Prospects and status for development of novel chemicals for IPM in cotton

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Abstract
Increasing concerns regarding food and feed safety, quality of groundwater and surface water, and resistance of insects to chemical pesticides, have provided added impetus to the development of integrated pest management (IPM) systems for cotton. The chemical industry is cognizant of these concerns and is directing increasing research resources to develop more selective, IPM-compatible pesticides through more rational approaches than those used previously. This paper discusses the status of current chemical control practices in cotton and describes several promising candidate control agents that could be compatible with IPM. The developing use of semiochemicals for insect control is also briefly discussed in terms of the potential of the IPM approach to reduce the application volume and frequency of conventional insecticides.

Keywords
IPM; new pesticides; natural products; pheromones; cotton

Introduction

Corn, soybeans, cotton and cereals constitute the most important crop plants in the United States. The Economic Research Service (ERS) of the US Department of Agriculture (USDA) forecast that approximately $5.5 \times 10^6$ hectares (ha) would be planted to cotton in the United States in 1990 (ERS, 1990).

In 1990 in the United States, 30% of insecticides was applied on cotton (ERS, 1990), namely, 1.5 kg a.i. ha$^{-1}$. Synthetic pyrethroids (SPs) constitute about one-half of the volume of all insecticides applied on cotton, and their application rates are low, ranging from 0.02 to 0.22 kg ha$^{-1}$ (Menn, King and Coleman, 1989). This high use of SPs on cotton assumes even greater significance, considering that in some parts of the Cotton Belt, especially in the Southeast, they may be applied as many as ten times per growing season.

The primary targets of chemical control in order of importance are the boll weevil (*Anthonomus grandis grandis* Boheman) and the 'Heliothis' complex, which comprises the tobacco budworm (*Heliothis virescens* (Fabricius)) and the bollworm (*Helicoverpa (Heliothis) zea* (Boddie)).

Despite intensive efforts in the integrated pest management (IPM) arena (Frisbie, 1985), heavy pesticide use in cotton still continues. Perhaps the greatest difficulty in developing IPM strategies that incorporate the use of conventional chemicals is rooted in the great diversity of cotton insect pests. These include not only the boll weevil and Heliothis complex but also intermediary and more regional pest species, such as the sweet potato whitefly (*Bemisia tabaci* (Gennadius)), Lygus species, including the tarnished plant bug (*Lygus lineolaris* (Palisot de Beauvois)), the pink bollworm (*Pectinophora gossypiella* (Saunders)), and spider mites. Complicating IPM efforts is the ability of the Heliothis complex to migrate long distances and the invasion of pest species from other croppings. The chemical industry, the major discoverer and developer of chemical insecticides, has long recognized cotton as a primary target for field-testing new insecticides; in fact, many insecticides in the United States were first registered for use on cotton, owing to the diversity of insect pests and relative ease of registration.

Current chemical control in cotton

An estimated 35 chemical insecticides are in current use to control various pests of cotton in the United States (Suguiyama and Osteen, 1988). The insecticides in greatest use, based on 1988 data, are: parathion (22.7%), methyl parathion (10.7%), azinphos-methyl (4.6%), dicrotophos (6.4%), acephate (2.6%) and SPs (21%), accounting for 68% of all insecticides applied on cotton (C. Giedraitis, personal communication, 1990).

Although the organophosphorus esters (OPs) are still the primary chemical weapons against the boll weevil and sucking insects, the SPs have in recent years become the major weapons against the Heliothis complex. The SPs appeared to be the ideal insecticides: effective at low rates; fairly non-persistent in the environment, and low in cost, based on use pattern. However, as early as 1985–1986, control failures with SPs were reported in Texas (Bull and Menn, 1990). It appears now that genes for SP resistance are present in populations of the Heliothis complex in the United States, and it is likely that resistance to those insecticides will continue to build up as a consequence of intensive use pattern (Bull and Menn, 1990). It appears now that genes for SP resistance are present in populations of the Heliothis complex in the United States, and it is likely that resistance to those insecticides will continue to build up as a consequence of intensive use pattern (Bull and Menn, 1990). Although the resistance phenomenon portends economic difficulties for cotton production, it may in the long term catalyse the development of biological control agents and more selective chemical insecticides that can be used in IPM systems for cotton.
Table 1. Primary stages involved in discovery and development of a pesticide

<table>
<thead>
<tr>
<th>Activity</th>
<th>Time frame (months)</th>
</tr>
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<tbody>
<tr>
<td>Synthesis and initial bioscreen</td>
<td>18</td>
</tr>
<tr>
<td>Advanced bioevaluation</td>
<td>24</td>
</tr>
<tr>
<td>Development</td>
<td>40</td>
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<td>Field trials</td>
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<td>Formulations</td>
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<tr>
<td>Metabolism and environmental studies</td>
<td></td>
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<tr>
<td>Toxicology (acute and chronic)</td>
<td></td>
</tr>
<tr>
<td>Test marketing and sales</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>96</td>
</tr>
</tbody>
</table>

Discovery of new chemical insecticides

Discovery and successful market introduction of a synthetic chemical pesticide has been likened to the development and successful launching of a spaceship; both projects are highly creative, interdisciplinary, costly, and unpredictable. In the case of the pesticide, more competition and time are involved, owing to the uncertainties of the registration process.

Details of the research and development process to bring a new pesticide to market were extensively reviewed in numerous articles, including those by Braunholz (1981), Menn (1983) and Menn and Henrick (1985). Table 1 shows the four stages for producing and bringing one successful candidate to market. It has been estimated that costs of developing a new pesticide have increased from USS21 x 10^6 to USS50 x 10^6 and the success rate has changed from 1 in 20000 to 1 in 40 000 (Braunholz, 1981; Menn and Henrick, 1981; Menn, 1983; R. F. Flattum, personal communication, 1990).

Owing to societal, regulatory and environmental considerations and pressures, the industry has been emphasizing development of more selective insecticides that harmonize control with relative safety to beneficial insects and other non-target organisms. Because of these constraints, very few insecticides have appeared on the market in recent years: in fact, in 1990, there was not a single new insecticide undergoing registration review for cotton in the United States.

A cardinal requirement for continued use of existing insecticides or introduction of new compounds is that their direct and/or indirect effect on beneficial insects and mites be determined (Croft and Brown, 1975; King, 1986; Croft, 1990; Elzen and King, 1991).

Laboratory and field evaluations are important for providing information on the overt and latent capability of insecticides to reduce populations of beneficial insects and mites. Metabolic studies are also important, because they can provide information for predicting the potential hazard of an insecticide and/or its metabolites to these beneficial organisms. Krieger, Feeny and Wilkinson (1971) have shown that certain beneficial insects have more limited detoxifying capacity than their lepidopterous hosts. The latter have evolved a greater variety of oxidative, reductive and hydrolytic enzymes capable of processing a much broader array of plant constituents than their parasites and/or predators.

Generally, OP insecticides have taken a heavier toll of beneficial insects than SPs and formamidines. Beneficial insects are relatively spared if SPs are used in late season only, as beneficials occur in reduced numbers in the late season (Croft and Whalon, 1982; Elzen and King, 1991). Beneficials are of prime importance in the early season, when host populations are still relatively low. Chlor-dimeform (Galecron) was a particularly useful insecticide and miticide in IPM programmes because it is a behaviour-modifying agent that has an indirect ovicidal and larvicidal action (Hollingworth and Lund, 1982); however, chlor-dimeform was recently deregistered in the United States. A related compound, amitraz (Mitac, Ovasyn), may possibly replace chlor-dimeform in some applications. Amitraz is active against a broad range of spider mites, and against the whitefly [Bemisia tabaci (Genn.)], it is a first-instar larvicidal and ovicidal against the Heliothis complex (Peregrine, 1989).

Approaches to discovery of selectivity

Most synthetic chemical pesticides were discovered through empirical synthesis coupled with broad-spectrum short-term-exposure screening tests on target insects. Screening tests that include non-target beneficial insects and mites are conducted only sparingly in industry, and most of the useful information on the response of beneficials to new insecticides has come from universities and the USDA, Agricultural Research Service (ARS). An example of such information was reported by Plapp and Bull (1978), among others, who showed that SPs were reasonably well tolerated by an important predator of the Heliothis complex in cotton. This information was most helpful in developing a mid-season to late-season IPM strategy for applying SPs on cotton.

The growing emphasis on selective insect control that is compatible with IPM practices has had a marked impact on the chemical industry: it has strongly influenced research thinking and redirection of resources. As a result, more directed approaches for discovering selective insecticides are being used. These approaches include (1) the synthesis of highly active analogues of biologically active compounds, the direction of the synthesis being guided by the results of quantitative structure–activity relationship (QSAR) analyses, (2) the discovery of natural-product insecticides and also the synthesis of their highly active analogues, and (3) use of a biorational approach to design and synthesize insecticides. These approaches have been described in detail by Morrod (1981) and Magee, Kohn and Menn (1985).

Directed synthesis

Once a highly active new class of insecticides has appeared in the patent literature, intensive efforts usually follow in competing industrial laboratories to synthesize analogues with even greater bioactivity through directed research. A
pertinent example is the synthesis of selective chitin-synthesis inhibitors that are analogues of diflubenzuron and other benzoylphenylureas (Verloop and Ferrell, 1977) (Figure 1).

Diflubenzuron, an insect growth regulator that interferes with chitin biosynthesis in insects, was introduced by Duphar B. V. in 1973. It eventually found a practical niche in cotton production by controlling the boll weevil and armyworms. In subsequent years, thousands of analogues were synthesized in industry with varying degrees of efficacy and selectivity. In the 1980s, a new compound that retains the benzoylphenylurea core was introduced by Duphar B. V. under the name andalin (PH 70-23) (Figure 1). This compound is also targeted as a cotton insecticide and miticide that is compatible with IPM; it is applied at the rate of 40–50 g a.i. ha⁻¹.

Another example of directed synthesis involves a new thiourea-derived insecticide and miticide that is active against hemipterous insects in cotton and compatible with IPM. This compound, diafenthiuron (Figure 2), was introduced by Ciba-Geigy AG. Interestingly, this compound exerts its action through photoconversion in sunlight and metabolism in insects and mites to the more reactive carbodiimide (DFCD). DFCD is more toxic than the parent compound to bulb mites [Rhizoglyphus echinopus (Fumouze and Robin)] and two-spotted spider mites (Tetranychus urticae Koch). Kadir and Knowles (1990) reported that DFCD was a potent agonist of octopamine-activated adenylate cyclase: thus, they concluded that DFCD is an octopamine agonist.

Undoubtedly, other new candidate insecticides are being tested world wide on various crops, including cotton. However, if Sps are excluded, only very few representatives of novel classes of insecticides have been described. The paucity in new insecticide discovery is probably attributable to increased confidentiality because of patent competition and difficulty in discovering selective, cost-effective insecticides that harmonize with IPM.

**Natural products**

Natural products derived primarily from plants and microorganisms have provided a vast storehouse of bioactive substances. However, only a few of these have been developed as agricultural insecticides to date.

**Synthetic pyrethroids (SPs)**

Currently, the SPs are the premier cotton insecticide in the world. In 1987, the value of the agricultural SP market reached US$1.5 × 10⁹, which represented ~25% of the global sales of insecticides (Morton and Collins, 1989). In the United States, the SPs are the dominant group of insecticides registered and used against lepidopterous larvae in cotton, primarily to control the Heliothis complex. Currently, ten SPs [bifenthrin, cyfluthrin, cypermethrin, esfenvalerate, fenvalerate, flucythrinate, karate (lambda-cyhalothrin), permethrin, and tralomethrin] are recommended for application in mid-season to late season. If used according to this schedule, there is a better likelihood of delaying the development of resistance to these valuable insecticides and of protecting beneficial insects in the early season (Bull and Menn, 1990; Elzen and King, 1991).

**Avermectin insecticides and miticides**

The avermectins are a novel class of lactones that are natural products derived by fermentation of the soil micro-organism Streptomyces avermitilis. The discovery of these microbial products was reported by Campbell et al. (1984). Members of these macrocyclic lactones were shown to possess outstanding anthelmintic (ivermectin) and insecticidal and miticidal activities (abamectin).

The mode of action of the avermectins is different from that of most other insecticides. They induce paralysis by inhibiting signal transmission at the neuromuscular junction and potentiating a GABA-like action on the GABA-receptor/chloride-ion-channel complex (Campbell, 1981). More recently, Turner and Schaeffer (1989) reported that high-affinity binding by avermectin causes greater membrane permeability to chloride ions that is independent of gaba-ergic chloride ion channels. The avermectins are biologically active in all organisms with a gaba-ergic system. Selectivity and differential toxicity of these compounds are probably a function of uptake, differential
metabolism and mode of delivery. The structures of avermectin B1 (abamectin) and an analogue, EMA (MK-243) are shown in Figure 3. Abamectin consists of approximately 80% of component a, where R = C₂H₅, and 20% of component b, where R = CH₃. Abamectin is primarily a broad-spectrum miticide, providing long residual control of spider mites on cotton. The miticide is active through translaminar foliar uptake; it disappears rapidly from the surface of cotton leaves but is retained in the epidermal cells, the feeding site of spider mites. Because of this translocation, abamectin is relatively non-toxic to predators and parasites and fits well in IPM programmes. In the course of chemical-modification studies on abamectin to optimize activity against lepidopteran larvae, it was discovered that substituting an amino group for an OH moiety at the 4"-position in the terminal disaccharide moiety of abamectin (Figure 3) produced a remarkable increase in selective toxicity against major lepidopteran larval pests of cotton (Dybas et al., 1989).

Dybas et al. (1989) determined the toxicities of EMA (MK-243), abamectin, two carbamates, and two SPs in tests with the larvae of three major lepidopteran cotton insect pests (Table 2). The LC₉₀ values showed that EMA was significantly more toxic to the three lepidopteran species than the other pesticides. It is remarkable that, against cotton bollworm, EMA was 205 times more toxic than cypermethrin when larvae fed on treated leaves. As a contact insecticide, however, EMA was only slightly more toxic than the SPs. Nevertheless, because of its unique mode of action, EMA should be extensively tested under field conditions and in various formulations for selectively controlling lepidopterous larvae in cotton.

Azadirachtin

Azadirachtin (AZ) is a tetranortriterpenoid (limonoid). Its structure was fully elucidated by Bilton et al. (1987) and is shown in Figure 4. AZ is the most important insect-active component of the seeds of the neem tree, or Indian lilac (Azadirachta indica), belonging to the Meliaceae (mahogany) family; there is a long history of folklore medicine and insect control associated with the neem tree. The properties and potential of neem in insect management were recently reviewed by Schmutterer (1990).

AZ acts as an insect growth regulator, apparently by blocking the action of the moulting hormone ecdysone. It also has a phagorepellent action in locusts and other insects. In addition to AZ, other neem seed kernel extracts and extracts of neem leaves have been shown to produce a variety of repellent, oviposition inhibition, feeding deterrent and morphogenetic effects in various insects. Currently, only the most active insecticidal ingredient, AZ, has been registered for non-food use on ornamental crops. Under the trade name Margosan-O, AZ is used against the greenhouse whitefly (Trialeurodes vaporarhium (Westwood)), the sweet potato whitefly, mealybugs, leafminers, and several lepidopterans at rates of 20–50 g AZ ha⁻¹. A strain of the sweet potato whitefly has become a major pest of cotton in the western United States and appears to tolerate most insecticides. Price and Schuster (1990) reported promising control of second-stage nymphs of the sweet potato whitefly with single foliar spray applications of 220 p.p.m. AZ Margosan-O to poinsettias. Promising control was also reported on tomatoes by Schmutterer (1990). These results suggest that AZ should be extensively tested for whitefly control on cotton.

Neem-based pesticides have proved to be relatively harmless to many beneficial insect parasites and predators.
and also to honey bees. The weak contact toxicity and selective mode of action are probably significant contributors to this bioactivity profile (Schmutterer, 1990). Neem-based pesticides also have a favourable acute toxicity profile in warm-blooded animals and fish, and a rapid disappearance rate in the environment.

**Bacillus thuringiensis (B.t.)**

Great hopes were generated, in past years, of controlling the Heliothis complex in cotton with spray formulations of spores of *Bacillus thuringiensis* Berliner var. kurstaki; however, field trials conducted over several seasons with strains HD-1 and HD-263 failed to provide economic control (Menn et al., 1989). Although *B.t.* is a relatively effective stomach poison, a residual contact insecticide is required to control the Heliothis complex effectively. *Heliothis* larvae feed sparingly on foliage and rapidly invade squares and bolls, thus escaping surface residues.

Renewed interest in *B.t.* has been generated recently, spurred by advances in biotechnology. Through genetic engineering, the *B.t.* delta-endotoxin gene has been successfully expressed in cotton plants, producing transgenic plants that are toxic to lepidopterous larvae feeding on cotton. Currently, field trials are under way in Mississippi to evaluate protection of transgenic cotton plants from attack by first-instar larvae of *Heliothis virescens*. These trials are being conducted co-operatively in the United States by the Monsanto Agricultural Company, St Louis, Missouri, and the USDA, ARS, Crop Science Research Laboratory, Mississippi State, Mississippi (J. N. Jenkins, personal communication, 1990).

However, one cannot exclude the possibility that resistance might develop to the expressed *B.t.* endotoxin protein in cotton plants in the Heliothis complex. Resistance to *B.t.* has been reported already in several species of lepidopterous insects (Georgiou, 1990). Recently, Gould (1991) proposed an interesting strategy to delay onset of resistance to transgenic plants by providing refuge of non-transgenic plants in a given cropping, thus reducing the resistance selection pressure. However, actual field trials will be necessary to test this and any other hypothetical strategies.

**Biochemical design**

Most insecticides were discovered by the empirical or random synthesis-and-screen approach. However, as discussed earlier, more and more resources and attention are being directed toward biochemistry and physiology in designing novel pesticidal molecules. It was this cogent biorational approach that led to the design and synthesis of juvenoids that disrupt insect development (compounds mimicking the action of juvenile hormones) (Menn and Henrick, 1981). Unfortunately, many of the juvenoids are photolabile and become inactive as insectostatic agents.

A recent breakthrough was the discovery of the first potent non-steroidal agonist of ecdysone (Wing, Slavecki and Carlson, 1988). This compound, RH-5849 (1,2-dibenzoyl-1-tert-butylhydrazine) (Figure 5), was discovered as a result of a long-term biorational programme to discover antijuvenile or moulting hormone inhibitors at the Rohm and Haas research laboratories. When injected into larvae of *Manduca sexta* (Linn.), RH-5849 was 50 times more active than 20-hydroxyecdysone in initiating premature moulting. It was even more effective in larval diets, where it was 670 times more active than 20-hydroxyecdysone in initiating premature moulting. Similar activity was determined in members of three other lepidopteran families – Noctuidae, Pyralidae and Pieridae (J. A. Svoboda, personal communication, 1989).

Biochemical studies (Wing, 1988) established that RH–5849 is a true ecdysone agonist and does not compete directly with ecdysone for target tissues. Although similar in chemical structure to the benzoylphenylureas that interfere with chitin biosynthesis, RH–5849 has a markedly different mode of action. The novel and selective mode of action of RH–5849, which results in rapid cessation of feeding regardless of age or instar, suggests that this compound, and possibly more active analogues, should be field-tested in IPM programmes for cotton. However, like the avermectins, this class of ecdysone agonists may suffer from the drawback that they are primarily active through ingestion; experience has shown that the most successful insecticides against lepidopterous pests of cotton exert their primary action through contact. Nevertheless, as seldom do such exquisitely selective compounds come along, every opportunity should be afforded to exploit their unique action through further synthesis of analogues and extensive field-testing in cotton.

**Semiochemicals**

Semiochemicals, including pheromones, attractants, feeding stimulants and arrestants, have been used in cotton and other crops for a number of years, primarily for monitoring population densities of several pest species. Only very recently has the technology of using semiochemicals to disrupt mating and to mass-trap insect pests become economically feasible for controlling two major North American pests of cotton – the boll weevil and the pink bollworm.

In the Mississippi Delta cotton region, McKibben, Smith and McGovern (1990) developed an attracticide trap for the boll weevil in which 40 μg grandlure (a four-component attractant for the boll weevil), feeding stimulants and cottonseed oil, were mixed with 1 g cyfluthrin formulated in polyvinyl chloride, with natural shellac, as a binder, and a green pigment. This mixture is
applied to wooden stakes placed vertically in the field at the rate of two stakes ha\(^{-1}\). This trapping system has proved highly efficient in mass trapping of both sexes of the boll weevil; the stakes need to be recharged with the mixture every 4 weeks. This selective population-management system has the potential to become important for controlling boll weevils during a 2-month period in the early season and may significantly reduce the need for large-scale treatments with insecticides.

In recent years, the cotton acreage in Arizona, the Imperial Valley of California, and the northeastern valleys of Mexico have drastically decreased or disappeared altogether because of the ravages of the pink bollworm. A new technology, based on mating disruption, that had its genesis in the pioneering research of Shorey and co-workers (Shorey, Gaston and Kaae, 1976) is now coming to practical realization. Large-scale field trials are currently under way in the Parker Valley of Arizona to evaluate the commercial potential of several formulations of gossypolure to disrupt early-season mating and, thus, to preclude the need for treating the cotton fields with insecticides early in the season (Brosten and Simmonds, 1990).

Staten et al. (1987) obtained promising field results in the Imperial Valley of California and in the Mexicali Valley, Mexico, with hand-applied PBW-ROPE dispensers containing 78 mg 96% (Z, Z) and (Z, E) isomers of gossypolure in a ratio of 49:51, respectively. Field labourers placed the dispensers around the stem of individual plants at the first-flower-bud stage and at a rate of 1000 ha\(^{-1};\) the dispensers reduced the need for insecticide applications by 41% and resulted in a 97% reduction in trap catches of the moths in August.

Commercial control by mating disruptions of the pink bollworm has already been demonstrated in Egypt, using slow-relative release formulations of gossypolure (Critchley, Campion and McVeigh, 1989).

It is evident from the foregoing that semiochemical technology may have an economic future in IPM programmes. It may help to improve the quality of the environment by greatly lowering the volume of chemical pesticides.

The increased emphasis on IPM and environmental, economic and social pressures and demands are causing dynamic changes in the development of new chemicals for insect and mite control. The most obvious outcome is a drastically reduced number of new chemical compounds appearing in the marketplace. Several of the new chemical insecticides and miticides described here would seem to be compatible with biological control agents and semiochemicals in improved pest management systems for cotton. However, extensive field experience will be required to verify this.

**Notes**

At a later date, this paper, in a slightly different version, will also appear as part of the US Department of Agriculture’s publication on the proceedings of the Soviet-American Symposium on Cotton IPM, held in Tashkent, USSR, September 3–6, 1990.

Mention of trade names or commercial products is solely for the purpose of providing specific information and does not imply recommendation or endorsement by the US Department of Agriculture.

**References**


Staten, R. T., Flint, H. M., Weddle, R. C. et al. (1987) Pink bollworm (Lepidoptera: Gelechiidae) large-scale field trials with a high rate gossypolure formulation. *J. Econ. Entomol.* 80, 1267–1271


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