Dodhylex™ active

Global Technical Bulletin

FMC An Agricultural Sciences Company

Dodhylex™ active is not yet registered for sale or use in any country. No offer for sale, sale, or use of this product is permitted prior to issuance of the required registrations by the relevant regulatory entity.

Introduction & Overview

FMC's tetflupyrolimet herbicide, trademarked Dodhylex™ active, is the first new mode of action (MOA) herbicide introduced in over 30 years. Dodhylex™ active will provide season-long control of key grass weeds in rice regardless of cultivation method, including direct-seeded and transplanted *japonica* and *indica* varieties.

Dodhylex™ active belongs to a new herbicidal class of aryl pyrrolidinone anilides that interferes with *de novo* pyrimidine biosynthesis via inhibition of the dihydroorotate dehydrogenase enzyme that is localized to the mitochondria in the plants and is the first active ingredient in HRAC/WSSA Group 28. This novel active molecule was discovered at the FMC Stine Research Center and is proprietary to FMC Corporation. Intellectual property rights for this novel proprietary chemistry are protected by a solid patent portfolio (more than ten patents filed, first publication June 2015).

Annual grass weed control is the highest commercial value and market proposition for Dodhylex™ active (Figures 1 and 2). As the only herbicide in HRAC Group 28, Dodhylex™ active provides a new rotational tool for resistance management to help growers across a wide range of agronomic practices. To date, no resistance to this site of action has been reported, and Dodhylex™ active has been able to control herbicide-resistant populations, a key unique benefit. Dodhylex™ active provides good to excellent control of grass weeds that can have a significant impact on crop yield, including *Echinochloa* spp., *Digitaria* spp., *Setaria* spp., *Apera* spp., *Leptochloa* spp., *Ischaemum rugosum*, *Brachiaria* spp., *Poa annua* and suppression of *Lolium* spp. The spectrum of broadleaf and sedge species is more limited, but it includes a few key broadleaf and sedge species in rice, such as *Monochoria* spp. and *Fimbristylis* spp.

Key Attributes of Dodhylex™ active

- Novel MOA dihydroorotate dehydrogenase (DHODH) in pyrimidine biosynthesis pathway, proprietary chemistry area for FMC. Dodhylex™ active is the only herbicide classified by Global HRAC in Group 28.
- Outstanding residual control product (50 days+) of key grass weeds (ECHSS, LEPSS), some sedges (FIMMI) and BLWs (MOOVA).
- Excellent safety to both transplanted or direct-seeded *japonica* and *indica* rice under diverse soil types and environmental conditions.
- Ideal complementary mixing partner with other pre-emergence and post-emergence herbicides.
- Consistent weed control under diverse agronomic and water management practices.
- Unique MOA with no evidence of cross-resistance with existing classes of herbicides, thereby an excellent tool for resistance management, controlling widespread ALS, ACCase, HPPD, propanil, quinclorac and glyphosate-resistant weeds.
- Low use rates resulting in better environmental stewardship.
- Favorable toxicology, ecotoxicology and environmental fate profile.

Figure 1.

Dodhylex™ active control of *Echinochloa crus-galli* and *Leptochloa panicoides* in a field trial conducted in Arkansas, USA.

Figure 2.

Dodhylex™ active control of *Echinochloa crus-galli* and *Leptochloa chinensis* in direct-seeded *Indica* rice in China.

Registrations

FMC Corporation is working towards registering Dodhylex™ active for use in all major rice-growing countries across the globe and other additional crops. Dodhylex™ active is not currently registered and is not available for sale in any country. The registration dossier for Dodhylex™ active and products containing Dodhylex™ active were submitted for review in the United States, Korea, India and Taiwan. This technical bulletin is provided for educational purposes only and is not meant to promote the sale of the product. This document is intended to summarize the inherent activity of the Dodhylex™ active molecule alone and the key features of its use. Information contained within this bulletin is presented in an understandable and usable way by both FMC internal and external audiences, including research and development, regulatory, marketing, and management.

Herbicidal Action

Biochemical Mode of Action

Dodhylex™ active inhibits the enzyme dihydroorotate dehydrogenase (DHODH), the fourth step in the *de novo* pyrimidine biosynthesis pathway. It is a potent, low nM inhibition confirmed on heterologously expressed and purified enzymes. The mode of action was determined and validated internally in FMC by multiple approaches:

- Screening of EMS-treated seeds and SNP analyses
- Biochemistry experiments with recombinant enzyme
- Nutrient reversal experiments
- Metabolomic analyses of treated plants

Pyrimidine nucleotides are an important part of normal cellular functions, such as DNA and RNA synthesis, and the metabolism of cellular components, such as polysaccharides, glycoproteins and phospholipids.

Plants can synthesize pyrimidines de novo or break down cellular components like RNA that are no longer needed (i.e., salvage them from larger molecules). Because the de novo pathway is energetically expensive, cells utilize it only when they are rapidly growing and dividing. Mature cells can meet their metabolic needs using salvaging processes that do not utilize the DHODH enzyme, the target of Dodhylex™ active. This means the herbicide is most active against weed seedlings when most of the cells in the seedling are rapidly growing and dividing. The blockage of pyrimidine biosynthesis after Dodhylex™ active application interrupts normal cellular function, resulting in the cessation of plant growth and/or seedling emergence.

The patent on MOA was published in 2016: https://patents.google.com/patent/WO2017075559A1/en

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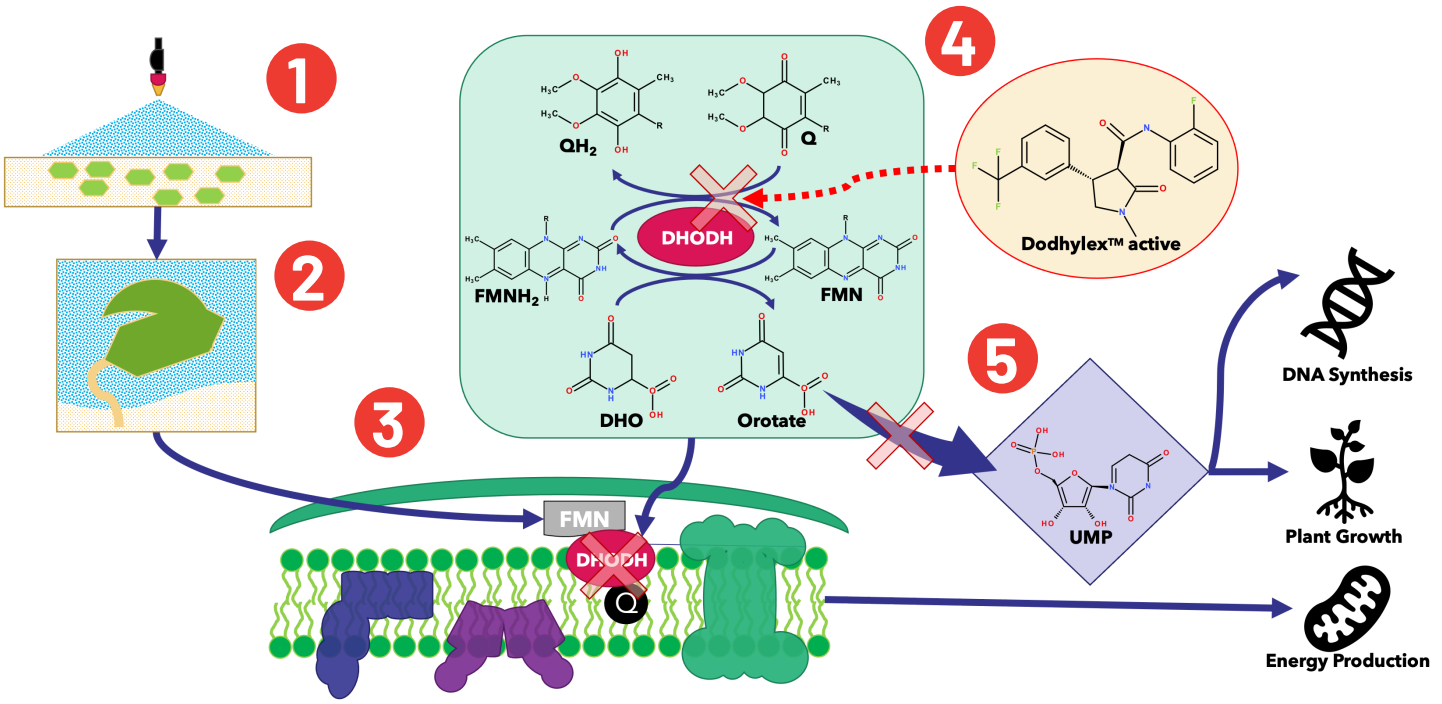
Herbicidal Action (continued)

Overview of Mechanism of Action

The mechanism of action of Dodhylex™ active (tetflupyrolimet) is depicted below in the diagram:



1. Dodhylex™ active is applied to the soil (or emerging weeds) where seedlings are germinating.
2. Dodhylex™ active forms a layer in the upper surface of the seedbed where germinating seedlings grow into the treated layer, and soil moisture will move it to the seedling.
3. DHODH resides on the outer surface of the inner mitochondrial membrane within proximity of complex II and III of the electron transport chain; it complexes with FMN and quinone to function.
4. Tetflupyrolimet interacts with the DHODH enzyme, occupying the quinone binding site and thus preventing the conversion of dihydroorotate into orotate.
5. In the absence of orotate, de novo uridine monophosphate (UMP) cannot be produced, and subsequent downstream products and processes, including DNA/RNA synthesis and plant growth, are impaired. Energy production via the electron transport chain may also be affected.

Herbicidal Action (continued)

Herbicide Symptomology

Products containing Dodhylex™ active can control susceptible weed species when applied either pre-emergence or post-emergence. In the latter case, applications to young weeds (generally up to 3-leaf stage) are effective since plants still utilize de novo pyrimidine biosynthesis to support plant growth.

Following pre-emergence applications, weed seeds of susceptible species germinate and start growing utilizing pyrimidines stored in the seed. Dodhylex™ active inhibits and stops their growth as soon as their metabolism requires additional synthesis of nucleotides from the de novo pathway, preventing weeds from emerging.

The symptoms observed in emerged plants are generally the same regardless of the application timing. These symptoms include but are not limited to stunting, deformed growth, inability to properly unfold leaves, dark and purple pigmentation, and necrosis.

Figure 3.

Effect of Dodhylex™ active on *Digitaria insularis* roots compared to an untreated plant (left) and *Echinochloa oryzicola* from a rice field in Japan (right).

Herbicidal Action (continued)

In addition, one of the most typical symptoms caused by Dodhylex™ active is the inhibition of root growth (or root pruning), confirming previous research that has found that root tissues are more impacted by changes in pyrimidine biosynthesis than shoot tissues. In some cases, while the plant's aboveground parts may appear unaffected, the root system is completely stunted and necrotic. Root pruning may also cause additional symptoms that are typically associated with drought stress, such as wilting and necrosis.

Most weeds die within seven to ten days from the onset of symptoms. However, some plants might remain stunted for longer periods, as the salvage metabolism of pyrimidines may be sufficient to maintain life but not enough to sustain new growth and are outcompeted during crop canopy closure.

Figure 4.

Typical symptoms caused by post-emergence applications of Dodhylex™ active on *Echinochloa crus-galli*, including leaf circling, purple pigmentation of stem and leaf curling.

Uptake and Translocation

While Dodhylex™ active herbicide can be absorbed by different plant tissues, its primary route of uptake is via root absorption. Dodhylex™ active is absorbed by germinating roots and hypocotyl/coleoptile tissues and is then passively distributed through the plant via the water transpiration stream in the xylem. In the case of post-emergence applications, Dodhylex™ active can also be absorbed by leaf tissues, but it does not translocate through the phloem. Studies conducted in greenhouse conditions showed that post-emergence weed control is achieved through a combination of root and foliar uptake.

Biological Profile

Weed Control

Products containing Dodhylex™ active can be applied as a pre-plant, pre-emergence or early post-emergence product to control various annual grasses and a few broadleaf and sedge species. The performance of Dodhylex™ active herbicide in weed control programs and with multiple partners has been validated with over 2,500 field trials completed to date; information presented here strictly refers to the stand-alone abilities of Dodhylex™ active.

Optimal application timing of the target weeds:

- **Grasses:** Pre-emergence to 3-leaf stage (depending on application method and cultural practices)
- **BLWs:** Pre-emergence to cotyledons stage

The following tables provide a listing of weeds that, based upon internal results, have been found to be susceptible to products containing Dodhylex™ active at anticipated label use rates. The following table is intended as a reference guide only and should not be constructed as an endorsement of weed control. Always read and follow product labels, as well as local regulations and requirements related to the application of products containing Dodylex™ active.

Examples of key grass weeds effectively controlled include:

Scientific name	*(Common English name)*
Echinochloa crus-galli	(Barnyardgrass)
Echinochloa colona	(Junglerice)
Echinochloa oryzoides	(Early watergrass)
Echinochloa oryzicola	(Late watergrass)
Leptochloa chinensis	(Chinese sprangletop)
Leptochloa fascicularis	(Bearded sprangletop)
Leptochloa panicoides	(Amazon sprangletop)
Digitaria sanguinalis	(Large crabgrass)
Ischaemum rugosum	(Saramollagrass)
Brachiaria plantaginea	(Alexandergrass)
Setaria faberi	(Giant foxtail)
Setaria viridis	(Green foxtail)
Poa annua	(Annual bluegrass)
Apera spica-venti	(Silky windgrass)
Lolium multiflorum	(Italian ryegrass)
Panicum spp.	(Panicum)

Examples of broadleaf weeds and sedges controlled include:

Scientific name	*(Common English name)*
Monochoria vaginalis	(Monochoria)
Fimbristylis miliacea	(Globe fringerush)

Control of weeds resistant to current commercialized herbicides:

Dodhylex™ active has demonstrated excellent control of grass, BLW and sedge weed species, which have developed increased tolerance or resistance to other actives of ALS, ACCase, HPPD, glyphosate, quinclorac, propanil, and other current commercialized MOA herbicides.

Use rates:

Rates range from 75 to 250 g ai/ha, depending on use patterns (pre-emergence vs. post-emergence application), agronomic and water management practices, with a maximum of 2 applications per cropping season and maximum rate of 400 g/ha per year. Always follow the actual label of the product for directions of use.

Biological Profile (continued)

Crop Selectivity

Dodhylex™ active herbicide has excellent crop safety on transplanted or direct-seeded *indica* and *japonica* rice biotypes grown globally. Crop selectivity in rice is due to the lower binding affinity of Dodhylex™ active to rice DHODH enzyme. *In vitro* studies showed that Dodhylex™ active activity in *Setaria italica DHODH enzyme* is approximately fivefold greater than that of rice enzymes. When used following label instructions, products containing Dodhylex™ active can be used on all rice varieties and hybrids across the globe.

Transplanted rice was tolerant to Dodhylex™ active at all the rates tested, including 5X of high use rate. On the other hand, in case of wet conditions (after significant rain events) and cold temperatures, direct-seeded rice may show transient phytotoxicity symptoms when Dodhylex™ active herbicide is applied at rates higher than the proposed label rate (1.25X and higher, Figure 5). In these conditions, full crop recovery has been observed in 14 to 28 days.

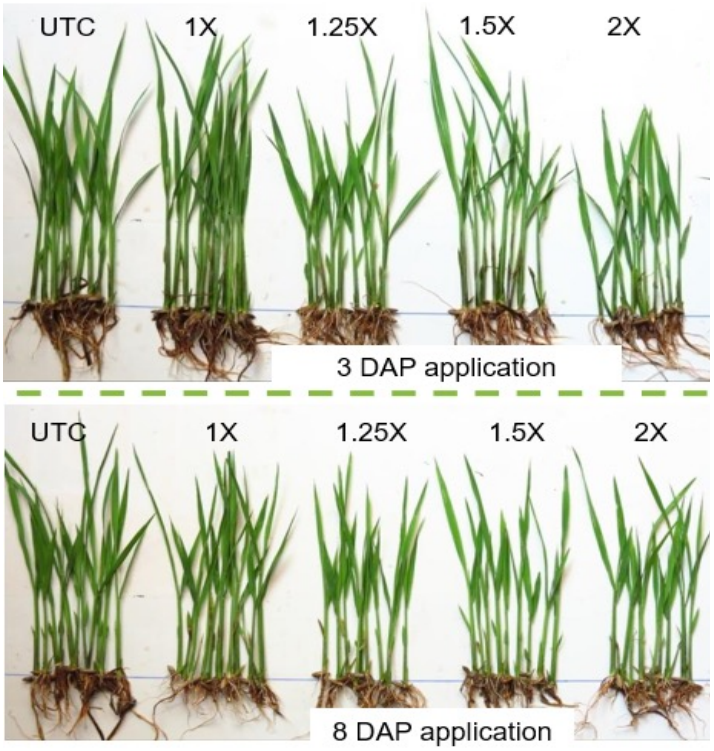


Figure 5.

Effect of Dodhylex™ active on direct-seeded rice. The picture was taken three days after treatment from a trial conducted in Vietnam.

UTC = Untreated Control

DAP = Days After Planting

Additional crops, such as sugarcane, soybean, cotton, sunflower and maize, have also shown tolerance to pre- and post-emergence applications of Dodhylex™ active.

Directions for Use

Formulations

In support of the global and regional launch of Dodhylex™ active, the following solo product formulations have been developed.

TABLE 1: LIST OF DODHYLEX™ ACTIVE SOLO FORMULATIONS

Formulation Type	Active Ingredient Content
Suspension Concentrate (SC)	400 g/L
Granule (GR)	0.5% and 1%

Mixing Instructions

Products containing Dodhylex™ active have performed like other known products of similar formulation type during the preparation of spray tank solutions. All solutions containing Dodhylex™ active require constant agitation and should be used or disposed of within a single working day (<24 hours).

Water hardness (PPM of CaCO3) and solution pH did not affect Dodhylex™ active formulations under lab conditions. If water quality is a concern within the targeted market, it is highly recommended that, at minimum, a jar test with local water is assessed for potential incompatibility concerns.

Standard mixing order should be followed to properly suspend and avoid physical incompatibility of Dodhylex™ active formulations in most standard spray equipment, and local labels must always be followed. The following outlines the minimum requirement for mixing with Dodhylex™ active-based products:

- The tank and spray equipment should be clean and free from all residues.
- Fill the tank with a minimum of 50% of the required water volume; begin agitation.
- Add any soluble powders (SG/SP).
- Add any dry powders (DF/WG).
- Add dispersed liquid formulations including Dodhylex™ active SC formulations (SC/F/SE/EW/CS).
- Add remaining emulsifiable concentrates (EC/EW/OD) or solutions (S/SL).
- Add any required adjuvants.
- Add the remaining water to the tank.

Directions for Use (continued)

Tank Clean-Out Guidance

Standard tank clean-out procedure should be followed to adequately remove Dodhylex™ active residues from the tank and spray equipment; at minimum, FMC requires triple rinsing of all tank components following the applications.

The following procedures are the minimum requirement for clean-out; consult local requirements for additional needs:

- All spray mixtures should be sprayed completely out of the tank through the boom/nozzles in a designated clean-out area.
- A minimum of 20% tank capacity of clean water is recommended for the initial cleanout; the tank should be rinsed and recirculated throughout the tank systems (all appropriate valves open).
- Spray out the tank solution in a designated clean-out area.
- Remove, clean and rinse all screens and the boom end caps; flushing of the boom may be required; reattach all pieces.
- Perform a second rinse of the system with 20% of the tank volume; spray the solution in a designated area.
- Add tank cleaning agent and follow instructions per the manufacturer's recommendations.
- Perform a final rinse of the system with 20% of the tank volume; spray the solution in a designated area.
- Check all nozzles/screens for particulates that may have accumulated; physically clean as appropriate.

Compatibility

Dodhylex™ active herbicide has shown good mixability with most herbicide partners under good agricultural practices. It can be applied in tank mix combinations with major pre-emergence and post-emergence herbicides in rice. When tank mixing, follow label directions for each herbicide label.

Adjuvant Recommendations

No specific adjuvants are needed when products containing Dodhylex™ active are applied directly to the soil as a pre-emergence herbicide. Field and laboratory/greenhouse tests have shown that the core types (NIS, COC or MSO) can be used with Dodhylex™ active for post-emergence uses. Given the various adjuvants available in different markets, the country and regional product manager must evaluate their use.

Directions for Use (continued)

Application Method

Products containing Dodhylex™ active herbicide can be successfully applied using different application methods based on the formulation type and the local rice-growing system, including knapsack sprayers and spreaders, boom sprayers, aerial and drone applications.

Because of its low vapor pressure, the role of vapor drift in the off-target movement of Dodhylex™ active herbicide is likely to be limited. The risk of particle drift varies greatly depending on the formulation type and the application method used. In general, granule formulations are not considered important sources of drift, even when applied aerially. On the other hand, liquid formulations may pose a greater risk of drift in the case of aerial applications.

To reduce the potential for drift, the most effective strategy is to apply the largest droplet size possible and to conduct the application using the following optimal conditions:

- Use a medium or coarser droplet size.
- Use the lowest spray pressure recommended for the nozzle to produce the largest droplets.
- For aerial applications: orientate the nozzles to minimize the effects of air shear; use shorter booms; make applications at the lowest height possible.
- Avoid making applications when relative humidity is low and temperatures are high.
- Do not spray in conditions of temperature inversion.

The risk of drift causing significant damage is directly related to the level of susceptibility of non-target plants to Dodhylex™ active herbicide. While research has shown that downwind drift deposits from a boom sprayer typically range from 1% to 8% of the application rate, it is also possible that some non-target areas receive higher doses due to environmental and spray conditions. The susceptibility of non-target crops commonly grown in areas adjacent to rice is shown in Table 2.

TABLE 2: CROP RESPONSE TO POST APPLICATIONS OF DODHYLEX™ ACTIVE IN FIELD CONDITIONS

Crop	Rate Tested (g ai/ha)	Crop Response
Almond	1.25 to 12.5	No crop response
Corn	6.25 to 250	No crop response
Cotton	6.25 to 250	No crop response
Peanut	6.25 to 250	No crop response
Pistachio	1.25 to 12.5	No crop response
Plum	1.25 to 12.5	No crop response
Sorghum	6.25 to 250	No crop response
Soybean	6.25 to 250	No crop response
Walnut	1.25 to 12.5	No crop response

Environmental Factors

Environmental factors, especially soil moisture, soil type, seedbed conditions and, in the case of rice, flooding time, are all key factors influencing the efficacy and crop safety of Dodhylex™ active.

Soil texture and organic matter content affect Dodhylex™ active's efficacy in pre- and post-emergence applications. Studies conducted in greenhouse conditions showed that to achieve a similar level of weed control, soils with fine texture (clay) and high organic matter content (>3%) require higher doses of Dodhylex™ active than soils with coarser texture and lower organic matter content (<3%).

Data from greenhouse and field studies show that soil moisture plays a significant role in Dodhylex™ active's efficacy in pre- and post-emergence applications. When applied pre-emergence, Dodhylex™ active achieved significantly higher levels of *Echinochloa crus-galli* control when soil saturation was at least 75%. For post-emergence applications, the best results were obtained when the soil was completely water-saturated.

The effect of flood timing on efficacy and crop safety is species-specific. However, the best results were generally achieved with flooding or flushing immediately after the application with Dodhylex™ active.

Stewardship

Resistance Management

FMC is committed to effectively managing weed resistance through integrating cultural and chemical control measures. Dodhylex™ active (tetflupyrolimet) is the only herbicide classified by Global HRAC as a Group 28, and due to its novel MOA, there are no reported cases of weed species that have developed resistance to it.

Global HRAC Classification:

Dodhylex™ active (tetflupyrolimet) (Chemical Family: Aryl pyrrolidinone anilide)	28 HRAC/WSSA

Based on genomics work done by FMC internally, Dodhylex™ active is considered a low-risk herbicide for weed resistance development. Due to its mode of action and primarily pre-emergence application timing, resistance development is expected to be slow. Products containing Dodhylex™ active are an excellent foundation for any weed management program by offering a robust resistance profile and residual control at early stages of crop development, thereby optimizing the conditions for a following post-emergence herbicide. Products containing Dodhylex™ active should be used as part of an integrated weed management program incorporating cultural, biological and other chemical management practices for long-term resistance management and sustainability. Such practices include but are not limited to using label rates, correct weed identification, application at target weed growth stages, good water management practices, field scouting, calibration of spray equipment, and following rotational practices listed on the label.

Stewardship (continued)

The following practices are recommended to prevent weed resistance:

Weed Management

- Use herbicide management program with multiple modes of action for controlling target weeds. Products containing Dodhylex™ active can be applied in tank mix combinations with major pre-emergence and post-emergence herbicides in rice, providing multiple MOA for controlling key weeds in rice. Dodhylex™ active has an excellent residual control profile, and a timely application of post-emergence herbicide is a recommended practice.
- Use mixtures or sequential treatments of alternate mode of action herbicides to control target weeds. Rotate products containing Dodhylex™ active with other MOA herbicides for weed management
- Do not use more than two applications of products containing Dodhylex™ active in a single rice-cropping season.
- If resistance or increased tolerance is suspected, treat weed escapes with an efficient herbicide/non-chemical management method to eradicate weed escapes to prevent seed production.

Proper Application Timing

- Apply products containing Dodhylex™ active at labeled rates and the recommended stages of weed growth as stated on the label. Due to its MOA, limit the application of products containing Dodhylex™ active to pre-emergence up to the 3-leaf stage of target weed species.

Field Scouting

- Scout fields before and after herbicide application to ensure proper weed identification, target weed stages for application and detect weed escapes. If a potentially resistant weed or weed population has been detected, use available control methods to avoid seed dispersion in the field.
- Early detection and eradication of possible resistant weed species is critical to prevent or delay resistance development.

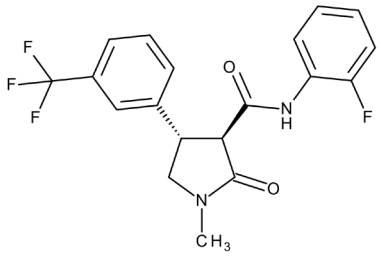
Integrated Management Practices

- Use alternative weed management practices, such as crop rotation, mechanical cultivation and use of weed-free clean seed for planting.
- Clean equipment before moving between fields to minimize dispersion of weed seed.
- Manage weeds around the fields to reduce weed seed production and potential spread in the field.
- Start with a weed-free field for planting rice using mechanical tillage or pre-plant herbicide application.

Report any incidence of suboptimal performance of products containing Dodhylex™ active to your local FMC Corporation representative.

Technical Information

Physical and Chemical Properties

Physical Properties - Technical Active Ingredient	
Global Brand Name	Dodhylex™ active
Code/Experimental Name	TVE29
ISO Name	Tetflupyrolimet
CAS Number	2053901-33-8
Chemical Formula	C19H16F4N2O2
IUPAC Name	(3S,4S)-N-(2-fluorophenyl)-1-methyl-2-oxo-4-[3-(trifluoromethyl)phenyl]pyrrolidine-3-carboxamide
Chemical Class	Aryl pyrrolidinone anilide
Structure	
Molecular Weight (g/mol)	380.3
Appearance	White, off-white or pink solid
Water Solubility (mg/L)	4.7
Vapor Pressure (mPa)	4.8 x 10^{-8} (PAI)
Henry's Law Constant (20°C, Pa m3/mol)	3.9 x 10^{-6} (PAI) at pH 7
Boiling Point (°C)	ND; starts to decompose at 380°C (PAI)
Melting Point (°C)	137.8 -139.1
Flammability	Not highly flammable (TGAI)
Explosive Properties	Not explosive (TGAI)
Auto Ignition Temperature	Not tested, TGAI is a solid material
Oxidizing Properties	Not oxidizing (TGAI)
Specific Gravity (Relative Density @20°C)	1.417 (TGAI)
Surface Tension (20°C)	67.8 mN/m (PAI)
Decomposition Temperature (°C)	380°C (PAI)
Stability pH	6.69 (TGAI)
KowLogP (20°C)	3.33 (PAI)
pKa	12.8

Technical Information (continued)

Environmental Fate

Soil Degradation, DT_{50} (days) @20°C, pF2.0	64 (lab, geomean)
Mobility, Koc (mL/g)	657 (geomean)

Toxicological Properties

Acute – Oral LD_{50} (mg/kg)	>5000 (GHS no category)
Acute - Dermal LD_{50} (mg/kg)	>2000 (GHS no category)
Inhalation LC_{50} (mg/L)	>5.08 (GHS no category)
Eye Irritation	Mildly irritating (GHS no category)
Skin Irritation	Slightly irritating (GHS no category)
WHO Classification	U (unlikely to present an acute hazard)

Eco-Toxicological Properties

Fish – 96 hour LC_{50} (mg/L)	5.9
Daphnia - Acute 48 hour EC_{50} (mg/L)	5.85
Algae - 72 hour EC_{50} (mg/L)	4.7
Earthworms - 14 day LC_{50} (mg/kg dw soil)	>1000
Birds - Acute Oral LD_{50} (mg/kg)	>2000
Honeybees - Contact 48 hour LD_{50} (µg as/bee)	>100
Honeybees - Oral 48 hour LD_{50} (µg ai/bee)	>119

This technical bulletin is intended for use only as a guide in providing general information about Dodhylex™ active. It must be emphasized that products containing Dodhylex™ active must be used in accordance with local regulations and registrations. We strongly recommend that users read, understand, and follow all label directions, warnings and precautions prior to using products containing Dodhylex™ active.

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