Insecticide Mixtures and Resistance Management – Updated Guidance

August 30th 2023

IRAC
Insecticide Resistance Action Committee

IRAC Statement: Insecticide Mixtures

Insecticide* mixtures (tank-mix or pre-formulated mixture) are used for many different reasons. When used as part of a rotation program, mixtures may provide an additional benefit for resistance management.

- The following considerations are important when using insecticide mixtures for insecticide resistance management (IRM):
  - Insecticide mixtures should contain active ingredients with different modes of action (MoA) for a resistance management benefit to occur.
  - Mixtures with active ingredients that have a different product brand name, but the same IRAC MoA classification are not suitable for resistance management.
  - For tank mixes follow the label instructions for each of the mixture components.
  - Individual insecticides selected for use in mixtures should each be effective against the targeted insect life stage.
  - Simultaneous exposure of the target insects to both insecticides is required.
  - There should be limited or no cross-resistance** between the two or more insecticides used within the mixture.
  - Mixtures will be most effective if resistance in the target insects to both active ingredients is absent or very low.
- IRAC does not support the repeated use of the same mixture as the sole method of pest control.
- All insecticide applications should only be made when necessary and should be carried out as part of an IPM (Integrated Pest Management) program.

If not stated differently, the above recommendations are made for the use of mixtures for resistance management in a single target pest scenario and for combinations of compounds that don't act synergistically.
* Including acaricides
** Resistance conferred by the same mechanism of resistance to two or more insecticide modes of action.

Insecticide Mixtures and Resistance Management – Key Considerations

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Insecticide Mixtures: Introduction

- The combined application of two insecticides* with different modes of action (MoA) is an increasingly common approach to insect pest management. Insecticide mixtures (tank-mix or pre-formulated mixture) are applied to crops for pest management for many different reasons. These reasons include to broaden spectrum, to combine different technical characteristics of insecticides, or to combine two modes of action to control species where single compound applications do not provide sufficient control. Mixing insecticides, may also offer a benefit for insecticide resistance management (IRM).
- Because it is very difficult to set up realistic empirical field experiments, these benefits have been studied and discussed by many authors using computer models.
- In the present slides IRAC presents an up-dated mixture statement and the key considerations supporting it.
- IRAC International and pest management researchers have based their opinions on theoretical and practical experiments, however IRAC International fully acknowledges that more research in this area and, in particular, more practical evidence is needed to fully understand the challenges and benefits of using insecticide mixtures as part of a IRM program.

* Including acaricides

Insecticide Mixtures: General Advice

- Whatever the reason for selecting single or multiple active ingredients is, it is important that growers/advisors/applicators carefully consider their choice of insecticide products and their potential impacts. All insecticide applications should only be made when necessary and should be carried out as part of an integrated pest management (IPM) and IRM program.

Insecticide Mixtures: Key Considerations

1. Should individual insecticides selected for use in mixtures be highly effective and equally effective?

- The relationship between insecticide effectiveness (dose/concentration) and resistance risk is complex and depends upon multiple variables, such as mode of reproduction and inheritance, pest immigration rates, level of exposure, and the dominance of the resistance gene/genes.
- As for solo compound applications, when using tank mixes, and when some of these variables (particularly dominance of the resistance gene) are not known, IRAC still recommends the individual mixture compounds to be applied at rates/concentrations that provide effective control of the target pests.
- Considerations based on theoretical models:
  - For mixtures with components that are applied below their label dose, some recent models suggest that reducing the effectiveness (e.g. dose) of insecticide applications and increasing the immigration of susceptible individuals or allowing a high escape rate, may delay resistance in the treated population better than label dose mixtures (Helps *et al.* 2020; Sudo *et al.* 2018).
  - When highly effective insecticide rates are utilized with high coverage (exposure), selection favors only the most resistant individuals (homozygotes) to survive, which can result in the rapid development of resistance within the pest population. Lower doses of insecticides inevitably kill fewer insects, potentially allowing both resistant and susceptible insects to survive. With lower doses, insect populations may recover quickly, but the resistance evolution is unlikely to be faster than with higher doses (Helps *et al.* 2020; Sudo *et al.* 2018).
  - Because lower doses are less likely to select for highly resistant individuals, it is not evident that under all circumstances high doses are required for a resistance management benefit of an insecticide mixture (Helps *et al.* 2020; Sudo *et al.* 2018) .
- For mixtures to provide a benefit for IRM, equal effectiveness is advantageous but not essential (South & Hastings 2018). In a mixture with components that are differently effective, the more effective compound (faster resistance) may protect the less effective compound (slower resistance) (South & Hastings 2018).

Insecticide Mixtures: Key Considerations

2. Why should mixtures of compounds for which there is cross-resistance** be avoided when seeking IRM benefits?

- When mixtures provide an additional benefit for IRM, they do this based on the principle of redundant kill. Redundant kill means that individual target insects that carry a resistance gene for one MoA are still fully controlled by the other MoA. Redundant kill is most effective, if there is very little or no cross-resistance between the individual mixture components for the targeted pest(s).

** Resistance conferred by the same mechanism of resistance to two or more insecticides.

Insecticide Mixtures: Key Considerations

3. Why is simultaneous exposure of the target insects to both insecticides important?

- Ideally, the two insecticide components of a mixture should have the same or very similar durations of effect (residual activity) (South & Hastings 2018), with the aim to expose target insects simultaneously. This means that both insecticides prevent the survival of insects which are resistant to either insecticide (redundant kill) over the entire length of a treatment window (pest generation). However, if this is not the case, a mixture might still provide some additional benefit for IRM, if the insecticide components are both active, the mixture provides overall good control, and is embedded in a rotation scheme.

Insecticide Mixtures: Key Considerations

4. Why are mixtures more effective if resistance in the target insect to both active ingredients is very low?

- As for single compound rotations, insecticide mixtures benefit IRM most when the proportion of insects carrying a resistance gene against each mixture component is very low, and insects carrying both resistance genes are extremely rare (Tabashnik, 1989). Under such conditions mating between insects carrying resistance genes for both mixture components, leading to fully resistant offspring will be very unlikely. Nevertheless, mixing insecticides in cases where partial resistance is already developing against one of the mixture components might still provide some benefit for IRM (Bourguet et al., 2013), such as a mixture with a newer insecticide showing low resistance in pest populations and an older insecticide showing higher resistance in pest populations (South and Hastings, 2018).

Insecticide Mixtures: Key Considerations

5. What role does an insects' mode of reproduction play in resistance management?

- As for IRM in general, modelling indicates that reduced exposure and a high level of immigration favors the use of mixtures for IRM most when the targeted pest species is diploid and sexually reproducing, because of the recombination of resistance genes with susceptible genes (Helps *et al.* 2020; Sudo *et al.* 2018). This is for example the case in caterpillars, beetles, flies, mosquitos and stinkbugs. For non-sexually reproducing pest such as aphids, mixtures provide less benefit for IRM. In addition, haplodiploid insects (i.e. species where males are haploid) such as thrips tend to also develop resistance faster, because a resistance gene always causes functional resistance in haploid individuals (Sudo *et al.* 2018 and Helps *et al.* 2020).
- In cases where target populations are not very mobile and mate locally (such as thrips and mites), the effect of immigration is lacking, leading to increased risk of resistance build up (Sudo *et al.* 2018).

Insecticide Mixtures: Key Considerations

6. Why are immigration rate and exposure important factors when using mixtures in the context of resistance management?

- Models suggest that two parameters, i) effectiveness and ii) exposure, have a significant impact on whether mixtures can have an IRM benefit over sequential deployment of insecticides. Under conditions where effectiveness is high and exposure incomplete, mixtures provide an additional benefit for IRM. In modelling scenarios, reducing exposure below 90% of the population was found to always delay resistance (Madgewick, and Kanitz, 2022). In contrast, increasing exposure of a target insect population to an insecticide reduces the proportion of susceptible versus resistant genotypes that survive treatment, thus resistance could evolve faster.
- In sexually reproducing diploid insects, immigration of non-exposed susceptible insects into a treated population has a similar effect as reduced exposure, making susceptible insects available for mating with insects that carry a resistance gene (Sudo *et al.* 2018). If the resistance gene is not highly dominant, the resulting offspring will be functionally susceptible, and the development of resistance could be delayed.
- Importantly however, when using conventional insecticides under realistic scenarios, reduction of exposure and effectiveness can be tolerated only to limited level. We can assume, that in a classical foliar spray application at recommended label dose, a small percentage of a pest population may survive.

Insecticide Mixtures: Key Considerations

7. Why is the level of effective dominance of the resistance gene important when using mixtures in the context of resistance management?

- As for IRM in general, dominance of the resistance gene in diploid insect populations plays an important role in determining the benefit of insecticide mixtures. Any optimal management strategy must be robust against high levels of dominance. At a high level of effective dominance, a mixture as part of a rotation scheme might likewise not provide an additional benefit for IRM, because heterozygote insects resulting from individuals carrying a dominant resistance gene that mate with susceptible individuals are not functionally susceptible. In the field insecticide resistance genes are often effectively dominant (Roush, 1998, Bourget *et al.* 1996).
- Effective dominance is dose-dependent and also depends on environmental factors. The higher the dose, the more likely heterozygotes are killed; therefore the allele becomes effectively recessive. Effective dominance is also dependent on the mechanism of resistance (i.e. loss of function versus gain of function).

Insecticide Mixtures: References

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