REVIEW

Insect Growth Regulators for Insect Pest Control*

Hasan TUNAZ**
Kahramanmaraş Sütcü İmam University, Faculty of Agriculture, Department of Plant Protection, Kahramanmaraş - TURKEY

Nedim UYGUN
Çukurova University, Faculty of Agriculture, Department of Plant Protection, Adana - TURKEY

Abstract: Insecticides with growth regulating properties (IGR) may adversely affect insects by regulating or inhibiting specific biochemical pathways or processes essential for insect growth and development. Some insects exposed to such compounds may die due to abnormal regulation of hormone-mediated cell or organ development. Other insects may die either from a prolonged exposure at the developmental stage to other mortality factors (susceptibility to natural enemies, environmental conditions etc) or from an abnormal termination of a developmental stage itself. Insect growth regulators may come from a blend of synthetic chemicals or from other natural sources, such as plants. The chemical composition of hormones indigenous to insects is now being studied and used as a basis for developing analogs or mimics against insects. The similarities, however, in certain aspects of biochemistry among vertebrates and invertebrates may result in the limited development of IGRs. Environmental contamination also creates a hurdle as well as a challenge for industries to develop compounds that provide a more environmentally or ecologically sound insect pest control.

Key Words: Insect growth regulators, insect pests, insect hormones, diflubenzuron

Zararlı Böceklerin Mücadelesinde Böcek Büyüme Düzenleyicileri

Özet: Büyüme düzenleyici özellikleri olan insektisitler, biyokimyasal yollarla büyüme ve gelişme için gerekli olan sistemleri düzenliyerek veya önleyerek böceklerde etkili olurlar. Bu maddeler hücrelerin ve organların gelişiminde etkili olan hormonların anormal çalışmasına neden olurlar ve böylece, hedef alınan böcekleri öldürürler. Diğer bazı böceklerde de, gelişme dönemlerinin uzaması sonucu doğal düşmanlar ve çevre koşulları gibi diğer ölüm faktörleri nedeniyle ölümler meydana gelir. Böcek büyüme düzenleyicileri ya sentetik kimyasalların karışımından ya da değişik bitkilerden doğal olarak elde edilmektedir. Günümüzde, böcekler üzerinde etkili olan ve böcek hormonlarını taklit eden bu maddelerin kimyasal yapıları çalışılmakta ve zararlı böceklere karşı yeni maddelerin geliştirilmesinde kullanılmaktadır. Ancak, omurgalılar ve omurgasızlar arasındaki biyokimyasal benzerlikler bu maddelerin geliştirilmesini sınırlandırmaktadır. Zararlı böcek mücadelesinde kullanılan kimyasal bileşimlerin meydana getirdiği çevre kirliliği bu maddeleri üreten sanayiyi engellemekte ve dolayısıyla çevre açısından daha az zararlı kimyasal bileşimlerin üretin çalışmalarına geçilmesine neden olmaktadır.

Anahtar Sözcükler: Böcek büyüme düzenleyicileri, zararlı böcekler, böcek hormonları

Introduction

A new approach to insect pest control is the use of substances that adversely affect insect growth and development. These substances are classified as "insect hormone mimics" or "insect growth regulators" (IGRs) owing to their effects on certain physiological regulatory processes essential to the normal development of insects or their progeny. They are quite selective in their mode of action and potentially act only on target species (Table 1).

The action of IGRs, however, should not be confused with other synthetic insecticides, such as organophosphates and carbamates, since these chemicals interfere with other physiological processes but do not regulate the development of normal insects. An IGR, therefore, does not necessarily have to be toxic to its target, but may lead instead to various abnormalities that impair insect survival (Siddall, 1976). Interestingly, most of the IGRs that have shown effectiveness against insect pests cause

---

Table 1. Insect growth regulators and their activity for insect pest control

Name	Activity
Bistfluron	Chitin synthesis inhibitor
Buprofezin	Chitin synthesis inhibitor
Chlorfluazorun	Chitin synthesis inhibitor
Cyromazine	Chitin synthesis inhibitor
Diflubenzuron	Chitin synthesis inhibitor
Flucycloxuron	Chitin synthesis inhibitor
Flufenoxuron	Chitin synthesis inhibitor
Hexaflumuron	Chitin synthesis inhibitor
Lufenuron	Chitin synthesis inhibitor
Noyaluron	Chitin synthesis inhibitor
Noyiflumuron	Chitin synthesis inhibitor
Penfluron	Chitin synthesis inhibitor
Teflubenzuron	Chitin synthesis inhibitor
Triflumuron	Chitin synthesis inhibitor
Epofenonane	Juvenile hormone mimic
Fenoxycarb	Juvenile hormone mimic
Hydroprene	Juvenile hormone mimic
Kinoprene	Juvenile hormone mimic
Methoprene	Juvenile hormone mimic
Pyriproxyfen	Juvenile hormone mimic
Triprene	Juvenile hormone mimic
Juvenil hormone I	Juvenile hormone anolog
Juvenil hormone II	Juvenile hormone anolog
Juvenil hormone III	Juvenile hormone anolog
Chromafenozide	Molting hormone agonist
Halofenozide	Molting hormone agonist
Methoxyfenozide	Molting hormone agonist
Tebufenozide	Molting hormone agonist
α-ecdysone	Molting hormone anolog
Ecdysterone	Molting hormone anolog
Diofenolan	Molting inhibitor

the rapid death of the insect through failure of a key regulatory process to operate or function. IGRs generally control insects either through regulation of metamorphosis or interference with reproduction (Riddiford and Truman, 1978). Compounds developed to disrupt metamorphosis ensure that no reproductive adults are formed. Those that specifically interfere with reproduction may include the development of adults with certain morphogenetic abnormalities that reduce their reproductive potential. Adults may be sterile or possess abnormally developed genitalia, which hinders the mating process or the capacity to produce fertile offspring.

To be compatible with the existing strategies in an integrated pest management (IPM) program, each component of the program should have a characteristic selectivity to its target species. Emphasis on selective insect pest control practices markedly impacted the approaches that the chemical industry adopted in developing novel insecticides. Pesticide regulation (e.g., EPA) emphasized the discoveries or synthesis of compounds (IGRs) that are specific to the target species and do not adversely (or at least minimally) affect beneficial and non-target species. As a result, direct approaches for discovering selective insecticides are being used, namely: 1) synthesis of active analogs of biologically active compounds guided by the results of quantitative structure-activity relationship (QSAR) analyses; 2) discovery of insecticides from natural products, as well as synthesis of their highly active analogs; and 3) application of a bio-rational approach to design and synthesize insecticides (Morrod, 1981; Magee et al., 1985).

Discovery of Insect Growth Regulators (IGRs)

The first account of the potential use of IGRs in insect control was in 1956, when juvenile hormone (JH) was isolated from the abdominal crude extract of the male Cecropia moths *Hyalophora cecropia* (L.). Topical application of the hormone prevented metamorphosis and subsequent multiplication of the insect. However, it was not observed until discovery of the "paper factor" in 1965 because the "paper factor" led to an understanding of the potential use of JH in insect development. Researchers at Harvard observed that cultures of the linden bug, *Pyrrhocoris apterus* L., which originally came from Czechoslovakia, had low egg hatch rates and that supernumerary larvae, rather than adults, were formed. Their investigations later showed that the abnormality observed was caused by the material in the paper towels (Scott, brand 150) used in the rearing jars. The active component of the paper towel, which was later identified as juvabione, came from the balsam fir, *Abis balsamea* (L.), the main pulp tree used in the United States paper industry (newspapers , magazines, etc.). Juvabione is a methyl ester of domatuic acid proven to be a very specific juvenile hormone mimic of the hemipteran family Pyrrhocoridae. The discovery of this highly specific substance led to industrial interests in JH as a tool in developing IGRs.

In addition to plant-derived insect growth regulators, other compounds are synthesized based on an

understanding of the biochemistry and physiology of insect development, rather than the empirical or random synthesis and screen approach of pesticide discovery. This direct approach, coupled with the available techniques, led to the design or synthesis of more selective analogs with potential compatibility with integrated pest management (IPM) programs.

Major Groups of Insect Growth Regulators

Since the target sites of common insecticides on insects and mammals are known to be similar, it is desirable to develop insecticides whose primary target site does not exist in mammals for selective toxicity. IGRs may belong to this type of (selective) insecticides and can be grouped according to their mode of action, as follows: chitin synthesis inhibitors (i.e. of cuticle formation) and substances that interfere with the action of insect hormones (i.e. JHs, ecdysteroids) (Table 1).

Chitin synthesis inhibitors

The insect cuticle serves as an interface between the living animal and its environment; and forms the exoskeleton, supporting the linings of the gut, respiratory systems, reproductive ducts, and some gland ducts. It consists primarily of protein and chitin fractions. The latter comes in 3 forms, α, β, and γ chitin, and is the β-(1,4) glycoside polymer of N-acetyl-D-glucosamine. In additional to the insect and crustacean cuticles, chitin is present in cell walls of fungi and protozoa, but is absent in vertebrates and higher plants. Synthesis of chitin depends on the action of the extra cellular enzyme chitin synthesis attached to the plasma membrane. However, this enzyme is produced as a zymogen (inactive) in the endoplasmic reticulum of the epidermis and has to be activated by proteases for chitin synthesis (Hepburn, 1985). Since proteases are important for activating chitin synthesis zymogens, these enzymes become potential targets for regulation by certain compounds, along with other key regulatory steps in the biosynthesis of chitin.

The first chitin synthesis inhibitor introduced into the market as a novel insecticide was benzoylphenylurea, diflubenzuron (Figure, 1a) (Miyamoto et al., 1993). It was considered a potent compound against larvae of common cutworm, *Spedoptera litura* (Fabr.) and *Cydia pomonella* L. (Miyamoto et al., 1993). Some of the structural modifications (derivatives) of the compound are more active than the parent compound.

Aside from Lepidoptera, diflubenzuron has also been effective against Coleoptera and Diptera (Göktay and Kısmalı, 1990). Diflubenzuron and its derivatives were effective against insect pests and mites infesting field crops, and were relatively harmless to beneficial insect species. On the other hand, buprofezin, another chitin synthesis inhibitor, was used against homopteran pests including nymphs of brown planthoppers, *Nilaparvata lugens* (Stal.), leafhoppers, *Nephotettix cincticeps* (Uhler), whiteflies, *Bemisia tabaci* (Gennadius), and scale insects, *Trialeurodes vaporariorum* (Westwood), attacking fruit crops and certain species of Coleoptera and Acarina (Asai et al., 1985; Elsworthip and Martinez, 2001).

Lefunuron, an orally administrated chitin synthesis inhibitor, was also used against fleas (Smith, 1995), and it inhibited chitin synthesis and influenced the development of eggs and larvae. Female fleas biting lufenuron-treated animals produced infertile eggs as well as inhibiting larval development when feeding on "flea dirt" that contained blood from the treated insect. This observation was probably because of lufenuron, which is not significantly metabolized and is thus excreted into the feces. Different groups of insect growth regulators, such as juvenile hormone analogues, chitin synthesis inhibitors, and one triazine derivative, were tested in a special larvicidal test. The chitin synthesis inhibitors were quite effective against multi-resistant *Musca domestica* strains, except for one strain with strong resistance against chitin synthesis inhibitors, developed after extensive treatments with benzoylphenylureas for several years (Pospischil et al,, 1997).

Mode of action of chitin synthesis inhibitors (CSIs)

Most CSIs are primarily used as larvicides. Treated larvae develop until molting, but fail to ecdyse due to inhibition of the synthesis of new cuticle, specifically, chitin biosynthesis. Diflubenzuron, for instance, when directly applied to *Manduca* epidermal cells in vitro, inhibited endocuticular deposition (Miyamoto et al., 1993). Moreover, chitin precursors of *Pieris* larvae (^{14}C-glucose), *Manduca* larvae (^{14}C-glucosamine), *Mamestra* larvae (^{14}C-acetylglucosamine) and *Spodoptera* (Boisduval) larvae (^{14}C-UDP-N- acetyglucosamine) were not incorporated into chitin in the presence of chitin synthesis inhibitors.

Although the precise mode of action of diflubenzuron and other CSIs is still unknown, 3 hypothetical target
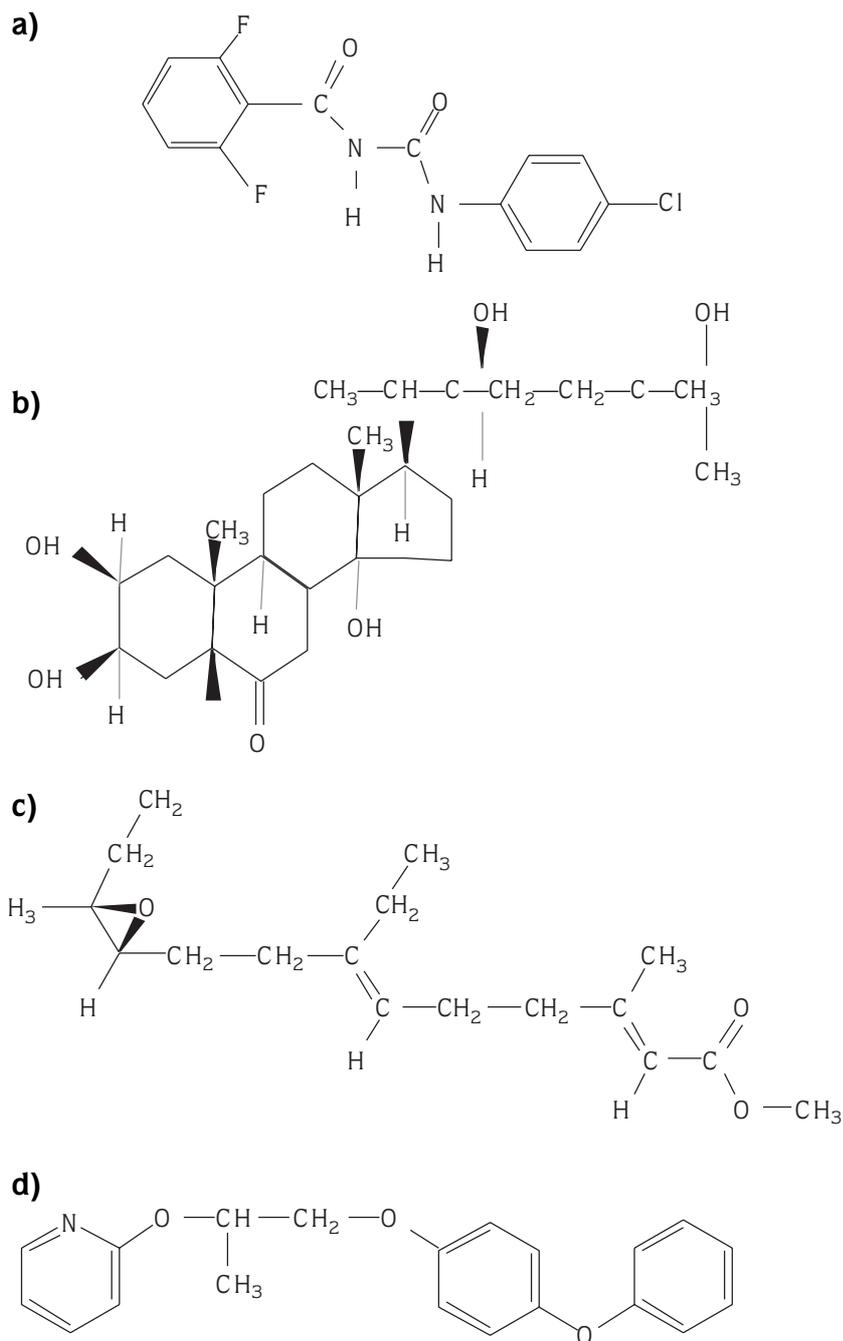
Figure 1. Structure of some insect growth regulators (a, diflubenzuron; b, ecdysone; c, juvenile hormone; d, pyriproxyfen).

sites have been proposed, namely: inhibition of chitin synthetase (or its biosynthesis), inhibition of proteases (or its biosynthesis), and inhibition of UDP-*N*-acetylglucosamine transport through the membrane (Miyamoto et al., 1993).

It seems unlikely, however, that the active metabolite hypothesis (i.e. action of proteases on zymogens) is correct because studies using diflubenzuron showed fast in vivo inhibition of chitin synthesis, while its metabolism in insects was relatively slow (Miyamoto et al., 1993).

Although Leighton et al. (1981) suggested that diflubenzuron inhibited chitin synthesis (i.e. by interfering with proteolytic activation of the zymogens), neither the presence of such zymogens in insects nor the inhibition of insect proteases has been found.

Eto (1990) further indicated that the most probable mechanism proposed is the disruption of the accessibility of the substrate. This hypothesis was demonstrated in a study using isolated *Mamestra brassicae* (L.) larval midgut tissue (Mitsui et al., 1984). It was shown that diflubenzuron inhibited the incorporation of ^{14}C-labeled glucosamine or N– acetlyglucosamine into the chitin of the peritrophic membrane, when applied to either side of the insect midgut epithelial cell layers. However, when UDP-*N*-acetlyglucosamine was applied inside the midgut, diflubenzuron did not inhibit chitin biosynthesis. These results suggested that the compound interferes with the transport system of UDP-*N*-acetlyglucosamine across the biomembrane (Eto, 1990). The release of UDP-*N*-acetylglucosamine from the epithelial cells was inhibited by diflubenzuron (Mitsui et al., 1984). Similarly, in vivo chitin synthesis from N–acetylglucosamine of *N. lugens* nymphs was selectively inhibited by buprofezin (Izaha et al., 1985).

Substances interfering with the action of insect hormones

Growth and development of insects are under the control of hormones, including prothoracicotrophic hormones (PTTH) (brain hormone), ecdysteroids, and juvenile hormones (JH). The peptide hormone PTTH secreted from the brain controls the secretion of the molting hormone (ecdysone) (Figure 1b) from the prothoracic gland. Ecdysone is responsible for cellular programming and, together with JH, initiating for the molting process. When JH levels secreted from the corpora allata are high, the epidermis is programmed for a larval molt, otherwise, the epidermis is programmed for metamorphosis. JH is virtually absent in the pupae, but is present in adults to serve some functions in reproduction. Thus, JH suppresses pupation and induces vitellogenesis during the reproductive stage of the insect (Eto, 1990).

There are several known insect JHs (i.e. JH I-III, JH 0, and *iso*-JH 0) (Figure 1c) synthesized and secreted from the corpora allata (Miyamoto et al., 1993). Any disturbance in the normal hormone balance may cause a crucial disorder in the growth and development of insects. JHs control a number of processes such as embryogenesis, molting and metamorphosis, reproduction, diapause, communication, migration/dispersal, caste differentiation, pigmentation, silk production, and phase transformation. Although JHs showed insect-specific control potential, their instability and synthetic difficulties did not allow the use of JH itself for pest control. Instead, many JH analogs (or mimics) (JHAs) became attractive candidates for pest control because of the ease of synthesizing these analogs and their which was action more selective than those of other peptide and steroid hormones (Eto, 1990). The first compound introduced into the market was methoprene. This is a terpenoid compound used primarily against household pests because of its low activity against agricultural pests and low residual on plants under field conditions (Smith, 1995). Methoprene is now being incorporated in dog and cat collars as well as being added to these animals' coats to control fleas (Smith, 1995). Other IGRs available for use against household and agricultural pests are fenoxycarb and pyriproxyfen. For example, when fenoxycarb was tested in the laboratory for ovicidal properties on *Cydia pomonella* L., by dipping apples in solutions with fenoxycarb, it acted as an excellent ovicidal product with an LC_{50} value of 0.05 ppm (Charmillot et al., 2001).

Mode of action of juvenile hormone analogs (JHAs) (including ecdysteroid) and anti-JHAs

JHAs are more effective at the beginning stage of metamorphosis and embryogenesis in insects, such as freshly ecdysed last larval instars, freshly ecdysed pupal instars, and deposited eggs. Thus embryogenesis is disrupted when young eggs are treated with JHAs. Application to early last instar larvae would result in the development of supernumerary instars, whereas treatment at the later stage would result in abnormal pupation and development of larval-pupal mosaics or intermediates (Koçak and Kılınçer, 1997).

The effectiveness of JHAs depends on the timing of application. This is apparent in studies involving the tobacco hornworm larva, *M. sexta*. It was shown that in the last instar larvae JH disappeared just after or within a few days of final molting to larvae. JH titer in the hemolymph began to decline at day 2 (Miyamoto et al., 1993). In this species, the release of prothoracicotrophic hormone occurred on day 3 to stimulate the prothoracic

glands to secrete small amount of ecdysone. This surge of ecdysone without JH induced commitment from larval development to pupal development, suggesting that application of JHAs after pupal commitment had no effect on morphological changes. Thus, the sensitive period of the last instar larvae to JHAs is between the disappearance of JH and before the appearance of the small surge of ecdysteroid (Riddiford, 1976; Miyamoto et al., 1993). No normal adults develop when pupae are treated with JHAs. The adult stage is generally insensitive to JHAs, but some insect species become sterile when JHA is applied (Retnakaran et al., 1985).

Application of pyriproxyfen [[2-[1-methyl-2(4-phenoxyphenoxy)ethoxy]pyridine]] to the last instar larvae of the tobacco cutworm, *S. litura* (100μg), hornworm, *M. sexta* (10 μg) (Hatakoshi et al., 1988) and the German cockroach, *Blattella germanica* (L.) (10-100μg) (Reid et al., 1994), induced molting of larvae into supernumerary larvae. The brains of these larvae were presumed to be activated to secrete prothoracicotrophic hormone when a high dosage of pyriproxyfen is introduced. Ecdysteroid titer peaked in the penultimate larval instar and pyriproxyfen induced larval molt. Both pyripoxyfen (Figure 1d) and fenoxycarb induced significant developmental delays and levels of morphogenetic wing twisting in the German cockroach (Reid et al., 1994). Twisted-wing adults were incapable of successful reproduction when treated with 10-100 μg of the compounds; however, the mating of lightly affected adults (below 10 μg) with normal adults did not inhibit reproduction. Pyripoxyfen and fenoxycarb were also shown to suppress egg hatch in pear psylla, *Casopsylla pyricola* (Foerster) (Higbee et al., 1995), and egg hatch and adult formation in *B. tabaci* (Ishaaya and Horowitz, 1992) and *Haematobia irritans* (L.) (Bull et al., 1993). Similarly, pyripoxyfen and methoprene had an obvious lethal effect on the egg hatching of *Ziposcelis entomophila* (Enderlein) (Ding et al., 2002).

Azadirachtin (AZ), a tetranortriterpenoid limonoid from the Indian neem tree (*Azadirachta indica* A. Juss.), is another active ingredient of IGRs commercially available as Align and Margoson-O (Wells et al., 1993). Neem-or AZ based IGRs are very selective ecdysone antagonists and have a broad spectrum of activity. They were found to have a very broad spectrum of activity against agricultural, stored product and house-hold pests (Awad et al., 1998), and several other insect species and

plant pathogens including fungi, viruses and protozoa (Mordue and Blackwell, 1993; Riba et al., 2003). A detailed description of the known action of AZ based pesticides as IGRs was reviewed by Ascher (1993), and Mordue-Luntz and Balckwell (1993).

Another compound, buprofezin, a chitin synthesis inhibitor, has been shown to suppress insect oviposition and egg fertility (Asai et al., 1985; Uchida et al., 1987). The inhibition of oviposition in *N. lugens* females was correlated with inhibition of prostaglandin E_2 (PGE_2) biosynthesis from arachidonic acid (Uchida et al., 1987). However, the inhibitory effects of buprofezin were reversed or counteracted by treating the insect with the molting hormone 20-hydroxyecdysone. These results thus suggest that buprofezin acts on the metabolism or receptors of ecdysteroids, because of its effects on both cuticle formation and oviposition (Eto, 1990).

The action of anti-JHs is accomplished by competing with JH in binding to the JH receptors or to the JH-carrier proteins, injuring the corpora allata cells, or interfering with JH biosynthesis (Leighton et al., 1981). Therefore, if we consider the mechanism of action of anti-JHs, as mentioned above, other JHAs may also function as anti-JHs. There are JHAs that compete with JH at the receptor site and become feedback inhibitors of JH biosynthesis. An example is ETB [ethyl 4-(2-pivaloyloxybutyloxy)-benzoate], which showed JH agonist and antagonist activities in *M. sexta* larvae (Staal, 1986).

Bowers et al. (1976) recognized that the first anti-JH, precocene I and II (derived from *Ageratum houstonianum* Mill), included precocious metamorphosis in young nymphs of the milkweed bug, *Oncopeltus fasciatus* (Dallas). Nymphs treated with this anti-JH developed into sterile adults by skipping one or more instars. The ensuing adults of precocene-treated female nymphs had less developed corpora allata and ovaries. JH treatment did not restore the development of corpora allata, but it did that of the ovaries. This irreversible damage to the corpora allata was attributed to the biological alkylation of allatal macromolecules by precocene after activation into epoxides or quinone methides (Bowers, 1982). Nonetheless, this anti-JH did not make it into the commercial market because of its lack of activity against most holometabolous insects.

KK compounds, such as KK-42 (1-benzyl-5-[(E)-2,6-dimethyl-1,5-heptadienyl] imidazole), the phenyl

derivatives of substituted imidazoles, inhibited JH biosynthesis and in vitro ecdysone synthesis, suppressed the in vivo increase in hemolymph ecdysteroid titers leading to larval ecdysis, and retarded ovarian growth and adult emergence in newly ecdysed pupae in silkworms (Kadono-Okuda et al., 1987). KK-42 was also shown to inhibit JH biosynthesis and to delay or inhibit ecdysteroid production in European corn borer larvae, *Ostrinia nubilalis* (Hubner) and desert locust females, *Schistocerca gregaria* (Gelman et al., 1995; Wang and Schnal, 2001).

Potential Effects of IGRs on Non-Target Organisms (NTOs)

Chitin synthesis inhibitors

Chitin is a very important constituent of the cell walls of fungi and green algae, and in the integuments of invertebrates (arthropods), but it is absent among vertebrates. Since arthropods share a similar molting process, species-specificity to chitin synthesis inhibitors is less pronounced than that of JHAs (miyamoto et al., 1993).

Among the species in aquatic ecosystems affected by IGRs, crustaceans and a few other aquatic species are the endangered organisms sensitive to chitin synthesis inhibitor applications. This is because insects and crustaceans contain the same molting hormones. For instance, diflubenzuron (at ppm levels) affected the survival, larval development, regeneration and reproduction of macrocrustaceans (Nimmo et al., 1980). Miura and Takahashi (1974) reported that crustaceans and shrimp were extremely sensitive to diflubenzuron, showing LC_{50} of about 0.1-1.0 ppm, which is comparable to the mosquito LC_{50} of about 0.7 ppm. In addition to the direct effects of CSIs in aquatic ecosystems, the reduction of aquatic organisms (which are an important component in the food chain) shifted the feeding habits of other species. The bluegill sunfish, *Lepomis macrochirus* Rafinesque, shifted its feeding habits from feeding on cladocerans (e.g. crustaceans) and copepods to chironomid midges and terrestrial insects (Ables et al., 1977).

The effects of diflubenzuron on terrestrial NTOs, however, tend to be minimal compared to the effects of conventional insecticides. Adults of *Trichograma pretiosum* (Riley), *Apantels marginiventris* (Cresson), and *Voria ruralis* (Fallen) as well as the survival of the F1 generation were not affected (Wilkinson et al., 1978). A

decrease in egg hatch was observed in the lacewing *Chrysopa carnea* Stephens, and in the nymph survival of *Gaucheries punctipes* (Say) due to diflubenzorun treatment (Apperson et al., 1978; Medina et al., 2002). In addition to the diflubenzuron effect on terrestrial NTOs, 2 ecdysone agonists, halofenozide and methoxyfenozide, caused premature induction of larval molting and incomplete pupation in affected larvae of the multicolored Asian lady beetle, *Harmonia axyridis* (Carton et al., 2003).

Juvenile hormone analogs

Methoprene (Altosid ®EC4) showed no adverse effects on Rotifera, Platyhelminthes, Nematoda, Mollusca, Arachnida, or Pisces. Field applications do not produce long-term disruptions in the population levels of crustaceans, altough at multiple applications of 302g a.i./ha to experimental ponds, it significantly affected the populations of certain aquatic insects (e.g. the mayfly, *Callibaetis pacifucis* Seeman, the dytiscid beetle, *Laccophilus sp.* and the hydrophilid beetle, *Tropisternus lateralis* (F.) (Norland and Mulla, 1975).

With respect to predators, the lacewing, *Chrysopa carnea* Stephens, and lygaeid bug, *Geocoris punctipes* (Say), tolerated high doses of JHAs. However, the lady beetle *H. convergens* and *Coccinella septempunctata*, were sensitive to many JHAs (Hodek et al., 1973; Kısmalı and Erkin, 1984). In other studies, the effects of JHAs were enhanced depending on the methods of application. For instance, the topical application of methoprene did not affect the predaceous mite *Amblyseius brazilli* except at concentrations as high as 1000 ppm, but with methoprone-treated pollen at 100 ppm egg laying was inhibited (El-Banhawy, 1977).

Similarly, JHAs did not show significant adverse effects on parasites. The LD_{50} for eggs of the gypsy moth, *Porthetra dispar* L., was 6.3 ng/egg, but the dose that produced deleterious effects on the egg parasites, *Ooencyrtus kuwanai* (Howard), was 63 ng/egg (Granett and Wesoloh, 1975). Hydroprene, triprene, and kinoprene were found to adversely affect *Aphidius nigripes* Ashmead, the parasitoid of the potato aphid, *Macrosiphum euphorbiae* Thomas (McNeil. 1975), but the overall adverse effects of JHAs on parasitoids were less than those of broad-spectrum conventional insecticides.

Many highly eusocial bees such as honeybees (Apinae) and stingless bees (Meliponinae) practice age polyethism, in which different groups of individuals perform a different ensemble of tasks as they age. Young workers, for example, are responsible for brood and queen care and nest maintenance, while older workers are involved in foraging activities. Since JH is involved in the regulation of age polyethism in the honeybee, *Apis mellifera* L. (Robinson and Ratnieks, 1987), it is probable that JHAs will have adverse effects on this species. Indeed, the topical application of 200 μg methoprene to adult worker honeybees caused a premature shift from the brood nest to food storage region, precocious foraging behavior, and premature production of alarm pheromones. At the same time, efficient pollination of insect-pollinated crops can be achieved due to the induced foraging effects of JHAs. Although treatment significantly shortened the life span of worker honeybees (Robinson, 1985), bumble bee broods fed with a sucrose solution containing pyriproxyfen or fenoxycarb developed normally (DeWael et al., 1995).

Neem-or AZ based IGRs are highly selective, but their potential adverse effects on beneficial organisms cannot be discounted. Isolated cases of ecdysial failure in certain parasitoids were reported. However, this type of IGR is generally safe for non-target and beneficial organisms (e.g., honeybees, parasitic wasps, spiders, earwigs, ants, and predaceous mites) (Mordue and Blackwell. 1993).

Resistance to Insect Growth Regulators

There were predictions that insects could not become resistant to their own hormones, since no demonstrable proof of the evolution of any new JH by insects has been advanced (Bowers, 1990). According to laboratory experiments, however insects can develop resistance to JHAs. However, no serious field resistance to JHAs has been reported to limit their use in pest control.

Cross-resistance between organophosphates, benzoylphenylureas or diflubenzuron has been suspected among organophosphate-resistant populations of the codling moth, *Cydia ponomella* (L.) (Moffit et al., 1988). Zhang et al.(1998) also investigated cross-resistance to IGRs in the pyriproxyfen-resistance housefly,*Musca domestica* populations. They showed that although the housefly which possessed 880-fold resistance to pyriproxyfen had no cross-resistance to diflubenzuron, it showed medium cross-resistance to 2 other juvenile hormone analogs, fenoxycarb and methoprene. Elbert

and Nauen (2000) tested buprofezin and pyriproxyfen against second instar nymphs and eggs of the tobacco whitefly, *Bemisia tabaci.* Their results showed there was lower buprofezin resistance while pyriproxyfen resistance was not obvious. The ineffectiveness of diflubenzuron in controlling the tufted apple bud moth, *Platynota idaeusalis* (Walker), was attributed to the increased levels of enzymatic detoxification, which were also observed in organophosphate-resistant insects (Biddinger et al., 1996). The resistance in these chitin inhibiting types of IGRs indicated that multi-resistance factors (generally enzymatic detoxification) that allow insects to metabolize various groups of insecticides may confer some cross-resistance to benzoylphenylureas and probably other IGRs. The carboxylesterase activity that contributed to the resistance of the tufted apple bud moth to organophosphates may also be important in conferring resistance or tolerance to diflubenzuron in various strains of the tufted apple bud moth (Biddinger et al., 1996).

Conclusion

Most synthetic insecticides are toxic to all animals including human beings. Although many insecticides can be used safely, a few are persistent in the environment and a small number have multigenic, carcinogenic and teratogenic effects on human beings and domestic animals. Furthermore their magnification in the food chain sometimes threatens non-target organisms. These facts have become of deep concern to agricultural and health scientists, producers and consumers alike.

Based on the previous discussion, IGRs represent the newest of all approaches to operational and commercial insect control. Their species or stage-specificities that were higher than those of conventional insecticides offer a good alternative for a selective insect pest control that is in harmony with existing IPM programs. IGRs generally have a good margin of safety for most non-target biota including invertebrates, fish, birds, and other wildlife. They are relatively safe for human beings and domestic animals. Although CSIs are broad-spectrum compounds, the mode of action between the targets and non-target organisms (e.g., crustaceans) should be considered. Similarly, JHAs are generally selective, but the last stage of some NTOs will potentially suffer morphogenetic effects or anomalies, while crustaceans will probably have defective reproductive systems (albeit reversible).

The use of JHAs in some species may be impractical for use under field conditions since the most damaging stage of some insect pests is in the entire larval stage, while JHAs are most effective at the last larval instar. In other situations, JHAs could be especially useful in mosquito control programs because JHAs do not induce quick mortality to preimaginal stages or larval mosquitoes. This is a desirable feature of JHAs in mosquito control because the larvae are an important food source for fish and wildlife (Mulla, 1995). The effects of JHAs are transient and thus acceptable due to their high degradability and non-lethal and reversible effects on most aquatic arthropods. This will make it easier for JHAs to be registered for mosquito and midge control, without large -scale experimental trials for risk assessment before registration. In order to protect plants from the feeding stages of insects, anti-JHs have been synthesized to interfere with the biosynthesis, secretion and transport or action of JH. This would most likely complement the drawback of JHAs, which are most effective against late last instar larvae. Clarifying the primary site of action, and the recognition and elimination of non-essential side action are important for designing selective insecticides. Commercial JHAs are very safe for the environment. Therefore, these will potentially contribute to developing control agents with reduced environmental impacts. While insects will certainly continue to be devastating pests, more effective IGRs will be discovered and will continue to have devastating effects on their target insects.

Acknowledgments

References

Ables, J., R. Jones and M.J. Bee. 1977. Effect of diflubensuron on beneficial arthropodos associated with cotton. Southwest Entomol. 2: 66-72.

Apperson, C.S., C.H. Schaefer, A.E. Colwell, G.H. Werner, N.L. Anderson, E.F. Dupras Jr. and D.R. Longanecker. 1978. Efeects of diflubenzuron on Chaocorus astictopus and nontarget organisms and persistence of diflubenzorun in lentic habitats. J. Econ. Entomol. 71: 521-527.

Ascher, K.R. 1993. Nonconventional insecticidal effects of pesticides available from the neem tree, *Azadirachta indica*. Arch. Insect Biochem. Physiol. 22: 433-449.

Asai, T.A., M. Kajihara, F. Fukada and S. Makekawa. 1985. Studies on the mode of action of buprofezin II. Effects on reproduction of the brown planthopper, *Nivaparvata lugens* Stal (Homoptera: Delphacidae). Appl. Entomol. Zool. 20: 111-117.

Awad, T.I., F. Önder and Ş. Kısmalı. 1998. *Azadirachta indica* A. Juss (Meliaceae) ağacından elde edilen doğal pestisitler üzerinde bir inceleme. Türk. Entomol. Derg. 22: 225-240.

Biddinger, D.J., L.A. Hull and B.A. Mcpheron. 1996. Cross-resistance and synergism in azinphosmethyl resistant and susceptible strains of tufted apple bud moth (Lepidoptera: Tortricidae) to various insect growth regulators and avarmectin. J. Econ. Entomol. 89: 274-287.

Bowers, W.S., T. Ohta, J.S. Cleere and P.A. Marsella. 1976. Discovery of insect anti-juvenile hormones in plants. Sci. 193: 542-547.

Bowers, W.S. 1982. Toxicology of the precocenes, In: Insecticide mode of action (Ed. J.R. Coats,). Acad. Press, New York. pp. 403-420.

Bull, D.L. and R.W. Meola. 1993. Effect and fate of the insect growth regulator pyriproxyfen after application to the horn fly (Diptera: Muscidae). J. Econ. Entomol. 86: 1754-1760.

Carton, B., G. Smagghe and L. Tirry. 2003. Toxicity of two ecdysone agonists, halofenozide and metoxyfenozide, against the multicolored Asian lady beetle, *Harmonia axyridis*, (Col., Coccinallidae). J. App. Entomol. 127: 240-242.

De Wael, L., M. De Greef and O. Van Laere. 1995. Toxicity of pyriproxyfen and fenoxycarb to bumble bee brood using a new method for testing insect growth regulators. J. Apic. Res. 34: 3-8.

Ding, W., E. Shaaya, J.J. Wang, Z.M. Zhao and F. Goa. 2002. Acute lethal effect of two insect growth regulators on *Liposcelis entomophila* (Psocoptera; Liposcellididae). Zool.Res. 23: 173-176.

Elbert, A. and R. Nauen. 2000. Resistance of *Bemisia tabaci* (Homoptera: Aleyrodidae) to insecticides in southern Spain with special reference to neonicotinoids. Pest-mgt-Sci. 56: 60-64.

El-Banhawy, E.M. 1977. Growth inhibition of the predaceous mite *Amblyseius brazilli* (Mesostigmata: Phytoseiidae) by a synthetic juvenile under laboratory conditions. Entomophaga, 22: 429-434.

Ellsworthip, P. and C.J.L. Martinez. 2001. IPM for *Bemisia tabaci*; A case study from North America. Crop Protection. 20(9): 853-869.

Eto, M. 1990. Biochemical mechanism of insecticidal activities, In: Chemistry of Plant Protection (Eds. G. Haug and H. Hoffman,). Springer Verlag. 6: 65-107.

Gelman, D.B., R.A. Bell, A.B. DeMilo and J.P. Kochansky. 1995. Effect of KK-42 on growth, development, molting, and metamorphosis of the European corn borer, *Ostrinia nubilalis* (Hubner). Arch. Insect Biochem. Physiol. 28: 1-15.

Göktay, M. and Ş. Kısmalı. 1990. Diflubenzuron'un böcekler üzerindeki etkisi. Türk. Entomol. Derg. 14: 53-64.

Granett, J. and R.M. Wesoloh. 1975. Dimilin toxicity to the gypsy moth larval parasitoid, *Apanteles melanoscelus*. J. Econ. Entomol. 68: 577-580.

Hatakoshi, M., I. Nakayama and L.M. Riddiford. 1988. The induction of an imperfect supernumerary larval molt by juvenile-hormone analogs in *Manduca sexta*. J. Insect Physiol. 34: 373-378.

Hepburn, H.R. 1985. The integument, In: Fundamentals of Insect Physiology (Ed. M.S. Blum,). John Wiley and Sons, New York. pp. 139-183.

Higbee, B.S., D.R. Horton and J.L. Krysan. 1995. Reduction of egg hatch in pear psylla (Homoptera: Psyllidae) after contact by adults with insect growth regulators. J. Econ. Entomol. 88: 1420-1424.

Hodek, I., Z. Ruzicka and F. Sehnal. 1973. Termination of diapause by juvenoids in two species of ladybirds (Coccinellidae). Experientia. 29: 1146-1147.

Ishaaya, I. and A.R. Horowitz. 1992. Novel phenoxy juvenile hormone analog (pyriproxyfen) suppresses embryogenesis and adult emergence of sweet potato whitefly (Homoptera: Aleyrodidae). J. Econ. Entomol. 85: 2113-2117.

Izawa, Y., M. Uchida, T. Sugimoto and T. Asai. 1985. Inhibition of chitin biosynthesis by buprofezin analogs in relation to their activity controlling *Nilaparvata lugens* Stal. Pestic. Biochem. Physiol. 24: 343-347.

Kadono-Okuda, K., E. Kuwano, M. Eto and H. Yamashita. 1987. Anti-ecdysteroid action of some imidazole derivatives on pupal-adult development of the silkworm, *Bombyx mori* (Lepidoptera: Bombycidae). Appl. Entomol. Zool. 22: 370-379.

Kısmalı, Ş. and E. Ekin. 1984. Juvenil hormon analoglarının bazı yararlı böceklerin gelişmesi üzerine etkileri. II. *Coccinella septempunctata* L. 'nın larva gelişmesi üzerine etkisi. Türk. Entomol. Derg. 8: 231-236.

Koçak, E and N. Kılınçer. 1997. Juvenil hormon analoğu methopren' in pamuk yaprak kurdu (*Spodoptera littoralis* Boist. (Lep.: Noctuidae)' na etkileri: I. pupa ve yumurta etkiler. Bitki Kor. Bült. 37: 163-172.

Leighton, T.E., D. Marks and F. Leighton. 1981. Pesticides: Insecticides and fungicides are chitin synthesis inhibitors. Sci. 213: 905-907.

Magee, P.S., G.K. Kohn and J.J. Menn.1985. Approaches to rational synthesis of pesticides. ACS Symp. Ser.., ACS, Washington, DC. 255: 1-207.

McNeil, J. 1975. Juvenile hormone analogs: Detrimental effects on the development of an endoparasitoid. Sci. 189: 640-642.

Medina, P., G. Smagghe, F. Budia, P. Estal, L. Tirry and E. Vinuela. 2002. Significance of penetration, excretion, and transovarial uptake to toxicity of three insect growth regulators in predatory lacewing adults. Arch. Insect. Biochem. Physiol. 51: 91-101.

Mitsui, T., C. Nobusawa and J. Fukami. 1984. Mode of inhibition of chitin synthesis by diflubenzuron in the cabbage armyworm, *Mamestra brassicae* L. J. Pestic. Sci. 9: 19-26.

Miura, T. and R.M. Takahashi. 1974. Insect development inhibitors; Effects of candidate mosquito control agents on non-target aquatic organism. Environ. Entomol. 3: 631-636.

Miyamoto, J., M. Hirano, Y. Takimoto and M. Hatakoshi. 1993. Insect growth regulators for pest control, with emphasis on juvenile hormone analogs: Present status and future prospects. ACS Symp. Ser., ACS, Washington, DC. 524: 144-168.

Moffit, H.R., P.H. Westigard, K.D. Mantey and H.E. Van DeBaan. 1988. Resistance to diflubenzuron in codling moth (Lepidoptera: Tortricidae). J. Econ. Entomol. 81: 1511-1515.

Mordue-Luntz, A.J. and A. Blackwell. 1993. Azadirachtin: An update. J. Insect Physiol. 39: 903-924.

Morrod, R.S. 1981. Lead generation: Designing the right approach. Phil. Trans. Roy. Soc. Lond. B. 295: 35-44.

Mulla, M.S. 1995. The future of insect growth regulators in vector control. J. Ames. Mosq. Cont. Assoc.11: 269-273.

Nimmo, D.R., T.L. Hamaker, J.C. Moore and R.A. Wood. 1980. Acute and chronic effects of dimilin on survival and reproduction of *Mysidopsis bahia*, *In*: Aquatic Toxicology, ASTM STP 707 (Eds. J.G. Eaton, P.R. Parrish and E.C. Hendricks,). American Society for Testing and Materials, Philadelphia, PA. Pp. 366-376.

Norland, R.L. and M.S. Mulla. 1975. Impact of altosid on selected member of an aquatic ecosystem. Environ. Entomol. 4: 145-152.

Pospischil, R., K. Szomm, M. Londershausen, I. Schroeder, A. Turberg and R. Fuchs. 1997. Multiple resistance in the larger house fly, *Musca domestica* in Germany. Pest. Sci. 48: 333-341.

Reid, B.L., V.L. Brock and G.W. Bennett. 1994. Development, morphogenetic and reproductive effects of four polycyclic non-isoprenoid juvenoids in the German cockroach (Dictyoptera: Blattellidae). J. Entomol. Sci. 29: 31-42.

Retnakaran, A., J. Granett and T. Ennis. 1985. Insect Growth Regulators, In: Comprehensive Insect Physiology, Biochemistry and Pharmacology (Eds. G.A. Kerkut and L.I. Gilbert,). Pergamon Press, Oxford. 12: 529.

Riba, M., J. Marti and A. Sans. 2003. Influence of Azadirachtin on development of reproduction of *Nezara viridula* L. (Het., Pentotomidae) J. Appl. Entomol. 127: 37-41.

Riddiford, L.M. 1976. Hormonal control of insect epidermal cell commitment *in vitro*. Nature.259: 115-117.

Riddiford, L.M. and J.W. Truman. 1978. Biochemistry of Insect Hormones and Insect Growth Regulators, In: Biochemistry of Insects (Ed. M. Rockstein,). Acad. Press, New york. pp. 307-357.

Robinson, G.E. 1985. Effects of a juvenile hormone analogue on honey bee foraging behaviour and alarm pheromone production. J. Insect Physiol. 31: 277-282.

Robinson, G.E. and F.L.W. Ratnieks. 1987. Induction of premature honey bee (Hymenoptera: Apidae) flight by juvenile hormone analogs administered orally or topically. J. Econ. Entomol. 80: 784-787.

Siddall, J.B. 1976. Insect growth regulators and insect control: A critical appraisal. Environ. Health Press.14: 119-126.

Smith, C.A. 1995. Searching for safe methods of flea control. J.Am.Vet. Med. Assoc. 206: 1137-1143.

Staal, G.B. 1986. Anti-juvenile horone agents. Ann. Rev. Entomol. 31: 391-429.

Steelman, C.D., J.E. Farlow, T.P. Breaud and P.E. Schilling. 1975. Effects of growth regulators on *Psorophora columbiae* (Dyar and Knab) and non-target aquatic insect species in rice fields. Mosq. News. 35(1): 67-76.

Uchida, M., Y. Izawa and T. Sugimoto. 1987. Inhibition of prostaglandin biosynthesis and oviposition by an insect growth regulator, buprofezin, in *Nilaparvata lugens* Stal. Pestic. Biochem. Physiol. 27: 71-75.

Wang, F. and F. Schnal. 2001. Effects of the imidazole derivative KK-42 on the female and embryos of *Schistocerca gregaria*. Entomol. Sci. 4: 387-392.

Wells, S.A., J. Immaraju, W.S. Ruggero and R. Nelson. 1993. Align, a new insect growth regulator that shows potential for control of cotton pests. Proc. Beltwide Cotton Conf., Memphis, TN. 1: 43-44.

Wilkinson, J.D., K.D. Biever, C.M. Ignoffo, W.J. Pons, R.K. Morrison and R.S. Seay. 1978. Evaluation of diflubenzuron formulations on selected insect parasitoids and predators. J. Ga. Entomol. Soc. 13: 227-236.

Zhang, L., H. Kenji and S. Toshio. 1998. Cross-resistance to insect growth regulators in pyriproxyfen-resistant housefly. Appl. Entomol. Zool. 33: 195-197.