New Insecticide Chemistry for Australian Cotton IPM.

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Abstract

New insecticide technology is needed in the Australian cotton production system to reduce reliance on old chemical groups and to maintain profitability. Conventional insecticides provide us with the backbone of insect control in cotton and will remain as integral and necessary tools for incorporation into integrated pest management (IPM) programs in the future. Several new classes of insecticides such as the oxadiazines, phenylpyrazoles, avermectins, neonicotinoids, spinosyns, pyrroles and diacylhydrazines have new modes of action and offer great promise for the future of insecticide resistance management (IRM) and IPM in cotton. Generally these toxicants are more environmentally acceptable than existing insecticide chemistry; because they offer greater specificity to target pests, have greater intrinsic activity, achieving acceptable insect control at low field use rates and because they degrade rapidly in the environment to harmless metabolites.

Introduction

New insecticide technology is needed in the Australian cotton production system to reduce reliance on old chemical groups and maintain profitability. Despite the fact that a wide variety of insecticides have been registered for the control of insect pests of Australian cotton, current management is heavily dependent on insecticides from five classes; single representatives from the organochlorine class, (endosulfan), and formamidine (amitraz) classes, and several from the carbamate, organophosphate, and pyrethroid classes. All of these are nerve poisons whose mode of action depends on binding at one of only four target sites in the insect's nervous system: endosulfan at the gamma-aminobutyric acid (GABA) gated chloride channel, amitraz at the octopamine receptor, organophosphates and carbamates at the acetylcholinesterase receptor and the pyrethroids at the voltage gated sodium channel. Heavy selection pressure on these relatively few target sites has contributed to problems of resistance. Nowhere is this resistance problem more acute than in efforts to control *Helicoverpa* spp. in Australian cotton.

The ability of Heliothine pests to develop resistance to conventional insecticides has been well-documented around the world over the past 30 years (McCaffery 1998). With the exception of formamidines, Australian field populations of *H. armigera* have developed resistance to all of the above chemical groups (Forrester 1994, Gunning personal communication). Genetic engineering has provided transgenic cotton expressing the *Bacillus thuringiensis* Cry 1Ac delta endotoxin, with insecticidal efficacy against *Helicoverpa* spp. However, the robustness of this technology and a current lack of understanding of how to exploit it to its full potential under Australian conditions, means that additional, novel foliar insecticides for control of Lepidopteran pests are needed. Field trials need to be performed on

both conventional and Ingard/Bollgard Bt cotton varieties in order to provide data for the selection criteria of supplemental insecticides for use in transgenic cotton crops.

A major advance on the part of most agrochemical companies is the acceptance that the development of resistance to any new insecticide is a probability rather than a possibility (Thompson 1996), and their co-operation and support of research through organisations such as the Insecticide Resistance Action Committee (IRAC). New insecticides will be most cost-effective and under reduced selection pressure for resistance if they can be launched with proactive 'anti-resistance' guidelines included on the label and targeted against pest populations with background of susceptibility to existing chemical groups. When available, new insecticides with novel modes of action will provide the necessary addition tools to allow effective rotation of insecticide groups, essential for successful implementation of IRM programs. Thus preservation of remaining efficacy of 'old' chemical groups will have as much bearing on the sustainability (and cost) of new technologies as the initial use of the new products themselves.

The 'special needs' for new insecticides in Australian cotton are very similar to those for other modern high input cotton production systems around the world. In addition to providing cost-effective control of target pests, desirable criteria for novel insecticides would include the need for additional early season products that are less disruptive to beneficial insects and therefore more compatible with IPM, insecticides that will complement other new technologies including transgenic Bt cotton, and with new modes of action to which *Helicoverpa* spp. are not resistant. A barrier for several promising technologies, for example improved strains of foliar Bts and a number of baculoviruses, remains their stability under Australian cotton-growing conditions, which include high ambient temperatures, high ultra-violet (UV) light and a rapidly growing cotton plant which causes growth dilution of insecticide deposits. Increasing environmental concerns are also high on the list for insecticide choice, and when existing products such as endosulfan and methyl parathion are under review, the cotton industry has to take the initiative to research and develop their eventual replacements. As part of this brief review of 'New Insecticide Chemistry for Australian Cotton IPM', we will limit the discussion to novel conventional insecticides (rather than bioinsecticides) and place special emphasis on those compounds that are destined for use in Australian cotton in the near future.

Insecticides acting at target-sites in the nervous system

The nervous system of insects has provided the majority of target sites for insecticides to date. Insect nervous systems are highly specialized and very sensitive, with numerous potential sites for insecticide action (Bloomquist 1996). Disruption at one of any one of these sites can lead to 'knock on effects' in other parts of the nervous system, magnifying the effect of the toxin. Nerve poisons produce rapid symptoms of intoxication, lack of co-ordination, antifeedant effects, paralysis and death. It is ironic that a significant barrier to the acceptance of new insecticide groups (particularly those that do not act on the nervous system), are product expectations that end-users grew accustomed to in the early days of the fast-acting and highly efficacious 'pyrethroid era'. Despite problems of resistance at a number of existing nerve target sites, the diversity of binding domains at existing sites, along with an increasing awareness of novel target sites, means that nerve poisons continue to make up the majority of new insecticides.

Insecticides acting at nerve sodium channels

The voltage gated sodium channels represent one of the most successful insecticide target-sites to date and is shared by both DDT and the pyrethroids. Insecticides from both of these groups hold sodium channels open, causing a prolonged influx of sodium ions into the nerve, resulting in repetitive nerve firing, paralysis and death. Only a small percentage (<1%) of the sodium channels need to be directly affected by the insecticides before their abnormal functioning generates additional action potentials and release of synaptic messengers. Both metabolic and target-site resistance mechanisms are well established for DDT and the pyrethroids in many insect pest species. In some cases metabolic resistance to pyrethroids may be overcome by the use of synergists and some of the candidate synergists that are currently undergoing commercial research and development show promise for use in Australian cotton. To date there is no evidence to suggest that synergists improve efficacy against the pyrethroid target-site mechanism (known in some insect species as *kdr*) which is thought to confer cross resistance between the current members of the pyrethroid class. However there is considerable evidence to suggest that distinct binding domains exist within the sodium channel which can provide additional targets for novel insecticides (Bloomquist 1996). Several candidate insecticide groups including the isobutylamides (also known as the N-alkyamides), trihaloimidazoles and oxadiazines have either a primary or secondary mode of action at the voltage-gated sodium channel, but at sites separate from that of DDT and the pyrethroids (Forrester 1994).

Indoxacarb is the first of a promising new group of insecticides, the oxadiazines, with a new mode of action caused by binding at a new site of the sodium channel. Insecticides in this group and the related chemistry dihydropyrazoles, hold sodium channels closed, preventing the influx of sodium ions into the nerve cell, which suppresses the generation of action potentials. Indoxacarb is a pro-insecticide which is bioactivated by esterase/amidase enzymes inside an insect following ingestion (Wing *et al.* 1998). This may contribute to its greater selectivity than the pyrethroids, and relative selectivity against beneficial insects. No cross-resistance has been reported between indoxacarb and existing insecticide groups including the pyrethroids. Bearing in mind the high use of pyrethroids and current prevalence of a number of different pyrethroid resistance mechanisms in major insect pests (particularly in *H. armigera*), the possibility of cross-resistance warrants thorough investigation before widespread commercial use of this valuable new insecticide class. In theory, insects with metabolic resistance due to high expression of esterase enzymes, including some populations of *H. armigera* (Gunning personal communication) may show negative cross-resistance to indoxacarb (increased susceptibility compared with susceptible insects), and this possibility warrants further investigation. Indoxacarb is currently undergoing field trails for use in cotton in both Australia and the US (trade name 'Steward'). Initial results have confirmed a favorable environmental profile, selectivity towards beneficial insects and high insecticidal efficacy against a range of target pests. As such indoxacarb may provide a valuable tool for the management of insecticide-resistant populations of *H. armigera* in Australian cotton.

Insecticides acting at nerve GABA receptors

The GABA and glutamate receptors activate channels that allow negatively charged chloride ions to flow into the nerve cell and counteract nerve excitation. Artificial blockage of the GABA gated chloride channels (for example by endosulfan or phenylpyrazoles), prevents this feed-back mechanism and results in over-excitation of the nerves. In contrast, artificial

stimulation of the GABA gated chloride channels (by avermectins), leads to over-inhibition of the nerves, lethargy and paralysis (Salgado 1997).

Fipronil is the first highly successful member of a new group of insecticides the phenylpyrazoles, which are highly potent blockers of the GABA-gated chloride channel. This broad-spectrum insecticide is highly active via ingestion, contact and systemic routes, and should provide control of insects which are resistant to carbamate, organophosphate and pyrethroid insecticides. However the mode of action of fipronil is very similar to that of the cyclodienes (e.g. dieldrin and endosulfan) and although it is thought to bind to the GABA receptor at a distinct site from the cyclodienes and picrotoxin, the phenomenon of cross-resistance between these insecticide groups has been reported in the laboratory and requires careful monitoring in the field. Phenylpyrazoles have good activity against a wide range of soil and foliar-feeding (particularly sucking) agricultural pests, including aphids, leafhoppers, planthoppers, chewing Lepidoptera (unfortunately not *Helicoverpa* spp.), Coleoptera and Diptera (Hamon *et al.* 1996). Fipronil could become available for use in cotton in a number of formulations, including a seed dressing ('Cosmos'), an in-furrow treatments a well as a foliar spray ('Regent').

The avermectins are extremely active insecticides belonging to the macrolide chemical class, acaricides and antihelminthics which were originally microbiologically derived from a Japanese strain of *Streptomyces avermitilis*. Their primary mode of action appears to be as GABA agonists, opening GABA gated chloride channels, stimulating the presynaptic release of GABA and depressing nerve excitation Dunbar *et al.* 1996). So far, two members of the group have been successfully commercialised; Ivermectin for control of animal parasites and abamectin (avermectin B1) as a miticide for use in agriculture. The success of abamectin has been limited by its rapid degradation under field conditions, although in some instances this short persistence could be seen as an advantage for use in IPM programs. Abamectin, ('Agrimec') is weakly active against most Lepidoptera but shows good activity against *H. puctigera* in Australia, suggesting a promising early season fit for use in cotton. Structure activity studies have identified semi-synthetic analogs of abamectin, MK-243 and MK-244 (emamectin benzoate, 'Proclaim' in the US). Emamectin benzoate has far superior efficacy against a range of other Lepidopteran pests including *H. armigera* while retaining modest acaricidal activity (Dunbar *et al.* 1996) and is currently undergoing field trials in Australia.

Insecticides acting at nerve synapses

Disruption of the nerve synapse has provided the other main target site for insecticide action which is shared between the organophosphates and carbamates. Nerve signals are carried across the tiny (30nm) gap between two nerve cells (the synaptic cleft) by a number of chemical messengers, called neurotransmitters. One of the most important of the neurotransmitters is acetylcholine which is made up of acetic acid and choline joined by an ester bond. Depolarization of the presynapse by the influx of sodium ions leads to the release of acetylcholine which moves across the synaptic cleft and binds to post-synaptic nicotinic acetylcholinesterase receptors. These then open sodium channels allowing for the relay of the nerve signal in the post-synaptic nerve cell. Following the delivery of this chemical message, the ester bond of acetylcholine is cleaved by the enzyme acetylcholinesterase and the synapse is restored to its resting state. Organophosphate and carbamate insecticides bind to the acetylcholine esterase enzyme preventing degradation of the neurotransmitter which builds up,

causing prolonged excitation of the nerve (Salgado 1997). As is the case with the voltage gated sodium channel, insecticide resistance mechanisms are well established for organophosphates and carbamates in many insect pest species. The target-site resistance mechanism (insensitive acetylcholinesterase) can confer cross resistance within the organophosphate and carbamate groups, but available evidence suggests that a number of distinct binding domains exist at the post-synaptic nicotinic acetylcholinesterase receptor, and these provide additional targets for novel insecticides.

Imidacloprid is the first of a group of 'neonicotinoid' insecticides with a novel mode of action that is similar to the natural product nicotine. They are mimics of acetylcholine, stimulating the depolarization of the postsynaptic nerve cell and exciting the nerve. Imidacloprid features low mammalian toxicity (compared to nicotine), and high insecticidal efficacy against a range of target pest species including Homoptera, Hemiptera, Coleoptera and Diptera (McNally and Mullins 1996). It is particularly active against sucking pests via ingestion, contact and systemic routes, including efficacy against pests that are resistant to organophosphate and carbamate insecticides. No cross resistance has been reported between imidacloprid and other classes of insecticides, although independent selection for resistance has already occurred in some instances. Imidacloprid is currently available for use in Australian cotton as a seed-treatment ('Gaucho'), which provides several weeks of residual pest control, and formulations for use as foliar sprays ('Provado and Confidor') are close to registration. Several other neonicotinoid insecticides are also undergoing development for use in cotton, including acetamiprid ('Rescate 200'), thiomethoxan ('Cruiser'), nitenpyram and diacloden.

The spinosyns are a new class of insecticides derived by fermentation from the metabolites of a new species of Actinomycetes, *Saccharopolyspora spinosa* with a novel mode of action, high insecticidal activity, very low mammalian toxicity and a favorable environmental profile (Sparks *et al.* 1997). The primary mode of action of Spinosad (a mixture of spinosyn A and D) is as a nicotinic acetylcholine receptor agonist, but unlike nicotine and the neonicotinoids (e.g. Imidacloprid), it binds at a novel site of the postsynaptic nicotinic acetylcholine receptor, prolonging the action of acetylcholine without competing for its binding site (Salgado 1997). It is mainly active via ingestion, but has some secondary contact activity, and has good efficacy against pests that are resistant to organophosphate, carbamate and pyrethroid insecticides (Sparks *et al.* 1997). They are very active against a range of agricultural insect pests, particularly against Lepidoptera including *H. punctigera* and *H. armigera,* pose a moderate risk to beneficial Hymenoptera and thrips spp., but are relatively safe to other beneficial insects including predatory bugs and beetles (D. Murray, L. Wilson, personal communication). Spinosad has only recently become available for use in cotton as the foliar spray ('Tracer') and as an 'IPM friendly' heliothicide without existing resistance problems, it represents a welcome addition to the Australian IRM strategy.

Insecticides acting at other target-sites in the nervous system

Octopamine receptors are another existing insecticide target-site, that may serve as the target for new insecticide groups. The formamidine insecticides, amitraz and chlordimeform, are both octopamine agonists, causing excitation of the insects central nervous system, hyperactivity and eventual death. A new insecticide sharing this mode of action is the thiourea compound, diafenthiuron, which is activated by UV light to a stable and highly active carbodiimid derivative, with strong vapor and translaminar insecticidal activity. It provides

residual control of a range of sucking pests, chiefly mites, aphids, jassids and whitefly and has recently been released for use in Australian cotton as 'Pegasus'.

Pymetrozine, trade name 'Chess' in Australia, 'Fulfill' in the US, is a novel pyridine insecticide with systemic activity against aphids, whitefly and jassids. The mode of action of pymetrozine is not yet wholly understood, but it is thought to act at a target-site in the nervous system causing unique antifeedant effects which ultimately results in death of the effected insects by starvation (Forrester 1994).

Insecticides disrupting mitochondrial respiration

Disruption of any of the number of steps involved in mitochondrial respiration provides targets for insecticides that are not prejudiced by existing cross resistance to nerve poisons. Re-oxidation of NADH to NAD+ involves loss of electrons via the electron transport chain and transfer of energy through oxydative phosphorylation to the high energy bonds of ATP. Blockage of an insect's electron transport system or oxydative phosphorylation arrests energy production which ultimately leads to death. Existing mitochondrial respiration insecticides include the bioinsecticide rotenone, which disrupts the electron transport chain in a similar way to a number of recently developed acaricides (e.g. fenazaquin and tebufenpyrad) and the stomach poison hydramethylnon, which currently provides alternate chemistry for use in baits in IRM strategies for pubic health pests (Forrester 1994).

Pyrrole insecticides were developed from structure activity studies following the discovery of insecticidal properties of a natural product, dioxapyrrolomycin, isolated from a strain of *Streptomyces,* which uncouples the electron transport chain from oxydative phosphorylation (French *et al.* 1996). The first commercial product from this class, chlorfenapyr, has not yet received full registration for cotton, but is available on a limited basis as 'Pirate' in the US, and 'Intrepid' in Australia. Chlorfenapyr is predominantly a stomach poison, but also shows limited contact activity and is a pro-insecticide which is bioactivated by monooxygenase enzymes following uptake into an insect. It controls adults, nymphs and larvae (very little ovicidal activity) of over 70 species from Lepidoptera, Coleoptera, Thysanoptera, Orthoptera, Isoptera and Hymenoptera and Acarina (S. Jones personal communication). Initial studies with metabolically resistant insects expressing high monooxygenase activity have shown negative cross-resistance to pyrroles and the possibility of improved efficacy against some metabolically resistant field populations of *H. armigera* warrants further investigation in Australia. Chlorfenapyr has excellent miticidal efficacy and promising activity against a broad spectrum of pests including *Helicoverpa* spp. (French *et al.* 1996). Recent unconfirmed reports suggest that larval *H. armigera* exposed to sub-lethal doses of chlorfenapyr have reduced fecundity as adults (R. Gunning personal communication) and confirmation of this effect could represent an significant additional attribute for use in cotton IRM.

Insecticides disrupting growth regulation

Insect development and growth is regulated by a number of hormones and neurohormones which provide targets for insecticides. Juvenile hormone (JH) and 20-hydroecdysone are primarily involved in the regulation of insect metamorphosis and moulting (at moulting high titres of JH preserve the insect in an immature stage and low titres initiate metamorphosis to the adult stage). However alongside other insect hormones, they play additional important roles in a number of processes including maturation, embryogenesis, reproduction, diapause

and behavior. Due to their poor UV persistence, low intrinsic activity and narrow window of efficacy, early JH analogs (methoprene, hydroprene and kinoprene) achieved limited success in control of insect pests of crops. Later developed, more active compounds including pyriproxyfen (for whiteflies and aphids) and the non-neurotoxic carbamate, fenoxycarb, (as an ovicide against Heliothis) may find a place in future cotton IRM programs (Forrester 1994). One of the most promising and recent additions to this class of insecticides are the diacylhydrazines; tebufenozide ('Confirm'), methoxyfenozide ('Intrepid' in the US, RH 2485 in Australia) and halofenozide. These act as ecdysone agonists, disrupting moulting in a range of Lepidopteran pests, including several major pests of cotton (tebufonozide has high efficacy towards *Spodoptera* spp., whereas methoxyfenozide has improved efficacy against *Helicoverpa* spp. (Harrison *et al.* 1997). The diacylhydrazines are stomach poisons, which are reported to be highly selective, causing minimal disruption of beneficial insects. In addition to its novel mode of action, RH 2485 may provide Australian cotton with a much needed 'soft option' for the control of Lepidopteran pests .

The amino-polysacchararide, chitin, is an essential structural component of insect exoskeletons, mouthparts and peritrophic membranes. Benzoylphenylureas (also known as acylureas) including the product 'Dimilin', inhibit chitin production and cause insecticidal effects due to malformations in moulting, and disruption of the peritrophic membrane causing leakage of gut contents into the haemolymph. Recent developments in this class of insecticides include trials to investigate possible synergistic interactions between Dimilin and transgenic cotton, and the development of 'second generation' of acylureas and include a number of highly active products (chlorfluazuron, teflubenzuron, hexaflumuron, and flufenoxuron), with broad spectrum activity predominantly against mites and sucking pests. Higher rates of chlorfluazuron ('Helix') showed promising activity as a stomach poison of Lepidopteran pests, including *H. armigera.* The product's novel mode of action., good persistence and low toxicity to non-target species gave it a useful fit for control of *H. armigera* in late season 'cut-out' cotton in Australia (Forrester 1994). The withdrawal of chlorfluazuron from Australian cotton in 1994, resulting from the detection of residues accumulated in cattle fed with cotton trash represented a significant loss from the IRM strategy program and new, less persistent acylureas may be developed for use in cotton in the future. Indeed one novel chitin disrupting compound, buprofezin ('Applaud'), shows promising activity against a range of sucking pests including whiteflies.

Conclusions

A variety of promising new insecticide chemistry is becoming available for use in Australian cotton pest management. Only through the wider use of these products by growers and consultants will develop a sufficient knowledge-base to determine their most cost-effective fit for Australian cotton. Further field trials need to be performed in Australia to compare the efficacy of existing and novel insecticides on conventional versus Ingard/Bollgard Bt cotton varieties. These trials should provide data to answer two questions; first, how the products perform under Australian conditions rather than extrapolation of the results of overseas (predominantly US) work and second, to provide data for the selection criteria of supplemental insecticides for use in transgenic cotton crops. New (affordable) insecticides should provide alternatives to old chemical groups, reducing reliance on them while maintaining the profitability of cotton production. Several new classes of insecticides offer great promise for

the future of cotton IPM because their selectivity should allow more effective preservation of early-season beneficial insect spp. in both conventional and transgenic cotton. Where appropriate, these data should provide enough cost-effective alternatives to allow a repositioning of older, overused broad-spectrum insecticide groups to their optimal places in the IRM strategy. Several new groups with novel modes of action show promising efficacy towards *Helicoverpa* spp. which should help to alleviate current difficulties in the management of these major pests. None of these new insecticide groups are 'resistance proof'. The arrival of new insecticides should provide a further incentive to maintain current efforts aimed at the preservation of the efficacy of older chemical groups since they will allow more options for the effective rotation of insecticides with different modes of action through the IRM strategy. The cotton industry's enthusiasm for any one (or all) of these new technologies must not be allowed to result in their initial over use, so that the early development of resistance by major pest species can be avoided and the new chemistry can provide cost-effective insect control for the future.

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