Efficacy Data Required For Tank Mixtures and Sequences of Pesticides

When and why must data be supplied

For information on whether the actual data supporting a tank-mixture needs to be supplied or whether compatibility assurance statement can be submitted instead see The Applicant Guide (the revised Registration Handbook). The Applicant Guide states that data must be supplied with the first recommendation of convenience tank mixes for a product containing an active substance where no previous tank mixes have been approved. Data are needed to demonstrate that chemical, physical or biological incompatibility does not occur when pesticides are applied in mixture. With sequences there is only a risk of biological incompatibility occurring.

This guideline does not cover chemical and physical compatibility testing which must be considered for convenience and positive tank-mix recommendations – see instead – Physical and Chemical Properties section of the Data Requirements Guidance.

Biological incompatibility may be defined as, when two or more pesticides 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 post-emergence leading to crop damage).

Evidence on biological compatibility is a requirement of COPR, the Efficacy guidance clarifies that this information is also required under PPPR.
What extent of data is needed for a convenience tank-mixture?

Deciding on the need for testing

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 pesticides are somewhat more common.

For any new herbicide it should therefore be anticipated that biological incompatibility could occur. This means that initially recommended convenience tank-mixtures with any other type of pesticide, adjuvant or other tank-mix ingredient, e.g. nutrient, should be examined in field tests.

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, particularly those with herbicides. Which representative mixtures to test should depend, where appropriate, on previous experience with related or similar active substances.

Once information has been accumulated on an active substance and related active substances, the need for testing of further convenience mixtures can be judged on a case by case basis using the experience gained. Unless problems are seen it is unlikely that any further testing will be needed, particularly for mixtures that do not contain herbicides or plant growth regulators.

Type of testing

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

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

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.

**What data are needed for a convenience sequence**

In general, for a convenience sequence as long as a suitable interval is allowed between applications to prevent antagonism or reduced crop safety, then trials work would not be required. An interval of two weeks or greater is considered to be 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**

Positive tank-mixtures and sequences can be defined as where a benefit is claimed from applying the mixture or sequence, 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. 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. In some cases use is only recommended in mixture with another pesticide product or adjuvant, in which case all effectiveness and crop safety testing, including yielded trials, should include the mixture. In other cases mixtures are only recommended for certain instances, for example, for improved control of a certain pest. In these cases then more limited effectiveness and crop safety evidence would be required to support the claim being made and to demonstrate lack of biological incompatibility. In this case yielded trials would only be required where crop damage is above that expected when the products are applied alone.

Other aspects

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

- 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 PSD Efficacy Guideline 303.

- 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 PSD Efficacy Guideline 302.