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ADEPIDYN™ Fungicide: A New Broad Spectrum Foliar Fungicide for Multiple Crops

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ABSTRACT

ADEPIDYN™ is the new carboxamide fungicide discovered by Syngenta, which is the first member of a new chemical subgroup among the succinate dehydrogenase inhibitor (SDHI) fungicides, the N-methoxy-(phenyl-ethyl)-pyrazole-carboxamides. The ISO common name for ADEPIDYN™ fungicide is pydiflumetofen. The compound was selected based on its particular strength against *Fusarium* species, especially those involved in Fusarium Head Blight of cereal crops. It possesses high binding properties to the complex II enzyme. It also delivers a very high efficacy against many leaf spot pathogens (such as *Cercospora spp.*, *Alternaria solani* and *Venturia inaequalis*) setting a new performance standard in various crops (such as apples, wheat and peanuts). Further, it provides excellent control of powdery mildews across multiple crops. In addition, ADEPIDYN™ is highly active on difficult to control pathogens such as *Botrytis cinerea, Sclerotinia sclerotiorum,* and *Corynespora cassiicola*, that cause severe damage on important crops. This spectrum makes it the ideal fungicide to complement the Syngenta fungicide portfolio and to introduce a new mode of action for Fusarium control. The observed movement of ADEPIDYN™ fungicide combined with excellent quantitative rainfastness provides long lasting activity. It can be safely mixed with various other active ingredients, which allow ADEPIDYN™ fungicide formulations to provide activity against a comprehensive spectrum of pathogens on a wide range of crops and also provide a tool for the management of fungicide resistance in the target populations.

INTRODUCTION

The fungicide class of the succinate dehydrogenase inhibitors (SDHI), or carboxamides, have become more important in recent years. After the introduction of Carboxin in 1966 (Schmeling & Kulka 1966), mainly used in seed treatment, Furametpyr (Reinheimer et *al*. 2007) the first pyrazole carboxamide fungicide was registered in 1996. In 2003, Boscalid was

introduced, which broadened the spectrum of use (Stammler et *al*. 2007). Between 2010 and 2012 Syngenta launched 3 members of the SDHI class: The first compound was Sedaxane, used as seed treatment with a broad spectrum for seed and soil borne diseases, such as *Microdochium nivale*, *Rhizoctonia solani* and smuts (Zeun et *al*. 2012). Sedaxane was closely followed by Isopyrazam, the broad spectrum solution in cereals controlling *Zymoseptoria tritici*, rusts, and recently in fruit and vegetables, targeting *Venturia inaequalis* and powdery mildews (Harp et *al*. 2011). In 2012 Benzovindiflupyr, with the tradename SOLATENOL™ was introduced to control soybean rust, and a broad spectrum of other diseases (Guicherit et *al*. 2014). Currently more than 15 different SDHI fungicides are on the market covering activity on a wide range of plant pathogens, from Ascomycetes, Deuteromycetes and Basidiomycetes. However, some pathogens/pathogen groups are still difficult to control either due to lack of intrinsic activity or due to sub-optimal physical-chemical properties. ADEPIDYN™ widens the spectrum significantly, brings in a significant improvement of activity, and will be an enrichment of the tool set for modern agriculture to combat many severe diseases.

ADEPIDYN™ - MEMBER OF A NEW GROUP AMONG SDHI FUNGICIDES

ADEPIDYN™ (APN) is the trade mark of Pydiflumetofen, a N-methoxy-(phenyl-ethyl)-pyrazole-carboxamide within the succinate dehydrogenase inhibitor (SDHI) fungicides class (Fig 1). It interferes with ubiquinone reduction in complex II of the respiration chain and because this reaction is coupled with succinate oxidation it affects the Krebs cycle as well as respiration. ADEPIDYN™ has a clear and well defined binding cavity similar to other SDHI (Scalliet et al. 2012) and is a single mode of action fungicide. The water solubility (2.5 ppm) and the log P (3.77) are in the range of other modern SDHIs currently in use for foliar application. The chemical structure is characterized by the hydrophilic difluoromethyl

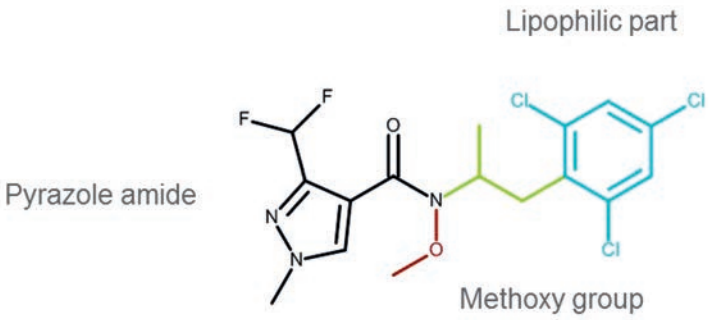

Figure 1 Chemical structure of ADEPIDYN™ (Pydiflumetofen), a N-methoxy-(phenyl-ethyl)-pyrazole-carboxamide within the succinate dehydrogenase inhibitor (SDHI) fungicides class, characteristic elements are highlighted in different colors: the pyrazole amide in black, the lipophilic part in blue, the stretched linker in green and the methoxy moiety in red.

pyrazole acid constituting the toxophore, coupled to a N-methoxy amine moiety and a stretched linker to the hydrophobic tri-chloro substituted phenyl ring. The intrinsic activity at the target enzyme reflects the high potency even compared to other highly active SDHI molecules. For both *Botrytis cinerea* and *Fusarium graminearum* species, the IC 50 was below 3 nM indicating high and specific binding to SQR pocket of complex II.

BIOKINETIC CHARACTERISTICS OF ADEPIDYN™

The molecule is well suited for agricultural usage due to its physio-chemical characteristics. The uptake, movement, partitioning and rainfastness of ADEPIDYN™ have been measured in several plant species, such as wheat, soybean and apples. Radioactive labeled compound was added in droplets to the base of wheat heads and over time course of 14 days, the movement into the heads was measured (Fig 2). Leaf uptake was assessed by using soybean trifoliates, where droplets of radioactive compound were placed in the center of the leaves and the uptake and movement measured over 7 days. The movement and uptake of ADEPIDYN™ showed to be similar or slightly better as compared to standard triazoles used in both crops.

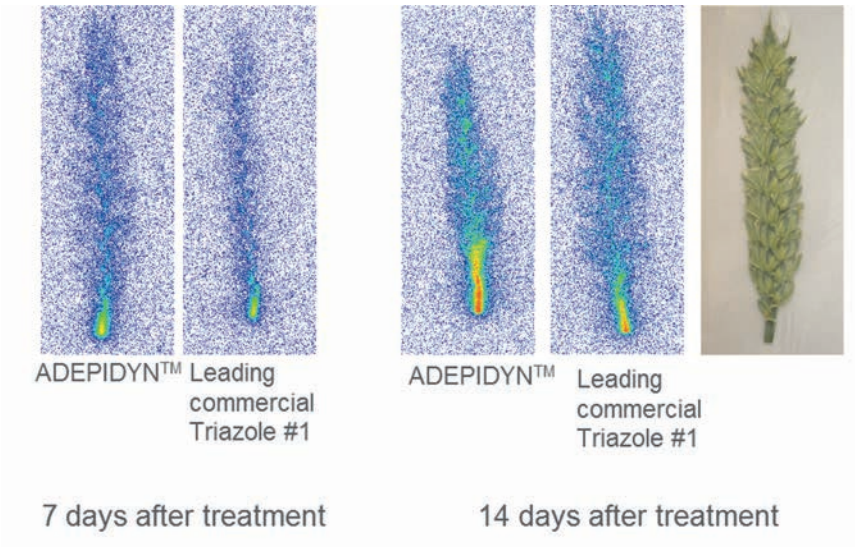

Figure 2 Translocation of ADEPIDYN™ over time in wheat heads using ^{14}C ADEPIDYN™ compared to ^{14}C commercial triazole #1 with movement measured after application to petioles.

The partitioning characteristics of ADEPIDYN™ was evaluated applying non-radioactive compound on soybean leaves and separately measuring the amount of fungicide on the surface, in wax/cuticle and leaf tissue. Assessments were done 6 hours, 1, 3 and 7 days after treatment. The uptake into the wax layer is very rapid since after 6 hours the majority is already in the cuticle (>80%), the rest is equally distributed either on the surface (8%) or in the tissue (8%). Over the course of the 7 days the total amount of compound recovered decreases,

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due to smaller amounts in the tissue and the wax. The absolute amount in the tissue remained stable and therefore increased proportionally to about 16%.

The rainfastness was measured on apple seedlings using a specially constructed “rain tower”. ADEPIDYN™ was applied solo, using the planned commercial SC200 formulation, as well as in mixture with Difenoconazole, in comparison to different SDHI products already in the market. Measurement of remaining compound was done after 20 mm rain 1 hour after foliar spray. APN retention either in the solo or in the mixture formulation was approximately 70% whereas the retention for either Difenoconazole (in the mixture formulation) or other market SDHI formulations was around 50%.

PHYSIOLOGICAL MOA OF ADEPIDYN™

Inhibition of complex II affects a fundamental process necessary for all life stages of fungal pathogens. However, as for other respiration inhibitors, the major effect is on energy demanding processes, such as germination and germ-tube growth at which stages many pathogens do not have yet access to nutrients. Studies were performed with *Alternaria solani*, and *V. inaequalis in vitro* on water agar (Fig 3). *A. solani* spore germination was not inhibited even at high ADEPIDYN™ or other SDHI fungicide concentrations (10 to 40 % inhibition at 100 mgL^{-1}). Germ-tube elongation of *A. solani* was strongly reduced by ADEPIDYN™ at 0.01 mgL^{-1}. Other SDHI fungicides needed 0.1 to 1 mgL^{-1} for a comparable inhibition of germ-tube elongation. Mycelium growth was inhibited most strongly by ADEPIDYN™ (more than 80 % at 1 mgL^{-1}) compared to other SDHIs (40 to 70 % inhibition at 1 mgL^{-1}). In contrast, spore germination of *V. inaequalis* was already completely inhibited at 0.01 mgL^{-1} of APN. Spores of *A. solani* are multi-cellular and 109-115 µm of 18-26 µm in size, whereas *V. inaequalis* spores are uni-cellular and only 20-30 µm by 7-9 µm in size. Whether a difference in availability of resources, difference in accessibility of the SDHI compounds to the target, or timely usage of the complex II explain the observed germination response is not yet elucidated. Important for disease control is that SDHI fungicides and especially APN inhibit early steps in the disease cycle of pathogens very efficiently.

SPECTRUM AND EXAMPLES OF BIOLOGICAL PERFORMANCE OF ADEPIDYN™

Many tests have been performed to profile the spectrum, activity and performance of ADEPIDYN™. These include tests in micro-titer plates with liquid growth medium and with leaf disks, followed by small plant screens in the greenhouse, to field trial in many countries around the world. The spectrum of ADEPIDYN™ spans mainly the ascomycetes, and combines high activity towards many very important pathogens such as *Z. tritici*, *Blumeria graminis*, *Pyrenophora* (*Drechslera*) *tritici-repentis, Uncinula* (*Erysiphe*) *necator* and *A. solani*. In addition, ADEPIDYN™ has high activity against difficult to control pathogens such as *B. cinerea*, *Sclerotinia sclerotiorum* and as novelty also against *Fusarium* spp. For

Fusarium head blight a special 24-well assay using spikelets was developed. ADEPIDYN™ showed almost full control of *F. graminearum* and *F. culmorum* down to 20 mgL^{-1}. Control of *B. cinerea* was assessed in greenhouse on tomato seedlings showing that rate per rate ADEPIDYN™ was significantly more active than the cyprodinil/fludioxonil mixture (Switch) and the activity stayed at high level until late evaluation timings.

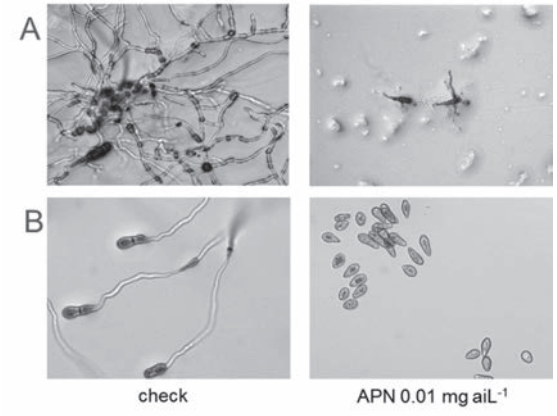

Figure 3 Effect of ADEPIDYN™ on A: *Alternaria solani* germ tube growth at 0.01 mg aiL^{-1} and B: Germination inhibition of *Venturia inaequalis* conidia by 0.01 mg aiL^{-1}.

FIELD TRIAL EXPERIMENTS

The results of many field experiments in different countries confirmed the activity and the spectrum of ADEPIDYN™.

Fusarium head blight (FHB) control by ADEPIDYN™ was compared in the field to two different standard DMI fungicides in 5 trials with 4 replicates of each treatment. Severity in untreated plots was approximately 25% on average (Fig 4). APN reached on average 90% disease control with a relatively small variation between the trials. The higher activity of APN compared to other fungicides used to control FHB is probably explained by its high intrinsic activity and good redistribution properties.

The superior activity of ADEPIDYN™ to control grey mold on grape bunches (*B. cinerea*), apple scab on leaves and fruits (*V. inaequalis*) and early blight on potatoes (*A. solani*) was shown in 12, 12 and 8 trials, respectively.

In addition, many more field trials were conducted to elucidate the ADEPIDYN™ activity against an even wider range of diseases. For example, on soybeans the control of *Cercospora sojina* (frog eye leaf spot) and *Corynespora cassiicola* (target spot) is improved by using ADEPIDYN™ in spray programs compared to current solutions. This is especially important since QoI resistance has spread for both diseases and a new mode of action is required

(FRAC). Furthermore, high performance against corn pathogens such as *Cercospora zeae-maydis* and *Exserohilum turcicum* could also be demonstrated.

With the broad spectrum activity of ADEPIDYN™ towards ascomycete diseases, this new fungicide complements the spectrum of the current Syngenta fungicides portfolio by filling important gaps of difficult to control pathogens.

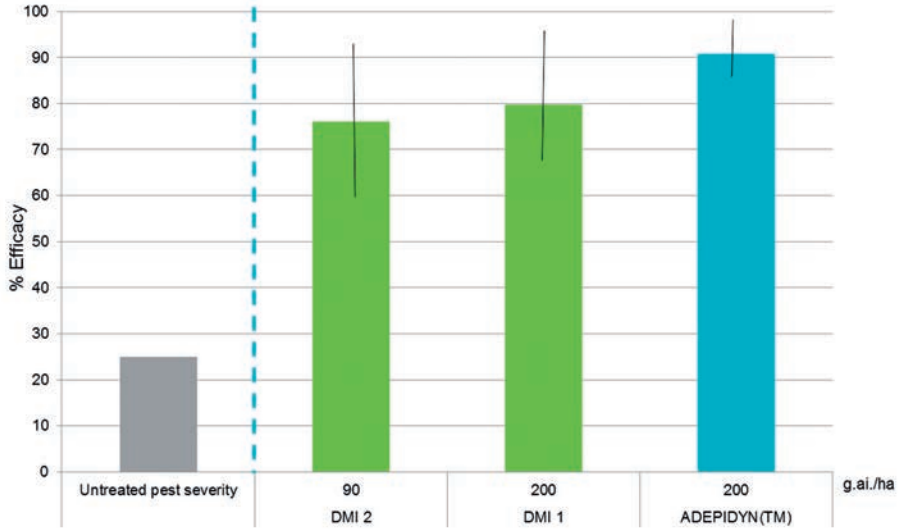

Figure 4 ADEPIDYN™ activity on Fusarium head blight in wheat measured as % efficacy on ears. Average of 5 trials. Bars indicate the variation (95% confidence level).

SUMMARY AND CONCLUSIONS

ADEPIDYN™ is the next generation SDHI fungicide comprising a new chemical group of N-methoxy-(phenyl-ethyl)-pyrazole-carboxamides. ADEPIDYN™ has a broad and unique disease spectrum for multiple crops with superior intrinsic activity, a balanced distribution in plants, excellent quantitative rainfastness and residual activity. ADEPIDYN™ constitutes a new mode of action for Fusarium Head Blight control. It fills current industry gaps in disease management. ADEPIDYN™ is not cross resistant to QoI's, DMI's, AP's and PP's. However, ADEPIDYN™ is cross resistant to other SDHI's, with genotype specific differences (Scalliet *et* al. 2012, Syngenta internal data) and will be embedded into the general and specific resistance management recommendation for SDHI fungicides agreed and published by FRAC (FRAC 2016).

ADEPIDYN™ is a strong partner for mixtures within the Syngenta portfolio and therefore enables versatile products to address farmers' urgent needs.

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