a product label recommends a mixture or sequence with one or more other PPPs and a benefit is claimed from this in terms of pest control or biological activity, over the products applied alone. The benefit can be control of pests not claimed on either label, greater control of pests claimed already, or to achieve the same effect with lower doses of the products.

Positive tank-mixtures

Positive tank-mixtures must be shown both to be physically and chemically compatible and biologically compatible (effective and crop-safe) and therefore these mixtures require a CAS and efficacy data. Example 'positive' tank-mixture claims:

- To improve the control of [pest], use in mixture with 1.0 l/ha 'APHICIDE'
- Common poppy and common field speedwell are susceptible when Product X is tank-mixed with 1.0 l/ha Product Y
- Where creeping thistle is a special problem, a tank mixture of 5 litres/ha Product X with Product Y at 0.5 litre per hectare, is recommended. This mixture may improve control of black bindweed over that provided by Product X alone
- If annual broadleaved weeds are beyond the cotyledon to first true leaf stage, but do not have more than two true leaves, or where dry conditions persist, a 3-way tank mixture of 5 litres Product X + 5litres Product Y + 0.5litres Product Z per hectare, will give the best results

In addition to the physical and chemical compatibility data required for convenience tank-mixes (see above), where a positive tank-mix recommendation is being made, additional biological compatibility (efficacy) data will be required to support the proposed positive tank-mixes.

Typically to support a positive mix claim, the standard requirement is that each positive claim(s) is supported by the provision of effectiveness and crop safety data. Where the positive claim(s) relates to pest (s) which are currently authorised on at least one of the product labels, it would be sufficient to provide field trials data conducted in a single season. Typically, this should include a minimum of 5 fully supportive trials for each positive claim. Where a claim is made for a new pest, the standard UK data requirements would apply, which is based around 10 fully supportive trials for a major pest, or 3 fully supportive trials for a minor pest. However, it is advisable for applicants to seek advice first as the number may also be dependent on other factors (for example, whether a field or protected situation, whether there may be other existing claims on relevant species etc). It would be expected that trials should include the currently authorised dose of each product and the proposed mixture dose so that the claimed benefit(s) can be clearly demonstrated. Trials should preferably be located in the UK or another EPPO Maritime country at sites where the target biology, growing conditions, agronomic practice and resistance status can be shown to be comparable to those prevalent in the UK. Further advice is given in EPPO standards PP 1/241(2) 'Guidance on comparable climates', and PP 1/226(2) 'Number of trials'.

Any positive tank-mixture recommendations must be within the authorised conditions of use of the product to be included in the positive tank-mix recommendation. In other

words, the details of the partner product must be checked to ensure that if the tank mixture is used it does not contravene any of the conditions of authorisation of the partner product.

In some cases, where use is **only** recommended in mixture with another plant protection product or adjuvant, all effectiveness and crop safety testing, including yielded trials, should include the mixture.

Positive sequences

A positive sequence is where there are enhanced on-label claims of effectiveness from a sequence compared to when a product is applied alone or for programmes of PPPs used in sequence. In these situations, efficacy data will be required to support the proposed sequence. As this is in effect a new recommendation the normal programme of trials, usually conducted over two years, examining crop safety and efficacy is required; the extent of data required depending on the specific claims being made.

Other aspects

A number of other areas need to be considered when a label recommends a convenience or positive tank-mixture or sequence:

- Following crops – increased risk to following crops needs to be considered if both active substances are similar in activity and pose a risk to similar crops, e.g. two sulfonylurea herbicides cannot be applied in mixture and sequence without specific supporting evidence, see 'Guideline 303 Effects on NonTarget Crops of Highly Active Herbicides - Including Mixtures and Sequences
- Resistance – uses of mixtures or sequences of active substances with different modes of action is normally seen as a positive step for avoidance of resistance, as long as activity is against the same target pest. On the other hand, sequences of pesticides with the same mode of action that are active against the same pests may increase the risk of resistance. It should be considered whether recommending such sequences is in line with any resistance management strategy that has been drawn up
- Change in formulation – The direct biological interaction between two pesticides is not normally related to formulation and where a change in formulation occurs no further data would normally be required. Where a negative interaction might be caused by increased uptake due to high levels of surfactant present in a formulation, then consideration should be given as to whether any change in formulation in this could make this problem worse

- Cleaning of application machinery – problems can be caused or made worse by mixtures, see EPPO standard PP1/292(1) - Cleaning pesticide application equipment (PAE) – efficacy aspects

Further information

For information about health and safety, or to report inconsistencies or inaccuracies in this guidance, visit www.hse.gov.uk.

This guidance is issued by the Health and Safety Executive. Following the guidance is not compulsory, unless specifically stated, and you are free to take other action. But if you do follow the guidance you will normally be doing enough to comply with the law. Health and safety inspectors seek to secure compliance with the law and may refer to this guidance.

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