The Presidential Green Chemistry Challenge Awards Program
Nomination for the 2012 Awards

Chlorantraniliprole: Increased Food Production, Reduced Risks, More Sustainable Agriculture

December 23, 2011

Primary Sponsors:

Rik L. Miller
President
E.I. du Pont de Nemours and Company
DuPont Crop Protection
4417 Lancaster Pike
Chestnut Run Plaza, 705/1S11
Wilmington, DE 19805
(302) 999-5518
Rik.L.Miller@usa.dupont.com

Linda J. Fisher
Vice President and Chief Sustainability Officer
E.I. du Pont de Nemours and Company
DuPont Safety Health & Environment
1007 Market Street
DuPont Building, Room 6074
Wilmington, DE 19880
(302) 774-6074
Linda.J.Fisher@usa.dupont.com

Contact Persons:

Richard A. Carver, Ph.D.
Senior Product Registration Manager
E.I. du Pont de Nemours and Company
DuPont Crop Protection
Stine-Haskell Research Center
1090 Elkton Road S300/415
Newark, DE 19711
(302) 451-4517
Richard.A.Carver@usa.dupont.com

Michael D. Woodward, Ph.D.
Global Registration Manager
E.I. du Pont de Nemours and Company
DuPont Crop Protection
Stine-Haskell Research Center
1090 Elkton Road S300/408
Newark, DE 19711
(302) 366-6396
Michael.D.Woodward@usa.dupont.com

Chlorantraniliprole:
Increased Food Production, Reduced Risks,
More Sustainable Agriculture

Recent Milestones

The first U.S. EPA registration was granted in May 2008. Since its introduction, products containing chlorantraniliprole currently are the fastest growing crop protection products in the world and are registered in 82 countries, with registration pending in 21 other countries. In 2011, more than 20 million farmers used products containing chlorantraniliprole. In the United States, more than 400 crops and other uses are listed on the registered product labels.

Award Category

Focus Area 3: Industry Sponsor for a technology. This nomination is not eligible for the small business award or the academic award.

Primary Focus Area

Design of greener chemicals

Description of Research, Development or Aspects Occurring Within the United States

All research and development described in this nomination occurred within the United States.

Abstract

One in six of the world's people is starving and nearly half the population is malnourished. The United Nations estimates that food production must increase by 70% to feed everyone. While farmers in the United States and around the world strive to provide enough food, they continue to struggle to overcome insects that damage crops and limit food production.

Lepidopteran insects are the second-largest group of insects in the world. The caterpillar larvae of many lepidopteran species are major pests in agriculture, defoliating plants and attacking fruit and root systems. Insects consume 20% of the world's crops; lepidopteran pests are likely responsible for 30% to 40% of that damage. In many developing countries, lepidopteran insects consume 50% of all crops.

While insecticides are available to control these pests, many may have toxicity profiles higher than desired or pose other risks to the environment. DuPont redesigned its new active ingredient discovery process, integrating chemistry and biology with toxicological, environmental and site-of-action studies to simultaneously provide lower-toxicity products and optimize product performance. The resulting active ingredient, chlorantraniliprole, has excellent toxicological and environmental profiles, and is one of the most potent and efficacious insecticides ever discovered.

While highly effective in controlling food-destroying insects, chlorantraniliprole has set new standards for environmental stewardship and low toxicity. It is a precedent-setting new tool for the advancement of sustainable agriculture. Its selective action, which targets damaging insects, is chiefly responsible for its inherent low toxicity to non-target species. Its broad spectrum of control and low use rates make chlorantraniliprole an ideal replacement for more toxic and less selective pesticides in many important global markets. The benefits of chlorantraniliprole extend to workers, the public, and the environment.

Chlorantraniliprole:
Increased Food Production, Reduced Risks,
More Sustainable Agriculture

As the world's population swells from 7 billion people today to a projected 9 billion by 2050, hunger threatens to become a global crisis if it is not addressed in multiple ways with worldwide collaboration. Already, one in six people is starving and nearly half are malnourished. The United Nations estimates that food production must increase by 70% to feed everyone. While farmers in the United States and around the world strive to provide enough food, they continue to struggle to overcome insects that damage crops, significantly reducing their ability to produce fruits, vegetables, nuts and other foods.

Lepidoptera are the second-largest group of insects in the world. The caterpillar larvae of many lepidopteran species are major pests in agriculture, defoliating plants and attacking fruit and root systems, making plants less able to produce according to their genetic potential and wasting valuable resources. Most crops are attacked by at least one species of lepidopteran insect, and some develop resistance to pesticides after repeated use, requiring discovery and development of new pesticides to control them.

The United Nations Food and Agriculture Organization (FAO) estimates that herbivorous insects consume 20% of the world's crops; lepidopteran pests are likely responsible for 30% to 40% of that damage. In many developing countries, lepidopteran insects are responsible for consuming 50% of all crops. Growers must spend nearly $6 billion (USD) every year to manage lepidopteran pests — about 50% of expenditures on all insect control products.

Need for New Solutions

There is ever-increasing demand to replace older, more toxic pesticides (organophosphates, carbamates, pyrethroids) with lower-toxicity-profile and targeted (selective) products. Selective insecticides control the damaging or hazardous targeted insects, while not affecting most other species, including humans who live and work near application sites, and beneficial insects, such as bees that pollinate crops and parasitic wasps that prey on damaging insects. Target selectivity is one of the most critical factors impacting mammalian toxicity for insecticides.

Organophosphate (OP) insecticides are the most commonly used pesticides in the world. They are relatively inexpensive, highly effective with broad-spectrum activity and less prone to resistance issues that have occurred with some other pesticides. However, OPs may pose significant hazards. They are related to potent nerve agents and overexposure by misuse can result in effects on the nervous system that can persist for weeks or years, or even death.

In the United States and other well-regulated countries, all registered pesticides must comply with high standards for registration and use. However, OPs are one of the most common causes of pesticide poisoning around the world and have been claimed to be linked to neurophysiological effects in farmers, attention deficient syndrome in children and development of cancer. In some countries, suitable protective clothing is not always used when these products are applied. As a result, farmers and applicators have potential for increased exposure to OPs and the potential negative effects. OPs are being addressed by the U.S. Environmental Protection Agency (EPA) and other countries' regulatory groups, with the goal of reducing or eliminating their use.

Other solutions have been raised over time, but must be joined by additional options. In 1999, for example, spinosad was a new, precedent-setting, natural insecticide that received a Green Chemistry Challenge Award. Spinosad effectively controlled lepidopteran insects with a new mode of action and a favorable health and environmental profile. However, since spinosad was developed, DuPont has made significant strides in identifying and developing products with new modes of action, such as

chlorantraniliprole, that set even higher standards for efficacy, environmental impact and sustainability, resulting in a rapid and record-setting global adoption rate.

Chlorantraniliprole is a major new broad-spectrum insecticide discovered and developed by DuPont to replace OPs and other potentially less desirable insecticides. It represents a significant advancement in both efficacy on target insect pests and development of products with excellent environmental profiles. Chlorantraniliprole mainly targets lepidopteran insects, not non-target organisms, including bees and other beneficial insects. Chlorantraniliprole controls destructive insects that have become resistant to other insecticides, giving fruit, vegetable and nut growers a much-needed new option for controlling chewing insects where other insecticides now fail to achieve control and crops are lost. Chlorantraniliprole was registered by the EPA as a Reduced Risk pesticide for a number of uses and as a replacement for older, more toxic insecticides, including OPs.

These Texas cabbages in the center row were protected from diamond back moth and cabbage looper by 5 g/hectare of chlorantraniliprole.

Applying Green Chemistry Principles to Discovery

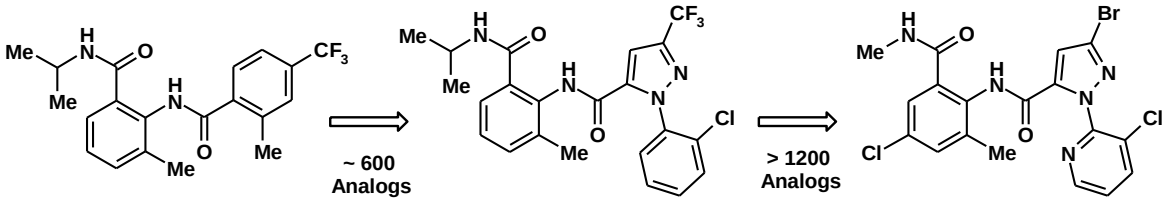
DuPont Crop Protection develops, manufactures and sells crop protection products around the world, enabling production of safe, high-quality, abundant food. DuPont is committed to supporting sustainable agriculture by developing products that are not only effective in controlling insects, weeds and plant disease, but also enhance environmental stewardship.

Historically, the design of new crop protection products has been a stepwise process consisting of optimization of biologically active leads toward commercially viable use rates followed by thorough evaluation of health and environmental attributes to ensure compliance with regulatory requirements. With this approach, the best candidates in terms of both biological performance and health and environmental stewardship have not always been identified. DuPont Crop Protection fundamentally redesigned this process, integrating chemistry and biology with toxicology, environmental and site-of-action studies. The redesigned process applied green chemistry principles and elevated key health and environmental characteristics to the same level of importance as pesticidal activity. With discovery of a novel series of highly active diamide insecticides, DuPont researchers created an optimization program that balanced efficacy with an excellent environmental profile and low toxicity.

An Advanced Molecule Designed for Safety and Performance

In early 2000, DuPont's Insecticide Discovery Group discovered a novel class of anthranilic diamides, DD-01 (see chart below), with promising activity against key lepidopteran species. Advancement of insecticidal activity proceeded rapidly; however, some issues associated with the potential for slow soil degradation and higher than anticipated mammalian toxicity were identified. In fact, the most active early candidate, DD-02, showed minimal environmental breakdown and raised some toxicity concerns. The new

discovery process of continuous compound redesign, coupled with intensive evaluation of compound health and environmental attributes in upfront screens, helped overcome those issues and resulted in the final molecule, chlorantraniliprole.



The illustration above shows some of the progress within the optimization program from discovery of the earliest leads (DD-01) through identification of advanced candidates (DD-02), and ultimately to the discovery of chlorantraniliprole. Identification of very high levels of insecticidal activity was achieved rather quickly, within the first 600 analogs, and with fairly significant structural changes. The fine-tuning required to identify chlorantraniliprole took approximately twice as many analogs, due to the need to maximize properties of each critical attribute. The resulting product, chlorantraniliprole, is one of the most active and least toxic chemical insecticides ever discovered.

In parallel with the ongoing chemistry program, the mode of action was identified: Anthranilic diamides perturb insect muscle contraction through unregulated activation of ryanodine receptors, which causes paralysis. The insects cease feeding, which stops crop destruction, and then die. This mode of action is very different from that of OPs and promised to have a significantly lower toxicity profile to non-target organisms. Chlorantraniliprole was found to be 2,000 times less potent against human ryanodine receptors than insect ryanodine receptors. This strong differential selectivity is a major factor contributing to chlorantraniliprole's low toxicity to mammals.

Comparison of Insect Selectivity for Various Insecticides*			
Insecticide	**Chemical Class**	**Target**	**Selectivity Factor**
chlorantraniliprole	diamide	ryanodine receptor	>2000
chlorpyrifos-oxon	organophosphate	acetylcholinesterase	0.3
bendiocarb	carbamate	acetylcholinesterase	4.1
carbaryl	carbamate	acetylcholinesterase	2.8
fipronil	pyrazole	GABA receptor	135
imidacloprid	neonicotinoid	nicotinic acetylcholine receptor	565

*Selectivity factor is calculated as Human EC_{50}/Insect EC_{50} (obtained from published data). EC_{50} refers to the concentration needed to induce 50% of the maximal response at the target site.

Depending on the species tested, chlorantraniliprole has the lowest or among the lowest toxicity profiles of all insecticides, including insecticides derived from natural sources. Signal words like "Caution," "Warning," and "Danger" on the product label indicate the level of acute hazard of each product. Of the more than 5000 insecticide products registered by EPA, only 25 products are so low in acute toxicity that their labels contain no signal word and 15 of them use chlorantraniliprole as the sole active ingredient.

Chlorantraniliprole was designed to meet the goals of both environmental stewardship and performance. The work required collaboration of teams from synthetic chemistry, analytical/environmental chemistry, entomology, biochemistry, toxicology, and regulatory groups and spanned two years of

discovery work. The combination of outstanding insecticidal activity, favorable environmental attributes and a detailed understanding of the mode of action in insects and mammals as the basis for development of this new product was a direct result of the redesigned process and intense effort from the beginning of the program.

Favorable Environmental Profile

Chlorantraniliprole provides excellent control of damaging lepidopteran pests to protect plants and increase the global food supply. It is usually one to two orders of magnitude more effective against target pests when compared to commercial standards (e.g., carbamates, pyrethroids and OPs). This increased efficacy allows chlorantraniliprole to be applied at much lower rates and translates into immediate reduced-risk benefits with significantly less material entering the environment. For example, on tree fruits such as apples in the United States, 100 grams/hectare of chlorantraniliprole replaces up to 2200 grams/hectare of an OP. And on rice in Asia, 25 grams/hectare of chlorantraniliprole replaces up to 2200 grams/hectare of an OP.

Added Peace of Mind About Overall Safety for Crops and Workers

Personal protective equipment (PPE), including chemical-resistant gloves, footwear, coveralls, and protective eyewear, are required by the EPA and other countries' regulatory agencies to protect workers while handling pesticides. Product labels for the majority of OP products, for example, require users to wear a considerable degree of protection to meet appropriate worker protection standards. Although PPE is effective when properly used, local working conditions often make PPE uncomfortable and cumbersome. Consequently, some workers, particularly those in developing countries, choose not to use PPE. The best solution is to develop products that do not require specialized PPE.

When applying chlorantraniliprole, no personal protective equipment is required, since the EPA has identified no oral, dermal or inhalation hazards with its use. This designation points to a significantly reduced potential for risk to workers and others near fields where crops are grown. This freedom from personal protective equipment is especially important in developing countries where OPs are used extensively but enforcement is difficult due to the cost and availability of protective clothing and equipment and the hot climate.

After a pesticide is applied, farm workers must wait until the regulated re-entry interval period has passed before they can return to work in the fields. Farmers who choose to not follow this time interval risk unsafe worker exposure. After chlorantraniliprole-containing products are applied to crops, workers and others can re-enter fields in as little as four hours — the shortest re-entry interval allowed by EPA. This flexibility gives growers significant additional peace of mind about overall safety for food crops and workers and helps farms enhance productivity while protecting food supplies from damage.

Flexible, Targeted Application

Another way to reduce the potential for human exposure to pesticides is to apply products systemically, through crop roots. However, few active ingredients effective on insects that feed on foliage, including lepidopteran pests, maintain their effectiveness after soil applications. Chlorantraniliprole is different. Its root-uptake systemic action means it can be applied via drip chemigation (adding chemicals to soil-applied irrigation water) and provide excellent control of lepidopteran insects that feed on foliage. Applying chlorantraniliprole through drip chemigation reduces potential exposure to workers, bystanders (including children), and most non-target organisms. No other commercial insecticide offers this application method for lepidopteran control. Other products must rely only on foliar sprays applied with sprayers, mist blowers, or even aircraft, which can contribute to airborne pesticides that can drift to off-target areas.

Protecting Beneficial Insects and Preventing Resistance

Many beneficial insects and other non-target species, such as honeybees, earthworms and insect predators, are critical to healthy ecosystems and global food production. Nonselective pesticides, like OPs, indiscriminately harm these organisms.

DuPont chlorantraniliprole products have negligible effects on honeybees. Growers who use wild bees or commercial hives to pollinate their crops are assured that pollinators will not be affected. This is particularly important given the widespread presence of colony collapse disorder, which has dramatically reduced bee populations in many regions. Chlorantraniliprole has no application restrictions for bees. It is two or more orders of magnitude less toxic to honeybees than other insecticides available for the same use. In addition, chlorantraniliprole is essentially non-toxic to earthworms, most beneficial soil organisms and plants.

Many growers use integrated pest management (IPM) programs to help prevent development of resistance to overused active ingredients and to reduce the amount of pesticide introduced to the environment. The goal with IPM is to use as many different control mechanisms as possible, combining use of pesticides and targeted pests' natural predators, as well as other production techniques, to thwart insects. Even though chlorantraniliprole is extremely potent on target pests, it has negligible impact on key beneficial arthropods, including parasitoids and predators. These insects aid in natural control of problem insects. While controlling lepidopteran insects, chlorantraniliprole does not contribute to flare-ups in populations of piercing arthropod pests, such as aphids, mites, scales, whitefly or hoppers, as frequently happens with other insecticides. With chlorantraniliprole, there is very low risk to parasitic wasps, in contrast to other insecticides. This impressive selectivity to beneficial arthropods, along with its robust pest control and favorable environmental profile, establishes chlorantraniliprole as an excellent fit for IPM programs.

Green Chemistry Manufacturing Principles

Green chemistry principles were integrated into the design and development of the convergent commercial process for the manufacture of chlorantraniliprole to minimize organic solvents, recover and recycle solvents, minimize waste and eliminate regulated waste products, and establish inherently safer reaction conditions.

Rapid Adoption of Green Chemistry Reduces Risk

Adoption of this new technology has been swift and extensive. Chlorantraniliprole products are now registered in 82 countries, with action pending in 21 other countries. In 2011 alone, more than 20 million farmers and 400 crops benefitted from insect control due to chlorantraniliprole, enhancing our ability to feed the growing world population while preserving and protecting our natural resources and providing a safe environment for the people who live and work in crop production areas.

Since 2008, chlorantraniliprole-containing products have achieved significant adoption by growers, approaching 10% of total insecticide use on key crops in the United States. Globally, these products are the fastest growing family of insecticides.

Reduction in use of organophosphates and other less favorable insecticides is now occurring; the EPA has ordered phaseout of the OP azinphos-methyl by Sept. 30, 2012, due to risks to human health and aquatic ecosystems. By registering chlorantraniliprole under its Reduced Risk pesticide program, the EPA Reduced Risk Committee anticipated that chlorantraniliprole would be a major alternative to azinphos-methyl for insect control.

In China, registration of chlorantraniliprole-containing products was granted just 45 days after submission (versus the normal two-year review), based on their unique profiles. Registration of fipronil, the leading product for controlling lepidopteran pests in rice but with a higher toxicity profile, was then cancelled

by the Chinese regulators. Additionally, DuPont packages chlorantraniliprole products in packets as small as 5 millliliters to cost-effectively meet local farmers' needs on typical, small 1- to 2-hectare farms. As evidenced by the sale of 35 million packets in China, farmers have responded to this opportunity by adopting the benefits of chlorantraniliprole products to protect their crops. A similar situation exists in India, where 350,000 liters of these products were sold in 2011 in packages as small as 10 milliliters. This scenario is repeated in countries throughout Asia and Africa where farmers are now able to use chlorantraniliprole-containing products to improve their crop yield, reduce their exposure risk, and ultimately improve their quality of life.

In the Pacific Northwest, the apple tree on the right was protected from codling moth damage with an application of 50 g/hectare of chlorantraniliprole. The tree on the left was untreated, allowing codling moths to feed on the tree's fruit.

Most Important: More Food, Better Quality of Life

Chlorantraniliprole creates value for farmers through improved plant health, which translates to greater crop yields. Farmers in the United States produce significant portions of the world's food. Increased yields enhance export opportunities and help fill gaps in food needs in many other countries. Farmers in developing regions grow food to sustain their families. Any surplus above their immediate need can be sold and converted to disposable income to enhance quality of life and provide education for their children.

Farmers around the world are describing the benefits of using products that contain chlorantraniliprole. Their comments provide a snapshot of how these products are improving their businesses, enriching their families' quality of life, and helping to feed the world. Typically, comments convey these impressions:

I apply less insecticide to the environment with fewer insecticide sprays overall.

I see more bees and other beneficial insects in my orchards.

I save fuel, conserve water, and cause less soil compaction because I am making fewer passes over the field by using drip applications.

Effective insect control helps me increase my crop yields with minimal investment.

Summary

Chlorantraniliprole has set new standards for environmental stewardship and pest management efficacy. It is an important new tool for the advancement of sustainable agriculture. Its selective action, which targets insects, is chiefly responsible for its inherent low toxicity to non-target species. Its broad spectrum of control and low use rates make chlorantraniliprole an ideal replacement for more toxic and less selective materials in many important global markets. The benefits of chlorantraniliprole extend to workers, the public and the environment as we strive to feed the world's growing population.