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class of larvicides

Spinosad: A New Active Ingredient for Public Health

Natular™ larvicides introduce an entirely new active ingredient to public health markets. It's derived from a naturally occurring bacterium: *Saacharopolyspora spinosa*, meaning "spiny sugar". It is one of only five active ingredients to receive the Presidential Green Chemistry Award.

Spinosad is also considered an EPA Reduced-Risk active ingredient. When it was first registered in 1997 for the agricultural markets, spinosad was reviewed as a Reduced-Risk Pesticide. The goal of this program is to quickly register commercially viable alternatives to riskier conventional pesticides. This ensures that these Reduced Risk pesticide products get into the marketplace as soon as possible.

Spinosad has since been labeled in more than 85 countries and on over 250 crops. Natular™ larvicides are the first public health label for spinosad and also the first aquatic use pattern with the active as well.

At several levels, Natular™ larvicides offer truly advanced differentiation among larvicides. From a performance perspective, they offer the first new active ingredient in years. The benefit of which is compounded by the fact that active also introduces a new class of chemistry, Group 5, to mosquito control as well as a new mode of action. This makes them powerful resistance-fighting solutions to help assure established larvicides can be used effectively for years to come.

The reduced-risk chemistry of spinosad provides the perfect balance of efficacy and environmental stewardship, as all domestic formulations of Natular meet standards for use in and around organic food production.

Spinosad has an excellent safety record. It breaks down quickly and does not bioacumulate in the environment.

New Mode of Action

Spinosad has a novel mode of action that makes it ideal for rotational use. It shows no cross-resistance with existing chemistries used for mosquito control. Spinosad alters the function of insect nicotinic acetylcholine receptors in a unique action causing continuous nervous impulses. This constant involuntary nervous stimulus causes paralysis and death. This action results primarily by ingestion, as well as contact with the active.

New Class of Chemistry

Spinosad is classified as a Group 5 Insecticide, a class unique and distinct among all other public health larvicides.

Group 5 Insecticides

Spinosad is classified as a Group 5 insecticide by the Insecticide Resistance Action Committee, which means its mode of action is unique. Spinosad acts as a nicotinic acetylcholine receptor allosteric activator, impacting mosquito larvae by stimulating the nervous system.[2]

[2] http://www.irac-online.org/documents/MoA%20classification_June08_v6%200.pdf, information gathered July 30, 2008

Formulated with Organic in Mind

In 1999, spinosad received the Green Chemistry Award from the US EPA, and in 2002, it was approved by the US Department of Agriculture's National Organic Standards Board for use in certified organic agriculture as a natural product. In addition *all ingredients* in Natular™ formulations are either NOP listed or included on the EPA's List of Minimal Risk Inert Ingredients.

All Natular™ formulations for domestic use are currently under review by the Organic Materials Review Institute (OMRI). Once approved, OMRI listing certifies that the formulated products meet the stringent requirements for use in and around organic agriculture.

OMRI, a nonprofit, independent reviewing organization ensures the processes used to develop and manufacture Natular larvicides prevent any risk of cross-contamination.

The criteria met by Natular formulations make them excellent choices for labeled environmentally sensitive habitats and for the growing number of communities with green or sustainable practice guidelines.

Frequently Asked Questions

Q. *What is the active ingredient in Natular™ larvicides?*
A. Spinosad. It is a naturally-derived active ingredient produced during fermentation by the soil organism, *Saccharopolyspora spinosa*. The natural metabolites produced during the fermentation process were termed "spinosyns". Spinosad is the collective term for the two most prominent and most active compounds in the fermentation broth (spinosyn A and spinosyn D). Hence the name "Spino**sad**"

Q. *How is the active ingredient manufactured?*
A. Spinosad is produced in a state-of-the-art fermentation facility in the United States, using natural feed-stocks to maintain the fermentation process.

Q. *Is spinosad new?*
A. No. Spinosad's first global registration was in 1996. Today it's used on more than 250 crops and in consumer and animal health uses in over 85 countries. Although Natular™ larvicides are the first public health usage of the active.

Q. *How does the active ingredient in Natular™ formulations control mosquito larvae?*
A. Spinosad has a novel mode of action; it alters the function of insect nicotinic acetylcholine receptors in a unique manner. Ultimately paralysis sets in upon ingestion and contact and the mosquito larvae don't recover.

Q. *Are Natular™ formulations suitable for use in organic agriculture?*
A. Yes. The active ingredient (spinosad) is listed as an *Allowed Substance* by the USDA National Organic Program (NOP) and all ingredients in NatularTM formulations are either NOP listed or included on the EPA's List of Minimal Risk Inert Ingredients. All Natular™ formulations for domestic use are currently under review by the Organic Materials Review Institute (OMRI). Once approved, OMRI listing certifies that the formulated products meet the stringent requirements for use in and around organic agriculture.

Q. *What does Group 5 Chemical mean on the Natular label?*
A. Group 5 is a designation by IRAC (Insect Resistance Action Committee), which is a global industry organization that promotes the development of insecticide resistance management strategies to maintain efficacy and support sustainable agriculture and improved public health. Each group has a distinctly different mode of action. Spinosad is the only active ingredient in Group 5 used for mosquito control. The benefit of this is that it has no cross-resistance with existing products – making Natular™ an excellent option for resistance management.

Q. *What exactly are the inerts in Natular™?*
A. It depends upon the formulation. The primary inert in one granular product is a non-GMO (non-genetically modified organism) corn cob, the other uses sand. The carrier for the tablets is a food-grade binder Natular™ EC formulations use natural plant oil extracts. All are in the EPA List of Minimal Risk Inert Ingredients or National Organic Program.

Q. *Do Natular™ larvicides control all of the important mosquito species?*
A. Natular™ formulations have been tested on 14 of the most common vector and nuisance mosquito species and Spinosad is effective against all of them. Given the fact that spinosad is a new active ingredient and has a completely unique mode of action; we expect to see consistent performance across all species.

Q. *Will Natular™ formulations control mosquitoes that carry the West Nile Virus and other mosquito-borne diseases?*
A. Yes. Natular™ formulations introduce a new active ingredient with a new mode of action to provide control of species that carry West Nile Virus and other mosquito borne diseases.

Q. *How do Natular formulations perform in habitats containing high organic matter?*
A. We have seen excellent results in habitats with high concentrations of organic debris with Natular™ formulations, e.g. polluted water, sewage lagoons, and waters with high concentrations of leaf litter or other organic debris.

Q. *How have Natular™ products performed in catch basins?*
A. Both the 30-day Natular™ T30 and Natular™ XRT have performed exceptionally well in catch basins – even in the face of significant rain events as well as wet/dry cycles. The 30-day Natular™ T30 provides 30 days of control, while the XRT has consistently reached full season limits with control up to 180 days.

Q. *How effective is Natular™ in an open / floodwater habitats with sunlight (Aedes vexans)*
A. Excellent, based on numerous cooperator and university trials.

Q. *How does varying amounts of sunlight affect the performance of Natular™ products?*
A. Natular formulations were developed specifically for use in natural mosquito habitats, with single- or multi-brood control objectives in mind. To date we have seen very uniform control levels regardless of sunlight intensity, and consistent with the labeled control claim of each Natular formulation.

Q. *What about resistance?*
A. The active ingredient in Natular™ products, spinosad, has not been used to control mosquitoes, hence there is no resistance to it. Spinosad is in a unique chemical class different from any other current products used in mosquito control, so there is no cross-resistance. Clarke will implement a resistance management program. To prevent resistance, Clarke will steward and monitor the applications of these products to ensure consistent use according to label directions.

Q. *What are the storage requirements for the products?*
A. You store these products as you would any other pesticide – A cool, dry place is recommended, avoid freezing of the liquid. Be mindful of preventing cross contamination with other pesticide products.

Q. *What is the ecological toxicity of the Natular™ formulations?*
A. Spinosad was registered under the US EPA Reduced Risk program and has favorable environmental characteristics compared to other mosquito larvicides. The active ingredient in Natular™ larvicides, spinosad, is well known to present a relatively low risk to beneficial and non-target insects compared to other broad-spectrum, insecticide products. Spinosad is not acutely toxic to terrestrial birds, wildlife, or to fish and most aquatic invertebrates. Extensive field experience indicates that spinosad's overall impact on beneficial insects is generally limited and transitory, and spinosad fits well into Integrated Pest Management (IPM) programs.

Q. *How do Natular™ products affect honey bees?*
A. Field testing has demonstrated that once liquid spray residues have been allowed to dry for up to 3 hours that spinosad is not harmful to foraging honeybees and bumblebees. Spinosad has been used extensively in more than 85 countries with over 250 registered crop uses since its first launch in agriculture without any reported adverse effects on bees. This would be applicable ONLY TO THE LIQUID formulation. Granular and tablet formulations will not pose a bee hazard.

Q. *Why are Natular™ formulations good rotational products?*
A. Natular™ formulations are the new standard in larvicide control and are excellent as rotational products because they contain a new active ingredient with a distinctly different mode of action. Natular™ products are a key component in rotational programs for larvicide control. Rotation will help preserve the continued use of existing products.

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Clarke®

An Introductory Profile for Natular™ Larvicides

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a n e w c l a s s o f l a r v i c i d e s

Green chemistry, also known as sustainable chemistry, is the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances. Green chemistry applies across the life cycle, including the design, manufacture, and use of a chemical product. Green chemistry technologies provide a number of benefits, including:

- *reduced waste, eliminating costly end-of-the-pipe treatments*
- *safer products*
- *reduced use of energy and resources*
- *improved competitiveness of chemical manufacturers and their customers.*

www.epa.gov/greenchemisry

green chemistry

Natular™: A New Class of Larvicides

Natular™ larvicides are the result of six years and over 35,000 man hours of development and regulatory review. The result is a full spectrum of larvicide formulations that set a new benchmark for mosquito control. They bring to the market:

- A new, Reduced-Risk active ingredient
- A new mode of action
- A new class of chemistry

Natular larvicides are formulated as sustainability solutions for greater application flexibility with precision performance.

The First Reduced-Risk Larvicide

In 1993, the U. S. Environmental Protection Agency created the Reduced-Risk Pesticide Initiative to "encourage the development, registration and use of lower-risk pesticide products, which would therefore result in reduced risks to human health and the environment when compared to existing alternatives."

Spinosad, the active ingredient in Natular™ larvicides, is one of only sixteen chemicals registered as a Reduced-Risk Pesticide, and the only larvicide for mosquito control. According to the EPA, the advantages of Reduced-Risk pesticides include:

- low impact on human health
- lower toxicity to non-target organisms (birds, fish, plants)
- low potential for groundwater contamination
- low use rates
- low pest resistance potential
- compatibility with Integrated Pest Management (IPM) practices[1]

[1] http://www.epa.gov/opprd001/workplan/reducedrisk.html, information gathered July 30, 2008

Formulations and Performance Fitting Any Habitat

Natular is available in six distinct, advanced formulations. Each offers exceptional handling characteristics, labeled for only protective eyewear PPE. This is due to the virtually dustless, nearly, non-chalking quality of the solid formulations.

Name	Formulation Type	Carrier & Appearance	Application Rate*	Bulk Density
Natular™ EC	Single brood liquid	Liquid, dark and slightly cloudy in appearance	1.3 - 2.8 fl oz / ac	9.68 lbs/gal
Natular™ G	Single brood granule	Granules made from organic, non-genetically modified corn cobs	3. 5 - 9 lbs/ac	33 lbs/cf
Natular™ T30	Multiple-brood 30-day tablet	A dust-free, pharmaceutical grade tablet	1 / 100 sf	6 g/tablet
Natular™ XRT	Multiple-brood extended release tablet	A dust-free, pharmaceutical grade tablet	1 / 100 sf	40 g/tablet
Natular™ XRG	Multiple-brood extended release granule	Granules made from silicone (sand)	5 - 20 lbs/ac	85 lbs/cf
Natular™ DT (not available in the U.S.)	Multiple-brood tablet for containerized water	Bi-layer tablets	1 / container	1.35 g/tablet
*depending on area of treatment				

Performance logged and observed in testing and early operational work has demonstrated consistent performance with exceptional control of larvae from first through early fourth instar stages. Spinosad begins to work immediately upon ingestion and contact with the first visible effects seen within hours of application. Optimal control is reached within 24-72 hours and is sustained at very uniform levels for the labeled control period.

Through 2008, Natular™ formulations have been very effective in a wide spectrum of habitats in more than 50 domestic tests and 15 international studies. Data has been gathered on 14 species and will be expanded in 2009 with operational applications.

Natular™ DT – Formulation Follows Function

In rural urban areas of Latin America and Asia, the need to treat water barrels and other containers with larvicides is crucial in the fight against Dengue, Yellow Fever and Chikungunya.

Clarke answered this need with a truly revolutionary formulation: the Natular™ DT bi-layer tablet. Each tablet just 12 mm (1/2 in) in size packs the larviciding power to treat a 200 liter barrel of water for 60+ days. The patent-pending formulation consists of two layers. The first is an effervescent layer that provides an immediately release of active to control existing larvae. The second layer slowly, visibly dissolves to provide control for 60+ days.

These tablets, shipped in packaging similar to the size and weight of a pound of coffee, can be stored and transported more easily than other larvicides, and the simple tablet eliminates human error in measuring and treatment schedules.

Natular DT has been sucessfully evaluated by WHOPES and is available for international use only.

Structure

Chemical name: *Saccharopolyspora spinosa*

Common name: spinosad, a patented combination of spinosyn A and spinosyn D

	spinosyn A	spinosyn D
Empirical Formula	$C_{41}H_{65}NO_{10}$	$C_{41}H_{67}NO_{10}$
Molecular Weight	731.98	746.00
Color and State	Crystalline Solid, White to Tan	
Vapor Pressure	2.4x 10^{-10} mmHg	1.6x10^{-10} mmHg
Melting Point C	84 - 100 C	161 - 170 C
Water Solubility pH 5 pH 7 pH 9	 290 235 16	 287 0.332 0.053

Environmental Impact

Spinosad is a highly selective insect control product with high potency for target insects but low toxicity toward mammals and other non-target organisms.

Species	Timeframe	Dose Rate
Bluegill Sunfish	96-hour LC 50	5.9 mg/L
Rainbow Trout	96-hour LC 50	30 mg/L
Sheepshead Minnow	96-hour LC 50	7.9 mg/L
Common Carp	96-hour LC 50	5.0 mg/L
Water Flea	48-hour EC50	1.5-14.0 mg/L
Grass Shrimp	48-hour LC50	>9.7 mg/L
Midge	25-day NOEC	0.002 mg/L
Bobwhite Quail	Acute LD50	>2000 mg/L
Mallard Duck	Acute LD50	>2000 mg/L
Microorganisms		No effect at 100 mg/L

Environmental Fate in Soil

Spinosad degrades readily in the soil environment and is non-persistent. Primary mechanisms of degradation are sunlight photolysis and microbial breakdown. Under field conditions, spinosad breaks down rapidly in the soil with observed half-lives of less than one day. Spinosad degrades into carbon dioxide and water by the soil microbial community.

Spinosad is moderately to strongly absorbed by soil particles and is considered to be "relatively immobile to immobile" with regard to leaching.

Environmental Fate in Water

In natural water systems, spinosad degrades rapidly in sunlight. A water column half-life of less than one day has been observed in artificial pond systems in outdoor conditions.

Fate in Animals

Because of its unique mode of action spinosad is highly selective to insects. In mammals, spinosad is not readily absorbed through the skin. Any minute amounts that are absorbed or ingested are rapidly metabolized to inactive byproducts, which are excreted. As a result, it has very low acute toxicity. In long term studies, no evidence of carcinogenicity, mutagenicity, or neurotoxicity has been observed.

Toxicity, Mutagenicity, Genotoxicity

The active ingredient in Natular™ larvicides, spinosad, is well known to present a relatively low risk to beneficial and non-target insects compared to other broad-spectrum, insecticide products.

Spinosad is not acutely toxic to terrestrial birds, wildlife, or to fish and most aquatic invertebrates.

Spinosad has been investigated in a battery of genotoxicity studies and has been found to possess no mutagenic potential.

Spinosad was registered under the US EPA Reduced Risk program and has favorable environmental characteristics compared to other mosquito larvicides.

Extensive field experience indicates that spinosad's overall impact on beneficial insects is generally limited and transitory, and spinosad fits well into Integrated Pest Management (IPM) programs.

The Spinosad Story: Spiny Sugar

The scientific name for spinosad tells its story. Sacchrapolyspora spinosa literally translates into "spiny sugar." In 1982, a vacationing scientist took a soil sample from a drum that was used to make rum in the Caribbean. The bacteria, S. spinosa, in the sample were fermented in a lab. The fermentation yielded spinosyn A and D.

spinosyn A
+ spinosyn D
= Spinosad

spinosad