# INSECTICIDE RESISTANCE MECHANISMS AND THEIR MANAGEMENT IN *HELICOVERPA ARMIGERA* (HÜBNER) A REVIEW

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## ABSTRACT

The development of insecticide resistance management strategies requires a comprehensive knowledge of mechanisms by which insects evolve insecticide resistance. *Helicoverpa armigera* has evolved resistance to almost all chemical groups directed towards it worldwide including organophosphates, carbamates, and pyrethroids. The judicious use of chemicals can greatly help to preserve the usable life span of insecticides. This requires a knowledge of mechanisms of resistance which can prevent un-necessary use of a pesticides to which insects had already evolved or can evolve resistance. The literature review on insecticide resistance, mechanisms and resistance management will help design robust and effective control strategies against *H. armigera*. This purpose gives such a review.

**KEYWORDS:** *Helicoverpa armigera;* insecticides; pesticide resistance; Pakistan.

## INTRODUCTION

*H. armigera* has received a great attention due to an important pest of a number of cash crops. The mainstay for *H. armigera* control has been the use of chemicals. Almost 30 percent of all pesticides used worldwide are directed against *H. armigera* which resulted into high levels of resistance in this pest. Insecticide resistance in *H. armigera* is widespread problem in Pakistan, China, India, Australia, Thailand, and Indonesia (2, 3, 5-7, 9, 13, 14, 16, 31-33, 38, 41).

Resistance to an insecticide may be defined as “the ability of an insect population to survive a dose of poison that is lethal to the majority of individuals in a normal population of the same species” (12). Resistance may also be defined as” when the failure of an insecticide (applied at its normal rate) to control a population of insects is due to a genetically transmitted capacity to tolerate more insecticide than normal, then insecticide resistance is said to have occurred” (36). The evolution of resistance to a particular insecticide by *Helicoverpa / Heliothis* resulted in high levels of cross-resistance to other insecticides within the same class of insecticide (1, 71). Studies on pyrethroid resistance strains during 1985 and 1986 demonstrated varying levels of resistance to organophosphates and carbamates in

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pyrethroid-resistant *H. virescens* (22). Leonard *et. al.* (53) reported a broad spectrum cross-resistance to permethrin, cypermethrin, fluvalinate, bipenthrin, esfenvalerate, and deltamethrin in *H. virescens* while cross-resistance to lambda = cyhalothrin was consistently low.

*H. armigera* has been subjected to intense selection pressure with a range of pesticides and thus, developed significant levels of resistance to insecticides applied for its control.

**Resistance to organophosphates(OPs)**

*H. armigera* is generally considered to be relatively susceptible to OP insecticides. However, the highest levels of endosulfan resistance (>50-fold) were recorded in 1974 following several years of endosulfan use in the field. The highest level of resistance recorded after 1984 was 23-fold and selection with endosulfan increased this to 163-fold. Following an insecticide resistance management strategy from 1986 to 1990, level of resistance declined in Australia (41).

High levels of resistance to monocrotophos and low level of resistance to chlorpyriphos and profenophos were reported from Pakistan (4). In another study, low to moderate levels of resistance to OPs in *H. armigera* was documented from India, Pakistan and Thailand (15, 60).

**Resistance to carbamates**

Wu *et al.* (89, 90) reported significant level of resistance to methomyl in *H. armigera* from Shandong province (China). Resistance to methomyl and thiodicarb in *H. armigera* from New South Wales (Australia) was documented in 1986 and 1993, respectively (39, 44). A low-level resistance to thiodicarb was documented from Pakistan (4). However, a high level of resistance in *H. armigera* populations from cotton growing areas of Andhra Pradesh, India has been reported (14, 15). Resistance in *H. virescens* against methomyl is due to a single autosomal incompletely dominant gene (75).

**Resistance to pyrethroids**

The earlier resistance to DDT in *H. armigera* and *H. virescens* should have warned us to the potential for pyrethroid resistance as the same mechanism confers resistance to both DDT and pyrethroids (64, 70, 81). *Heliothis* control difficulties with pyrethroids were reported for the first time from Imperial

Valley, California during 1978 (59, 85). Resistance to pyrethroids was first detected in *H. armigera* in Australia in January 1983 in the irrigated area of Emerald in the Central Highlands of Queensland. Significant yield losses of cotton, soybeans and sorghum were documented which was confirmed in subsequent laboratory tests. Low to moderate levels of resistance was found throughout the eastern Australia (mainly NSW and Queensland) (26, 31, 43).

Mortality of third instar larvae of *H. virescens* was reduced to 40-50 percent compared with a susceptible strain from Mississippi (54). Similar results were reported from the Imperial Valley of California in 1979, 1980, and 1981 (58).

When populations of *H. armigera* from Sweet Corn in Victoria, Australia, were tested for resistance frequencies to fenvalerate using a diagnostic dose in an adult vial test, they were found higher than those in the cotton growing regions of northern Australia, where resistance to pyrethroids had been documented in 1983. Adults were much more resistant to fenvalerate than larvae. However, no significant differences in the development times and pupal weights of resistant and susceptible *H. armigera* were detected on corn (34). *kdr* resistance to fenvalerate is inherited in *H. armigera* as an autosomal and incompletely recessive trait (76).

Resistance to delta-methrin and cypermethrin in *H. armigera* was reported from West Africa (56). In follow up studies it was further documented that oxidases, which provided resistance by degradation of pyrethroids in resistant individuals, also activate triazophos in its toxic oxon form resulting in a negative cross-resistance (57). Pyrethroid resistance in *H. armigera* in Spain was not as high or widespread compared with other area of the world (84).

**Mechanisms of resistance to insecticides in *H. armigera***

The development of resistance management strategies requires a comprehensive knowledge of mechanisms by which the insect evolves insecticide resistance (47). The evolution of resistance by an insect to an insecticide may involve several mechanisms. When an insect comes in contact with the insecticide resistance may first evolve by reducing the penetration of insecticide through the cuticle. If the insecticide enters the organism, modifications of target-sites or metabolism may result in target-site or metabolic resistance (involving detoxification). In some cases, the insecticide may be excreted from the insect body. Moreover, some insects may become functionally resistant by avoiding the insecticide e.g., behavioral resistance.

Three mechanisms of resistance against pyrethroids in *H. armigera* were found at the onset of pyrethroid resistance in 1983 in Australia, namely, reduced penetration, reduced nerve sensitivity and another factor that was synergisable by Piperonyl Butaoxide (Pbo) (37).

**Mechanisms of resistance to organophosphates (OPs)**

*(I). Mechanisms involving target-site resistance (insensitive acetylcholinesterase) to OPs*

Acetylcholine enzyme (AchEs) acts by hydrolyzing excess neurotransmitter (acetylcholine) in some synapses of the nervous system. OP insecticides act by blocking AchE (65) and has been well studied in a number of insects including *H. virescens* and *H. armigera* (20, 45, 51). Point mutations are considered to be the main cause of reduced sensitivity of AchE to OPs (63). The biochemical analysis of resistance in laboratory selected monocrotophos resistant cotton bollworm (RR: 200) and the susceptible strain revealed that insensitive acetylcholinesterase was involved (73).

*(II). Mechanisms involving metabolic resistance to OPs*

Metabolic resistance can significantly decrease the susceptibility of insects to insecticides. Metabolic resistance to OPs in *Heliothis/ Helicoverpa* is believed to be due to enhanced metabolism of insecticides that decreases the attainment of the effective amount of insecticides that can kill insects. Three major detoxifying enzymes are associated with insecticide resistance (21, 67): (a) cytochrome P450 monooxygenases (CYPs), (b) glutathione-*S*-transferases (GSTs), (c) esterases (ESTs). At least one of these stated enzymes in insects is involved in detoxification of insecticides. Enhanced detoxification is usually involved in the evolution of resistance.

Detoxifying CYPs are a superfamily of important enzymes that catalyze multiple oxidative reaction and are capable of metabolizing a variety of endogenous and exogenous substrates. Increased CYP activities were expressed in insecticide-resistant *H. virescens* (91). P450 monooxygenases were involed in the metabolism of OPs in insecticides (21, 72, 88).

GSTs are a family of enzymes that catalyze the conjunction of glutathione with electrophilic substrates such as insecticides (91). Resistance to OPs is considered to be due to metabolism of these compounds by glutathione-*S*-transferases (88). Harold and Ottea (49) reported glutathion-*S*-transferases involved in resistance to profenofos in *H. virescens.*

Esterases are a large group of proteins (25) that share a highly catalytic domain characterized by an a/b hydrolase fold in three-dimensional structures (66). Esterase-mediated metabolic resistance is widespread and has been detected in almost all pests and against all classes of insecticides containing an ester moiety. Moreover, Harold and Ottea (49) also reported high frequencies of profenofos resistance correlated with GST in larvae of *H. virescens*. Esterases are usually named according to the substrates they hydrolyze, such as phosphorotriester hydrolase (PTEH, EC 3.1.1.2), AchE, or amidases mid carboxylesterases. Increased esterase activity toward model (non-insecticidal) substrates is associated with resistance to OP insecticides (91).

**Mechanisms of resistance to cyclodienes**

*Mechanisms involving target-site resistance (altered GABA receptor) to cyclodienes*

The chloride channel gated by the inhibitory neurotransmitter lambda-aminobutyric acid (GABA) is the major target site for a number of insecticides including cyclodienes (α-endosulfan), fipronil, lindane (18, 23), the spinosyn (86) and the avermectins (17). Reduced sensitivity of GABA-gated chloride channels as a resistance mechanism has been studied extensively only in cyclodiene (such as endosulfan)-resistant insects (19). Target-site insensitivity to cylcodiene action was inferred in adult *H. virescens* on the basis of highly correlated toxicities of dieldrin and endosulfan (51).

**Mechanisms of resistance to Carbamates**

*(i) Mechanisms involving target-site resistance (insensitive acetylcholinesterase) to carbamates*

Insensitive acetylcholinesterase was a major mechanism of resistance to methomyl, carbaryl, thiodicarb, and pyrethroid-resistant populations of *H. virescens* (91). Similarly, resistance to thiodicarb in Australian *H. armigera* population was due to a form of acetylcholinesterase that is insensitive to both thiodicarb and methomy (60). Target site resistance to carbamate is similar to organophosphate.

*(ii). Mechanisms involving metabolic resistance to carbamates*

Esterase-mediated metabolic resistance is widespread and has been detected in almost all pests and all classes of insecticides containing an ester moiety. Enhanced esterase and monooxygenase activity have been shown to be mechanisms of resistance to carbamates. Zhao *et al.* (91) reported increased esterase activities that were associated with resistance to carbamates.

**Mechanisms of resistance to Pyrethroids**

*(i) Mechanisms involving target-site resistance (nerve insensitivity) to pyrethroids*

This mechanism of resistance is not specifically defined. However, it may involve a reduction in the number of sodium channels (69, 76), changes in the fluidity of nerve membranes (24) or changes in the voltage-sensitive sodium channels that alter the binding characteristics for insecticides (77). The main targets for pyrethroids and DDT are voltage-sensitive sodium channels (11, 80). Reduced sensitivity of sodium channels to pyrethroids is expressed in pyrethroid-resistant *H. virescens* (61, 68). Ahmad *et. al.* (8) reported nerve insensitivity in a pyrethroid and DDT-resistant Thai strain of *H. armigera*. Similarly, West and McCaffery (87) documented high levels of nerve insensitivity to pyrethroids and DDT in Indian populations *H. armigera*.

*(ii). Mechanisms involving metabolic resistance to pyrethroids*

The major pyrethroid resistance mechanism in both larvae and adults of *H. armigera* involved oxidative metabolic detoxification via a monooxygenase system (33, 56). In addition, a low level PbO insensitive resistance (nerve insensitivity + penetration resistance factor) was also present (33). Resistance to pyrethroids mostly involved oxidation by the micosomal P450-dependent monooxygenases (or mixed function oxidases) and hydrolysis by esterases (60). However, glutathione-*S*-transferases do not seem to be involved in resistance to pyrethroids. Studies conducted on mechanisms of resistance to pyrethroids suggest that both oxidative and hydrolytic activity is involved in resistance to pyrethroids in *Heliothis/ Helicoverpa* spp.

Three mechanisms of resistance were reported with the first report of resistance to synthetic pyrethroids in Australia (35, 42, 43). A strong nerve insensitivity (super-*kdr*) and a penetration resistance (pen) were present alongwith a third factor overcome by PBO (Pbo) (35). Ahmad and McCaffery (10) documented a mechanism of reduced cuticular penetration to trans-cypermethrin in resistant strain of *H. armigera* from Thailand. Similar results

of reduced penetration of esfenvalerate were reported in resistant Australian *H. armigera* (40).

The ability of PBO to completely suppress resistance to pyrethroids in *H. armigera* population homozygous for a metabolic detoxification mechanism was presumably the evidence of the involvement of P450-mediated metabolic resistance (33, 52). Martin *et al.* (56, 57) reported *H. armigera* population evolved resistance to pyrethroids in West Africa via the overproduction of cytochrome P450 (oxidases) that increased pyrethroid metabolism.

**Insecticide resistance management strategies**

*H. armigera* was not a serious threat to cotton in Pakistan until late 1980s. However, indiscriminate use of chemicals on *H. armigera* particularly on cotton led to resistance to almost all classes of chemicals. *H. armigera* is a multi-resistant insect species, that is, it can express more than one resistance mechanism to a particular insecticide group. Insecticides resistance management strategies can vary from region to region and, may change in a pest population over time. The main emphases of any resistance management program are directed to (a) prevent resistance evolution in target insect pests, (b) slow down the rate of resistance evolution, and (c) conserve susceptibility in resistant populations.

The process of evolution of resistance in bollworms including *Heliothis/Helicoverpa* could be delayed only with the judicious use of insecticides in concert with non-chemical control tactics (74, 78; 79, 82). Several insecticide resistance management options are available for different resistance mechanisms in *H. armigera*:

*(i). Resistance management strategies for organophosphates*

Organophosphates have long been used for *H. armigera* control as an effective larvicidal chemical. The use of OPs increased rapidly with an increase in resistance to pyrethroids, endosulfan and carbamates. Low level of resistance to OPs has been reported from Australia (45), however, Ahmad *et al.* (5) reported moderate to high levels of resistance to OPs in Pakistan. There was not a major control failure of OPs reported from the field populations (45). Therefore, OPs should be used judiciously in rotation with pyrethroids, and other new chemistries. In multi-pest situations, such as on cotton crop in Pakistan, there is tendency to use OPs as mixtures with pyrethroids. Mixtures (unless mixing pesticides do not have synergistic/ potentiating properties) may aggravate the resistance problem by resulting in

to multiple resistance. Thus, mixtures should only be used as a last resort if there are no alternatives available.

*(ii). Resistance management strategies for carbamates*

There is a low level resistance to carbamates in Pakistani populations of *H. armigera* which is an encouraging news for the farmers. Therefore, it becomes important to preserve effectiveness of carbamates against *H. armigera*. The best-bet strategy to conserve susceptibility to carbamates such as Thiodicarb, is to limit its use to a single application, alone or in mixture per season. Thiodicarb is one of a few insecticides that can still provide an effective control of *H. armigera* with a long residual action. Since there are no reports of cross-resistance to pyrethroids or OPs (3), thiodicarb can be alternated with these two chemical groups. Moreover, to avoid the overuse of Thiodicarb, non-chemical IPM practices based on non-chemical, rotating this chemical with new chemistries and timely spray of carbamates keeping in view the early instars may help preserving its efficacy (6).

*(iii). Resistance management strategies for pyrethroids*

In response to a high level of pyrethroid resistance in Australia, an insecticide resistance management strategy was implemented which restricted the use of pyrethroids to only one of the 4-5 generations of *H. armigera* produced per year. This strategy was a conservative one that needed little information about the population biology of *H. armigera*. This strategy is based on factors that influence the evolution of resistance (30). A similar strategy for managing insecticide resistance in *H. armigera* was introduced in Israel. The main objectives of this strategy were to restrict the use of pyrethroids and endosulfan to short period during cotton season to delay the onset of resistance and to preserve beneficial control agents. The second goal of the strategy was to prolong the lifespan of new insecticides by optimizing their use through monitoring field pest tolerance (50).
Tang (83) suggested that the use of pyrethroids against *H. armigera* should be restricted for a given period of the year. It was further recommended to use insecticides with no history of cross-resistance or rotation with insect growth regulators and *Bt*.

In the Mfo (mixed function oxidases) strain, the major shift in resistance phenotype (33-fold resistance) was due to a single major gene with incomplete dominance (27, 28).

Pbo being an effective esterase inhibitor and a synergist of pyrethroids, is believed to facilitate pyrethroid penetration through the cuticle of resistant *H. armigera* (32, 40, 46). Pbo synergised the effects of synthetic pyrethroid, fenvalerate 1000-fold and can therefore, eliminate resistance entirely (28). Moreover, non-toxic doses of organophosphate as synergists for pyrethroids also showed excellent levels of pyrethroid synergisms against resistant *H. armigera* (46).

**Table 1. Possible mechanisms of resistance to the major insecticide groups**

| Mechanism (s) | Chemical group to which resistance evolves | References |
|---|---|---|
| Acetylcholinesterases | Organophosphates<br>Carbamate | (45, 73) |
| GABA/ Chloride channel | Cyclodiene<br>Fipronil<br>Spinosyn,<br>Avermectin | (17, 18, 23, 86) |
| Mixed function oxidases | Carbamates<br>Organophosphates<br>Pyrethroids | (62) |
| Glutathion-*S*-transferases (including DDT dehydrochlorinases) | DDT<br>Organophosphate | (21, 67) |
| carboxylesterases | Carbamates<br>Pyrethroids<br>Organophosphate | (62, 91) |
| Sodium ion channel | DDT<br>Pyrethroids | (10, 76, 80) |

The increase in resistance alleles could be countered by dilution as a result of immigration of susceptible moths from non-sprayed cultivated or non-cultivated host plants which act as natural refuge (29, 48, 55).

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