

Bupirimate (NIMROD): a unique fungicidal mode of action and solution in the Oidium diseases control

Areas of Bupirimate usage and importance to crop protection

Bupirimate is one of the most important fungicides for the control of Powdery mildew diseases in a large number of crops such as pome fruits, cucurbits, strawberry and various other berries, grapes, vegetables and ornamentals.

Based upon contact, translaminar, systemic and vapour activity, Bupirimate offers a unique method for effective and proven control of Oidium disease. Both from a resistance management point of view and because of its unique activity, the use of Bupirimate cannot be missed in the currently registered uses in Europe.

Introduction

IUPAC name:

5 Butyl-2-ethylamino-6-methylpyrimidin-4yl- dimethylsulfamate

Chemical class:

Pyrimidinol (2-Aminopyrimidine)

Trade names: NIMROD

Formulations: 250 g/L EC

Mode of action: NIMROD, a formulation containing 250 g/L Bupirimate, exhibits a fungicidal activity unique through its pyrimidine chemistry.

Bupirimate has a four-ways action activity on Powdery Mildew (hereinafter PM), providing ERADICANT and PROTECTANT activity against PM (different disease agents) in a very wide range of crop situations; mainly in pome fruits, stone fruits, berries, vine, fruiting vegetables and ornamentals (such as roses, begonias, chrysanthemum).

Disease control is achieved by interaction of direct protection and eradication through systemic and translaminar action. Bupirimate is apparently translocated in the plant xylem. i.e. movement occurs with the translocation stream upwards in the stem and towards the margins of leaves:

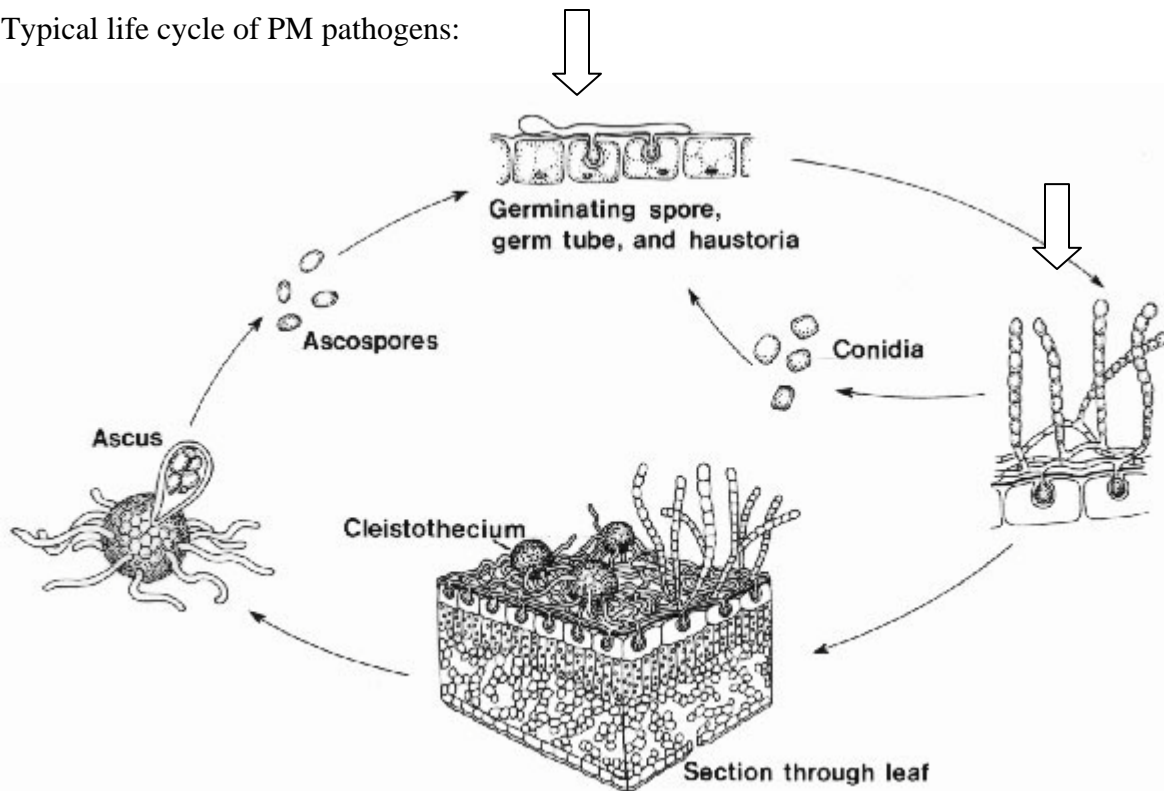
- **SYSTEMIC:** after application Bupirimate rapidly spreads through the leaf to give rainfast protection against disease; Bupirimate moves freely within sprayed leaves and from sprayed green stems to leaves. Systemic and trans-laminar activity has been shown against powdery mildew of apple, cucumber and vine;
- **TRANSLAMINAR:** Bupirimate passes through the leaf to control mildew on the unsprayed surface. Translocation within stems and leaves is likely to be an important

factor contributing to the excellent performance of the Bupirimate sprays against PM under field conditions. As PM penetrate only the superficial cells it can be assumed that Bupirimate applied to one surface of the leaf reaches the outer layer of cells at the opposite surface;

- **VAPOUR:** vapour action helps to give effective control where foliage is dense and complete spray cover is difficult.

Other uses include inhibits PM fungus at various stages; spore germination, formation of appresoria, formation of haustoria, some effect on hyphal growth, anti sporulant. Bupirimate is metabolized to Ethirimol in the plant tissues. Ethirimol inhibits Adenosine-deaminase (ADA-ase) in the nucleic acid synthesis in the fungus cell thus disrupting Purine metabolism in the fungus cell

Typical life cycle of PM pathogens:



Comparative mode of action of commonly used fungicides to control PM

Products	NIMROD	Strobilurins	SBIs (triazoles, pyrimidines, imidazoles)
Active ingredient	Bupirimate	Azoxystrobin, Kresoxim metyl,	Fenarimol, Cyproconazole,

		Trifloxystrobin, etc.	Flusilazol, Tetraconazole, Tebuconazole, Triadimenol, etc.
Mode of action	Synthesis of nucleic acids in the fungi	Respiration	Biosynthesis of sterol in membranes
Site of action	Adenosine-deaminase (ADA-ase)	binding to the mitochondrial bc ₁ complex, subsequently blocking electron transfer and ATP synthesis.	C14- demethylase

Consequently, Bupirimate is an excellent choice in spray programmes to complement fungicides with alternative modes of action, such as demethylation inhibitor products or strobilurines.

Resistance management

Bupirimate belongs to the FRAC group 8, which includes other 2 fungicides, dimethirimol and ethirimol, both now not authorized in Europe. Bupirimate is therefore the only member left of this family.

Resistance to this group of fungicides is thought to be controlled multi-genically (Hollomon 1981).

Resistance to this class of fungicide was studied intensively in the 1970's and 1980's. The focus of the studies was resistance to ethirimol in barley powdery mildew populations in the UK (Shepard *et al.* 1975, Heaney *et al.* 1984). Resistance to dimethirimol was also reported in populations of cucurbit PM (*Sphaerotheca fuliginea*) in the Netherlands (Schepers 1984) and Japan (Ohtsuka *et al.* 1991).

No cases of resistance have been reported in the last 15 years.

Indeed Bupirimate it is always used only as part of a season long control programme (primarily in alternation with other cross-resistance groups). As a consequence it continued to maintain high levels of sensitivity and thus current levels of effectiveness in the long term should be maintained too.

Resistance develops relatively slowly if selection is excessive and can be reversed if selection is relaxed. In this respect Bupirimate provides an easier resistance management challenge than more modern mildewcides such as the strobilurins, where resistance development can be rapid and may be stable.

No cross resistance with other chemical families have been observed.

IPM compliance

Bupirimate is actually included as a key product in the IPM PM spray programs for most of the crops its use is authorized. Bupirimate use is suggested either in alternation with other fungicides or in mixture.

Besides the reasons described in this document, another important advantage is Bupirimate selectivity on beneficials. Bupirimate has negligible effect on bees and beneficial arthropods (eg. predatory mite *Typhlodromus pyri*, *Coccinella septempunctata*, *Orius spp*, *Bombus terrestris*) commonly present in orchards and field crops.

Toxicological and Environmental profile compared to commonly used fungicides

Bupirimate is not classified for human health. Appropriate protective equipment allows safe uses of the Bupirimate formulated products in the target crops.

Bupirimate will fit the approval conditions of the new PPP legislation as briefly summarized as follows.

A new dossier was prepared and submitted in June 2009 for annex 1 registration and currently reviewed by ESFA.

The information submitted allows establishment of clear endpoints for ADI, for AOEL. No ARfD is deemed necessary to be assigned.

In addition, Bupirimate is meeting all criteria for approval related to human health, fate and behavior in the environment:

- not carcinogenic, mutagenic or toxic to reproduction class 1 or 2
- not an endocrine disruptor
- no persistence , no bioaccumulation, no toxic (not a POP, PBT, vPvB substance)
- no relevant metabolites
- no groundwater contamination

None of the conditions for candidate for substitution as described in the new regulation replacing 91/414 are met and therefore Bupirimate is very unlikely be subject to a comparative assessment and its substitution principle.

Bupirimate does not cause harmful effects to the environment when used as recommended.

Use recommendations and controlled diseases

Crop	Common name	Latin name
Apple	Powdery Mildew	<i>Podospharea leucotricha</i>
Pear		<i>Podospharea leucotricha</i>
Stone fruits		<i>Sphaerotheca pannosa</i> <i>Podospharea tridactyla</i>
Cucurbits		<i>Erysiphe cichoracearum</i> <i>Sphaerotheca fuliginea</i>
Rose		<i>Sphaerotheca pannosa</i>
Pepper		<i>Levillula taurica</i>
Tomato, Eggplant		<i>Levillula taurica</i>
Strawberry		<i>Sphaerotheca macularis</i>
Artichoke		<i>Levillula taurica</i>
Hops		<i>Sphaerotheca humuli</i>
Mango		<i>Oidium mangifera</i>
Currant		<i>Sphaerotheca mors-uvae</i>
Goosberry		<i>Sphaerotheca mors-uvae</i>
Vine		<i>Uncinula necator</i>

Bupirimate is actually registered in many European countries on more than 20 crops, many of them to be considered minor crops. In some case its authorization was obtained with the support of specific countries programs aimed to register plant protection products on minor crops, with the regulatory local authority and farmer association contribution.

Rates and PHIs

Rates and pre-harvest intervals vary according to the target diseases and crops. The following Bupirimate rates of application may be used as a guideline.

Crop	Application Rate (as Bupirimate g/ha)	Per-harvest interval (days)
Apple	125 – 450	1 - 14
Pear	125 - 450	1 - 14
Stone fruit	150 - 450	7 - 14
Cucurbits	125 - 500	3 - 15
Ornamentals (Roses, etc.)	50 – 3000	n.a.
Pepper	250 – 750	3 - 7
Tomato, Eggplant	250 – 750	3 - 15
Artichoke	250	7

Strawberry	250 - 350	3 - 7
Hops	350	14
Gooseberry	175 – 375	14
Raspberry	275 – 375	8
Blackberry	275 – 375	3
Blackcurrants	375 - 700	7
Vineyards	225 – 500	14

Bupirimate and its metabolite ethirimol residues decline quite quickly, allowing to spray it with a quite short pre-harvest interval.

Phytotoxicity

Not phytotoxic effects to the above mentioned crops, if used according to recommendations, have been observed.

Easy to measure and mix formulation

Bupirimate is formulated as an easy to measure and liquid (emulsifiable or oil water) formulations.

Compatibility

Bupirimate is compatible with most of fungicides, insecticides and adjuvants, with very limited exceptions on some crops. Therefore, also from this point of view, Bupirimate should be considered a very flexible fungicide.

Recommendations by crops

1. apples and pears

Benefits of NIMROD (Bupirimate)

- Proven performance against mildew
- Unique mode of action, excellent choice in spray programs to complement other fungicide types (use in conjunction with a mildewcide of alternative mode of action, eg a SBIs)
- Adjust application rates to suit spray intervals
- Very short PHI interval (14 days)
- Comprehensive tank mix recommendations
- Timing: apply from green cluster until extension growth ceases (apple) or from white bud stage or when mildew appears and repeat as necessary certainly until after the fruitlet stage to prevent fruit infection (pear).

2. strawberry and various berries

Benefits of NIMROD (Bupirimate)

- Proven performance against mildew
- For disease resistance management, excellent choice in spray programs to complement other fungicide types (use in conjunction with a mildewcide of alternative mode of action, eg a SBIs type)
- Very short PHI interval (3 days)
- Timing: apply at the first sign of disease from just before blossom and repeat 10 to 14 days intervals if necessary.

3. cucurbits, melon, courgettes

Benefits of NIMROD (Bupirimate)

- Proven performance against mildew
- For disease resistance management, excellent choice in spray programs to complement other fungicide types (use in conjunction with a mildewcide of alternative mode of action, eg a SBIs type)
- Very short PHI interval (3 days)
- Timing: apply at the first sign of disease from just before blossom and repeat at 14 days intervals if necessary.

4. stone fruits (peach, apricots)

Benefits of NIMROD (Bupirimate)

- Proven performance against mildew
- For disease resistance management, excellent choice in spray programs to complement other fungicide types (use in conjunction with a mildewcide of alternative mode of action, eg a SBIs)
- Very short PHI interval (14 days)
- Timing: apply at the first sign of disease before blossom and repeat at 10 to 15 days interval.

5. Grapes

Benefits of NIMROD (Bupirimate)

- Eradicant and preventive proven performance against mildew
- For disease resistance management, excellent choice in spray programmes to complement other fungicide types (use in conjunction with a mildewcide of alternative mode of action, eg a SBIs)
- Very short PHI interval (14 days)
- Timing: apply at the first sign of disease from blossom and repeat 4-5 days intervals if necessary.

6. Ornamentals (Roses, Chrysanthemum, Begonias other ornamental and forestry plants

- Proven performance against mildew

- For disease resistance management, use in spray programmes with alternative mode of action types (use in conjunction with a mildewcide of alternative mode of action, eg a SBIs)
 - Specific recommendation for Roses, Christanthemum and Begonias .
 - Safety used on a wide range of Ornamental and Forestry plant
 - Timing: apply before or at the first sign of disease and repeat 4-5 days intervals.
7. Processed food crops: tests have shown that Bupirimate does not cause taints in crops following treatments.

Bupirimate strenghts and relevance for growers

The information provided demonstrates the importance of Bupirimate use through the application of the products NIMROD 250 EC and NIMROD 250 EW as an essential part of powdery mildew control schemes.

The Bupirimate toxicological and environmental properties, and its unique mode of action provides a consistent eradicant, and protectant efficacy while products of other chemical groups lose efficacy and become sensitive to resistance.

Moreover, the use of Bupirimate becomes imperative when powdery mildew is already established in fields and other products are not effective or can only present protectant activity while a curative activity is required.