SYNERGISM OF PERMETHRIN BY FORMAMIDINES IN *HELIOTHIS VIRESCENS*[1]: A COMPARISON OF CHLORDIMEFORM, AMITRAZ AND A METABOLITE

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ABSTRACT

Laboratory tests were conducted to evaluate the ability of three formamidines to synergize permethrin in tobacco budworm (TBW), *Heliothis virescens* (Fabricius), using a topical application of 1:1 wt/wt ratio of permethrin + formamidine against third instar larvae of susceptible and resistant strains. There was no synergism found with the permethrin + formamidine combinations against the susceptible strain, a slight synergism was found in a field strain, and an increased synergism was shown in the resistant strain, in which chlordimeform (CDF) and N'-(2,4-dimethylphenyl)-N-methylformamidine (SN-49844), a metabolite of amitraz, showed higher degrees of synergism than amitraz. Amitraz and SN-49844 were also tested for synergism with permethrin against larvae of a cross-bred strain between a laboratory resistant and a laboratory susceptible culture. The compound SN-49844 showed synergism of 1.8-fold and amitraz showed no synergism at all. Selection of larvae of the cross-bred strain of TBW using permethrin ± formamidine mixtures at LD_{80} for four generations produced strong tolerance to permethrin regardless of the agents used in the selection. After four generations of continuous selection pressure, the LD_{50} in the F_5 generation had increased by 100-fold with permethrin alone, 122-fold with permethrin plus amitraz and 180-fold with permethrin plus SN-49844 as compared to the F_1 generation. A test for cross-resistance to cypermethrin and to methyl parathion in the permethrin-selected strain of TBW showed resistance levels of 58-fold and 48-fold in that order compared with the susceptible TBW.

INTRODUCTION

The development of resistance is a major problem in the use of pesticides, particularly for insecticides and acaricides used in the management of cotton pests. *Heliothis virescens*, the tobacco budworm (TBW), is currently the most damaging late season pest of cotton in the USA (Reed and Pawar, 1982) and has shown resistance to most insecticide classes (chlorinated hydrocarbons, carbamates and organophosphates) (Adkisson 1968, Plapp 1971, Plapp 1972).

The introduction of the pyrethroids in 1977 offered an opportunity to manage insecticide resistance because they proved to be highly effective at low doses against many insects such as the TBW, which were resistant to other insecticides. Nonetheless, a gradual increase in the tolerance of TBW to pyrethroids has been documented in some areas (Allen et al. 1987, Plapp et al. 1987, Roush and Luttrell 1987, Leonard et al. 1987). This led to research to try and extend the commercial life of pyrethroids by using insecticide synergists. Formamidines have been reported to synergize the toxicity of pyrethroids to arthropods (Plapp 1976, 1979, Ditrich et al. 1981, El-Guindy et al.1981, Bodnaryk 1982, Rajakulendran and Plapp 1982, El-Sayed and Knowles 1984a, b). Crowder et al. (1984) demonstrated that the use of chlordimeform (CDF) in combination with pyrethroids may prevent or delay the development of resistance in TBW. Unfortunately CDF has been shown to cause cancer in laboratory rats and has been removed from the market. Safer synergists could facilitate practical insect control by reducing the dosage rate of expensive pyrethroids and by maintaining the pyrethroid activity spectrum.

[1] Lepidoptera: Noctuidae

The purpose of our study was to test for synergistic abilities of two formamidines, amitraz and one of its metabolites N'-(2,4 - dimethylphenyl)-N-methyl formamidine (SN-49844), compared with that of CDF in both susceptible and resistant laboratory strains of TBW, and also an Arizona field strain. Synergistic abilities of amitraz and SN-49844 were also compared on a cross-bred strain of resistant (R) and susceptible (S) strains of TBW. In a companion study we investigated the potential for enhancing resistance by selecting with 1:1 (wt/wt) mixtures of permethrin + amitraz, permethrin + SN-49844 and a comparative selection with permethrin alone. Additonally, we determined the potential for cross-resistance to cypermethrin and methyl parathion in the F_{77} generation of the permethrin-selected strain of TBW.

MATERIALS AND METHODS

Four strains of TBW were included in the bioassays. The susceptible strain (USDA(S), a laboratory strain maintained in the lab for more than 220 generations with no exposure to insecticides) was obtained from the USDA Agricultural Research Service Honeybee Biology and Biological Control Laboratory in Tucson, Arizona. A field strain (FS) was collected from Laveen, Arizona in 1988 and reared for 5 - 7 generations in the laboratory, and a resistant strain (PSHI(R)) (permethrin resistant, selected over 70 generations at LD_{80}) was obtained from the University of Arizona Campus Agricultural Center, Department of Entomology. A cross-bred strain (PSDA) was developed by crossing either sexes of the susceptible and the resistant laboratory strains. The strains were maintained on modified lima bean diet (Patana 1969). The insecticides used in this study were technical grade permethrin (Pounce; F.M.C. Corp. Agricultural Chemical Division; Middleport, NY 14105; 96.5%), cypermethrin (Cymbush; ICI Incorporated, Biological Research Center, Goldsboro, North Carolina, 17530; 76.5%), and methyl parathion. The formamidines used were technical grades of chlordimeform (CDF), amitraz, and N-(2,4-dimethylphenyl-N-methylformamidine (SN-49844), a metabolite of amitraz (Knowles and Gayen 1983) all obtained from NOR/AM Chemical Company, (3509 Silverside Rd., Wilmington, DE 19803) (Fig. 1). The test procedure used was similar to that recommended by the Entomological Society of America (Brazzel 1970). Technical grade materials were dissolved in acetone and one microliter (ul) of solution was applied to the dorsal surface of 22 $\pm$ 5 mg third-instar larvae using a motor driven micro-applicator. The average weight of larvae was determined from a sample of about 15% of the larvae to be treated. All insecticides with or without synergists were tested on all four TBW strains. Insecticides plus synergists were tested at a 1:1 (wt/wt). In Arizona, the recommended application rate for permethrin is 0.2 lb ai/A, and for CDF is 0.25 lb ai/A. This gives an approximate ratio of 1:1 Permethrin:CDF. In our experiment we used 1:1 wt/wt ratio so as to simulate field conditions. Similar ratios with CDF have also been used by previous researchers (Plapp, 1976, Crowder et al. 1984). Four to five different concentrations were used for each insecticide or insecticide + formamidine combination in addition to the controls. Control larvae, to compare with the insecticide alone treatments, were treated with only acetone. For the permethrin plus formamidine treatments, control larvae were treated with the highest test concentration of formamidine used in the 1:1 ratio.

The treated larvae were maintained at 80°F and mortality was recorded at 72 hours after treatment. Larvae were classed as dead if they failed to respond to probing with a blunt probe. Moribund larvae were counted as dead after 72 hours. The 72 hours data were used to compute the probit analysis (Finney 1971).

Dosage ranges (mg/larva) used depended not only upon the specific insecticide used but also and primarily on the particular strain of larva: USDA, 0.4-6.4; FS, 0.63-12.7; PSDA, 1.29-64.5; and PSHI, 116-28,000. LD_{50} values were reported in micrograms (μg) of insecticides per gram (g) of larvae body weight to compensate for variation in the size of the larvae used. Data from all tests were corrected for control mortality with Abbott's (1925) formula. The synergism levels were calculated by dividing the LD_{50} for the insecticide alone by the LD_{50} for the insecticide with the synergist. The 95% confidence limits were used for determining differences among the LD_{50} values, where no overlap indicates a significant difference.

RESULTS AND DISCUSSION

The dosage-mortality data of permethrin on the four strains is shown on Table 1. Mortality in all the controls in all tests ranged from 1-3%. There was no significant difference between the LD_{50} value of the FS and that of the cross-bred strain. The PSHI showed very high levels of resistance to permethrin with a resistance factor of 5900-fold as compared with the susceptible USDA strain. Table 1 compares the dosage mortality ratios for the cross-bred strain (PSDA) and the parent strains. The F_1 of the cross between the resistant and the susceptible strains produced a 700-fold decrease in the LD_{50} to permethrin compared with the resistant parent but was still significantly more resistant than the susceptible parent (9-fold).

TABLE 1. Dosage-Mortality Data of Permethrin on Different Strains of Tobacco Budworm.

Strain[d]	n[a]	LD_{50}[b] (95% CI)	LD_{95} (95% CI)	Slope (SE)	RF[c]
USDA (S)	875	0.67 (0.36-1.06)	23 (9.9-120)	1.1 (0.08)	1.0
FS	600	5.42 (4.76-6.18)	30 (21-40.5)	2.2 (0.17)	8.1
PSHI (R)	750	3933 (3384-4571)	27000 (21000-35000)	2.0 (0.15)	5900
PSDA F_1	710	5.79 (4.63-7.25)	158 (94-266)	1.1 (0.11)	8.6

[a] n = Number of larvae tested excluding controls.
[b] LD_{50} and LD_{95} are expressed in μg of toxicant/g of larvae
[c] RF = Resistance Factor =(LD_{50} of Strain)/(LD_{50} of USDA(s))
[d] USDA(S) = susceptible lab strain, FS = field strain, PSHI(R) = permethrin high resistant strain, PSDA = cross-bred strain between USDA (S) and PSHI (R).

The extent of cross-resistance to cypermethrin and methyl parathion in the permethrin-selected strain of TBW is shown in Table 2. This strain has previously undergone seventy-six continuous generations of selection pressure with permethrin. The degree of tolerance with this strain to cypermethrin was compared with data from a 1981 field population of TBW, collected from Maricopa, Arizona (L.A. Crowder, personal communication). Similarly, the degree of tolerance to methyl parathion was compared with a 1974 domestic strain (Watson et al. 1986). The permethrin selected strain showed a 58-fold and a 48-fold resistance to cypermethrin and methyl parathion respectively.

TABLE 2. Relative Cross-Resistance to Cypermethrin and Methyl Parathion in Permethrin-Selected (PSHI(R)) Larvae of the Tobacco Budworm.

Insecticide	Susceptible		PSHI (R)[b]		RF[c]
	LD_{50}[a] (95% CI)	Slope (SE)	LD_{50}[a] (95% CI)	Slope (SE)	
Permethrin	0.67 (0.4-1.1)	1.1 (.08)	4681 (3625-5774)	1.9 (0.17)	7000
Cypermethrin	8.0[d] (7.7-9.49)	3.1 --	463 (351-613)	1.1 (0.11)	58
Methyl-Parathion	11.5 (9.4-11.7)[e]	2.5 --	555 (447-689)	1.2 (0.11)	48

[a] LD_{50} = μg/g of larva
[b] PSHI = Permethrin high resistant strain
[c] RF = Resistance Factor = (LD_{50} of Resistant Strain)/ (LD_{50} of susceptible strain)
[d] Crowder (1981 Field strain; personal communication)
[e] Data from Watson et al. (1986)

The synergistic levels of the three formamidines on permethrin against different strains of TBW are shown in Table 3. The 1:1 (wt/wt) mixtures of permethrin plus formamidines showed increased toxicity in the permethrin resistant strain of the TBW. Compared with CDF and SN-49844, amitraz showed a lower degree of synergistic ability. There was no synergism obtained when permethrin plus any formamidine was used against the laboratory susceptible strain. Synergism values for the field and the cross-bred strains ranged from 1.1 - 1.7 and 0.6 - 1.8 respectively with all the formamidines.

TABLE 3. Synergism Ratios (SR) for Permethrin:Formamidine Mixtures Against Different Strains of Tobacco Budworm.

Strain	Treatment			
	Permethrin	Permethrin + CDF	Permethrin + Amitraz	Permethrin + SN49844
USDA (S)				
LD_{50}[a] ± CI	0.67(0.36-1.06)	1.51(1.35-1.69)	1.62(1.43-1.84)	1.50(1.32-1.71)
Slope (SE)	1.1(0.08)	2.6(0.18)	2.2(0.17)	2.4(0.18)
SR[b]	1.0	0.44	0.41	0.45
Field strain				
LD_{50} ± CI	5.42(4.76-6.18)	3.20(2.16-4.85)	4.77(4.29-5.31)	4.79(4.21-5.45)
Slope (SE)	2.2(0.17)	1.5(0.12)	2.5(0.22)	2.0(0.18)
SR	1.0	1.7	1.1	1.1
PSHI (R)				
LD_{50} ± CI	3933(3384-4571)	415(348-496)	2870(2120-3919)	337(267-425)
Slope (SE)	2.0(0.15)	1.8(0.12)	1.4(0.15)	1.8(0.12)
SR	1.0	10	1.4	12
PSDA				
LD_{50} ± CI	5.79(4.63-7.25)	---	9.64(6.4-14.1)	3.21(2.28-4.23)
Slope (SE)	1.1(0.11)	---	1.1(0.13)	1.4(0.12)
SR	1.0	---	0.6	1.8

[a] LD_{50} = in μg of toxicant/g of larvae, ± 95% confidence interval
[b] SR = Synergism Ratio = LD_{50} of Permethrin/(LD_{50} of Permethrin + Formamidine)

Selection of the cross-bred TBW larvae with permethrin ± formamidine mixtures at LD_{80} for four generations produced strong tolerance to all mixtures used. After four generations of continuous pressure, the LD_{50} values of the synergists plus permethrin on the F_5 had increased by 100-fold with permethrin alone, 122-fold with permethrin plus amitraz and 180-fold with permethrin plus SN- 49844 compared to the LD_{50} value of the F_1 generation (Table 4).

The dosage-mortality data of permethrin on the PSHI (R) show that an Arizona field collected TBW strain could be selected for very high permethrin-resistance in the laboratory. This strain has a resistance factor of 5900 - fold compared with the susceptible laboratory strain. Although no failures to control field populations with pyrethroids have occurred in Arizona, failures have been documented in some areas in the US where pyrethroids have been extensively used. Plapp and Campanhola (1986) diagnosed permethrin resistance of 16-fold in populations of TBW from west Texas where control failures had occurred. Allen et al. (1987) reported more control failures in Texas during the 1985/86 season. Roush and Luttrell (1987) reported control failures at several locations in Mississippi during the 1986 season. Topical assays in the laboratory showed 5 to 23-fold resistance levels to pyrethroids in larvae from three of eight areas. Leonard et al. (1987) tested field strains of tobacco budworms collected in Louisiana, Texas, Arizona, and Mississippi during 1985 and 1986 and these insects exhibited moderate to high levels of resistance to fenvalerate (2 to 35-fold), permethrin (1 to 74-fold) and cypermethrin (2 to 9-fold). Except for these cases, the performance of synthetic pyrethroids on many cotton insects pests has been outstanding since their introduction into commercial pest management in 1977. Therefore, every effort must be made to extend their useful life by using them in a judicious manner.

Cross - resistance to cypermethrin and methyl parathion. Cross - resistance to cypermethrin and to methyl parathion in the permethrin selected strain of TBW was found to be high. In the F_{77} of this strain, LD_{50} values were 58-fold for cypermethrin, and 48-fold for methyl parathion as compared to a 1981 field collected susceptible strain and a laboratory susceptible strain, respectively.

Earlier studies by Crowder et al. (1979) reported low level cross-resistance to pyrethroids in TBW populations resistant to methyl parathion in Arizona. Similar results were obtained by Twine and Reynolds (1980) and Brown et al. (1982) in California and South Carolina, respectively. Priester and Georghiou (1980) demonstrated in studies with mosquitoes that selection for resistance with one pyrethroid confers at least partial resistance to many other

TABLE 4. Dosage-Mortality of Permethrin on the Cross-bred (PSDA) Strain of Tobacco Budworm Subjected to LD_{80} Pressure from Generation 1 - 4 Using Different Selecting Agents.

Selecting Agents		F(x)[a] 1	3	5
Control	LD_{50}[b] ± CI	5.79(4.63-7.25)	2.82(2.27-3.51)	2.57(2.26-2.93)
	slope(SE)	1.1(0.11)	1.3(0.11)	2.4(0.19)
	RF[c]	9.0	4.2	3.8
Permethrin	LD_{50} ± CI	5.7(4.63-7.25)	25.6(17.6-31.5)	632(450-859)
	slope(SE)	1.1(0.11)	1.1(0.14)	0.9(0.10)
	RF	9.0	37	900
Permethrin +Amitraz	LD_{50} ± CI	5.79(4.63-7.25	34.9(28.5-42.7)	717(578-890)
	slope(SE)	1.1(0.11)	1.4(0.16)	1.4(0.15)
	RF	9.0	52	1100
Permethrin + SN 49844	LD_{50} ± CI	5.79(4.63-7.25)	19.6(13.0-26.0)	1097(905-1330)
	slope(SE)	1.1(0.11)	10(0.14)	1.4(0.12)
	RF	9.0	29	1600

[a] F(x) = Generation where dose mortality regressions were completed
[b] LD_{50} is expressed in μg of toxicant/g of larvae; CI = 95% Confidence Interval
[c] RF = Resistance Factor = (LD_{50} of Fx)/(LD_{50} of USDA(S))

pyrethroids. Our results confirm these earlier observations in that the permethrin selected strain demonstrated resistance to another pyrethroid and to an organophosphate. Additionally, Crowder et al. (1984), working with the F_{12} (at 37-fold resistance level) of the same permethrin-resistant strain used in the current study, showed a 7.9-fold resistance to cypermethrin. Therefore, increasing levels of resistance to cypermethrin appears to accompany increasing selection for resistance to permethrin, but at a lower rate.

Inheritance of permethrin resistance in the tobacco budworm. The dosage-mortality regressions for the cross-bred strain show a large decrease in the LD_{50} value. The F_1 regression line lies closer to the susceptible than the resistant parent. This indicates that the resistance gene(s) of the permethrin selected strain are incompletely recessive. Earlier studies by Watson and Kelly (personal communication) involving crosses of the same strains have also indicated a large decrease in the LD_{50} value. Their results from the F_2 generation and from back-crosses with both the resistant and the susceptible parents suggest that more than one gene might be involved.

Only a few previous studies have analyzed the genetics of resistance factors in Lepidoptera. Liu et al. (1981), demonstrated that fenvalerate resistance in diamond back moth, *Plutella cylostella* was partially recessive and conferred by more than one autosomal gene. Past studies with TBW have addressed the inheritance patterns of resistance to methyl parathion (Whitten 1978) and methomyl (Roush and Wolfenbarger 1985). In both cases the authors concluded that resistance was conferred by a single autosomal gene of incomplete dominance. Payne et al. (1988) working with TBW demonstrated that permethrin resistance in the TBW was inherited as a single, major, incompletely recessive, autosomal factor which may explain why our F_1 cross was closer to the susceptible parent (9-fold difference) than the resistant parent (5900-fold difference).

Synergism of Permethrin by Formamidines. The results indicate no synergistic activity of permethrin by formamidine on the USDA(S) susceptible lab strain. However, some degree of synergism was observed on FS, PSDA, and the PSHI strain. Plapp (1979) reported in an earlier study a 1.8-fold synergism with a 1:1 mixture of permethrin plus CDF against a laboratory susceptible strain of TBW using the vial test. This synergism may be due to the behavioral effect of CDF. Increased movements of larvae within the vial allowed more contact with the insecticide and thus increased mortality. This is therefore a "behavioral synergism". Our studies also indicate that SN-49844 is a more promising synergist than amitraz and is equally effective as CDF against the resistant strain of TBW. Amitraz poorly synergized permethrin compared with its metabolite and CDF. Previous studies have shown that mixtures of pyrethroids and formamidines enhance toxicity to arthropods (Plapp 1976, 1979, Ditrich et al. 1981, El-Guindy et al. 1981, Bodnaryk 1982, Rajakulendran and Plapp 1982, El-Sayed and Knowles 1984a,b).

The physiological mechanism by which formamidines synergize other insecticides has not yet been determined. El-Badry et al. (1987) suggested that the mechanism associated with the synergism of pyrethroid activity by formamidines affects events in both pharmacodynamic and pharmacokinetic phases of pyrethroid actions. El-Badry and Knowles (unpublished data) observed that several formamidines synergized activity to a susceptible and to two resistant strains of the house fly. The resistance mechanism in one strain was nerve insensitivity and the other was mixed nerve insensitivity and enhanced detoxification. Results of a biochemical study indicated that the synergistic interaction between CDF and permethrin on the moth *Mamesta configurata* (Bodnaryk 1982) resulted from perturbation of octopaminergic transmission by the formamidine and cholinergic transmission by the pyrethroid. Chang and Plapp (1983) stated that the synergistic interaction between these two compounds in the TBW resulted from the fact that CDF increased the binding of permethrin to the presumed target receptors involved in nerve insenstivity. Gagne (1980) working with compounds other than pyrethroids found that CDF interferred with insecticide detoxification by TBW. The classical explanation of synergism of insecticides by other xenobiotics (e.g. piperonyl butoxide, PBO) remains that the synergist exerts its effect in the pharmacokinetic phase, usually by inhibiting degradation of the insecticide (Raffa and Priester 1985). More research work needs to be done to comprehensively elucidate the physiological mechanism by which formamidines synergize the activity of other insecticides.

Selection for resistance by formamidines. This investigation demonstrated that selection of permethrin resistance in the TBW might be enhanced (rather than repressed) by the addition of formamidines to the selecting agent when the resistant allele is present in high frequency. The F_1 of the cross between either sexes of PSHI (R) and USDA (S) had a resistance of 9-fold when compared with the USDA(S). This strain, when subjected to continuous selection (starting at F_1) with permethrin plus formamidines at LD_{80} for four generations, became resistant to permethrin at 1100, and 1600-fold for permethrin plus amitraz, and permethrin plus SN-49844, respectively. Selection at the LD_{80} level with permethrin alone caused 900-fold increase in resistance. These results indicate that the allele responsible for resistance was present in relatively high frequencies in the cross-bred strain. In the original selection studies, rapid development of resistance occurred after nine generations. Comparatively, a strain from the cross, that was not subjected to insecticides for four generations, showed only a 3.8-fold resistance to the laboratory susceptible parent in the F_5 as compared with 9-fold in the F_1.

These results suggest that when signs of resistance are observed in a population, resistance levels may increase rapidly when under strong selection pressure, especially in the presence of formamidine synergists like SN 49844. The best strategy to avoid resistance may be to switch to a different insecticide chemistry and refrain from using these type of synergists. Earlier studies by Crowder et al. (1984) indicated that induction of permethrin resistance in the TBW through selection might be delayed or prevented by the addition of CDF to the selecting agent. After eleven generations of selection with permethrin + CDF at LD_{80}, the LD_{50} of the F_{12} was 3.5μg as compared to 4.9 μg/g in the F_1. Even though their parent population was obtained from fields subjected to insecticide treatment, the R alleles were probably at a low frequency after rearing under laboratory conditions in the absence of selection.

Our results indicate that caution should be exercised under field conditions to ensure low levels of resistance. Resistance management strategies remain the greatest hope of extending the efficacy of pyrethroids. One tactic is the use of effective synergists, such as formamidines. However, this tactic may enhance the development of resistance, once the resistant alleles occur in high frequency in the population. Since cross-resistance is found among pyrethroids and between toxins of different classes, similar results of enhanced selection of resistance may occur with other synergist: insecticide combinations.

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