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Novaluron: Prospects and Limitations in Insect Pest Management†

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ABSTRACT

Biorational insecticides are a valuable insect pest management option for growers and pest management practitioners. Novaluron is a recently developed benzoylphenyl urea insecticide with excellent activity against several important insect pests. Through inhibition of chitin synthesis, larval insect stages are targeted with death from abnormal endocuticular deposition and abortive molting. This physiological specificity lends novaluron well to integrated pest management (IPM) programs, as toxicity to mammals, birds and other vertebrates is low, and adult beneficial insects, including predators, parasitoids and pollinators, are generally unaffected. Foliar applications have demonstrated prolonged persistence, providing long-lasting control for growers, and the mode of action of novaluron, completely different from that of commonly used neurotoxic insecticides, makes it a useful alternative insecticide for resistance management. However, there are several obstacles, many inherent to IPM, which may hinder the utility of novaluron. While its narrow spectrum of activity is a key attribute, paradoxically this may be a significant detractor for growers who prefer broad-spectrum control of multiple pests. As an insect growth regulator, timing of novaluron applications is often more restrictive and delayed insecticidal activity usually occurs. The purchase price of benzoylphenyl ureas is generally greater than that of conventional insecticides, which may limit the appeal of novaluron. Further, studies have shown that some beneficial organisms are susceptible to novaluron. Knowledge reviewed here will facilitate continued development and use of biorational compounds for IPM.

†Mention of a proprietary product or trade name does not constitute a recommendation of endorsement by the University of British Columbia or the University of Guelph.

Keywords: biorational insecticides, chitin synthesis inhibitor, constraints of IPM, insecticide selectivity, insect pest control, resistance management

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INTRODUCTION

It is not surprising that following the discovery of the insecticidal properties of the organochlorine insecticide DDT in 1939, and the organophosphorus and carbamate insecticides soon after, synthetic insecticides became the tool of choice in the battle against insect pests. Their ease of application, broad-spectrum activity, relatively low cost and rapid kill are attributes that continue to attract growers and other end users. The beneficial socioeconomic impact of synthetic insecticides has been staggering, as they have been instrumental in increased global production of food and fiber, and control of diseases of medical and veterinary importance. To be sure, no other single insect pest control tool developed thus far offers similar versatility and assurance of success.

However, like all tools, insecticides have limitations. The potential for adverse ecological and human health impacts as a result of excessive and indiscriminate insecticide use was dramatically introduced to the public in 1962 with the publication of Rachel Carson's *Silent Spring* (Carson 1962). At the same time, resistant insect pest populations were rapidly evolving, generating in some cases control problems of crisis proportions (Georghiou 1986). These pro-

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Invited Review

blems were principal drivers in the development of integrated pest management (IPM), a system emphasizing less disruptive control measures, with judicial use of pesticides as a last resort. Yet, after decades of research dedicated to eliminating or minimizing use of insecticides, they remain an integral component of most pest management programs.

It follows that “biorational” insecticides, having selective toxicity and modes of action different than those of neurotoxic insecticides, play an important role in IPM. Such compounds are designed to target pest species while permitting survival and contributions of natural enemies (e.g. predators, parasites and diseases) and other beneficial insects (e.g. pollinators). They often have utility in resistance management programs due to a lack of cross-resistance with broad-spectrum control products. Equally important, safety to pesticide applicators, the public and wildlife is greatly increased with biorational insecticides since biochemical sites not present in vertebrates are targeted.

Key constituents of the current suite of biorational insecticides are the so-called insect growth regulators, characterized by biological activity interfering with specific developmental processes in insects. Among these are the chitin synthesis inhibitors, represented largely by the benzoylphenyl ureas. Philips-Duphar scientists discovered the first benzoylphenyl urea analog, DU 19.111, almost inadvertently while exploring derivatives of the herbicide dichlobenil (van Daalen *et al.* 1972). As the chemistry and mode of action of benzoylphenyl ureas were unique, they were designnated a new class of insecticide (Retnakaran *et al.* 1985). An intensive effort to synthesize the optimal benzoylphenyl urea analog followed, which at the time was diflubenzuron. The search for more potent acylureas during the past three decades has resulted in synthesis of several analogs including chlorfluazuron, teflubenzuron, hexaflumuron, lufenuron and more recently, novaluron (Ishaaya and Horowitz 1998).

NOVALURON

General overview, mode of action, physical/chemical properties

Novaluron, (±)-1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)phenyl]-3-(2,6-difluorobenzoyl)urea (**Fig. 1**), is a benzoylphenyl urea recently developed by Makhteshim-Agan Industries Ltd. and is being distributed by Chemtura USA Corp, formally Crompton Co./Cie. It is a potent suppressor of important lepidopteran and coleopteran pests, and can provide control of several homopteran and dipteran pests. The compound has been formulated in the United States for use on food crops including apples, potatoes, sweet potatoes, and brassicas (Rimon® 0.83EC, 10% AI), ornamentals (Pedestal®, 10% AI) and cotton (Diamond® 0.83EC, 10% AI). Patents and registrations have been approved or are ongoing in several other countries throughout Europe, Asia, Africa and South America, as well as Australia (FAO 2003; PMRA 2006). The US Environmental Protection Agency (EPA) and Canadian Pest Management Regulatory Agency (PMRA) designated novaluron a “reduced-risk/organophosphorus alternative” as it exhibits low acute mammalian toxicity and no significant subchronic effects in mammals (EPA 2001; FAO 2003; FAO/WHO 2005; PMRA 2006). Overall, these agencies consider novaluron to pose low risk to the environment and non-

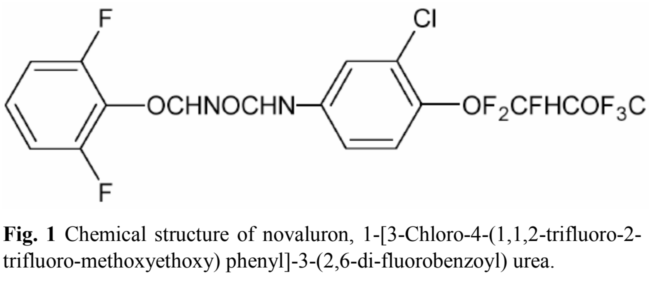

Fig. 1 Chemical structure of novaluron, 1-[3-Chloro-4-(1,1,2-trifluoro-2-trifluoro-methoxyethoxy) phenyl]-3-(2,6-di-fluorobenzoyl) urea.

Table 1 Physical and chemical properties of novaluron (Anonymous 2002; FAO 2003).

Property		Characteristics	
Physical state		Solid	
Colour		Pale pink	
Odour		Non-detectable	
Melting point		176.5-178.0°C	
Vapour pressure		1.6 x 10^{-5} Pa at 25°C	
Relative density		1.56 g/cm^3 at 22°C	
Partition coefficient		Log Pow = 4.3	
Solubility	Water	3 µg/L	
	Organic solvents	*n*-Heptane	8.39 mg/L
		1,2-dichloroethane	2.85 g/L
		Methanol	14.5 g/L
		Acetone	198 g/L
		Ethyl acetate	113 g/L
Stability	Hydrolysis in water	Stable at pH 5.0, slight hydrolysis at pH 7.0 and pH 9.0	
	Photolysis in water	Relatively stable at pH 5.0 under continuous radiation for 3 days	
	Air	½ life (photochemical degradation) = 2.4 h	
	Soil	Strong sorbtivity: Koc = 6650-11813	

target organisms, and value it an important option for IPM that should decrease reliance on organophosphorus, carbamate and pyrethroid insecticides.

No studies have specifically examined the mode of action of novaluron, but the general mechanisms and effects with benzoylphenyl ureas apply. These compounds do not readily inhibit chitin synthesis in cell free systems, nor do they block the chitin biosynthetic pathway in intact larvae (Oberlander and Silhacek 1998). Although a precise biochemical explanation of the insecticidal activity of benzoylphenyl ureas has been elusive, the most likely hypothesis is that they interrupt *in vivo* synthesis and/or transport of specific proteins required for assemblage of polymeric chitin (Oberlander and Silhacek 1998). At the organismal level, symptoms usually are expressed at molt when chitin is being actively produced and broken down (Mulder and Gijswijt 1973; Verloop and Ferrell 1977). Ultimately, the integrity of the endocuticle is compromised, resulting in disruption of ecdysis and eventual death in juvenile stages (Grosscurt 1978; Retnakaran *et al.* 1985). In general, only larvae are affected and all effects, including complete molt inhibition, partial molt inhibition, malformed pupae and failure to feed are due to malformation of the cuticle (Retnakaran and Wright 1987).

The physical and chemical properties, and environmenttal fate of novaluron have been evaluated as part of the registration process (EPA 2001; Anonymous 2002; FAO 2003; PMRA 2006). Novaluron has a low vapor pressure, low water solubility (3 µg/L), which is not affected by pH, and a relatively high Log P_{ow} of 4.3. Rates of hydro- and photolysis are slow and these processes are not expected to significantly degrade the compound in the environment. Novaluron has no adverse effects on soil respiration and N-mineralization, and it sorbs strongly to soils, a feature which is expected to reduce the likelihood of leaching and contaminating ground water systems (EPA 2001; Anonymous 2002; FAO 2003; PMRA 2006) (**Table 1**).

Prospects and limitations of novaluron

Novaluron is a welcome addition to the toolbox of pest management consultants and growers. Its mode of action, being different from that of broad-spectrum insecticides, should make it suitable for IPM and resistance management programs globally. Reliance on older broad-spectrum insecticides should be reduced through the introduction of novaluron and other reduced-risk products. However, certain intrinsic characteristics of the compound, as well as pragmatic agricultural and economic constraints, may limit its utility in some pest management systems.

The following discussion is an assessment of the prospects and limitations of novaluron in insect pest management based on data published in the peer-reviewed literature and regulatory documents, as well as our own observations and opinions. Throughout, the discussion is presented within the context of traits we feel are desirable of insecticides of agricultural and medical importance.

Activity against key pests

Of chief importance to growers is that the products they purchase provide effective, consistent control of target pests. New products that do not reduce risks of losses from pests confer little economic advantage over older products with proven efficacy.

When applied properly against susceptible pests, benzoylphenyl ureas have provided consistently good results (Granett 1987; Retnakaran and Wright 1987). Novaluron has demonstrated insecticidal activity against several important pests.[1] Its bioactivity is usually much greater than that of diflubenzuron and teflubenzuron, and it is at least as active as other recently developed acylureas, such as chlorfluazuron and lufenuron (Ishaaya *et al*. 1996, 1998). Like other benzoylphenyl ureas, novaluron acts primarily by ingestion against immature chewing stages, but does have improved contact toxicity (Ishaaya *et al*. 1996, 1998; Cutler *et al*. 2005a) and translaminar activity (Ishaaya *et al*. 2002), potentially broadening its application spectrum. Although acute lethal effects on adults are not seen, several investigations have demonstrated reduced egg production and/or viability from adults of pest insects exposed to novaluron.

In studies with lepidopteran pests, Ishaaya *et al*. (1996, 1998, 2003) reported that novaluron was highly active against *Spodoptera littoralis* (Boisduval) and *Helicoverpa armigera* (Hübner) larvae by ingestion, with persistent biological activity; 8 days after cotton leaves were treated in the field approximately 100% of exposed larvae died, while 30-60% of larvae died when exposed to foliage treated 15 days previous (Ishaaya *et al*. 1996). Hadapad *et al*. (2001) also showed *H. armigera* larvae were susceptible to novaluron, although lufenuron was more effective in laboratory experiments. *Spodoptera exigua* (Hübner) larvae are highly susceptible to novaluron (Ishaaya *et al*. 1998, 2002). Ingestion of sweet pepper or castor bean foliage treated with 0.27 or 0.50 ppm novaluron, respectively, resulted in almost 100% mortality and treatments of 5 ppm to sweet pepper plants provided effective residual control for 18 days (Ishaaya *et al*. 1998). Maxwell and Fadamiro (2006) found that ≤ 4 novaluron applications per season effectively maintained infestations of diamondback moth (*Plutella xylostella* (L.)), imported cabbage worm (*Pieris rapae* (L.)) and cabbage looper (*Trichoplusia ni* (Hübner)), below the economic threshold limit and resulted in increased marketable cabbage and collards. Cordero *et al*. (2006) suppressed lepidopteran pests with only one or two applications of novaluron to yield 89-97% marketable leaves on collards. Kumar *et al*. (2003) found that while novaluron alone provided 90% mortality of *P. xylostella* larvae, in combination with *Bacillus thuringiensis* only half the rate of novaluron was needed to give 100% mortality. Full-rate combinations of novaluron with malathion, carbaryl, azadirachtin, endosulfan, diflubenzuron and fenvalerate also resulted in complete control of *P. xylostella* larvae. However, in a study evaluating the efficacy of various insecticides on the stem borers *Diatraea saccharalis* (F.) and *Eoreuma loftini* (Dyar) in rice, Reay-Jones *et al*. (2007) reported that novaluron did not significantly reduce injury, demonstrating that lepidopteran pests are not always susceptible to the compound. They suggested that inadequate coverage or suboptimal exposure could have been responsible for the lack of control.

Novaluron provides effective, long-term control of Colorado potato beetle, *Leptinotarsa decemlineata* (Say) (Malinowski and Pawinska 1992; Cutler *et al*. 2007). In laboratory investigations, Cutler *et al*. (2005a) reported excellent residual and oral activity, and good direct contact toxicity against *L. decemlineata* larvae, as well ovicidal activity. Interestingly, *L. decemlineata* larvae from eggs treated with 1.0 ppm novaluron weighed significantly more than those from untreated eggs, providing evidence of a hormetic effect in this insect when exposed to low doses of novaluron. Further, adults produced fewer eggs and hatch of eggs was almost completely suppressed when adults were exposed to treated foliage (Cutler *et al*. 2005a). Good activity against the stored product beetle *Tribolium castaneum* (Herbst) was reported by Kostyukovsky and Trostanetsky (2006). Wheat flour and/or whole grains treated with 1.0 ppm novaluron caused complete mortality of third instars and hatch inhibition of eggs from exposed adults. Similar reductions in egg viability were observed after residual exposure of *T. castaneum* adults to novaluron (Kostyukovsky and Trostanetsky 2006).

In general, novaluron is expected to be most efficacious against chewing insect pests but activity against pests in orders Homoptera, Thysanoptera and Diptera has also been demonstrated. In laboratory and field trials the compound was a powerful suppressor of whiteflies, including sweet potato whitefly (*Bemisia tabaci* Gennadius) (Ishaaya *et al*. 1996, 2001, 2002, 2003), greenhouse whitefly (*Trialeurodes vaporariorum* (Westwood)) (Ishaaya *et al*. 1998, 2001, 2002) and silverleaf whitefly (*Bemisia argentifolii* Bellows and Perring) (Cloyd *et al*. 2004). On the other hand, Cloyd (2003) found in greenhouse trials that novaluron had no effect on citrus mealybug (*Planococcus citri* (Risso)) egg production, although egg viability from treated females and overall pest control was not determined. Seal *et al*. (2006) reported that novaluron generally reduced numbers of chilli thrips (*Scirtothrips dorsalis* Hood) on pepper with repeated applications, although some inconsistency occurred. Due to increased translaminar activity compared to other benzoyphenyl ureas, agromyzid leafminer (*Liriomyza huidobrensis* (Blanchard)) larvae are susceptible. Some mine formation occurred following novaluron treatments, but at 15-45 ppm pupation was significantly reduced and adult emergence was completely suppressed (Ishaaya *et al*. 1996, 2002). House fly populations may also be managed with novaluron. In the laboratory, Cetin *et al*. (2006) reported LC50 values of 1.66 and 2.72 ppm via ingestion and dipping methods, respectively, and > 80% larval mortality at 10 and 20 ppm.

The compound shows excellent potential for control of mosquitoes. In field experiments, Mulla *et al*. (2003) demonstrated that concentrations of 0.05-1.0 ppm novaluron inhibited second and fourth instar *Aedes aegypti* (L.) emergence by 86-96% for approximately 190 days, indicating exceptional long-term activity against this species. The compound also yielded good long-term control against natural populations of *Culex* spp. mosquitoes, suppressing larval emergence 14 days at concentrations of 1.25-5 ppb in microcosms (Su *et al*. 2003). Arredondo-Jiménez and Valdez-Delgado (2006) conducted a series of tests against *A. aegypti*, *Aedes albopictus* Skuse, *Anopheles albimanus* Wiedemann, *Anopheles pseudopunctipennis* Theobald and *Culex quinquefasciatus* Say in southern Mexico. In semi-field experiments, pupae of all species were highly susceptible to novaluron at 16.6 ppb or 55 ppb with adult emergence inhibited 90-97% for 14-17 weeks. In village-scale trials, applications of 600 ml/ha novaluron to natural breeding habitats within 1 km of neighbouring villages re-

[1] Product labels of Rimon, Pedestal and Diamond provide a complete list of insect pests, which the manufacturer claims, can be controlled with these formulations. Other reports on preliminary and routine screening for management of insects with novaluron occur in *Arthropod Management Tests* (http://www.entsoc.org/pubs/periodicals/amt/index.htm) and similar forums. As the primary focus of this review is peer-reviewed literature, these sources are not cited.

Table 2 Selectivity of novaluron towards beneficial arthropods.

Target Organism(s)	Exposure	Result	Reference
Aquatic invertebrates (several species)	Micro- and mesocosms	"Favorable margin of safety" (qualitative observations)	Su *et al.* 2003
Aquatic invertebrates (several taxa)	Aquatic experimental field plots	0.166 mg/L had no effect; 0.332 and 0.498 mg/L reduced non-target fauna	Arredondo-Jiménez and Valdez-Delgado 2006
Phytoseiid mites	Field (cotton)	No effects 6 weeks post-treatment	Ishaaya *et al.* 2001
Spiders, ladybird beetles	Field (cole crops)	No reduction in populations	Maxwell and Fadamiro 2006
Terrestrial arthropods (predators and parasites)	Field (citrus)	Reduced parasitoid emergence for 2 days post-application; reduced predatory mite nymph populations for 2 months post-application	PMRA 2006
Apis mellifera	Field (citrus)	Reduced brood development and colony strength	PMRA 2006
Atheta coriaria	Laboratory	Adults unaffected; larvae susceptible by direct contact	Jandricic *et al.* 2006
Bombus impatiens, *Megachile rotundata*	Laboratory	No mortality through direct contact	King 2005
Bombus terrestris	Laboratory	No acute toxicity to adults; reduced offspring from exposed workers; reduced egg hatch and larval development via contact and ingestion	Mommaerts *et al.* 2006
Encarsia formosa	Greenhouse (tomato)	No effect on populations and parasitism	Ishaaya *et al.* 2002
Podisus maculiventris	Laboratory	Nymph mortality via direct contact, treated foliage, and treated prey; reduced egg viability from exposed adults	Cutler *et al.* 2006
Stratiolaelaps scimitus	Laboratory	No mortality of protonymphs; no developmental effects	Cabrera *et al.* 2005
Trichgramma pretiosum	Laboratory	Parasitism, pupal development and emergence success varied with host and route of exposure	Bastos *et al.* 2006

duced *A. albimanus* larval populations for at least 8 weeks and sharply reduced densities of host-seeking adults (Arredondo-Jiménez and Valdez-Delgado 2006). Pestalto Environmental Products Inc. has recently developed a slow release novaluron formulation (in experiments concentrations ranged 0.1-149 ppb due to repeated refilling events in potable storage vessels) intended for mosquito control that causes 82-100% larval mortality for up to 8 months (R. Dupree personal communication).[2]

Selectivity favoring beneficial species

Insecticide selectivity is a cornerstone of IPM (Ripper 1956; Croft and Brown 1975). In addition to reducing toxicological risks to humans and wildlife, selective insecticides spare natural enemies of insect pests and pollinators, both of which can directly increase crop yields. By targeting biological receptors not present in vertebrates, novaluron is less hazardous to most non-target organisms than neurotoxic insecticides that may act on common biochemical targets or pathways. It has low acute and chronic mammalian toxicity and displays no developmental or reproductive toxicity (EPA 2001; FAO 2003; FAO/WHO 2005; PMRA 2006). The toxicity of novaluron to aquatic plants, birds, fish, earthworms and microflora is also low (FAO 2003), although there may be potential for bioaccumulation in fish in situations where applications are frequent and drift into aquatic habitats occurs (PMRA 2006). Novaluron is very toxic to aquatic crustaceans (FAO 2003). Given that the molecules rapidly dissipates from the water phase to sediment phase (see below), and that all life cycle stages of most aquatic crustaceans are in direct contact with sediment, these organisms are particularly susceptible (PMRA 2006).

Novaluron theoretically elicits physiological selectivity in favor of adult insects by targeting chitin synthesis, which predominately occurs at molt in juvenile insect stages. Indeed, several reports indicate novaluron has good selectivity favoring beneficial insects (**Table 2**). Ishaaya *et al.* (2001) sprayed cotton fields twice with field rates of novaluron, assessed phytoseiid mite populations (several species) six weeks later and found no differences between treated and untreated control plots. In a greenhouse experiment, Ishaaya *et al.* (2002) reported that a commercial rate of novaluron applied to whitefly (*T. vaporariorum*) infested tomato plants had no effect on populations and parasitism of the parasitoid *Encarsia formosa* Gahan, and eventually resulted in total suppression of the whitefly population. In laboratory experiments with the soil dwelling predatory mite *Stratiolaelaps scimitus* (Womersley), novaluron caused no mortality of protonymphs and, although molt was slightly delayed, no significant developmental effects were subsequently observed (Cabrera *et al.* 2005). While aquatic crustaceans are very susceptible to novaluron (FAO 2003), Arredondo-Jiménez and Valdez-Delgado (2006) found that 0.166 mg/L novaluron had no significant effect on non-target arthropods in aquatic experimental field plots, although concentrations 2- and 3-fold higher significantly reduced non-target fauna. Similarly, Su *et al.* (2003) suggested, based on qualitative observations in micro- and mesocosms, that novaluron had a favorable margin of safety for non-target aquatic invertebrates cohabiting with mosquito larvae. In field efficacy trials against lepidopteran pests of cole crops, Maxwell and Fadamiro (2006) observed no reductions in numbers of spiders or ladybird beetles in treated plots, suggesting no effect of novaluron on these predators. Other work has shown that adult bumble bees (*Bombus impatiens* Cresson) and leafcutter bees (*Megachile rotundata* (F.)) are unaffected by direct contact exposure to novaluron (King 2005).

The aforementioned studies confirm that novaluron exhibits selectivity in favor of some non-target organisms and beneficial insects, and demonstrate that it is compatible with many IPM programs. However, other investigations indicate that novaluron may be acutely and sublethally toxic to some beneficial insects (**Table 2**). In experiments with the predatory bug *Podisus maculiventris* (Say), Cutler *et al.* (2006) showed that nymphs were susceptible by direct contact, exposure to potato foliage, and through consumption of treated prey. Novaluron-treated *P. Maculiventris* eggs were able to hatch but neonates were thereafter unable to molt. Adult females caged with *L. decemlineata* larvae and novaluron-treated potato plants had reduced oviposition and egg viability compared to those caged with untreated potato plants (Cutler *et al.* 2006). Similarly, Mommaerts *et al.* (2006) found that while the maximum recommended field rate of novaluron was not acutely toxic to the bumble bee *Bombus terrestris* L., pronounced sublethal toxicity can occur. In their laboratory experiments there was a sharp reduction or complete suppression of male production in micro-colonies when workers were exposed to novaluron via direct contact, or treated sugar-water or pollen. Similar reductions or arrestment in egg hatch and larval

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development were also observed. In another field study, novaluron applied at 225 g AI/ha reduced honey bee brood development and colony strength (PMRA 2006).

Jandricic *et al*. (2006) found that while adult rove beetles (*Atheta coriaria* Kraatz) were unaffected by direct contact exposure to technical grade novaluron, third instars were highly susceptible. Bastos *et al*. (2006) showed that the toxicity of novaluron to *Trichogramma pretiosum* Riley depended on the host and/or mode of exposure. Although pupae developing in Angoumois grain moth (*Sitotroga cerealella* Olivier) eggs topically treated with novaluron were unaffected, adult emergence from Mediterranean flour moth (*Ephestia kuehniella* (Zeller)) eggs treated with novaluron was only half of that seen in controls. *T. pretiosum* adults offered novaluron-treated *S. cerealella* and *E. kuehniella* eggs were able to parasitize eggs over 80% of the time, but only 40% and 10%, respectively, of F_1 adults were able to emerge from these eggs (Bastos *et al*. 2006). In a field study, populations of *Lysiphebus* parasitoid wasps and *Amblyseius* predatory mites were reduced almost 90% for two months following two applications of Rimon 10EC at 225 g AI/ha (7-day interval) (PMRA 2006).

Thus, while selectivity following novaluron applications occurs, generalizations of selectivity cannot be inferred. When tested against pest insects, there are clearly interspecific differences in susceptibility to novaluron, but pronounced differences may also exist intraspecifically, varying across populations (Cutler *et al*. 2005b). There is no reason to suspect that susceptibility to novaluron should not also vary substantially among beneficial insects. Physiologically and pharmacologically, selectivity of novaluron favoring beneficial insects depends on many factors including rates of absorption through the cuticle following direct contact or gut wall after ingestion and metabolism after absorption.

Besides variable toxicology following exposure, selectively of novaluron also depends on ecological interactions and behaviors that may increase or decrease the probability of exposure. Insects found to be highly susceptible in the laboratory will suffer no adverse toxicological effects if not exposed to novaluron in the field. Differences in the life history, movement, and spatial and temporal distribution of pest vs. beneficial insects provide opportunities to time and place novaluron applications to minimize undesirable exposures. For example, buffer zones around fields and untreated crop refuges can reduce exposure for non-target arthropods. Temporal selectivity has been achieved with other benzoylphenyl ureas in specific cropping systems (Granett *et al*. 1976; Jones *et al*. 1983) and suggests that similar ecological selectivity could be important when applying novaluron.

Results from both laboratory and field experiments in different cropping systems are critical to accurately evaluate compatibility of novaluron with beneficial insects. Although the laboratory experiments cited are invaluable to understand mechanisms of toxicity and differential susceptibility depending on life stage or route of exposure, they greatly oversimplify and usually exaggerate exposure in the field. On the other hand, if selectivity is observed in the field, understanding mechanisms of selectivity deciphered through laboratory experiments may predict similar success in other field situations (Granett 1987).

Resistance management utility

A strategy within the IPM philosophy, resistance management contributes to the goal of implementing the best set of management tactics while minimizing socioeconomic and environmental impact. While increased concentrations and frequencies of insecticide application often follow control failures and accelerate resistance development, effective resistance management concurrently decreases rates of pesticide use and prolongs the efficacy of environmentally safe compounds (Denholm *et al*. 1998). Regrettably, insecticide resistance continues to be a serious obstacle in agricultural production and disease vector management (Whalon *et al*. 2006). It is therefore imperative that novel insecticides intended to reduce reliance on broad-spectrum neurotoxins have resistance management utility. Moreover, evaluation of resistance risks prior to widespread use of new compounds is being increasingly emphasized (Denholm *et al*. 1998).

Some work has investigated the resistance management potential of novaluron. Ishaaya *et al*. (2003) found that a *S. littoralis* field population and a *B. tabaci* laboratory colony with 1200- to 2000-fold resistance to the juvenile hormone mimic pyriproxyfen were not resistant to novaluron. Whiteflies with about 35-fold and 22-fold resistance to the neonicotinoids acetamiprid and thiamethoxam, respectively, also showed no cross-resistance with novaluron. In another study with different field populations, *S. littoralis* with 10-fold resistance to teflubenzuron, and *B. tabaci* with over 500-fold resistance to pyriproxyfen and 10-fold resistance to buprofezin (a thiadizine-like chitin synthesis inhibitor), were highly susceptible to novaluron (Ishaaya *et al*. 2002). Cutler *et al*. (2005b) found that adult *L. decemlineata* with 91-fold resistance to imidacloprid and 4-fold resistance to thiamethoxam produced larvae only 2.5-fold less susceptible to novaluron compared to a laboratory-susceptible stain. In a Canadian survey assessing susceptibility of 27 *L. decemlineata* field populations to novaluron, larval mortalities at a diagnostic concentration were 55-100%, but only 2 populations were significantly less susceptible than a laboratory-susceptible strain (Cutler *et al*. 2005b). Further, the diagnostic concentration used (2.38 ppm = LC98 of the laboratory-susceptible strain) was far less than exposure concentrations likely to be encountered in the field. Reuveny and Cohen (2004) found that the susceptibility to 1 ppm novaluron of larvae from a field population of codling moth (*Cydia pomonella* (L.)) exhibiting 7-fold resistance to azinphosmethyl, an organophosphorus insecticide, was not appreciably different from that of a laboratory colony.

These studies indicate novaluron could be an effective option for growers encountering pest populations resistant to neurotoxic insecticides and insect growth regulators. As a group, benzoylphenyl ureas traditionally have a good track record of providing control of pests where other insecticides have acted as selection agents (Retnakaran *et al*. 1985). This is not to say, of course, that novaluron is immune to resistance development. Although biochemical mechanisms of benzoylphenyl urea resistance are often different from those implicated in resistance to conventional compounds (Pimprikar and Georghiou 1979), the same mechanism may confer resistance to both benzoylphenyl urea and conventional insecticides. For example, organophosphorus, carbamate and organochlorine insecticide resistant house flies have exhibited cross-resistance to diflubenzuron (Cerf and Georghiou 1974; Oppennoorth and van der Pas 1977). This cross-resistance was attributed primarily to microsomal oxidases, enzymes that are widely used by insects to detoxify a number of plant toxins and insecticides. Cutler *et al*. (2005b) found that esterase-based detoxification, another common metabolic mechanism of resistance to many insecticides, was responsible for low-level tolerance to novaluron in an imidacloprid-resistant *L. decemlineata* population.

The persistence of biological activity of foliar-applied novaluron may also be important in the development of resistance to novaluron. Persistence has been cited as an important factor in the evolution of insecticide resistance since it prolongs selection for resistant individuals and eliminates susceptible homozygotes from exposed populations (Roush 1989). Several studies indicate that foliar applications of novaluron have biological activity that can persist for weeks (Ishaaya *et al*. 1996, 1998, 2001, 2002; Cutler *et al*. 2005a, 2007), which could accelerate evolution of resistance in target pests.

Nonetheless, novaluron possesses several important characteristics that may delay resistance development in insect pests (Cutler *et al*. 2005b). In addition to its mode of action being completely different from that of commonly used neurotoxic insecticides, its selective properties should allow survival of most natural enemies, providing an additional mortality factor for pests, which may reduce the need for repeated insecticide applications. As well, larval stages are often more sensitive to and less capable of developing resistance to insecticides than adults (Roush 1989); the mode of action of novaluron dictates that immature life stages are the predominant target. Further, since novaluron is non-systemic, refugia will exist in new plant growth (barring repeat application), permitting survival of susceptible genotypes and production of susceptible offspring in subsequent generations (Cutler *et al*. 2005b).

Environmental persistence and contamination

After killing the target pest(s), insecticides are ideally readily metabolized or decomposed to minimize exposure to non-target organisms and contamination of soil and water. The prolonged persistence of biological activity of foliar-applied novaluron suggests that extensive exposure to non-target arthropods could occur. However, no studies thus far have reported serious long-term adverse impacts of novaluron applications on beneficial arthropods.

Novaluron is stable under environmental conditions. No significant hydrolysis occurs at pH 5 and 7, and the first-order DT50 (dissipation time for 50% of the molecule) at pH 9 and 25°C is approximately 100 days (FAO 2003). Based on its low solubility in water (3 μg/L) and strong adsorption on to soil/sediment particles, however, novaluron is not expected to persist in water phase. The PMRA considers novaluron to be non- to slightly persistent in aerobic aquatic water/sediment systems with half-lives ranging 6-26 days (PMRA 2006).

The persistence of novaluron or its metabolites in soil depends on soil type and environmental conditions. The FAO indicates that the DT90 of novaluron in soil is > 100 days (FAO 2003). Transformation products of the parent molecule have been shown to accumulate and persist in soil under aerobic and/or anaerobic conditions in the laboratory, although such persistence was not seen in the field (PMRA 2006). Rotational crop studies with radio-labelled novaluron found that total radioactive residues (TRR) in soil declined from 98-99% on the day of application to 32-49% at final harvest, 127-195 days after application (FAO/WHO 2005). In the rotational crops spinach, turnip and spring wheat, TRR were low at 0.001-0.004 mg/kg, indicating that accumulation of novaluron, or its degradates, in rotational crops from use on primary crops under typical conditions is unlikely (FAO/WHO 2005). Under Canadian field conditions, novaluron is non- to moderately persistent in soils with DT50 values of 18-81 days (PMRA 2006). It sorbs very strongly to soils (FAO 2003; FAO/WHO 2005) decreasing concerns of leaching and water contamination through runoff events, and transformation in soil and aerobic water/sediment systems is usually rapid (PMRA 2006). Photolysis is expected to cause no significant environmenttal degradation with a DT50 of 139 days under natural summer sunlight (12 h daylight assumed).

In Canada, persistence of pesticides in soil, sediment and water are based on DT50 values as follows: < 15 days = non-persistent; 15-45 days = slightly persistent; 45-180 days = moderately persistent; > 180 = persistent. Other nations within the OECD have similar rankings systems, although some countries (e.g. Greece) classify pesticides with DT50s > 60 days to be persistent (OECD 2003). The classification of novaluron as non-persistent or persistent in soil or sediment may therefore vary among regulatory agencies. However, concerns of environmental persistence and contamination would not be expected to be a serious barrier to registration and use of novaluron in most countries.

Economic and 'ease of use' constraints

Ultimately, the use of any new insect pest control technology must make economic sense to end-users. In conventional agriculture, cost is normally second only to efficacy in terms of grower priorities that determine whether or not a particular pest control product will be used. Limited time and resources of growers usually dictate a preference for products that are cheap, easy to apply and broad-spectrum in activity, all characteristics of traditional neurotoxic insecticides. These are issues that may influence future use of novaluron in pest management programs.

The costs associated with developing benzoylphenyl ureas have generally been greater than those of neurotoxins (Granett 1987) and this means higher purchase costs for the grower. Novaluron is a relatively simple molecule and may not be that difficult or expensive to synthesize. However, the costs of developing and commercializing modern control agents is much higher than that of older materials that entered the market when there were far fewer regulatory hurdles to clear. The increased investment by agrochemical companies means that end users usually pay more for novel insecticides. Also, the total amount of active ingredient sold will influence purchase price for the grower. For top-selling insecticides, each kilogram of product bears a relatively small portion of the development cost, meaning end user costs can be kept relatively low. Sales of benzoylphenyl ureas have traditionally held a small share of global pesticide market. The commercialization of novaluron is unlikely to change this substantially, suggesting purchase prices will necessarily be higher to offset developmental costs. Still, novaluron is close to registration for several commodities in many countries and one would expect it to be competitive with other insecticides, especially if good efficacy against target pests is established.

It is ironic that while selectivity – the key constraint for use of insecticides in IPM systems – is generally achieved with novaluron applications and is the key advantage over broad-spectrum insecticides, this very characteristic may detract growers from using it in situations where several key pests require control. As pointed out by Granett (1987), growers usually prefer to use compounds that control multiple pests concurrently since such materials usually require less planning and, generally, fewer treatments. When using novaluron, growers might anticipate the need for additional pest control products or tactics. For example, key pests of potato throughout most of North America are *L. decemlineata*, potato aphid (*Macrosiphum euphorbiae* (Thomas)), green peach aphid (*Myzus persicae* (Sulzer)), potato leafhopper (*Empoasca fabae* (Harris)), tarnished plant bug (*Lygus lineolaris* (Palisot de Beauvois)) and tuber flea beetle (*Epitrix tuberis* Gentner). Several active ingredients are available that can control all or most of these pests, but novaluron provides effective control of *L. decemlineata* only (C. Cutler, personal observation). Further, for some crops/commodities where novaluron could be used, growers have the option of using systemic insecticides that may be applied to seeds or in-furrow, thereby providing protection upon plant emergence and avoiding foliar insecticide applications for several weeks. Despite the advantages novaluron can offer, faced with such a dilemma many growers may opt to use single broad-spectrum or systemic products.

The mode of action of novaluron also presents challenges related to application timing. Neurotoxins tend to affect all life-stages, permitting a broad temporal window of application. In contrast, novaluron acts predominately against immature stages and applications have to coincide with these stadia. Cutler *et al*. (2007) showed that while a 50 g AI/ha novaluron treatment to manage *L. decemlineata* was unsatisfactory when applied at observance of egg masses, an application only 7 days later, when second in-stars were observed, provided excellent protection. Thus, for the farmer, more time and resources may have to be allocated to monitoring of susceptible life stages to ensure application success with novaluron.

The speed of insecticidal action may be an additional use constraint (Granett 1987). Mortality following novaluron treatments is not usually seen until larval molt when chitin is being actively synthesized. Depending on the species and instar targeted this can take several days. For growers used to seeing neurotoxins work within hours of application, delays in insecticidal activity encountered with novaluron may be distressing. More importantly, in many situations delays in pest mortality are economically unacceptable as crop losses accelerate after action thresholds are exceeded.

In other ways, however, novaluron offers application flexibility equal to that of older broad-spectrum compounds. No special application equipment is required and mixtures/alternations with other pesticides are feasible (Kumar *et al*. 2003; Cutler *et al*. 2007). Novaluron is also rain-fast and highly resistant to photo-degradation, providing long-term pest control (Ishaaya *et al*. 1996, 1998; Cutler *et al*. 2005b, 2007), which may alleviate challenges of precisely timed applications. Although concerns of impacts on beneficial insects and resistance development increase with prolonged biological activity, in reality many growers would welcome the extended protection and flexible timing offered by persistent products. For example, Malinowski and Pawinska (1992) found that during field trials with potato in Poland spanning several years, a single novaluron treatment consistently suppressed *L. decemlineata* population densities below economic levels for the whole season. Prolonged efficacy can therefore result in fewer insecticide applications, resulting in reduced environmental contamination and grower exposure.

THE IPM CHALLENGE

This review focuses on the prospects and limitations of novaluron in IPM programs, but much of the discussion is not unique to this active ingredient. Perceived "operational inconveniences" such as temporal restrictions of applications and a limited activity spectrum are also considered by some to be weaknesses of some other insect growth regulators and biopesticides. However, as the research highlighted above attests, when applied properly novaluron can provide effective control of insect pests in a variety of cropping systems. Indeed, potential limiting factors with novaluron are probably based more on challenges inherent to IPM rather than the product itself.

Growers, the public, researchers, government agencies and agrochemical manufacturers all have a stake in IPM (Dent 2000). Each desires the development and use of consistent, profitable and environmentally-sound IPM methods, albeit their motives may differ. For agrochemical companies, constraints of commerce and responsibilities to shareholders mean development of efficacious compounds that will result in profits is usually of foremost interest. On the other hand, most consumers would likely cite human and environmental safety of insecticides as their top priority. Individual growers, who work to feed their own families but also must be sensitive to consumer concerns, certainly exist along a continuum between both extremes. Government and international agencies must work to benefit all other stakeholders. Complicating matters is the fact that within and among these interest groups, values encompasssing IPM inevitably shift over time and vary between regions and countries (e.g. Dent 2000). Thus, the success of any pest control technology depends to a large degree on the motives and interests of the parties involved and the resulting collective cost-benefit ratio of using that technology.

If novaluron or any other biorational pest control technology is to be fully used and adopted, a continued concerted effort towards the common IPM goal is required. And although design, management and implementation of IPM programs incorporating these new technologies is often slow and complex (Dent 2000), progress clearly is being made. Present day consumers are more informed than ever before on health and environmental issues, and potential hazards associated with some pest control measures. Their concerns can directly influence directives of other stakeholders. Most growers realize the days of insect control solely by calendar sprays of chemicals are over, appreciate benefits of the IPM approach to insect pest control and are receptive to desires of consumers. Furthermore, many older organophosphorus and carbamate insecticides have been or are being legislatively phased-out in some countries (e.g. passing of the US Food Quality Protection Act in 1996), and new reduced-risk products are being championed. Many countries/states have launched "minor use" programs that promote field research on new reduced-risk compounds and improve grower access to pesticides for use on minor crops. While agrochemical companies realize that they too must adapt to changing consumer values and regulatory environments, minor use programs provide additional incentives to develop and register biorational products for low acreage commodities with limited market potential.

Biorational insecticides are therefore likely to play an increasingly important role in insect pest management. Still, impediments to grower acceptance and access must be overcome to achieve optimal use of novaluron and similar products. Growers should be made aware of the alternatives and may require education to establish more sophisticated monitoring methods and sounder decision rules. As grower profit margins are usually extremely tight, the role of government and university extension personnel, as well as trade publications and newsletters, may need to be expanded to fill these knowledge gaps. Although many present day governments seem to be removing themselves from extensive activities, the environmental and human health benefits accrued should be incentive enough for governments to provide financial backing to educate growers and encourage IPM programs implementing biorational pesticides.

RECOMMENDATIONS FOR FUTURE WORK

The following are areas we feel require further study or work to maximize the utility of novaluron in insect pest management:

- The physiological selectivity of novaluron against larval or juvenile insects is significant but not absolute, and will vary among organisms and agro-ecosystems. It is necessary to identify non-susceptible beneficial insects, clarify their habitats and determine if susceptibility depends on the mode of exposure, differential metabolism or ecological factors. Timing, placement and rates of application may also need to be adjusted to minimize impacts. Critical study of the problem in both the laboratory and field is essential to fully characterize selectivity of novaluron in specific agricultural systems.
- There is a paucity of peer-reviewed environmental studies on persistence and potential impacts on non-target organisms other than terrestrial insects and mites. These issues deserve further examination. For example, novaluron dissipates rapidly from water phase into sediment, is highly toxic to many benthic arthropods and has potential to bioaccumulate in fish. This suggests that aquatic habitats subject drift during agricultural applications or those exposed to novaluron during treatments against mosquitoes could be at greater risk.
- Proactive resistance management is necessary to ensure consistent and enduring field efficacy of new materials. Studies that elucidate biochemical or behavioral mechanisms of novaluron resistance could be key to predict and prevent future control failures. Novaluron treatment alternations with insecticides from other classes should be encouraged and investigations into the viability of other strategies to minimize resistance development (e.g. maximizing non-chemical mortality, spot-treatments to provide refugia) should be explored.
- Although current agricultural research programs seems to be de-emphasizing detailed field-scale management studies, more of this type of work needs to be published

in peer-reviewed journals to clarify optimal insecticide application strategies in specific cropping systems. Merely documenting efficacy in short reports is useful but insufficient. Extension personnel and growers require concrete and practical decision rules to maximize efficacy and minimize resistance development. The field experiment approach taken has to be holistic with treatment recommendations based on the population dynamics and life histories of major pests and beneficial species within the agro-ecosystem. A provident manufacturer would do well to fund or undertake such work during the later stages of product development.

- Biorational insecticides like novaluron are only one of many insect management tools available. Potential niche markets where other pest management technologies are less used need to be identified and studied. At the same time, it is likely that novaluron could be used in concert with many of these technologies – e.g. transgenic crop varieties, semiochemical interference methods, biological and cultural control tactics – to maximize IPM objectives. Development of specific management programs integrating these strategies should be explored and encouraged.
- Growers who are satisfied with a pest management control product or strategy are generally unreceptive to change, and are unlikely to adopt new tactics they do not understand (Dent 2000). Governments, agrochemical companies, scientists and extension personnel therefore must increase their efforts to educate growers of the benefits and potential pitfalls encountered when using novaluron.

CONCLUSIONS

The benzoylphenyl ureas have proved very useful in controlling a wide variety of insect pests within and outside of IPM systems (Retnakaran and Wright 1987). Keys to their continued success are their specificity for larval/juvenile stages, low vertebrate toxicity and consistent field performance. Novaluron is one of the most recently developed benzoylphenyl urea analogs. Not yet registered in most countries, it has demonstrated excellent activity against many important insect pests. Though absolute selectivity towards target pests may not always be achieved, novaluron certainly confers substantial biorational advantages over broad-spectrum insecticides; beneficial insects should be often spared, risks to wildlife and humans will be low, and its unique mode of action will also make it a useful insecticide alternative in resistance management. Overall the chemical holds promise in insect pest management programs. Potential issues with selectivity, application timing and speed of action exist but can be overcome once the imperative of IPM is fully understood and continued efforts are made to educate growers of the benefits of using biorational insecticides.

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