

# Inatreq™ active

Technical Bulletin  
Cereals







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## Technical Bulletin

This technical bulletin represents a global overview of the technical attributes of Inatreq™ active (pronounced “INNA-trek”) relative to physical and chemical properties, biology and use, environmental fate, and toxicology.

This presentation is not intended to provide specific information relative to product use in different geographies.

This presentation is not a substitute for product labels. Consult your local country labels for specific product use.

## Presentation Disclaimers

Inatreq is currently not registered and is not available for sale. This is not an offer for sale.

The registration dossier for Inatreq was submitted for review in the European Union in December 2014.

This educational material is provided for informational purposes only and is not intended to promote the sale of product.

Any sale of this product after registration is obtained shall be solely on the basis of approved product labels, and any claims regarding product safety and efficacy shall be addressed solely by the label.





## Overview

Dow AgroSciences is excited to announce that our innovation efforts continue to generate market-focused opportunities for growth in both chemical and biological solutions with the advancement of a promising new cereal fungicide. Dow AgroSciences' fungicide business objective is to become a top player in the cereal fungicides market.

Inatreq™ active is an innovative new fungicide for the control of key diseases in cereals. The active is of natural origin with outstanding biology performance with a unique target site for cereal fungicides.

Inatreq is being evaluated globally in all major cereal fungicide markets, and will provide growers a powerful, new fungicide with a favorable environmental profile. It will be recommended in combinations or pre-mixes.

The new molecule ISO common name is Fenpicoxamid.

### Noteworthy Features – Key Attributes in Cereals

- **New patented chemistry** from Dow AgroSciences, chemical group: picolinamides
- **Novel fungicide with unique target site - Innovative resistance management tool**-binding site differs from all other current *Septoria tritici* modes of action (MoA) in the cereal fungicide market
- **Disease spectrum** –market leading activity on *Septoria tritici* (*Mycosphaerella graminicola*) with activity against rust and other diseases
- **Made in a single chemical modification of a natural product** produced by fermentation
- **Outstanding biology performance with strong residual protectant** properties as well as curative efficacy and local plant mobility (translaminar)
- **Application flexibility** with excellent crop safety: 2 applications in spring from BBCH 25 (mid tillering) up to BBCH 69 (end of flowering)
- **Favorable regulatory profile** – low mammalian toxicity and low persistence in the environment

### Formulation

New formulation chemistry has been developed to maximize the biological efficacy of the active ingredient. Inatreq will be offered in a range of formulation concepts to meet the various market needs of cereal growers.

- Inatreq will be used only in mixtures with other fungicides to deliver broad spectrum disease control and enforce a robust resistance management strategy for this unique molecule.
- Mixture partners may include triazoles, strobilurins or SDHIs.

Depending on the geography or premix combination, it will be offered as liquid formulations.

### Registrations

Dow AgroSciences is seeking to widely register Inatreq for use in all major cereal fungicide countries plus registrations in other countries where utility in additional crops is anticipated. Initial Inatreq registrations are anticipated in 2018.

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# Disease Control and Resistance Management

Inatreq™ active provides a unique mode of action for disease control in cereals. Based upon field trials, the following diseases will be controlled effectively by Inatreq at anticipated label use rates.

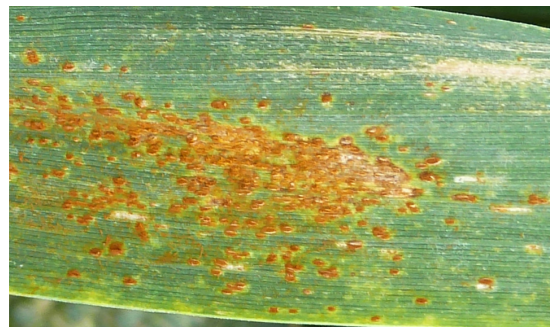
- Very strong residual protectant efficacy in wheat against *Septoria tritici* with activity on *Puccinia striiformis*, *P. recondita* and *Helminthosporium tritici-repentis*
- Curative activity against *Septoria tritici*
- Likely to be classified med/high resistance risk to *Septoria tritici* and will require a risk management strategy
- Shows no cross-resistance to existing cereal fungicide chemistries
- Compatible with other actives for tank mix flexibility



*Septoria tritici*, S. leaf spot



*Puccinia striiformis*, Yellow rust



*Puccinia recondita*, Brown rust



*Drechslera/Helminthosporium tritici-repentis* (DTR/HTR), Tan spot

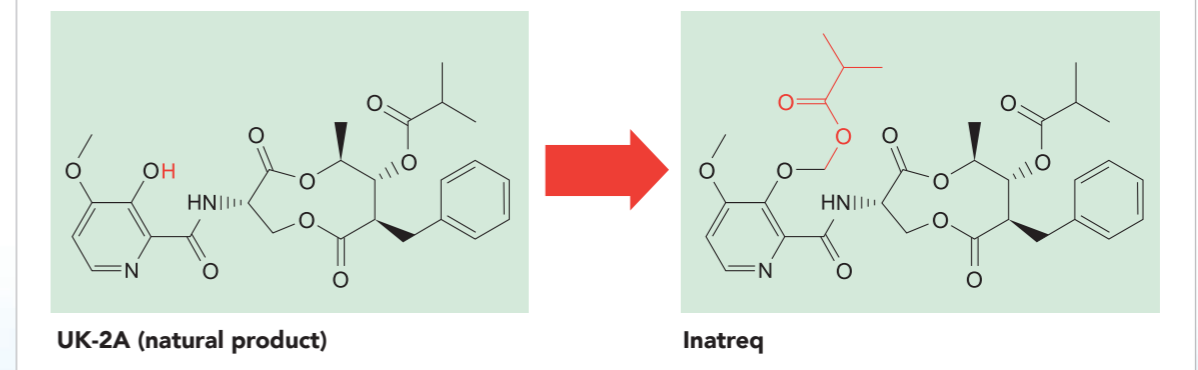
# Physical and Chemical Properties

Inatreq is derived from a natural product, UK-2A, produced by a soil borne *Streptomyces* species belonging to the phylum Actinobacteria. The original strain was isolated from a soil sample collected at Osaka University in Japan.

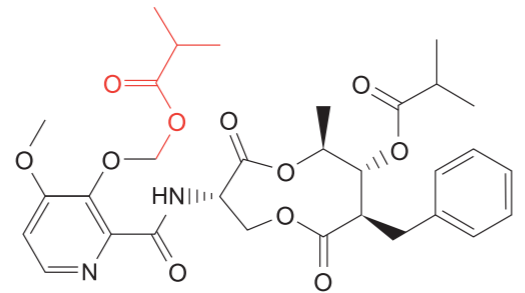


*Streptomyces* sp. 517-02 – the source of Inatreq

UK-2A is converted to Inatreq through a single chemical modification step post fermentation to enhance molecule stability and performance in the field (UV stability and physical properties).



## Description of Chemistry

Common Name	Fenpicoxamid (ISO provisionally approved)
Code Names Tested	DE-777, XDE-777, XR-777
Chemical Name (IUPAC)	(3S,6S,7R,8R)-8-benzyl-3-[[[4-methoxy-3-[[[2-methylpropanoyl]oxy]methoxy]pyridin-2-yl]carbonyl]amino]-6-methyl-4,9-dioxo-1,5-dioxonan-7-yl 2-methylpropanoate
CAS-Number	517875-34-2
Chemical Structure	
Chemical Family	Picolinamides
Empirical Formula	C <sub>31</sub> H <sub>38</sub> N <sub>2</sub> O <sub>11</sub>
Molecular Weight	614.64
Biological action	Fungicide
Mode of action	Respiration inhibitor at MET III (cyt. bc1 complex) - Qil
Plant translocation	Contact /residual and local plant mobility (translaminar)
Resistance group	Expected to be assigned to C4 #21 (2016/17)
Odor	Slight
Relative Density (20°C)	1.21
Melting Point	158.3°C
Boiling Point	Decomposes before boiling
Flammability	Not highly flammable
Explosive Properties	Not explosive
Vapor Pressure	1.2 x 10 <sup>-7</sup> Pa at 20°C

## Mode of Action

Inatreq™ active is the first member of a new class of cereal fungicides, the picolinamides.

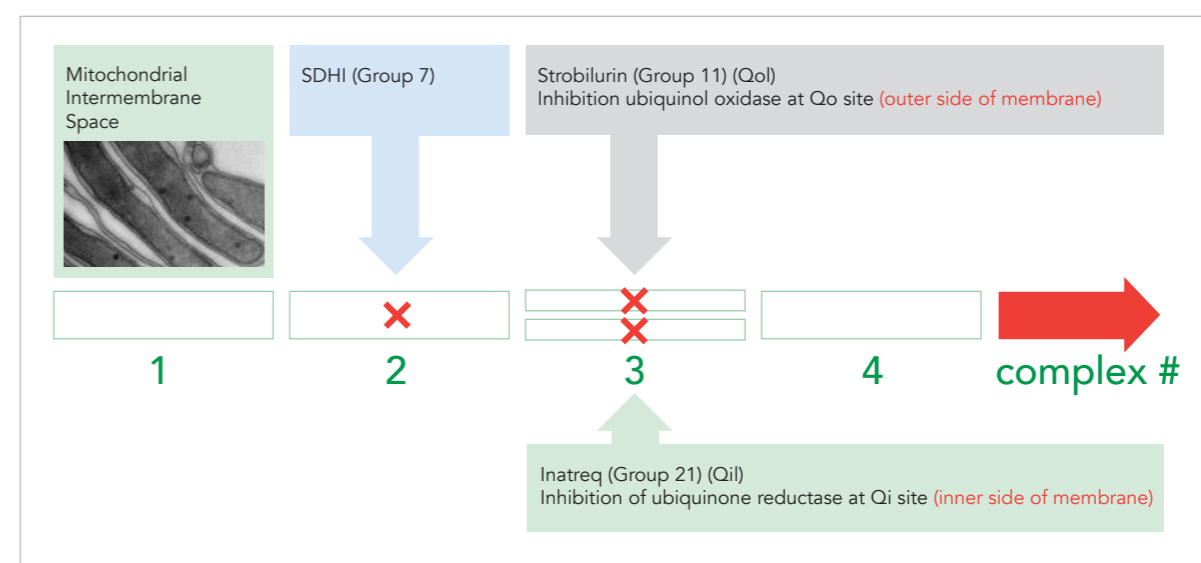
Inatreq is a Quinone Inside Inhibitor (Qil), expected FRAC MoA group C4 #21 (will be assigned in 2016/17). It inhibits mitochondrial respiration in fungi by blocking electron transfer in the respiratory chain, and binds to complex III (the bc1 complex) at the Qi site (the inner mitochondrial membrane).

**Note: Inatreq binds to a different site than the strobilurin Qo binding site.**

Inatreq will offer a new solution for control of *Septoria tritici* where resistance to other chemistries (e.g. strobilurins and triazoles) is a concern.

Inatreq shows good crop safety and disease control which can result in significant yield benefit.

Inatreq is best used as a protectant treatment or in the earliest stages of disease development.



Target site of **Inatreq**, SDHIs and strobilurins (Qo) in the mitochondria.

Inhibition of fungal mitochondrial respiration results in a reduction in the amount of ATP (Adenosintriphosphate) produced. As ATP is the main chemical energy carrier that drives the vital functions of cells, key biochemical processes are disrupted, growth is inhibited and the fungus dies.

In-vitro studies have shown that Inatreq is a potent inhibitor of spore germination and will also inhibit mycelial growth post germination thus explaining the outstanding protectant and strong curative properties observed when applied pre- or post-infection.



## Resistance Management

The unique target site of Inatreq™ active will be an innovative and effective tool in managing resistance when growers' choices are limited. Target site differs from all other current *Septoria* actives in the cereal market.

Inatreq should be used as part of an Integrated Crop Management (ICM) strategy incorporating other methods of control, including where appropriate, other fungicides with a different mode of action. Users should refer to current Fungicide Resistance Action Committee (FRAC) guidelines.

## Absorption and Translocation

### Behaviour on Leaf Surface after Application

Inatreq forms a tenacious deposit on the plant surface. Under greenhouse conditions, 90% of the material applied is still present 8 days after application. The majority of this material is associated with the plant surface and wax layers.

Inatreq redistribution across the plant surface is highly influenced by formulation type and based on this understanding, product performance has been optimized through specific formulation design.

### Penetration into Leaf Tissue

Inatreq penetrates into the leaves in small but biologically active quantities (up to a max. of 5% of the total applied after 48 hours). Penetration into leaves is influenced by formulation type.

It appears that the surface deposits act as a reservoir from which continuous penetration of the active occurs.

Once in the plant tissue, Inatreq is converted back into UK-2A, the natural product from which it is derived.

Studies with radiolabeled Inatreq and UK-2A have shown that, once inside plant tissue, UK-2A will show limited redistribution in an acropetal direction via the plant's vascular system.

In addition, bioassays have shown disease control on the abaxial (underside) leaf surface following application of Inatreq only to the adaxial (upper) leaf surface i.e. evidence of translaminar activity.

### Crop Tolerance and Plant Metabolism

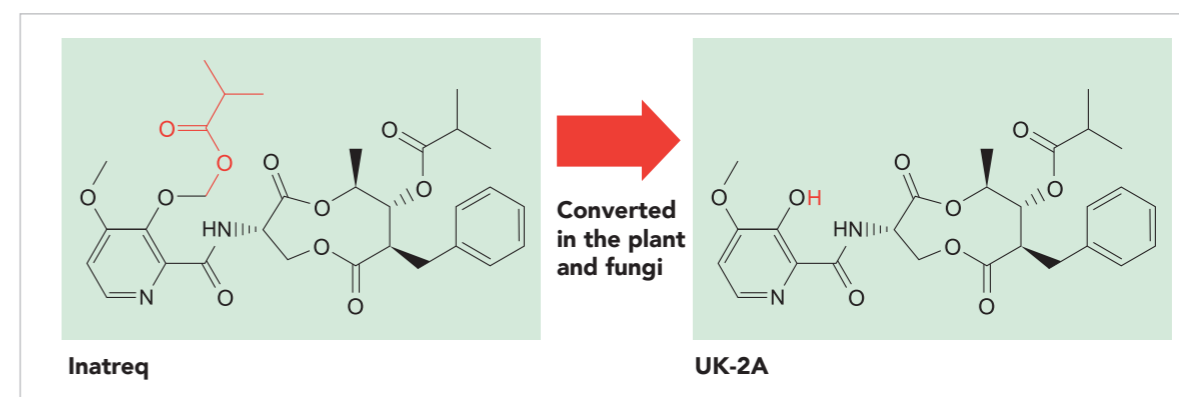
Spring and winter wheat, durum wheat, barley, rye and triticale show excellent tolerance to Inatreq.

Studies have shown that Inatreq is converted back into UK-2A within both plant and fungal tissue, thus activating its fungicidal activity.

This conversion occurs when Inatreq is taken up into the plant or fungal tissue. Inatreq on the leaf surface or bound to cuticular waxes is not converted to UK-2A. Plant metabolism studies show that at harvest more than 75% of Inatreq remains as parent.

Inatreq spray deposits are essentially a reservoir of material which is only activated to UK-2A once taken up into germinating fungal spores (**protectant activity**).

A small amount of Inatreq which penetrates into the leaf tissue are converted to UK-2A in the plant and/or when taken up by fungal tissue within the leaf (**curative activity**).



# Crop Specific Information

## Crops and Growing Conditions

Inatreq™ active can be used on all varieties of winter and spring wheat (soft and durum), rye and triticale.

### Timing

Best results are achieved from applications made as a protectant treatment or in the earliest stages of disease development following a disease risk assessment or the use of appropriate decision support systems. Timing is flexible, with optimal application timing T1 or T2.

### Crop Stage

Inatreq offers 2 applications in spring from BBCH 25 (mid-tillering) up to BBCH 69 (end of flowering), Interval between applications: min. 14 days.

### Rates of Use

Apply Inatreq at 75 to 130 grams of active substance per hectare.

## Mixing and Spraying

### Mixing Procedure

Sprayer is set to give an even application at the correct volume. Half the required volume of water is poured into the spray tank and agitation begins. The required amount of Inatreq is added to the spray tank and allowed to disperse before any other product is added. The rest of the water is added and agitation continues until thoroughly mixed. Agitation continues during spraying.

### Application Methods and Spray Quality

Typical application will be made with low pressure ground equipment. Sufficient spray volume (100-300 L/ha water) is used to provide thorough coverage and a uniform spray pattern. Only nozzle types and spray equipment designed for fungicide application are used. Low drift nozzles must be used to reduce potential buffer zone requirement to 5 m.

### Rainfastness

Inatreq has demonstrated favorable rainfastness.

### After Spraying

Thoroughly wash out sprayer according to manufacturer's guidelines and dispose of washing and clean containers according to DEFRA Code of Practice and local water authority guidelines.

# Toxicology

## Mammalian Toxicology

A complete set of mammalian toxicology studies was conducted with Inatreq in order to provide comparative information. The results are summarized below:

- Acute mammalian toxicity is very low by the oral and dermal routes of exposure
- Not irritating to the eyes, mild irritation to skin
- No skin sensitization
- Long-term toxicity and carcinogenicity studies did not demonstrate any potential for carcinogenicity

Inatreq has low acute mammalian toxicity\*:

Test (Species)	Results
Acute oral LD50 (rat)	>2000 mg/kg
Acute dermal LD50 (rat)	>5000 mg/kg
Dermal sensitization (rabbit)	Negative

Inatreq has low chronic mammalian toxicity\*:

Test (Species)	Results
Chronic 2 year (rat)	Not carcinogenic
Reproduction (rat)	Not a reproductive toxicant
Neurotoxicity (rat)	No adverse effects

\*Note: **Toxicity:** the degree to which a substance can harm humans or animals. **Acute toxicity:** involves harmful effects in an organism through a single or short-term exposure. **Chronic toxicity:** involves harmful effects in an organism over an extended period, usually upon repeated or continuous exposure.

Laboratory tests show no unreasonable adverse effects from Inatreq active:

- Not genotoxic
- Not immunotoxic
- Not neurotoxic
- Not carcinogenic
- Not a developmental toxicant
- Not a reproductive hazard



## Environmental Toxicology

Testing of Inatreq™ active indicates that the active ingredient exhibits very low acute toxicity to terrestrial species: mammals, birds, honeybees and earthworms. Inatreq exhibits high acute toxicity to fish and aquatic invertebrates and moderate toxicity to freshwater algae depending upon species.

Studies evaluated for Inatreq indicate:

- Exhibits very low toxicity to mammals
- Exhibits very low toxicity to birds
- Exhibits very low toxicity to honeybees and other non-target arthropods
- Exhibits very low toxicity to soil organisms like earthworms, collembola and soil mites
- Exhibits very low toxicity to non-target higher plants
- Exhibits high toxicity to fish and aquatic invertebrates\*
- Exhibits moderate to high toxicity to freshwater algae

\*Note: Use according to the approved label does not result in any risk to aquatic organisms when buffer zones and/or low drift nozzles are implemented.

## Environmental Fate

Laboratory and field studies have been conducted to determine the fate of Inatreq in the environment. Inatreq degrades rapidly in the environment to UK-2A which then degrades rapidly to pesticidally non-active compounds.

Dissipation of Inatreq occurs primarily through microbial degradation in the soil, hydrolysis and photolysis in water.

<b>Hydrolysis</b>	→ Lab half-life @ pH 7: 0.9 days
<b>Photolysis Water</b>	→ Lab half-life @ pH 7: 3.1 days
<b>Soil</b>	Aerobic lab half-life → Inatreq: 1.9 days → UK-2A : 2.3 days

## Soil Adsorption and Mobility

Laboratory studies have demonstrated an average Koc of 53173 mL/g indicating that Inatreq is strongly adsorbed to soil.

Laboratory studies have demonstrated an average Koc of 10040 mL/g for UK-2A indicating a similar sorption to soil as parent.

Both, Inatreq and UK-2A, demonstrate a very low potential for groundwater contamination according to EU simulation.

<b>Dissociation Constant (pKa)</b>	→ 2.4 @ 20°C
<b>Water Solubility</b>	→ 0.04 mg/L @ pH 7
<b>Octanol/Water cf. (log Pow)</b>	→ 4.4 @ pH 7



## Disclaimers

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