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Flufenerim, a Novel Insecticide Acting on Diverse Insect Pests: Biological Mode of Action and Biochemical Aspects†

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ABSTRACT: A new chemical compound was tested for its insecticidal activity against several major insect pests. The compound, called "flufenerim", has a core pyrimidine structure and an unknown mode of action and showed potent activity against the sweet potato whitefly *Bemisia tabaci* (Gennadius), the green peach aphid *Myzus persicae* (Sulzer), and the African cotton leafworm *Spodoptera littoralis* (Boisduval); however, it did not show any activity against two thrips species: western flower thrips *Frankliniella occidentalis* (Pergande) and tobacco thrips *Thrips tabaci* (Lindeman). The compound was relatively potent against the three tested pests and caused mortality rates that reached up to 100% at concentrations under 10 mg of active ingredient (ai) L^{-1}. The action of the compound was very fast, and mortality was observed within 48 h after exposure of the insects to treated leaves. A unique characteristic of this compound is its very short residual activity, which approximates to 4 days after application under laboratory conditions and to 2 days under outdoor conditions for both *B. tabaci* and *S. littoralis*. Although this new compound's mode of action is yet unknown, its rapid and potent action against sap-sucking pests suggests that it acts on a very important target site in the insect body and possibly could be applied very close to harvesting.

KEYWORDS: flufenerim, *Bemisia tabaci*, *Myzus persicae*, biological activity, ovicidal activity, cross-resistance

INTRODUCTION

One of the main drawbacks for using chemical insecticides is their toxicity to the environment, humans, and beneficial organisms. Repeated use of these insecticides is one of the main reasons for developing resistance among many insect pests. In most cases, the dynamics of resistance vary and may well depend on the insecticide, repeated use, the pest, and many other factors. Although many control methods and agents have been developed in recent years, some of which are in favor of the environment and beneficial organisms, including many biological control organisms,[1] organic insecticides,[2] and other physical and horticultural activities,[3] using and developing new chemical insecticides are still major activities for coping with insect pest damages in many agricultural systems. Furthermore, new chemical insecticides, which are based on better knowledge of their target sites, are being developed, and they constitute a major component in preventing and delaying resistance and increasing resistance incidences among insect pests. These newly developed biorational insecticides,[4,5] which are suitable for integrated pest management (IPM), and integrated resistance management (IRM) programs, have been developed in the past 20 years, and the structure of the active molecules in these insecticides is mainly based on targeting specific chemical compounds and essential systems for the normal development of the insect. The most commonly targeted sites are the nervous system, in the case of neonicotinoids,[6] the chitin synthesis system, in the case of the benzoyl phenyl ureas,[7] and the hormonal system, in the case of juvenoids and edysteroids.[8] Despite the potency and the specific activity of the newly developed insecticides, insect pests have developed resistance to all major insecticidal groups developed in recent years.[9] The resistance problems lead in many cases to field failures; however, these failures can be observed only many years after the first resistance incidence, and this depends on the dynamics of the pest populations, the genetics of the resistance developed, and the IRM strategies undertaken.

Developing new insecticides acting on selective targets in insects is of utmost importance for improving our pest management programs. In this paper we report the potency of a newly developed insecticide called flufenerim (Figure 1) against a diversity of important insect pests including the sweetpotato whitefly *Bemisia tabaci*, the green peach aphid *Myzus persicae*, and the African cotton leafworm *Spodoptera littoralis*. We report also preliminary results regarding flufenerim's mode of action in whiteflies.

MATERIALS AND METHODS

Insect Strains. A susceptible strain of *B. tabaci* (biotype B), used in all bioassays, was collected in 1987 from cotton fields and thereafter reared in isolation, with no exposure to any insecticides.[10,11] The whiteflies were reared on cotton seedlings (*Gossypium hirsutum* L. cv. Acala) under standard laboratory conditions of 26 ± 2 °C and a 14:10 h light/dark photoperiod. A susceptible strain of the green peach aphid *M.*

† Part of the Symposium on Pesticide Toxicology in Honor of Professor John Casida. I.I. collaborated with Professor Casida at the University of California Berkeley (1973−1985), where spent two sabbatical leaves, which were followed by two international cooperation projects (Binational Science Foundation (BSF) and Binational Agricultural Research and Development Fund (BARD)). During this period, they evaluated biochemical and biological aspects of novel insecticides such as benzoylphenyl ureas and pyrethroids and published 12 scientific papers and 8 scientific reports.

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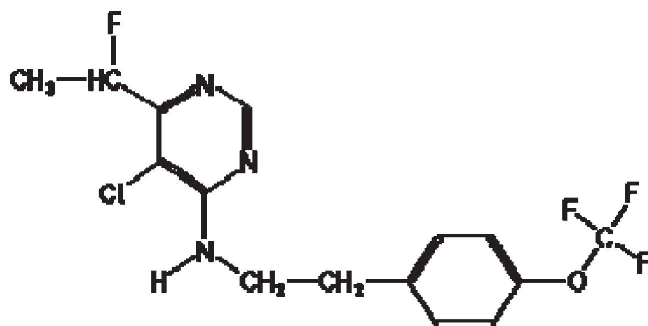


Figure 1. Chemical structure of flufenerim including a pyrimidine residue.

persicae was kept on mustard plants under standard laboratory conditions of 23 ± 2 °C and a 14:10 h light/dark photoperiod without any exposure to insecticides for the past 15 years. A susceptible strain of *S. littoralis* was kept for many years under laboratory conditions on castor bean leaves without any exposure to insecticides.

Flufenerim Solution. Flufenerim, a pyrimidineamine technical material, was provided by Makhteshim Chemical Works Ltd. Ten milligrams of flufenerim was dissolved in 1 mL of acetone and 0.5 mL of Tween 80. Distilled water was then added to 1000 mL, forming a concentration of 100 mg of active ingredient (ai) L^{-1}. This solution was then diluted with water to form the required concentration.

***B. tabaci* Rearing and Bioassays.** Cotton seedlings 20−25 cm tall were dipped in various concentrations of flufenerim, methomyl, or water (control) for 20 s, and then they were dried for 2 h in a fume hood as was previously described for foliar application of insecticides.[12] *B. tabaci* mated females (15−20, 3−5 days old), confined in clip-on-leaf cages,[10] were exposed to treated plants for 48 h under controlled conditions of 25 ± 1 °C and 65% relative humidity (RH). Adult mortality was then determined.

Effect of Flufenerim on *B. tabaci* Oviposition in Choice and Nonchoice Assays. One hundred female adults (3−5 days of age) were exposed separately to two cotton seedlings placed in a rearing box (60 × 40 × 40 cm) for 3 days in a choice experiment. One of the seedlings was sprayed until runoff with 10 mg of ai L^{-1} flufenerim, and the other was untreated. The number of eggs on each plant was determined after 3 days (Table 1). In another nonchoice assay, 100 female adults (3−5 days of age) were exposed to a cotton seedling treated with 10 mg of ai L^{-1} flufenerim in an insect-proof cage, and another 100 females of the same age were exposed to a similar untreated seedling in another cage. The number of eggs in each treatment was determined after 3 days of exposure (Table 1).

***S. littoralis* First-Larvae Mortality Bioassays.** Cotton leaves were treated with various flufenerim concentrations by dipping them in the compound for 20 s and then were air-dried for 2 h in a fume hood.[12] The leaves were exposed to first-instar *S. littoralis* (0−10 h old) for 3 days of feeding. Percent mortality was then determined. Experiments were done with five replicates of 10 larvae each.

***M. persicae* First-Nymph Mortality Bioassays.** Mustard leaves treated with various concentrations of flufenerim using the same methods used for *B. tabaci* and *S. llittoralis*[12] were placed separately in Petri dishes containing agar (to increase moisture). Ten first-instar nymphs were placed in each Petri dish. Mortality was determined after 72 h.

Flufenerim Residual Activity on *B. tabaci* Adults and *S. littoralis* Larvae under Laboratory and Outdoor Conditions. Cotton seedlings were treated with two concentrations of flufenerim, and control bioassays were performed with plants treated with deionized water (as indicated in each experiment under Results and Discussion).

Table 1. *B. tabaci* Oviposition on Treated and Untreated Cotton Seedlings with Flufenerim in Choice and Nonchoice Assays

	choice		nonchoice	
	treated	untreated	treated	untreated
total eggs[a]	1	234	0	530
eggs/female[b]	0.01	2.34	0	5.3

[a] Total eggs for 100 females in 3 days of assay. [b] Total eggs/female in 3 days of assay.

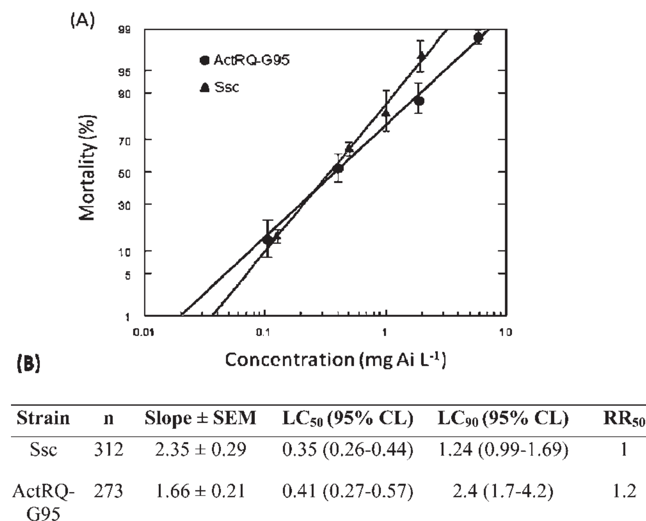
The treated plants were kept under standard laboratory conditions (25 ± 1 °C and a 14:10 h light/dark photoperiod) or under outdoor field conditions (average of 36 °C during the day and 15 °C during the night) and then exposed to *B. tabaci* females confined in clip-on-leaf cages for 48 h or to *S. littoralis* first instars for 72 h. *B. tabaci* or *S. littoralis* mortality was then determined. Each bioassay was performed in five replicates of 15−20 *B. tabaci* adults or 10 *S. littoralis* first instars.

Acetylcholine Esterase (AChE) Activity In Vivo and in Vitro. The effect of flufenerim on the activity of AChE activity was evaluated according to the Ellman method.[13] This assay was determined by using the enzymatic hydrolysis of the substrate analogue acetylthiocholine iodide (ATChI), which is determined colorimetrically at 405 nm by the absorbance of 2-nitro-5-thiobenzoate. Homogenates of 30 whiteflies were prepared in 1 mL of 0.1 M sodium−phosphate buffer, pH 7.2, containing 0.1% (w/v) Triton X-100 in an Eppendorf tube with a plastic pestle. After 20 min of solubilization on ice, the homogenates were centrifuged at 10000*g* and 4 °C for 5 min. The resulting supernatant was used as the enzyme source. One hundred microliter solutions of each ATChI and DTNB in buffer were added to an Eppendorf tube containing 50 μL of enzyme solution prepared in 50 μL of buffer, giving a final concentration of 0.5 mM each in a final volume of 300 μL. AChE activity was assessed at 23 °C. A stock solution of 100 ppm flufenerim was prepared, and subsequent lower dilutions for the AChE assay were prepared and added to the enzyme solution 20 min prior to the addition of the DTNB and ATChI solution. Both In Vivo and in vitro assays were performed to verify the activity of AChE. In the in vitro experiment, flufenerim was directly added to the enzyme solution for 20 min of preincubation, and then the enzyme was added for an additional 22 min with ATChI and DTNB; spectrophotometer measurements were performed at 405 nm. In the In Vivo experiment the same setup was conducted except that flufenerim was applied to cotton leaves and whiteflies were allowed to feed on these leaves for 48 h prior to performance of the AChE enzyme activity test. Flufenerim concentrations used in both the In Vivo and the in vitro experiments were 0.1, 0.25. 0.5, 1, and 2 mg of ai L^{-1}. All experiments were replicated three times.

Data Analysis. Probit analyses of the concentration-dependent mortality data were performed using POLO-PC,20 after correction with Abbott's formula. Failure of 95% confidence limits (CL) to overlap at a particular lethal concentration indicated a significant difference. All results comparing differences in adult or larval mortality were statistically analyzed using a paired *t* test with $\alpha = 0.05$. Error bars in all graphs represent the standard error of the mean (SEM).

RESULTS AND DISCUSSION

Effect of Flufenerim on *B. tabaci*, *S. littoralis*, and *M. persicae* Mortality. Female *B. tabaci* whitefly mortality rates were tested using the bioassays described under Materials and Methods. Figure 2 shows that flufenerim is very potent against whitefly adults, a concentration of 0.8 mg of ai L^{-1} resulting in 97% mortality. The LC_{50} value was 0.35 mg of ai L^{-1}, indicating a very active compound against *B. tabaci*. The potent activity



Strain	n	Slope ± SEM	LC_{50} (95% CL)	LC_{90} (95% CL)	RR_{50}
Ssc	312	2.35 ± 0.29	0.35 (0.26-0.44)	1.24 (0.99-1.69)	1
ActRQ-G95	273	1.66 ± 0.21	0.41 (0.27-0.57)	2.4 (1.7-4.2)	1.2

Figure 2. Log concentration−response curve (on a probit scale) for the effect of flufenerim after foliar application on mortality of a *B. tabaci* susceptible line and on a selection line for thiamethoxam (A). (B) LC_{50} and LC_{90} values of *B. tabaci* susceptible and resistant strain. Ssc, susceptible *B. tabaci* strain to all insecticides; ActRQ-G95, a resistant *B. tabaci* strain to thiamethoxam (commercial name Actara) from the Q biotype after 95 generations of selection in the laboratory conditions.

against *B. tabaci* adults resembles that of the thiamethoxam resistant group (∼800-fold resistance)[14] and suggests that flufenerim reaches its yet unknown target site and leads to rapid mortality, as observed with potent neonicotinoids and other insecticides that act probably on different target sites of the nervous system.

The rapid action of flufenerim was also observed when mortality of first nymphal stages of *M. persicae* (Figure 3) or first larval stage of *S. littoralis* (Figure 4) were tested using the bioassays described under Materials and Methods. Figure 3 shows that flufenerim is very potent against *M. persicae*, a concentration of 1 mg of ai L^{-1} resulting in about 90% mortality. The LC_{50} value was 0.39 mg of ai/L^{-1}, showing a very potent activity under laboratory conditions. The mortality was recorded 48−72 h after treatment for the different insects tested, suggesting a rapid action of the active material. The rapid action and mortality seen with *B. tabaci* suggest that flufenerim acts on a very important system, which leads to rapid death of the insect.

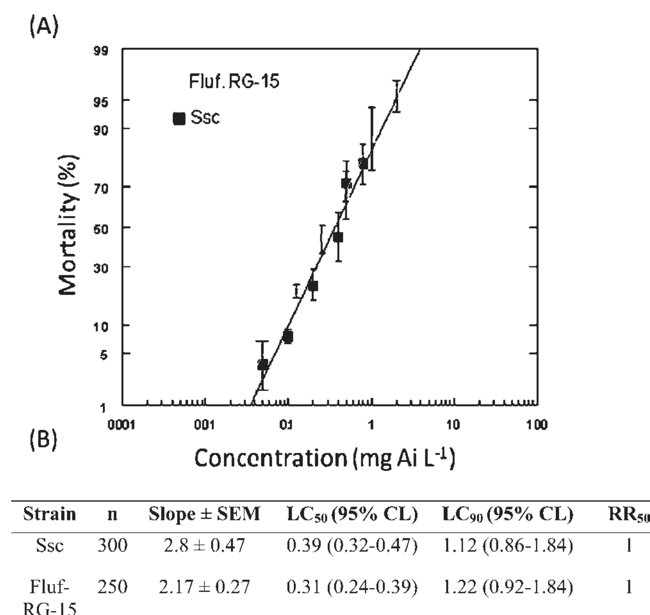
Similar to the effect on *B. tabaci* and *M. persicae*, flufenerim resulted also in a potent effect against the first larval stage of *S. littoralis*. Ninety percent mortality rates were obtained with a concentration of 6.32 mg of ai L^{-1}, and the LC_{50} value was 2.38 mg of ai L^{-1} (Figure 4). These values were somewhat higher than with whiteflies and aphids and suggest a reasonable activity against this pest.

Comparative Toxicity of Flufenerim and Methomyl on *B. tabaci* Adults and *S. littoralis* Larvae. We tested the toxicity of flufenerin against *B. tabaci* and *S. littoralis* and compared this toxicity to the effect of methomyl on the same insects. Methomyl is a carbamate and a commonly used insecticide against several insect pests, many of which are lepidopterans. Methomyl is known for its very short residual activity; thus, it is commonly used a few days before harvesting. For example, the effect of methomyl against fall armyworms in southern Florida in sweet corn was tested, and foliage fed to larvae 3 h after application (day 0) resulted in 50−60% mortality and 5−50% mortality at 1 and 2 days postapplication, suggesting that methomyl degrades very quickly after application, in field conditions.[15] We compared the toxicity of flufenerim and methomyl against *B. tabaci* adults and *S. littoralis* first-instar larvae. The results showed mortality rates of 94% when *B. tabaci* adults were exposed to 0.5 mg of ai L^{-1} flufenerim-treated leaves for 48 h and 90% mortality rates when *S. littoralis* first-instar larvae were exposed to the same concentration for 3 days. However, significantly lower mortality rates of 10 and 6% were obtained when methomyl was tested on both *B. tabaci* and *S. littoralis*, respectively, using the same concentration, suggesting a much lower potency of methomyl compared to flufenerim against both insect pests (Figure 5). Although methomyl belongs to an old class of insecticides relatively toxic to human and beneficial organisms, it is still widely used against many insect pests. The results we obtained here suggest that flufenerim could be a useful substitute for methomyl and other insecticides for use a short time before harvesting.

Effect of Flufenerim on *B. tabaci* Oviposition. We observed a strong effect of flufenerim on *B. tabaci* oviposition in two separate experiments. In the first experiment, whiteflies were released in an insect-proof cage in which untreated and treated cotton seedlings with 10 mg of ai L^{-1} of flufenerim were placed in the same cage. Whiteflies were given 3 days to choose and oviposit on either of the plants. The results showed that whereas 0.01 egg per female was laid on the treated plants, the whiteflies laid 2.34 eggs per female on the untreated plants, suggesting that the whiteflies did not choose and fed on the treated plants (Table 1) and that flufenerim causes a strong suppression of oviposition. In a complementary approach, a nonchoice assay, in which whiteflies were caged with either a treated or an untreated cotton seedling, was performed. Whereas the whiteflies did not lay any eggs on the treated plant, they laid 5.3 eggs per female on the untreated plants, again suggesting a strong oviposition suppression by flufenerim. The results we obtained here indicate that treated plants are not favored by adult *B. tabaci*, and thus fewer whitefly adults lay eggs on the treated plants. One explanation for this result is that adult whiteflies probe the treated plants by short feeding and then decide not to feed on them, and thus no eggs are found on these plants. It is unlikely that flufenerim causes oviposition suppression by a mechanism that affects egg development or the oviposition process in the female itself because very low concentrations of the compound are lethal to whitefly adults; thus, once feeding on treated plants, adult whiteflies are not able to lay eggs because of the high toxicity of the compound.

Flufenerim's Cross-Resistance and Selection for Resistance. To test whether flufenerim may have any cross-resistance with known insecticides, which may hint at its unknown mode of action, we tested its effect on a susceptible strain of *B. tabaci* and on a thiamethoxam (neonicotinoid) resistant strain. This strain exhibits 800-fold resistance to thiamethoxam, compared to the susceptible strains. When this strain was exposed to flufenerim, the LC_{50} value was 0.41 mg of ai L^{-1}, not significantly different from the LC_{50} value of the susceptible strain, which was 0.35 mg of ai L^{-1} (Figure 2). This result suggests no appreciable cross-resistance between flufenerim and thiamethoxam (neonicotinoid); thus, the target site of flufenerim is different from that of thiamethoxam. Despite this result, the target site of flufenerim might still be in the nervous system, however, different from that of neonicotinoids.

To test whether resistance against flufenerim can be obtained in *M. persicae* after gradual exposure to increasing concentrations

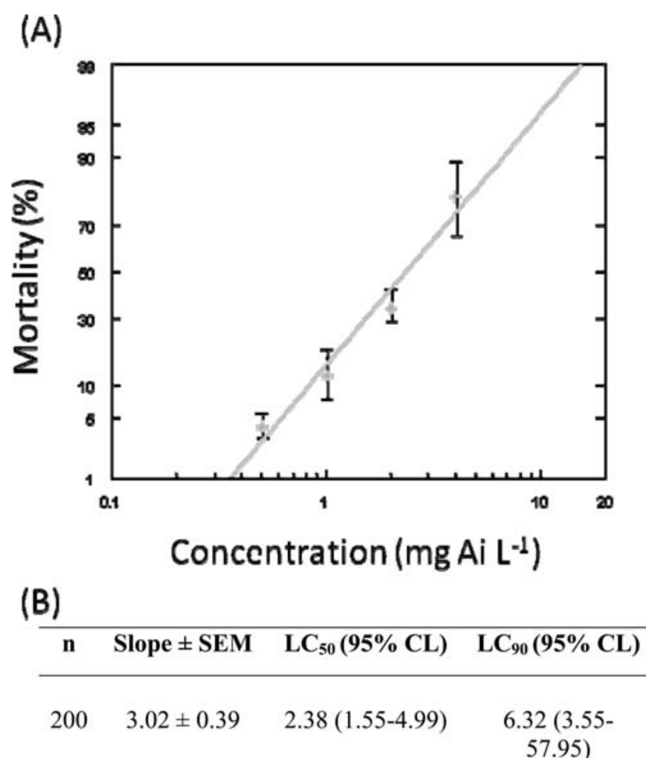


Strain	n	Slope ± SEM	LC_{50} (95% CL)	LC_{90} (95% CL)	RR_{50}
Ssc	300	2.8 ± 0.47	0.39 (0.32-0.47)	1.12 (0.86-1.84)	1
Fluf-RG-15	250	2.17 ± 0.27	0.31 (0.24-0.39)	1.22 (0.92-1.84)	1

Figure 3. (A) Log concentration−response curve (on a probit scale) for the effect of flufenerim after foliar application on *M. persicae* first nymphal stage susceptible line (Ssc) and on a selection line that was exposed to 0.1 mg of ai L^{-1} flufenerim for 15 generations (Fluf-RG-15) and then tested for mortality under different concentrations. (B) LC_{50} and LC_{90} values of flufenerim on *M. persicae* susceptible strain.

of the compound, we maintained a susceptible strain of *M. persicae* on a LC_{10} concentration and selected the individuals that survived this concentration for 15 generations.[14] After this selection, the susceptibility of the aphids remained unchanged (Figure 3). These results suggest that no appreciable resistance could be developed after 15 generations of exposure to sublethal concentrations of flufenerim. We obtained similar results with *B. tabaci* B biotype strain, which was selected under the same conditions and showed that no resistance could be development after more than 30 generations of exposure to flufenerim (Figure 4). These results suggest that under field conditions it is unlikely that resistance against flufenerim among *B. tabaci* and *M. persicae* will be developed within a short period of time. Resistance will be further delayed if flufenerim is used in an IRM program and in alternation with insecticides having different modes of action.

Residual Activity of Flufenerim. The residual activity of flufenerim on *B. tabaci* and *S. littoralis* was determined under both laboratory and outdoor conditions that simulate the field conditions. Under the laboratory conditions two concentrations and an untreated control were tested for each insect. As seen in Figure 6, for both *B. tabaci* and *S. littoralis*, flufenerim showed potent activity up to 4 days that reached up to 80% mortality rates when 20 and 16 mg of ai L^{-1} were used for *B. tabaci* and *S. littoralis*, respectively (Figure 6). After 4 days, the activity of the compound declined rapidly; however, for *S. littoralis*, it showed some activity that reached up to 55% mortality even after 7 days and up to 28% after 14 days (Figure 6). After 7 days, however, the activity was comparable to the untreated control when the compound was applied to *B. tabaci*. Under outdoor conditions, flufenerim showed high activity that reached 90% mortality at 30 mg of ai L^{-1} after 1 day of treatment; however, this activity declined rapidly to about 30% mortality after 2 days of treatment (Figure 6). The activity was higher against *S. littoralis* after 2 days



n	Slope ± SEM	LC_{50} (95% CL)	LC_{90} (95% CL)
200	3.02 ± 0.39	2.38 (1.55-4.99)	6.32 (3.55-57.95)

Figure 4. (A) Log concentration−response curve (on a probit scale) for the effect of flufenerim after foliar application on mortality of *S. littoralis* first larval stage susceptible line. (B) LC_{50} and LC_{90} values of flufenerim on *S. littoralis* susceptible line.

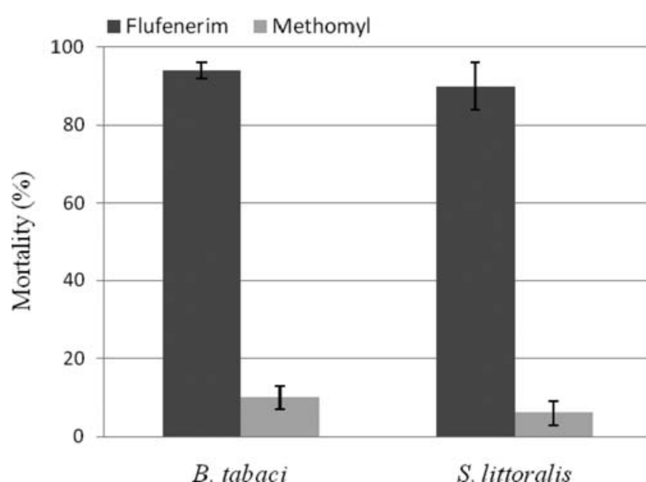


Figure 5. Mortality of *B. tabaci* and *S. littoralis* after 0.5 mg of ai L^{-1} felufenerim and methomyl application, in a leaf dip assay (see Materials and Methods for experiment details).

of treatment and reached >80% mortality with 16 mg of ai L^{-1}. This concentration is half the concentration used with *B. tabaci*, and the mortality rates were much higher. These results indicate that flufenerim has very strong activity 2 days after treatment, and the activity then declines rapidly, under outdoor conditions. The results also show that the compound reaches its target site more quickly in *S. littoralis* than in *B. tabaci*; thus, lower concentrations are needed for higher mortality rates. The reason for the short

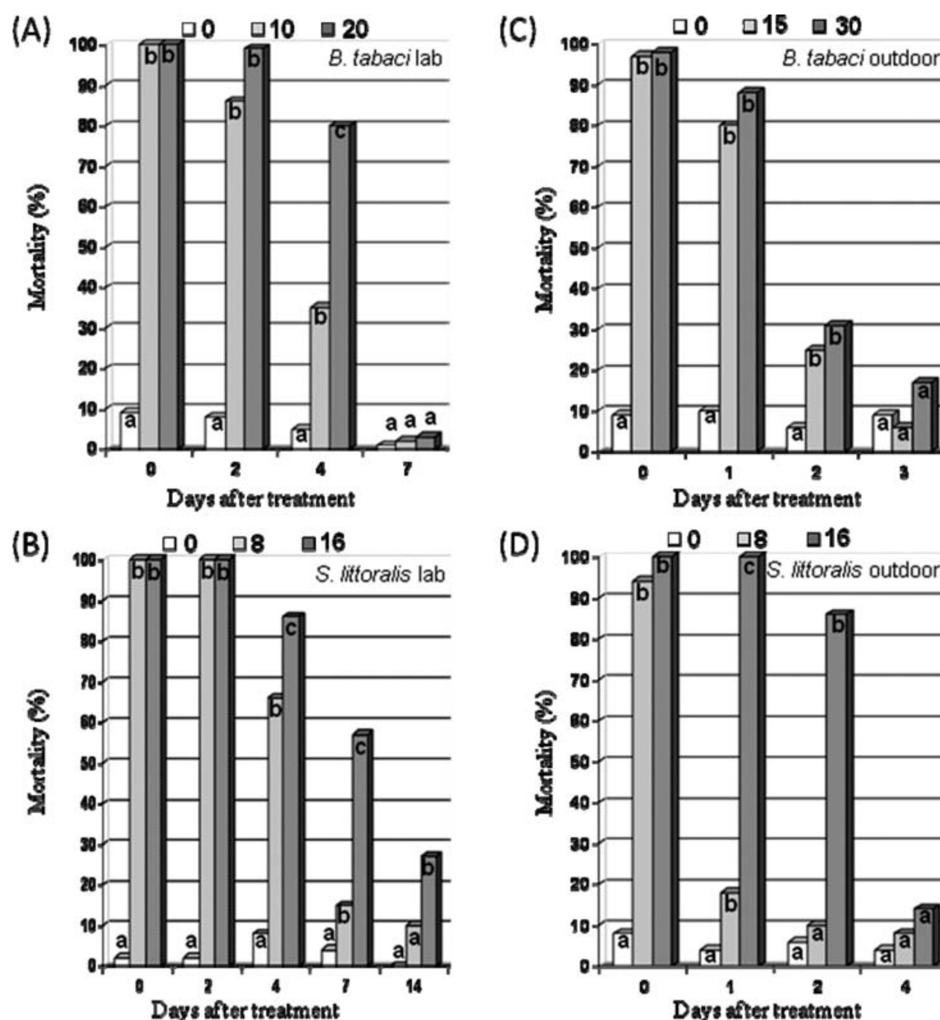


Figure 6. Residual activity of flufenerim on *B. tabaci* adults and *S. littoralis* first larval stage, expressed in percent mortality, under laboratory and outdoor conditions. The activity was tested according to the methods described in the text; two concentrations and untreated control were examined. Columns labeled by the same letter do not differ significantly at $P = 0.05$ in each tested concentration. The conditions for each experiment (outdoor or lab) and the concentrations tested (in mg of ai L^{-1}) are indicated at the top of each graph.

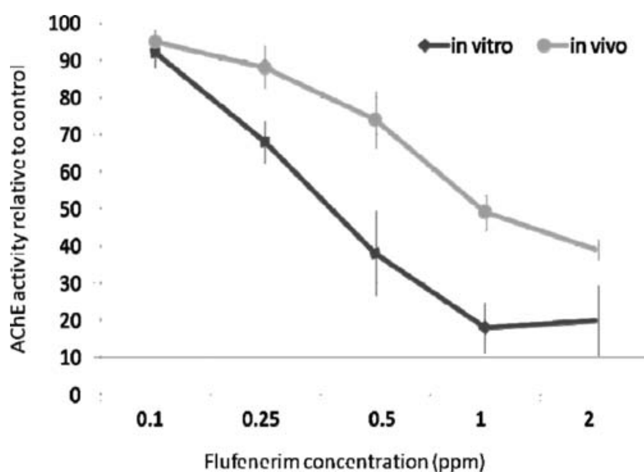


Figure 7. Effect of flufenerim In Vivo and in vitro on the activity of AChE in whiteflies.

residual activity of the compound might be the formulation that we used in our study. This formulation seems to lack long-term stability, which could be rectified by the addition of stabilizers in the final commercialized formulation. The short residual activity can be an important advantage for this new insecticide, especially if the active compound is rapidly degraded and thus could be applied with relatively short pre- and postharvest intervals in fresh herbs and vegetables.

Mode of Action of Flufenerim. Because the mode of action of flufenerim is not known, we started to screen possible target sites that might be affected after flufenerim application. A promising result was obtained when the activity of the AChE was measured. Figure 7 shows that in both the in vitro and In Vivo experiments, flufenerim caused significant reduction in the activity of AChE. Reduced activity of AChE may result in an increase of the level of the neurotransmitter ACh, affecting thereby the nervous system of the insect. The results we obtained here do not necessarily indicate a direct effect of flufenerim on AChE, and the reduced activity of the enzyme might be an indirect effect following the general toxicity of flufenerim on other biochemical systems in the insect, which are directly or indirectly linked to AChE. Further biochemical and genetic assays are in progress to elucidate more in-depth the flufenerim mode of action.

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