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Pesticide Mixtures and Rotations: Are these Viable Resistance Mitigating Strategies?

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ABSTRACT

Resistance to pesticides (in this case, insecticides and miticides) is a concern to producers associated with ornamental cropping systems such as greenhouses and nurseries. Resistance typically develops due to continually using insecticides and/or miticides with similar modes of action or chemistries in the presence of common detoxification pathways. Two strategies that have been suggested to mitigate resistance developing in arthropod (insect and mite) pest populations are the implementation of pesticide mixtures or pesticide rotations. However, the use of either strategy is still controversial as it is has not been adequately demonstrated quantitatively that these strategies actually mitigate resistance. Pesticide mixtures involve exposing individuals in an arthropod pest population to each pesticide simultaneously whereas pesticide rotations are the alternating use of pesticides with dissimilar modes of action. There are, however, a number of assumptions pertaining to both pesticide mixtures and rotations that dictate how successful these strategies may be in delaying the onset of resistance including 1) resistance associated with each pesticide is monogenic and independently genetically controlled, 2) individuals in the arthropod pest population with doubly-resistance genes or with multiple resistance mechanisms are rare, 3) a certain frequency or proportion of individuals in the arthropod pest population are left untreated due to the presence of refugia, 4) the pesticides used are equally persistent so that any individuals in the arthropod pest population are not exposed to just one pesticide for an extended length of time, and 5) the pesticides used have different modes of action. Either strategy of delaying or mitigating resistance should be incorporated with alternative pest management tactics such as cultural, sanitation, and biological control, which will reduce continued reliance on pesticides.

Keywords: cross resistance, insecticides, miticides, pest management, resistance mechanisms

CONTENTS

INTRODUCTION

Resistance to pesticides such as insecticides and miticides is always a concern because once arthropod (insect and mite) pest populations are no longer sufficiently suppressed with existing pesticides then management options become limited (McCord *et al*. 2002). The "selection pressure" exerted by a pesticide application may increase the frequency or proportion of individuals containing resistance genes (Comins 1977a). Furthermore, different mechanisms may confer resistance in various arthropod pest populations of the same species, and multiple resistance mechanisms may co-exist in certain arthropod pest populations (Forgash 1984; Brattsten *et al*. 1986). The primary resistance mechanisms associated with arthropod pests are metabolic detoxification and target site insensitivity (Oppenoorth 1985; National Research Council 1986a; Georghiou and Taylor 1986; Roush 1993; Jensen 2000). Metabolic resistance refers to the break down of the active ingredient by the arthropod pest. When the pesticide enters the body, enzymes attack and detoxify or convert the active ingredient into a non-toxic form (Jensen 2000). For example, detoxifying enzymes may convert insecticides, which are hydrophobic or "water-hating," to be more hydrophilic ("water-loving"). This usually makes the pesticide less biologically active and more readily excreted with waste products (Brattsten *et al*. 1986; Soderlund and Bloomquist 1990; Jensen 2000). The enzymes affiliated with metabolic detoxification include esterases, glutathione *S*-transferases, epoxide hydrolases, and cytochrome P450 dependent monooxygenases (mixed function oxidases) (Oppenoorth 1985; Brattsten *et al*. 1986; Soderlund and Bloomquist 1990; Ishaaya 1993; Roush 1993; Jensen 2000). In general, target site insensitivity involves interactions between the pesticide and the designated target site, which is similar to a key (pesticide active ingredient) fitting into a lock (the target site). A decrease in binding associated with target site insensitivity is similar to the lock having been changed so that the key no longer fits, and thus the pesticide is no longer effective (Mallet 1989). Most resistance mechanisms, in general, tend to be co-dominant to fully-dominant in expression, meaning that heterozygotes may display levels of resistance that are more similar to resistant than susceptible parents (Roush and Daly 1990).

Additional factors associated with resistance in arthropod pest populations are cross and multiple resistance. Cross resistance refers to a situation in which resistance to one pesticide confers resistance to another pesticide, even

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though the arthropod pest population has not been exposed to the second pesticide; and insensitivity to pesticides with similar modes of action or in the same chemical class due to a single resistance mechanism. However, this only addresses target site insensitivity. Cross resistance may also be due to common detoxification pathways associated with different pesticides (Cranham and Helle 1985; Georghiou and Taylor 1986; Roush 1993; Pedigo 2002). Multiple resistance, in general, refers to an arthropod pest population that is resistant to pesticides with discrete modes of action or across chemical classes associated with the expression of different resistance mechanisms (Forgash 1984; Brattsten *et al*. 1986; Georghiou 1986; Metcalf 1989).

The rate of resistance developing in an arthropod pest population is approximately proportional to the frequency of pesticide applications, especially when using those with similar modes of action (Forgash 1984; Tabashnik 1989). Two strategies that may delay or mitigate the onset of resistance developing in arthropod pest populations are the use of pesticide mixtures or rotations. There is already wide-spread use of pesticide mixtures among greenhouse producers, partly because combinations of selective pesticides may be required in order to deal with the arthropod pest population complex present in the crop (Tabashnik 1989; Ahmad 2004; Warnock and Cloyd 2005; Cloyd 2009). Typically, two pesticides are mixed together; however, it has been demonstrated that three or more pesticides (even fungicides) may be combined into a spray solution (Cloyd 2009). The implementation of pesticide resistance mitigating strategies is important for preserving the effectiveness of currently available pesticides (Hoy 1998). However, there is minimal evidence to suggest that either pesticide mixtures or pesticide rotations may actually delay or mitigate the onset of resistance (Immaraju *et al*. 1990). As such, this paper utilizes the scientifically-based literature to address the theoretical and realistic issues involved in mitigating resistance of arthropod pest populations using either pesticide mixtures or rotations in ornamental cropping systems.

PESTICIDE MIXTURES

A pesticide mixture entails exposing individuals in an arthropod pest population to each pesticide simultaneously (Tabashnik 1989; Hoy 1998). Pesticide mixtures may enhance arthropod pest population suppression due to either synergistic interaction or potentiation between or among the pesticides that are mixed together (All *et al*. 1977; Curtis 1985; Comins 1986; Ware and Whitacre 2004; Warnock and Cloyd 2005; Cloyd *et al*. 2007). Synergism refers to the toxicity of a given pesticide being enhanced by the addition of a less or non-toxic pesticide, or other compound such as a synergist (Chapman and Penman 1980; Ware and Whitacre 2004; Ahmad 2004). Potentiation alludes to an increased toxic effect on the arthropod pest population when mixing two active ingredients together (Chapman and Penman 1980; Marer 2000; Ahmad 2004, 2009). It has been proposed that pesticide mixtures may waive the onset of resistance development more effectively than rotating pesticides (described below) with different modes of activity (Skylakakis 1981; Mani 1985; Mallet 1989; Bielza *et al*. 2009).

Mixing pesticides with different modes of action may delay resistance developing within arthropod pest populations because the mechanism(s) required to resist each pesticide in the mixture may not be wide-spread or exist in arthropod pest populations (Georghiou 1980; Curtis 1985; Mani 1985; Mallet 1989; Ahmad 2004). As such, it may be difficult for individuals in the arthropod pest population to develop resistance to several modes of action simultaneously (Brattsten *et al*. 1986; Mallet 1989; Stenersen 2004; Yu 2008). Those arthropods present in the population resistant to one or more pesticides would likely succumb to the other pesticide in the mixture as long as pesticides with different modes of action are mixed together (Georghiou 1980; Mallet 1989; Yu 2008). For example, Crowder *et al*. (1984) reported that a mixture of chlordimeform (a formamidine) with the pyrethroid, permethrin, delayed resistance development in populations of *Heliothis virescens* (F.). However, pesticide mixtures may not always delay resistance (Burden *et al*. 1960). Attique *et al*. (2006) indicated that pesticide mixtures were less effective in delaying resistance in *Plutella xylostella* (L.) populations than applying insecticides separately. Furthermore, this approach may risk selecting for a detoxification mechanism that could allow survival to both pesticides (Stenersen 2004), and may actually enhance overall "selection pressure," thus accelerating the evolution of resistance (Curtis 1985; Brattsten *et al*. 1986; Via 1986).

The effect of pesticide mixtures is, however, unpredictable because differences in the mode of action do not necessarily guarantee a lack of common resistance mechanisms and may only reflect the specificity associated with enzymes responsible for detoxification (Sawicki 1981; Yu 2008). Moreover, the effects of pesticide mixtures may vary depending on the arthropod pest population as a result of differences associated with species, strain, and even biotype (Sawicki 1981; Georghiou and Taylor 1986; Ishaaya 1993). These differences could be related to physiology and the resistance mechanisms present in the population (Georghiou and Taylor 1977a; Brattsen *et al*. 1986). Also, resistance mechanisms typically do not respond to "selection pressure" or frequency of pesticide applications the same way based on the pesticide being applied. In fact, some resistance mechanisms may negate the advantages of pesticide mixtures (Tabashnik 1989; Stenersen 2004).

A notable aspect of pesticide mixtures is the opportunity for complex interactions, including synergism or antagonism. Two active ingredients may compete for or inhibit the same enzyme (e.g., esterase), which can increase the toxicity of the pesticide mixture (Kulkrani and Hodgson 1980). Synergism may occur when one pesticide interferes with the metabolic detoxification of another pesticide (Corbett 1974; Kulkrani and Hodgson 1980). Certain organophosphate insecticides bind to the active site on esterase enzymes responsible for detoxification of pyrethroid insecticides (Ascher *et al*. 1986; Ishaaya *et al*. 1987; Bynum *et al*. 1997; Gunning *et al*. 1999; Ahmad 2004; Zalom *et al*. 2005; Ahmad *et al*. 2008; Ahmad 2009), and so organophosphate insecticides can be useful synergists for pyrethroids (Chapman and Penman 1980; Brattsten *et al*. 1986; Ishaaya *et al*. 1987; Gunning *et al*. 1999; Martin *et al*. 2003; Zalom *et al*. 2005; Attique *et al*. 2006). This is one of the primary reasons why many manufacturing companies formulate organophosphate and pyrethroid-based insecticide mixtures to manage arthropod pest complexes and counteract resistance (Ahmad 2004). Examples of commercially available products for use in greenhouse production systems include Tame/Orthene TR* [fenpropathrin (pyrethroid) and acephate (organophosphate)] and Duraplex® TR** [chlorpyrifos (organophosphate) and cyfluthrin (pyrethroid). However, continued use of these pesticide mixtures may result in resistance to both modes of activity by arthropod pest populations, especially those that have the capacity of developing multiple resistance (Comins 1986; Metcalf 1989; Attique *et al*. 2006; Ahmad *et al*. 2008).

As with applications of individual pesticides, it is important to only mix together pesticides with different modes of action or those that affect different biochemical processes in order to mitigate resistance developing in arthropod pest populations (Cranham and Helle 1985; Cloyd 2009). Pesticide mixtures may delay or mitigate the onset of resistance under the following assumptions: 1) resistance associated with each pesticide in a mixture is monogenic (resistance

*Tame/Orthene TR (Total Release Insecticide) (Whitmire Micro-Gen Research Laboratories, Inc., St. Louis, MO).
**Duraplex® TR (Total Release Insecticide) (Whitmire Micro-Gen Research Laboratories, Inc., St. Louis, MO).

resulting from the expression of a single gene) and independently genetically controlled (Curtis 1985; Tabashnik 1989). In addition, there is no cross resistance among individuals in the arthropod pest population to the pesticides used in the mixture (Mani 1985; Comins 1986; Tabashnik 1989, 1990). These conditions are met when there are different target sites and detoxification enzymes implicated in resistance to the two pesticides. It is possible that under these given circumstances, individuals simultaneously possessing resistance mechanisms to both pesticides will be extremely rare (Curtis 1985; Brattsten *et al*. 1986; Mallet 1989; Roush 1993); 2) individuals in the arthropod pest population possess resistance genes that are exclusively recessive and/or individuals that are doubly-resistant are extremely rare. Evolution of resistance will be instantaneous if any survivors possess doubly-resistant genes or multiple resistance mechanisms (Curtis 1985; Comins 1986; Tabashnik 1989; Mallet 1989); 3) some individuals in the arthropod pest population are not treated or exposed to the pesticide spray mixture primarily due to the presence of refugia (Georghiou and Taylor 1977b; Brattsten *et al*. 1986; Tabashnik 1989, 1990), or there is immigration of and mating with susceptible individuals, which reduces the frequency or proportion of resistant individuals (or resistant genes) in the arthropod pest population (Comins 1977b; Georghiou and Taylor 1977b; Tabashnik and Croft 1982; Comins 1986; Georghiou and Taylor 1986; Mallet 1989; Jensen 2000; Stenersen 2004); 4) the pesticides mixed together are equally persistent so that the individuals in the arthropod pest population are not exposed to just one pesticide for an extended length of time (Forgash 1984; Curtis 1985; Tabashnik 1989, 1990; Roush 1993); and 5) mechanisms of resistance to each pesticide are present at such low frequencies that they may not occur together in any individuals in an arthropod pest population (Yu 2008).

In nearly all instances, the assumptions presented above are not realistic. It is possible that pesticide mixtures may promote the expression of multiple resistance, which could extend across other chemical classes resulting in specific arthropod pest populations being very difficult to manage (Forgash 1984; Brattsten *et al*. 1986; Ahmad 2004; Attique *et al*. 2006). For example, multiple evolutionary pathways exist that will eventually result in a pesticide-resistant arthropod pest population (Metcalf 1980; Georghiou 1983; Brattsten *et al*. 1986; Ishaaya 1993). Although pesticide mixtures may delay resistance due to target site insensitivity, which is usually specific to a particular class of pesticides, the use of pesticide mixtures enhances the selection for increased expression of metabolic enzymes that can simultaneously detoxify both pesticides (Roush and McKenzie 1987; Roush and Daly 1990; Roush and Tabashnik 1990; Stenersen 2004). Also, cross and multiple resistance may occur among some pesticides with similar modes of action (Stenersen 2004). Therefore, selecting for high levels of detoxification enzyme expression jeopardizes the usefulness of all pesticides, even those with new modes of action to which the arthropod pest population has not been previously exposed (Tabashnik 1989; Soderlund and Bloomquist 1990).

Additional problems associated with the assumptions of using pesticide mixtures are that the frequency of doubly-resistant individuals or those with multiple resistance mechanisms in the arthropod pest population may be extensive (Tabashnik 1989). This may be due to a history of pesticide exposure with the associated selection for resistance in previous arthropod pest generations, which implies that there may be some background levels of resistant traits or mechanisms in the arthropod pest population for each pesticide used in the mixture (Georghiou and Taylor 1977a). Finally, there is usually no refuge to preserve susceptible individuals (Georghiou and Taylor 1986; Tabashnik 1989), particularly in enclosed greenhouse production systems.

The question is then; is using pesticides in mixtures the most appropriate way to extend their usefulness, or is it preferable to apply them individually? Pesticide mixtures, in fact, may be more expensive than rotations (discussed below), especially if the pesticides that are mixed together are used at the highest recommended label rate (Curtis 1985; Comins 1986; Mallet 1989; Attique *et al*. 2006). As such, a common practice is too use reduced rates of each pesticide in the mixture although this may not mitigate resistance developing in arthropod pest populations (Suthert and Comins 1979). More sophisticated uses of pesticide mixtures will require a greater understanding of their interactions in order to optimize the dosage at below label rates when the components (active and inert ingredients) act synergistically (Tabashnik 1989; Attique *et al*. 2006). Pesticide mixtures may be an effective means of mitigating resistance as long as there is a high level of dominance in the arthropod pest population and immigration of susceptible individuals is prevalent (Mani 1985; Georghiou and Taylor 1986). Based on population genetic models, pesticide mixtures may effectively suppress resistance genes that are recessive and accord resistance to only one pesticide. However, it is possible that pesticide mixtures will select for dominant genes, which confer cross resistance (Tabashnik 1989). The rate of resistance development in an arthropod pest population to two or more pesticides in a mixture may take longer than when the pesticides are applied separately (National Research Council 1986b) although resistance to a pesticide mixture may occur at a similar rate as when the pesticides are applied individually (Kable and Jeffery 1980). Finally, the advantages of a pesticide mixture will only be sustained as long as resistance is not fully-dominant (Curtis 1985). Because the reliability of the pesticide mixture strategy depends on several assumptions, applying pesticides individually, by rotating those with different modes of action or that act on different target sites may be a more appropriate strategy (Roush 1993).

PESTICIDE ROTATIONS

Pesticide rotation is a temporal alternation of pesticides with different modes of action, and/or different resistance mechanisms or chemistries (Tabashnik 1989; Immaraju *et al*. 1990). Greenhouse producers often repeatedly use insecticides, with the same mode of action although there is information regarding the benefits of pesticide rotations (Immaraju *et al*. 1990). Coyne (1951) was the first to recommend pesticide rotation programs for resistance mitigation by rotating pesticides from different chemical classes (McCord *et al*. 2002). However, this approach is not appropriate since certain chemical classes have similar modes of action (e.g., organophosphates and carbamates), which results in increased "selection pressure" on an arthropod pest population and thus enhanced rates of resistance (McCord *et al*. 2002; Ware and Whitacre 2004; Yu 2008). The theory underlying the rotation of pesticides with different modes of action is that the frequency or proportion of individuals in the arthropod pest population resistant to one pesticide will decline when another pesticide, with a different mode of action, is being applied (Pimentel and Bellotti 1976; Georghiou 1983; Mani 1985; Tabashnik 1989; Mallet 1989; Hoy 1998). Also, individuals resistant to one pesticide may be lower in fitness than any susceptible individuals (Georghiou and Taylor 1986; Tabashnik 1989), based on the number of generations produced, such that the frequency or proportion of resistant individuals in the arthropod pest population decreases during the time period when the pesticide is not being applied (Mani 1985; Yu 2008). The reduced "selection pressure" associated with utilizing pesticides with discrete modes of action may lead to an increase in the usefulness of effective pesticides (McCord *et al*. 2002). However, continued "selection pressure," even when applying pesticides with dissimilar modes of activity may result in improved fitness via co-adaptation of the resistant genome thus leading to a higher stability of resistance (Georghiou and Taylor 1986). Therefore, pesticide rotation schemes should, in general, include as many pesticides with different modes of action as possible, particularly if resistance mechanisms and cross resistance cannot be identified (Georghiou 1983; Jensen 2000; Ahmad *et al.* 2001).

As with pesticide mixtures (discussed previously), there are a number of important assumptions that factor into how effective pesticide rotations are in mitigating resistance including 1) the pesticides must have different modes of action or select for different resistance mechanisms (Jensen 2000; Dekeyser 2005). This avoids continuous "selection pressure" on a particular trait or the expression of certain resistance mechanisms. Pesticide rotations across generations, in the case where generations overlap simultaneously during the growing season, may be more appropriate than rotations within a single generation (Roush 1989). The existence of traits or resistance mechanisms that lead to cross resistance among pesticides is similar to the use of pesticide mixtures (Comins 1986). If cross resistance is present in the arthropod pest population to two pesticides with similar modes of activity, then there would be no benefit to rotating the pesticides (Georghiou 1983; Comins 1986). However, Immaraju *et al.* (1990) indicated that rotations were a preferable option as opposed to pesticide mixtures despite the occurrence of cross resistance although no explanation was provided; 2) there is a genetic disadvantage or fitness cost associated with particular resistance mechanisms (Mani 1985; Roush 1993). Therefore, when a pesticide is not being applied, susceptible individuals will produce more offspring than those with the resistance trait or mechanism, and the frequency or proportion of the arthropod pest population harboring the resistance trait or mechanism will decline (Roush and Plapp 1982; Georghiou 1983); 3) some individuals in the arthropod pest population are not treated or exposed to pesticides used in the rotation program due to the presence of refugia, or there is immigration of and mating with susceptible individuals (Georghiou and Taylor 1986; Hoy 1998); and 4) the length of time or number of generations between applications of one pesticide with a specific mode of action is sufficient to allow resistance to decrease (Yu 2008). As the intervals between applications of pesticides with similar modes of action are increased, the frequency or proportion of resistant individuals in the arthropod pest population should diminish (Mani 1985; Hoy 1998). However, Stenersen (2004) suggested that rotating pesticides may not prevent the development of resistance if survival of heterozygotes is favored compared to susceptible individuals. Furthermore, pesticide rotations, depending on the frequency of applications within a given generation, may not decrease the rate of resistance development (MacDonald *et al.* 1983).

The assumptions for successful use of pesticide rotations to delay the onset of resistance have problems, as they did with pesticide mixtures (discussed previously). In both cases, any traits or resistance mechanisms such as enhanced expression of general detoxification enzyme systems can increase resistance selection for multiple components of a pesticide rotation program (Plapp 1984). Fitness costs do exist; however, this may vary in importance based on the pesticide and the number of generations in which resistance has been maintained within an arthropod pest population (Crow 1957). Furthermore, the number of offspring or young produced per female and generations per year will influence how effective pesticide rotations are in mitigating resistance because these factors often impact the frequency of pesticide applications (Tabashnik and Croft 1982; Georghiou and Taylor 1986; Croft and van de Baan 1988). Pesticide rotations may be regarded as a more viable strategy even if resistance is already present at low frequencies although no definitive explanation has been provided (Georghiou 1983; Metcalf 1983). In fact, pesticide rotations rather than pesticide mixtures are typically promoted in resistance management programs. For example, rotating pyrethroid-based insecticides along with organophosphate insecticides is a recommendation to alleviate resistance occurring in *Heliothis*/*Helicoverpa* populations (Sawicki and Denholm 1987).

SUMMARY

This paper presents information indicating that both pesticide mixtures and rotations may be viable strategies to mitigate resistance development in an arthropod pest population although this is still a controversial topic as it has not been adequately demonstrated quantitatively that either strategy may in fact mitigate resistance. Therefore, it is critical to understand the assumptions that must be fulfilled in order for these two resistance mitigating strategies to be successful (Tabashnik 1989). While pesticide mixtures may appear to be more effective in delaying resistance compared to pesticide rotations (Mani 1985), pesticide rotations may in fact be a more viable strategy to mitigate resistance because rotations reduce the overall use of favored (effective) pesticides (Sawicki 1981; Mallet 1989; Roush and Tabashnik 1990). Careful rotation of selective pesticides or those that may be integrated with biological control agents is especially important because parasitoids and predators (and even microbials such as beneficial bacteria and fungi) can suppress arthropod pest populations irrespective of the arthropod pests' resistance traits or mechanisms (Tabashnik 1986). Finally, either strategy for mitigating resistance must not divert attention from the implementation of alternative pest management strategies including cultural, sanitation, and biological control that can reduce reliance on pesticides, which is most effective in mitigating pesticide resistance (Georghiou 1983; Metcalf 1983; Tabashnik 1989; Roush 1989; Roush and Tabashnik 1990; Hoy 1998; Denholm and Jespersen 1998).

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