Dow AgroSciences

ISOCLAST™ ACTIVE TECHNICAL BULLETIN

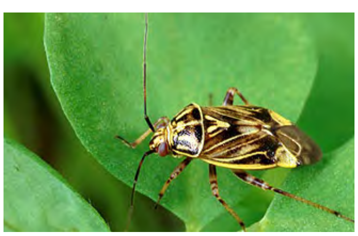
Solutions for the Growing World

Overview

Isoclast™ active (sulfoxaflor), discovered by and proprietary to Dow AgroSciences, currently is the sole member of a new chemical class of insecticides, the sulfoximines. Isoclast has been developed globally for use in major crop groups, including cotton, leafy and fruiting vegetables, apples, soybeans, rice (outside of the U.S.), cereals, citrus, cole crops, grapes, and other crops. Isoclast controls economically important and difficult-to-control sap-feeding insect pests including most species of aphids, jassids, leafhoppers, mealybugs, plant bugs, planthoppers, stink bugs, and whiteflies, and certain species of psyllids and scales.

Noteworthy Features

- Effective at low use rates
- Excellent knockdown and residual control
- Excellent translaminar and systemic activity
- Effective against insect pest populations resistant to other insecticides
- Valuable rotation partner with other chemistries
- Minimal impact on beneficial insects, including bees and natural enemies, when applicators follow label directions for use



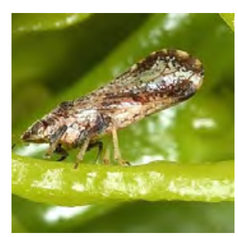
▲ Tarnished plant bug, *Lygus lineolaris*

▲ English grain aphid, *Sitobion avenae*

◀ Cotton aphid, *Aphis gossypii*

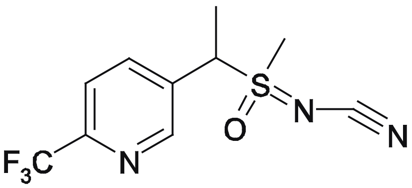
▶ Brown planthopper, *Nilaparvata lugens*

▶ Woolly apple aphid, *Eriosoma lanigerum*



▼ Asian citrus psyllid, *Diaphorina citri*

Discovery and Chemistry



The discovery of Isoclast™ active resulted from an investigation of the sulfoximines, which had not been examined extensively as crop protection chemicals, and therefore represented an opportunity for development of novel chemistry. The sulfoximine functional group offered a number of options for exploring a series of side chains known to have characteristics for agricultural uses. Early discovery-phase sulfoximine insecticides exhibited high levels of aphicidal activity in bioassays. Subsequent improvement in attributes resulted in the discovery of Isoclast, the first insecticide from the sulfoximine class of insecticides.

The Insecticide Resistance Action Committee (IRAC) has classified sulfoxaflor* (ISO common name) as a Group 4, Subgroup 4C insecticide. At the time of printing, sulfoxaflor was the only insecticidal active ingredient in this subgroup.

▲ Lettuce aphid, *Nasonovia ribisnigri*

▼ Bird cherry-oat aphid, *Rhopalosiphum padi*

▲ Southern green stink bug (nymph), *Nezara viridula*

▼ Citrus mealybug, *Planococcus citri*

▲ Cabbage aphid, *Brevicoryne brassicae*

▶ Green peach aphid, *Myzus persicae*

◀ Silverleaf whitefly, *Bemisia argentifolii*

*IRAC materials refer to Isoclast by its ISO common name, sulfoxaflor.

Mode of Action and Resistance Management

Available data indicate Isoclast™ active exhibits complex and unique interactions with insect nicotinic acetylcholine receptors (nAChR) that are distinct from those observed with neonicotinoids. Isoclast is a high-efficacy nAChR agonist with low affinity for the imidacloprid binding site.

Numerous studies have been conducted to determine whether insects resistant to other insecticides are cross-resistant to Isoclast. Available data for Isoclast indicate a broad lack of cross-resistance in many sap-feeding insect strains resistant to other insecticides. In several field studies, Isoclast controlled insect populations known to be resistant to neonicotinoids and to insecticides with other modes of action (e.g., carbamates, organophosphates, pyrethroids). The broad lack of cross-resistance between Isoclast and neonicotinoids is due primarily to differences in metabolism by monooxygenase enzymes, which are the predominant mechanism of insecticide resistance in the field. Laboratory studies have demonstrated a monooxygenase that degrades neonicotinoids has no effect on Isoclast. The novel chemistry of Isoclast and the lack of cross-resistance suggest that efficacy of Isoclast will be retained even in the presence of sap-feeding insect strains that are resistant to other insecticides, including neonicotinoids.

For reasons indicated in the preceding paragraphs, sulfoxaflor* was classified as a Group 4, Subgroup 4C insecticide in the Insecticide Resistance Action Committee Mode of Action Classification Scheme (Version 7.2, April 2012, http://www.irac-online.org). Sulfoxaflor is the sole member of this subgroup. Neonicotinoid insecticides are classified in Group 4, Subgroup 4A in the IRAC Mode of Action Classification Scheme.

Because of its unique properties and broad lack of cross-resistance, Isoclast will be a useful rotation partner with other insecticide chemistries, enhancing insect resistance management (IRM) strategies.

▲ Soybean aphid, *Aphis glycines*

▲ Citricola scale, *Coccus pseudomagnoliarum*

◀ Redbanded stink bug, *Piezodorus guildinii*

*IRAC materials refer to Isoclast by its ISO common name, sulfoxaflor.

How Isoclast™ Active Kills Insect Pests

Isoclast™ active kills insect pests both on contact and through ingestion to provide both knockdown and residual control. Isoclast displays translaminar movement (moves to the opposite leaf surface) when applied to foliage and is xylem-mobile.

Biological Activity

Background

Sap-feeding insects, especially those in the sub-orders Hemiptera and Homoptera, are among the most destructive insect pests in the world, annually causing economic losses in both row crops and horticultural crops. Management of sap-feeding insects often requires diverse and intensive control tactics, including the use of insecticides. Consequently, populations of sap-feeding insects have developed resistance to many insecticides representing a wide range of insecticide modes of action. Isoclast's efficacy and unique mode of action suggest that it will be a key tool for controlling economically important pests and a useful rotation partner in IRM programs.

Efficacy of Isoclast Against Insect Pests

Isoclast provides excellent efficacy against target pests at low use rates. Proposed application rates of Isoclast range from approximately 12 to 150 grams of active ingredient per hectare (0.011 to 0.133 pound of active ingredient per acre), depending on the target pest and the crop.

Field efficacy trials with Isoclast have been conducted worldwide on many crops against a wide range of sap-feeding insects. Results from these trials have revealed that Isoclast provides excellent control of many species of sap-feeding insects, including tarnished plant bug *(Lygus lineolaris)* and western tarnished plant bug *(Lygus hesperus)* in cotton; cotton/melon aphid *(Aphis gossypii)* in cotton and cucurbits; several species of aphids in cereal crops; soybean aphid *(Aphis glycines)* and stink bugs in soybean; green peach aphid *(Myzus persicae)* and whiteflies (*Bemisia* species) in multiple crops; Asian citrus psyllid *(Diaphorina citri)*, citrus thrips *(Scirtothrips citri)*, and several species of scales in citrus; woolly apple aphid *(Eriosoma lanigerum)* and other aphids in pome fruits; brown planthopper *(Nilaparvata lugens)* and other planthoppers in rice; blackmargined aphid *(Monellia caryella)*, grape leafhoppers (*Erythroneura* species), and several other sap-feeding species in tree nuts and vines; cabbage aphid *(Brevicoryne brassicae)* in cole crops; and lettuce aphid *(Nasonovia ribisnigri)* and other aphids in leafy vegetables. More pest species for which Isoclast provides excellent control are listed in the table on the next page. Isoclast does not control lepidopteran and coleopteran pests.

Partial List of Pests for Which Isoclast™ Active Provides Control

Crops *(partial list)*	**Key pests controlled**
Cereal	Aphids—Bird cherry-oat aphid *(Rhopalosiphum padi)*, English grain aphid *(Sitobion avenae)*, greenbug *(Schizaphis graminum)*
Citrus	Asian citrus psyllid *(Diaphorina citri)*; citrus mealybug *(Planococcus citri)*; citrus thrips *(Scirtothrips citri)*; scales—citricola scale *(Coccus pseudomagnoliarum)*, citrus snow scale *(Unaspis citri)*, Florida red scale *(Chrysomphalus aonidum)*
Cotton	Cotton aphid *(Aphis gossypii)*; cotton fleahopper *(Pseudatomoscelis seriatus)*; jassids, including *Amrasca devastans*; plant bugs—green mirid *(Creontiades dilutus)*, tarnished plant bug *(Lygus lineolaris)*, western tarnished plant bug *(Lygus hesperus)*; whiteflies, primarily *Bemisia* species
Fruits (pome—apples, pears)	Aphids—Apple aphid *(Aphis pomi)*, rosy apple aphid *(Dysaphis plantaginea)*, woolly apple aphid *(Eriosoma lanigerum)*; white apple leafhopper *(Typhlocyba pomaria)*
Fruits (stone)	Green peach aphid *(Myzus persicae)*
Potato	Aphids—Green peach aphid *(Myzus persicae)*, potato aphid *(Macrosiphum euphorbiae)*; potato leafhopper *(Empoasca fabae)*; potato psyllid *(Bactericera cockerelli)*
Rice	Green rice leafhopper *(Nephotettix cincticeps)*; planthoppers—brown planthopper *(Nilaparvata lugens)*, small brown planthopper *(Laodelphax striatellus)*, white-backed planthopper *(Sogatella furcifera)*; stink bugs
Soybean	Soybean aphid *(Aphis glycines)*; stink bugs—*Edessa* species, *Euschistus* species, redbanded stink bug *(Piezodorus guildinii)*, southern green stink bug *(Nezara viridula)*
Tree nuts and vines	Aphids—blackmargined aphid *(Monellia caryella)*, black pecan aphid *(Melanocallis caryaefoliae)*, yellow pecan aphid *(Monelliopsis pecanis)*; grape leafhoppers (*Erythroneura* species); grape mealybug *(Pseudococcus maritimus)*; walnut aphid *(Chromaphis juglandicola)*
Vegetables (cole)	Aphids—cabbage aphid (*Brevicoryne brassicae)*, green peach aphid *(Myzus persicae)*
Vegetables (cucurbit)	Cotton/melon aphid *(Aphis gossypii)*; whiteflies, *Bemisia* species, greenhouse whitefly *(Trialeurodes vaporariorum)*
Vegetables (fruiting)	Aphids—green peach aphid *(Myzus persicae)*, potato aphid *(Macrosiphum euphorbiae)*; whiteflies—*Bemisia* species, greenhouse whitefly *(Trialeurodes vaporariorum)*
Vegetables (leafy)	Aphids—foxglove aphid *(Aulacorthum solani)*, green peach aphid *(Myzus persicae)*, lettuce aphid *(Nasonovia ribisnigri)*

Impact of Isoclast™ Active on Natural Enemies of Insect Pests

Field studies have been conducted to measure the impact of Isoclast™ active on several predatory and parasitic arthropods (natural enemies): assassin bugs, big-eyed bugs, braconid wasps, green lacewings, lady beetles, minute pirate bugs (including *Orius insidiosus*), and spiders. When applied at field-use rates in these studies, Isoclast had no significant impact on population levels of any of the natural enemies measured. In addition, Isoclast has had no impact on beneficial mite species. Based on the results from these studies, as well as on observations from other field trials, use of Isoclast is not expected to cause outbreaks of secondary insect pests (often referred to as "flaring").

▲ Spider

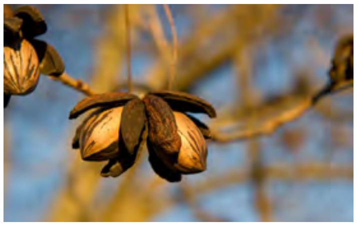
▲ Lacewing larva

▲ Damsel bug

▲ Lady beetle larva

Crop Tolerance

Tolerance of formulations of Isoclast is high for the many major crop species that have been tested. At labeled use rates, Isoclast exhibited no phytotoxicity in seedling emergence and vegetative vigor tests in ten crop species. No crop injury has been observed in any field trials over a range of environmental conditions, and no differences in varietal sensitivity have been observed. Since being registered in multiple countries, Dow AgroSciences has received no reports of any negative plant responses or phytotoxicity from application of Isoclast.



Mammalian Toxicology

Isoclast™ active exhibits low acute mammalian toxicity, and is non-genotoxic. Results from subchronic and chronic toxicity studies revealed the liver to be the primary target organ with effects of limited concern or no relevance to humans. Rat-specific neonatal effects occurred, but they did not occur in rabbits and are not relevant to humans. Chronic studies in rats and mice resulted in liver tumors after a lifetime of exposure to Isoclast; however, the underlying mechanism is well understood and Isoclast is considered to be non-carcinogenic to humans. Based on available data, use of Isoclast in the manner consistent with label directions represents low risk to humans.

Study	Animal or test system	Results
Acute oral LD_{50}	Rat	1,000 mg/kg
Acute dermal LD_{50}	Rat	>5,000 mg/kg
Acute inhalation LC_{50}	Rat	>2.09 mg/L
Dermal irritation	Rabbit	Minimal
Eye irritation	Rabbit	Slight
Skin sensitization	Mouse	None
4-week dietary exposure	Rat	NOAEL = 24.8 mg/kg bw/d
13-week dietary exposure	Rat	NOAEL = 6.36 mg/kg bw/d
4-week dermal exposure	Rat	NOAEL = 1,000 mg/kg bw/d
Developmental toxicity	Rat	NOAEL = 11.5 mg/kg bw/d
Genotoxicity	Ames test Chromosomal aberration Mouse micronucleus *(in vivo)*	Negative Negative Negative
Acute neurotoxicity	Rat	NOAEL = 25 mg/kg bw/d

Isoclast™ Active and Non-Target Organisms

Isoclast™ active does not persist in the terrestrial environment and degrades rapidly to products that exhibit low toxicity to non-target organisms. Consequently, when Isoclast is used according to label directions, exposure of non-target organisms to Isoclast is expected to be minimal. Based on available data, use of Isoclast in the manner consistent with label directions will not cause any unreasonable adverse effects in the environment.

Isoclast and Bees

The effects of Isoclast on honey bees *(Apis mellifera)* and bumble bees *(Bombus terrestris)* have been studied in laboratory experiments and in tunnel tests that simulate field conditions. In laboratory studies, Isoclast exhibits acute toxicity to bees when consumed by or applied directly to bees. However, in tests designed to mimic use conditions, toxicity of Isoclast to bees was significantly reduced after the spray droplets had dried.

Acute Toxicity (Laboratory Studies). Under laboratory conditions, Isoclast exhibited acute toxicity to bees when the bees were exposed by oral or contact routes of administration. Isoclast technical and formulated products had similar toxicities to honey bees. The primary metabolite was not toxic to honey bees. The following table shows available acute toxicity data.

Test material	Oral toxicity	Contact toxicity
Honey bee *(Apis mellifera)*		
Isoclast technical (95.6% a.i.)	48-hr LD_{50} = 0.146 µg a.i./bee	72-hr LD_{50} = 0.379 µg a.i./bee
SC formulation of Isoclast	48-hr LD_{50} = 0.0515 µg a.i./bee	48-hr LD_{50} = 0.130 µg a.i./bee
WG formulation of Isoclast	48-hr LD_{50} = 0.08 µg a.i./bee	48-hr LD_{50} = 0.244 µg a.i./bee
Bumble bee *(Bombus terrestris)*		
SC formulation of Isoclast	72-hr LD_{50} = 0.027 µg a.i./bee	72-hr LD_{50} = 7.554 µg a.i./bee

Based on data for technical materials reported in the US EPA Pesticide Ecological Effects Database (http://www.ipmcenters.org/ecotox), the laboratory contact toxicity of Isoclast is in the middle of the range of reported contact toxicity values for insecticides used to control sap-feeding insects.

Semi-Field and Tunnel Studies on Isoclast. Isoclast does not exhibit Extended Residual Toxicity on foliage. In semi-field studies during which honey bees were exposed to dried residues of Isoclast on alfalfa foliage that had been field-aged for 3, 6, and 24 hours, mortality rates of bees were significantly reduced at all three observation times. In tunnel tests in which honey bees from small colonies were allowed to forage among plants *(Phacelia tanacetifolia)* in plots treated with Isoclast™ active and commercially available insecticides, foraging activity by honey bees in Isoclast-treated plots was similar to foraging activity by bees in the non-treated controls. Foraging activity in plots treated with two commercially available insecticides in these same studies essentially ceased for several days. Based on available data for Isoclast, no long-term effects on brood development have been observed.

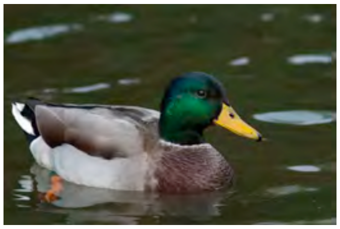
Summary. At the time of publication of this bulletin, the findings from all of the completed studies suggest that although Isoclast is acutely toxic to bees in laboratory studies, the risk of adverse effects on bees should be low under field conditions when applicators follow label directions for use. Because potential exposures to honey bees may vary among crops and field conditions at the time of application, it is important to read and follow all label directions regarding honey bees.

Isoclast and Other Non-Target Organisms

Acute and long-term environmental toxicology studies of Isoclast have been conducted to fulfill the requirements of the US EPA and other regulatory agencies. A summary of available data generated from these studies is presented in the following table.

Acute toxicity to birds	Oral LD_{50} = 676 mg/kg body weight (bobwhite quail)
Dietary toxicity to birds	5-day dietary LC_{50} >5,620 mg/kg diet (bobwhite quail, mallard duck)
Reproductive toxicity to birds	NOAEL = 81.2 mg/kg bw/d (bobwhite quail) NOAEL = 25.9 mg/kg bw/d (mallard duck) No reproductive effects were observed at any dosage
Acute toxicity to fish	96-hour LC_{50} >387 mg/L (rainbow trout) 96-hour LC_{50} >363 mg/L (bluegill sunfish) 96-hour LC_{50} >402 mg/L (common carp) 96-hour LC_{50} = 266 mg/L (sheepshead minnow)
Chronic toxicity to fish	NOEC = 5.05 mg/L (fathead minnow) NOEC = 1.21 mg/L (sheepshead minnow)
Acute toxicity to invertebrates	*Daphnia magna*—48-hour EC_{50} >399 mg/L Mysid shrimp—96-hour LC_{50} = 0.643 mg/L Eastern oyster—96-hour EC_{50} = 86.5 mg/L Earthworm—14-day LC_{50} = 0.885 mg/kg soil
Chronic toxicity to invertebrates	*Daphnia magna*—21-day NOEC = 50 mg/L Mysid shrimp—28-day NOEC = 0.114 mg/L *Chironomus riparius*—28-day NOEC = 0.0455 mg/L Earthworm—56-day NOEC = 0.1 mg/kg soil
Acute toxicity to aquatic plants	7-day EC_{50} >99 mg/L (*Lemna gibba*, duckweed)

Isoclast™ active exhibits very low acute toxicity to fish, freshwater crustaceans *(Daphnia magna)*, oysters, algae, and aquatic vascular plants. Midge larvae (*Chironomus* species) and the mysid shrimp *Americamysis bahia* (a saltwater free-swimming crustacean) may be considered sensitive to Isoclast. Isoclast exhibited effects on growth in long-term, early-life-stage toxicity tests in fathead minnows (freshwater fish) and sheepshead minnows (saltwater fish); slight effects on reproduction when applied at a high concentration of 100 mg/L in a lifecycle test on *Daphnia magna;* and effects on time to first brood in mysid shrimp.



Isoclast is considered to be slightly to moderately toxic to birds in acute oral toxicity studies. Isoclast did not exhibit any effects on reproduction in birds.

Environmental Fate

Microbial degradation is the predominant mechanism of degradation of Isoclast in the environment. Based on available data, use of Isoclast in the manner consistent with label directions represents a low risk to the environment.

Fate in Soil

Isoclast bio-degrades very rapidly in soil. The average DT_{50} in laboratory soil metabolism studies conducted in the dark was less than 1 day. Degradation also was rapid under field conditions, with an average DT_{50} of 4 days in field dissipation studies. Isoclast does not photo-degrade on soil surfaces. Despite its high water solubility and low soil sorption, the leaching potential of Isoclast is low because of its very rapid degradation in the soil. Consequently, Isoclast poses little threat to groundwater.

Fate in Water

Isoclast degrades slowly by photolysis in water. In the water phase of aerobic sediment/water systems, Isoclast dissipates and degrades through biological mechanisms with a half-life of 11 to 64 days. Considering both sediment and water phases, the degradation DT_{50} of Isoclast in sediment/water systems ranges from 37 to 88 days.




Fate in Plants

Metabolism of Isoclast™ active was studied in tomatoes, lettuce, succulent peas, and rice. Results from the studies showed that the metabolism of Isoclast is similar in all four crops. Although metabolites are produced, Isoclast generally accounts for the majority of residue in edible portions of crops.

Fate in Animals

The metabolism of Isoclast and one of its metabolites was studied in rats, ruminants, and poultry. In these animals, Isoclast is rapidly absorbed and rapidly eliminated with negligible metabolism. Isoclast did not accumulate in the animals' fatty tissues.


Fate in Air

The low vapor pressure and the estimated photochemical oxidation DT_{50} in air of less than 1 day indicate that levels of Isoclast in air following normal usage will be very low.

Formulations, Application, and Worker Safety

Dow AgroSciences has evaluated multiple formulations of Isoclast, including water-dispersible granular (WG) and suspension concentrate (SC) formulations. Additional formulations may be developed based on market needs. Global trade names will include Transform® and Closer®.

Refer to country-specific labels for information about application; Personal Protective Equipment (PPE) for product mixers, loaders, and applicators; and Re-Entry Intervals (REI). Also refer to country-specific labels for registered and recommended adjuvants that may be used to improve spray deposition, redistribution, and weatherability.

Physical and Chemical Properties of Isoclast™ Active

Chemical name (IUPAC)	[methyl(oxo){1-[6-(trifluoromethyl)-3-pyridyl]ethyl}-λ^6-sulfanylidene]cyanamide
Chemical name (CAS)	Cyanamide, N-[methyloxido[1-[6-(trifluoromethyl)-3-pyridinyl]ethyl]- λ^4-sulfanylidene]
Common name	Sulfoxaflor (provisionally approved by ISO)
Chemical class	Sulfoximine
CAS registry no.	946578-00-3
Empirical formula	$C_{10}H_{10}F_3N_3OS$
Structural formula	
Molecular weight	277.27 g/mol
Relative density	1.5191 g/mL at 20°C (purified)
Appearance	Off-white powder (solid)
Melting point	112.9°C
Boiling point	Decomposes at 167.7°C, before boiling
Flammability	Not highly flammable
Vapor pressure	$\leq 1.4 \times 10^{-6}$ Pa at 20°C
Octanol/water partition coefficient (log K_{OW}) at 19°C	pH 5: Log K_{ow} = 0.806 pH 7: Log K_{ow} = 0.802 pH 9: Log K_{ow} = 0.799
Dissociation constant (pKa)	>10 (does not fully dissociate within environmentally relevant pH ranges)
Hydrolytic stability (DT_{50})	Stable
Aqueous photostability (DT_{50})	Expected to be stable in sterile conditions
Soil photolysis (DT_{50})	Expected to be stable in sterile conditions (DT_{50} <1 day in aerobic soil in the laboratory)
Solubility in water (mg/L @ 20°C)	Purified water 670 mg/L Buffered water pH = 5 1,380 mg/L Buffered water pH = 7 570 mg/L Buffered water pH = 9 550 mg/L
Organic solvent solubility (g/L @ 20°C)	**Solvent** / **TGAI** Methanol 93.1 g/L Acetone 217 g/L Xylene 0.743 g/L 1,2-DCE 39.6 g/L Ethyl acetate 95.2 g/L Heptane 0.000242 g/L Octanol 1.66 g/L

Regulatory Information

On July 31, 2010, Dow AgroSciences submitted the application for registration of Isoclast™ active for a global joint review among the United States Environmental Protection Agency (EPA), the Australian Pesticides and Veterinary Medicines Authority (APVMA), and the Canadian Pest Management Regulatory Authority (PMRA). Since that submission, the US ESPA, APVMA, and PMRA have approved Isoclast registrations, and Isoclast has been registered for use in many other countries. Registrations of Isoclast will occur in additional countries as registration petitions are submitted, reviewed, and approved. Check with local Dow AgroSciences personnel for specific country registration status.

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Dow AgroSciences

Solutions for the Growing World

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