Bulletin OEPP/EPPO Bulletin (2012) **42** (3), 353–357 ISSN 0250-8052. DOI: 10.1111/epp.2608

European and Mediterranean Plant Protection Organization
Organisation Européenne et Méditerranéenne pour la Protection des Plantes

PP 1/277(1)

Efficacy evaluation of plant protection products
Evaluation biologique des produits phytosanitaires

Insecticide co-formulated mixtures

Specific scope

This standard provides guidance for the justification for using insecticide co-formulated mixtures, their potential advantages and disadvantages, plus an examination of the appropriateness of such mixtures in terms of resistance management. Based on these issues, a series of principles have been drawn up to form the regulatory framework for the decision making process in considering the approval of such mixtures. These principles should also act as a guide for trial design and the type of data required.

Specific approval and amendment

First approved in 2012–09.

Introduction

Insecticide co-formulated mixtures may be developed for a variety of reasons, including synergistic effects, improving efficacy against one pest or a range of pests, and other desirable properties such as flexibility of application. However, these benefits should also be balanced against potential compromises in effectiveness, e.g. when targeting multiple pests there may be conflicts for the individual species in appropriate application timings and threshold levels. Particular consideration should be given to indicate what benefits the mixture may deliver in comparison to a solo active product, to ensure there is no unnecessary over use of insecticides.

Insecticides are usually applied when appropriate thresholds (where available) are reached, and this will be dependent on favourable conditions for the pest during the growing period. Even for species considered as major pests, there may not be a need to use control measures every season. Where preventative treatments are used this tends to be either against virus vectors, or in high value crops where quality is economically important and therefore only very low levels of damage can be tolerated. Preventative treatments may also be used against pests for which no prognosis and no curative treatment is currently possible, such as for soil pest complexes, where there is a history and/or likelihood of detrimental yield affects.

The application of more than one insecticidal active substance may be used to broaden the spectrum of activity where more than one pest is present; to target more than one life stage of the pest; or to provide higher levels of control. Currently this can be achieved through the tank mixing of appropriate products. Resistance management with insecticides has conventionally been approached by the use of sequences of active substances with different modes of action, and not via the use of mixtures.

In contrast, herbicides are usually required to control a range of weeds, which are often present at the same time. Co-formulated products are designed to complement the range of activity of individual component active substances to control as broad a range of species as possible. The product of choice will depend on individual field situations and reflect the predominant weed species and competitiveness of the crop. Appropriate resistance management for herbicides may be addressed by using mixtures which combine active substances from different chemical groups with different modes of action, in order to control a specific target species that is at risk. Fungicides are also often co-formulated as mixtures. Again this is because they are commonly used against a disease complex and in order to provide both curative and preventative activity. Strategies for resistance management include using fungicides from different groups in alternation, or recommended formulated mixtures or tank-mixes.

There is commercial interest particularly in the potential of foliar co-formulated insecticide mixture products. In part this reflects the properties of newer active substances which, in order to meet regulatory requirements in other areas, may often have narrow pest spectra. For the reasons summarized above this needs careful consideration, both in terms of identifying justified uses, and their integration into resistance management strategies and complex crop protection programmes. This standard explores these issues in greater depth and provides a series of principles. These principles 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 insecticide co-formulated mixtures with respect to effectiveness

(a) Potential advantages (compared to solo active products)

- Combining insecticides with different properties, such as contact with systemic action or contact with vapour action, can be advantageous. Such a mixture may assist control of different stages of the same pest, particularly when the target is inaccessible due to either pest behaviour or crop structure. It may also be used to control different pests present on the crop at different times, e.g. a seed mixture treatment with more than one active substance where for example, one active substance targets soil pests and the other provides subsequent control of foliar virus vectors.
- The mixture may enhance the overall target spectra, allowing the control of a range of pests when they are present on the crop at the same time. This is particularly advantageous when there is little or no overlap in activity against pest species;
- Using two (or more) active substances in a mixture may provide more effective control than if applied singly in sequence. For example, the mixture may provide both a rapid action as well as more residual effects. This may provide benefits especially where rapid control, as in the case of virus vectors, is required. Or a longer lasting residual activity may allow fewer applications of a co-formulated mixture compared to solo products;
- In using active substances in combination, whether against a single pest or a pest complex, lower rates may be used compared to using products containing single active substances (additive or synergistic action);
- The mixture may provide higher and/or more consistent levels of control against the same species. This could be through synergistic effects, or complementary effects via two or more active substances targeting different life stages of the same pest. This could also allow for greater flexibility in treatment timing.

(There can be other more general advantages (operational or related to other aspects of the risk assessment) for co-formulated mixtures when compared to solo products. For example, less packaging, or reducing the number of operations for the operator.)

(b) Potential disadvantages of co-formulated insecticide mixtures with respect to effectiveness

- Most insecticide treatments are related to economic thresholds. The presence of two pests at threshold levels controlled by different active substances of a mixture may coincide. However in many cases it is possible that one active will be applied when its target pest either does not reach the treatment threshold, or indeed may not be present in the crop. Either situation would constitute an overuse or unnecessary use of insecticide and not be considered good agricultural practice;
- For many insect pests the application timing is critical in achieving an effective treatment, and additionally there may be a relatively short window within which treatments should be applied. Adults, but particularly juvenile stages, often quickly migrate or burrow into relatively inaccessible, sheltered parts of the crop. If the mixture is targeting different pests, the timing may not be optimal for all, resulting in reduced effectiveness;
- In many cases insecticide solo product labels have different individual doses recommended for different targets, even for individual species within a particular group. In this situation, when the mixture is targeting a wide range of pests, there will be less flexibility in being able to differentiate doses for individual species. A compromise in the dose of each active substance when combined in the co-formulated mixture may be needed, in order to prevent: overuse against some targets; unnecessary use (if the relevant pests for one active substance are not present); less than optimal doses being applied to other targets;
- Natural predators and parasites of insects are a key component of integrated pest management. The importance of integrated approaches is reflected in various National and International requirements and stewardship schemes, including the Directive 2009/128/EC on Sustainable Use of Pesticides (EC, 2009). Where mixtures are formulated to broaden the spectrum of activity, this may increase the potential detrimental effects on non-target organisms, and may do more overall harm than using single active products in sequence. The co-formulated insecticide mixtures could have the effect of preventing natural enemies from keeping a particular pest below the treatment threshold level, or may make the necessity of a subsequent follow-up treatment more likely. They may also prevent natural predators from killing any resistant or less susceptible individuals not controlled by the insecticide treatment;

- The use of mixtures may prevent subsequent use of one of the single active components because of regulatory limitations on that active substance.

Justification of co-formulated insecticide mixtures with respect to resistance risk and management strategies[1]

The use of mixtures for resistance management is based on the principle of 'redundant killing', i.e. killing the insect by more than one mechanism (mode of action). The use of mixtures, whether as a tank mix or formulated product is recognized as a potential modifier in a resistance management strategy for any pesticide. However, their usefulness as a resistance management strategy is dependent on certain criteria. EPPO Standard 213 *Resistance risk analysis* states that the active substances within the mixture should have different modes of action. It is recognized that the use of a mixture, particularly where actives act synergistically, may allow reduced doses. However, for resistance management purposes it is important that each active component significantly contributes to the control of the target pest(s), in both efficacy and (if relevant) pest spectrum.

The situation is more complicated where products have different spectra of control. The greatest consideration should be given to the most resistance prone organisms.

Alternation through the use of sequences is also a recognized modifier in resistance management. The alternating partners should be from different cross-resistance groups and work by reducing exposure, and consequently selection pressure. The lower the frequency of use within the sequence, the lower the resistance risk for any particular active substance.

The principle of redundant killing, by definition, means that the mixture will apply a higher total quantity of insecticidal active substances than is actually required to kill the target pest. Therefore an inappropriate mixture partner may not only be ineffective in resistance management, but may also constitute unnecessary use with up to double the amount of insecticide applied, and would be contrary to good agricultural practice.

Additionally, the benefits of using either mixtures or sequences in a management strategy may vary depending on the presence and type of resistance mechanisms present in the target(s). There may be less benefit if the resistance mechanisms span more than one mode of action (e.g. enhanced metabolism resistance) than where the mechanism has developed to a specific mode of action (e.g. target site).

Based on the above principles, the following need to be considered in terms of resistance management:

- In addition to the direct exposure of the target pest, incidental exposure to other pests present in the crop should also be considered. This particularly applies to species which have a broad range of host crops and a history of resistance development to a range of insecticides. Use of mixtures potentially increases the exposure frequency to any given active substance;
- Seed or soil treatments are justified where pest presence is predictable and likely to occur each season. However, the persistence of the active substance leads to an increase in exposure time, either to lethal or (at some point) sub-lethal doses. As such it may represent a high resistance risk. Their use in resistance management should therefore be considered carefully where pests are more sporadic in nature, and can be more appropriately controlled through foliar treatments as damaging population levels develop. Conversely they do not directly target foliar dwelling beneficial species, and so generally (although not always) may have a lower adverse impact on such species;
- Any advantage offered by a mixture in terms of resistance management is negated if a target pest has already developed practical resistance (See EPPO standard PP 1/213 *Resistance Risk Analysis*) to one of the partner active substances. To be a useful management strategy there should be no resistance in the target population to either active substance. This should be based on recently generated data as resistance development is dynamic and may change quickly;
- Potential problems discussed above may lead to unnecessary use of one active, use of inappropriate rates, or applications made at ineffective timings. All of these may increase exposure and therefore resistance selection pressure either directly to target pests, or indirectly to other potential pest species present in the crop at the time of application. Using active substances in mixtures reduces the ability to alternate with different modes of action. In many situations there will only be a limited number of available active substances, or one of the potential alternatives will already have resistance development in a range of species. The use of mixtures may often prevent alternation of active substances with different modes of action. This has an impact on resistance management, particularly if alternation is the more effective resistance strategy.

Principles to be considered for the justification and resistance management of insecticide mixtures, including generating data to demonstrate benefits of mixtures

The following key principles draw together the various issues discussed above. These considerations will vary depending on the properties and proposed uses/targets of the individual active substances. Applicants should consider these factors when developing insecticide mixtures and subsequently designing their efficacy field trials to support a formulated mixture. For example, when targeting a single pest it is important to include appropriate comparisons with

[1]See EPPO standard PP 1/213 *Resistance Risk Analysis*

formulations containing the single active substances, to demonstrate the additional benefits of using a mixture over each single active substance. Where formulated products are designed to increase pest spectra, it is important to demonstrate that the relevant pests will be present in the crop at significant levels, and that the timing of the application will be suitable for all. These data should support and identify those relevant targets where a co-formulated mixture is justified. The impact on resistance management, including potential benefits, should also be thoroughly examined:

- Within the regulatory framework and requirements for justified, sustainable pesticide use, the efficacy evaluation will consider the appropriateness of any mixture in terms of potentially increasing effectiveness of treatment; increasing insecticide use overall; and the impact that increased exposure may have on resistance selection pressure. As such there should be a demonstrable benefit in using mixtures compared to (available) single active products. The approval of a mixture should consider the justification of use alongside resistance implications, encompassing the positive and negative aspects of both;
- Mixtures targeting the same pest species could constitute potentially an overuse of insecticide unless there are demonstrable benefits above the use of single active products. For example, these benefits might include beneficial increases in levels of effective control, or improving virus protection. This would particularly apply to pests that are difficult to control, or those which cause significant economic damage to high quality crops. Applicants should be able to provide data and information to justify the 'benefit' of the mixture over the use of single active substances. The potential implications of the use of such a mixture on resistance management (positive or negative) should be considered. As such, the duration of control for the individual active substances within the mixture should be similar, and each component should have high activity in its own right against the target. The applicant should provide data/information to support these two points. Mixtures where there is no demonstrable benefit over the use of single active substances would not be approved. (Further information is available in EPPO Standard PP 1/213 *Resistance Risk Analysis*);
- Mixtures used to control a range of pests, especially where there is no overlap in the spectrum of activity, may be appropriate. This is dependent on specific criteria being met to ensure they will provide effective control, and additionally that they do not constitute unnecessary use. Namely, target pests controlled by the different active substances should be present in the crop, and at appropriate (threshold) levels justifying the need for control. The application timing should also be appropriate to all targets, without compromising effective control. There should be careful consideration of the benefit of using a formulated mixture rather than a tank mixture of single active products. In particular label wording may be appropriate to indicate the circumstances under which the product should be used (i.e. the factors discussed relating to relevant targets present in the crop at appropriate threshold levels and timings);
- The impact of any mixture on resistance management should be addressed. Where one of the active substances already has a history of resistance to the target pest(s), this reduces the potential benefit of a mixture as a resistance management strategy. This is particularly relevant where the incidence of resistance is widespread, i.e. the frequency of resistant genes to one of the active substances within the population is high. Furthermore the use of such a mixture, alongside single active products, will increase exposure and therefore selection pressure for the active where resistance has not yet developed. Mixtures containing actives substances of the same mode of action are not considered appropriate for resistance management. Mixtures where none of the active substances have a resistance history may provide a beneficial resistance management strategy, and may be particularly relevant for resistance prone insect species. This is dependent on the active substances meeting the appropriate criteria discussed in the EPPO Standard PP 1/213 (*Resistance Risk Analysis*) on resistance risk assessment and management strategies, and offering a demonstrable benefit as described in 'ii' above. The implications of using a mixture within an overall treatment regime should be addressed. This should include any initial seed/soil treatments, foliar applications of the relevant active substances as single products, and other non-chemical control measures. The use of the mixture may increase overall exposure to a particular active substance, and/or limit the scope to subsequently alternate with other active substances of different modes of action as part of the resistance strategy.
- Seed (and soil) treatments targeting a range of different pests (e.g. a soil pest complex) and subsequent foliar feeding pests may be appropriate. Mixtures to control a single pest should demonstrate the benefits of the mixtures compared to the single active substance. Seed (and soil) treatments are prophylactic in nature and therefore should target pests with a regular occurrence, either at a local or regional level and should also recognise the potential selection pressure through exposure to optimal and, as residues decline over time, sub-optimal rates. Sporadic pests are more appropriately controlled by curative, usually foliar, applications during the course of the season as populations develop. Consideration should be made of the resistance risk, and the extent of any selection pressure, both on target pests and indirect exposure to other foliar feeding pests. This will depend on the original seed treatment rate, and length of time before any subsequent exposure or any follow-up foliar treatment. When using an alternating strategy it is important to remember that the seed (soil) treatment is the first treatment in the programme.

Tank mixtures combining single active products

It is recognized that in practice the grower will have the option to use mixtures by combining single active substance products in the spray tank, where products with suitable active substances are available.

Tank mixes should offer benefits compared to single product use. However there are important differences between using tank mixtures of solo active products and co-formulated mixtures, particularly in the flexibility of use, which overcomes some of the issues described above. Firstly it will only be economic for the grower to use tank mixtures against more than one pest when they are all present in the crop at threshold levels. If the application timing is completely inappropriate for one of the pests then the grower has the option to spray against that pest on another occasion. Using tank mixtures of single active products allows the grower to apply each active substance at the optimal rate and timing against the target species present. A grower is unlikely to use more than one product against the same target species unless there is reason to believe more effective control can be achieved.

It should be noted that co-formulated products are optimized for both active substances in terms of retention, spreading and uptake by the plant and/or target. As such they will also tend to have fewer co-formulants than a tank mixture of single active products. All these factors may assist not only effectiveness, but also crop safety characteristics. (As well as reducing other potentially adverse factors which may have an impact on other areas of the risk assessment).

References

EC (2009) Directive 2009/128/EC of the European Parliament and of the Council of 21 October 2009 establishing a framework for Community action to achieve the sustainable use of pesticides. *Official Journal of the European Union* **309**, 71–86.