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EL-614, A NOVEL ACUTE RODENTICIDE

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Summary Eli Lilly and Company is currently developing EL-614, a novel, single feeding, acute rodenticide. This compound, α,α,α-trifluoro-N-methyl-4,6-dinitro-N-(2,4,6-tribromophenyl)-o-toluidine, has the unique property of being sufficiently toxic and acceptable to rats *(Rattus norvegicus)* that prebaiting is unnecessary. In non-choice feeding studies EL-614 at levels as low as 15 ppm exhibited total kill after feeding for 1 day, with none of the overt signs of toxicity found with many other acute rodenticides.

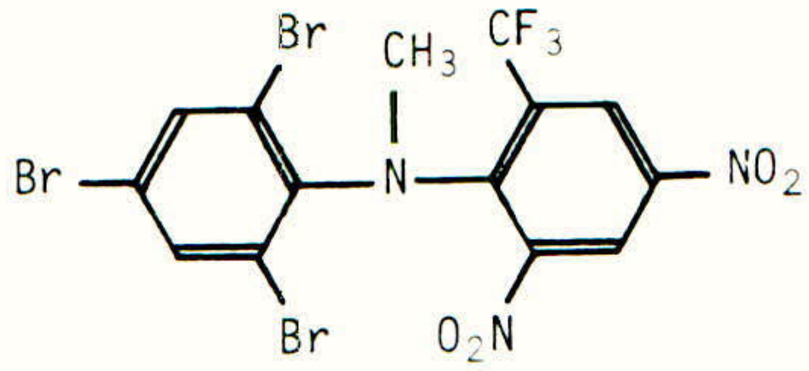
Résumé La société Eli Lilly est en train de developer EL-614, α,α,α-trifluoro-N-methyl-4,6-dinitro-N-(2,4,6-tribromophenyl)-o-toluidone, qui a la propriété unique d' être en même temps suffisament toxique et acceptable aux rats *(Rattus norvegicus)* de manière que l' utilisation des appats non poisonnés ne soit pas necessaire. Dans des essais où EL-614 a été administré aux rats dans la nourriture, une efficacité complète a été observéé après une journée à la dose de 15 ppm de matière active. Aucun de symptome visuels associes avec les autres raticides d'activitè aiguë n'a pas été observée.

INTRODUCTION

The discovery of warfarin in 1945 and the subsequent exploitation of anticoagulants as rodenticides dramatically increased the efficacy and safety of rodent control programmes and, at the same time decreased interest in acute poisons. With the discovery of rats and mice resistant to the effects of these anticoagulants interest was revived in rodenticides having a different mode of action. At Lilly, a programme was initiated to find a solution to the problem of anticoagulant-resistant rodents. The result of this effort has been the discovery and development of EL-614, an acute, single feeding rodenticide which is acceptable to rodents without prebaiting. Some of the results we have obtained with this compound will be described.

PHYSICAL AND CHEMICAL PROPERTIES

α,α,α-Trifluoro-N-methyl-4,6-dinitro-N-(2,4,6-tribromophenyl)-o-toluidine has the following structure:



Formula and molecular weight	$C_{14}H_7Br_3F_3N_3O_4$ 578.0
Physical state	Pale yellow, odourless, crystalline solid
Melting point	150-151 °C
Solubility	Soluble in chloroform, dichloromethane, acetone; moderately soluble in aromatic hydrocarbons; slightly soluble in saturated hydrocarbons; essentially insoluble in water.
Stability	Stable under normal storage conditions.

TOXICOLOGY

LD_{50} oral administration - polyethylene glycol solution of technical material

Rat *(Rattus norvegicus)*	2 mg/kg
House mouse *(Mus musculus)*	5 mg/kg
Cat	2 mg/kg
Dog	5 mg/kg
LD_{50} dermal administration male rabbits	1000 mg/kg

METHODS AND MATERIALS

Rodent bait was prepared either by mixing a solution of EL-614 in dichloromethane directly with the diet to make a final bait or by first preparing a concentrated bait (0.1%) and diluting it with diet to the desired levels. The diet used was either RT-10, a standard Lilly rat diet, or the diet, namely ground corn (65%), rolled oats (35%), corn oil (5%) and sucrose (5%), prescribed by the US Environmental Protection Agency (EPA). The acute toxicity was determined by feeding rats and mice varying concentrations EL-614 for up to 10 days in a non-choice test. The acceptability of EL-614 was determined in choice tests by allowing 10 males and 10 females of each

species to chose between treated and untreated diet. The animals were observed for 5 days post-test.

The efficacy of EL-614 against wild rats and mice was determined in a similar way with choice tests with wild captured or bred caged rodents. Limited field studies were conducted on station against natural infestations of animal facilities.

RESULTS AND DISCUSSION

EL-614 is toxic to rats at 15 ppm and to mice at 20 ppm in bait. Although toxicity is an essential prerequisite of any effective rodenticide, it is not by itself sufficient. A rodenticide needs also to be acceptable to rodents and have a delayed effect so as not to induce bait shyness. EL-614 has been shown by choice tests to satisfy these other requirements. The choice tests summarized on Tables 1-4 indicate that EL-614 has been effective on both the laboratory and wild varieties of both rats and mice. In most cases rats showed little or no discrimination between the treated and untreated diet. Male rats appear to be more susceptible than female rats. Mice discriminated against EL-614 more than rats, but even they consumed enough to be poisoned. The onset of symptoms appears to be delayed at least 12 h after ingestion by both rats and mice. One day's feeding seems adequate to kill most rodents. Only limited field testing of EL-614 has been undertaken to date. EL-614 was used to eliminate rat infestations in both chicken brooder houses and cattle feed pens, both cases in which alternate feeding was readily available. Although a pre-test census could not be taken, the number of carcasses found and a post-test census indicate that both rat colonies were eliminated.

Although EL-614 has been shown to be toxic to target and non-target animals alike, the low rates employed would require the ingestion of large amounts of bait by non-target animals to ingest a lethal dose (Table 5). The mode of action of EL-614 is not known at this time. It has been shown, however, not to act as an anticoagulant.

We are presently planning to field test EL-614 in the U.S.A. under an Experimental Use Permit Programme in a variety of locations against a variety of rodent problems. Some testing outside the United States against world rodent problems is also planned.

Acknowledgements

We thank Dr. William B. Jackson, Bowling Green State University (Ohio), for his help throughout the course of this work and for running the wild rodent choice tests.

Table 1

Summary of choice tests of EL-614 in diet achieving 100% kill (except as indicated) in laboratory rats *(Sprague Dawley* strain)

Concn. in diet (ppm)	Rats Sex	No.	Average initial weight (g)	Average diet consumed in 3 days (g) Control	Treated	Average amount of EL-614 consumed (mg/rat)	(mg/kg)	% EL-614 treated diet/ total diet	Average time to death (days)
50	M	5	195.8	0.6	7.0	0.35	1.79	92.0	1.8
	F	5	175.0	12.8	10.8	0.54	3.09	45.0	3.8
	Total	10	185.4	6.7	8.9	0.45	2.40	57.0	2.8
50	M	10	203.5	8.1	8.1	0.41	2.01	50.0	2.1
	F	10	188.4	15.2	16.7	0.84	4.46	52.0	4.4
	Total	20	196.0	11.7	12.4	0.62	3.16	51.4	3.25
50	M	10	189.4	9.0	8.5	0.43	2.25	48.5	4.0
	F	10	178.2	16.2	14.2	0.71	3.96	46.7	4.0
	Total	20	183.8	12.6	11.4	0.57	3.11	47.5	4.0
50	M	10	195.6	9.6	11.4	0.57	2.91	54.2	3.8
	F	10	173.2	15.2	14.7	0.74	4.26	49.0	3.9 *
	Total	20	184.4	12.4	13.1	0.66	3.59	51.3	3.85 **
50	M	10	191.7	10.2	9.7	0.49	2.53	48.7	4.0
	F	10	175.5	13.9	13.4	0.67	3.79	49.0	4.2
	Total	20	183.6	12.1	11.6	0.58	3.16	48.9	4.1
100	M	10	214.3	4.9	6.2	0.62	2.87	55.6	2.2
	F	10	196.3	13.6	13.4	1.34	6.81	49.5	3.0
	Total	20	205.3	9.3	9.8	0.98	4.75	51.3	2.6

* 90% kill

** 95% kill

Table 2

Summary of choice tests with 50 ppm EL-614 in diet achieving 100% kill in wild rats *(Rattus norvegicus)*

Rats		Average initial weight (g)	Average diet consumed in 3 days (g)		Average amount of EL-614 consumed		% EL-614 treated diet/ total diet	Average time to death (days)
Sex	No.		Control	Treated	(mg/rat)	(mg/kg)		
M	2	353	25.3	17.6	0.87	1.91	41.0	2.0
F	3	249	20.3	8.9	0.45	1.82	30.0	2.6
Total	5	290	22.2	10.8	0.54	1.86	32.0	2 4
M	5	286	19.0	15.6	0.78	2.99	45.0	2.6
F	5	270	16.1	20.2	1.00	3.91	55.7	2.2
Total	10	278	17.6	17.9	0.90	3.45	50.4	2.4

Table 3

Choice test of EL-614 in diet in laboratory mice (*Swiss-Webster* strain)

Concn. in diet (ppm)	Mice		Average initial weight (g)	Average diet consumed in 3 days (g)		Average amount of EL-614 consumed		% EL-614 treated diet/ total diet	% mice killed	Average time to death (days)
	Sex	No.		Control	Treated	(mg/mouse)	(mg/kg)			
50	M	10	25.3	3.4	3.7	0.18	7.22	51.8	100	3.0
	F	10	23.6	2.7	3.7	0.18	7.71	57.4	90	3.2
	Total	20	24.5	3.1	3.7	0.18	7.47	54.5	95	3.1
75	M	10	23.4	3.6	3.6	0.27	11.6	50.2	100	2.8
	F	10	23.0	3.0	3.9	0.29	12.7	56.0	80	2.9
	Total	20	23.2	3.3	3.7	0.28	12.2	53.0	90	2.8
100	M	10	22.6	2.2	2.6	0.26	11.5	54.9	100	2.7
	F	10	22.5	3.9	3.1	0.31	13.5	44.2	80	2.6
	Total	20	22.6	3.0	2.8	0.28	12.5	48.5	90	2.7

Table 4

Summary of choice tests with 50 ppm EL-614 in diet achieving 100% kill in caged wild house mice *(Mus musculus)*

Mice		Average initial weight (g)	Average diet consumed in 3 days (g)		Average amount of EL-614 consumed		% EL-614 treated diet/ total diet	Average time to death (days)
Sex	No.		Control	Treated	(mg/mouse)	(mg/kg)		
M	3	21.6	3.5	1.4	0.07	3.30	28.5	2.7
F	2	19.0	4.0	1.7	0.08	4.37	29.2	3.0
Total	5	21.0	3.7	1.5	0.08	3.57	28.8	2.8

Table 5

Relative dietary quantities (g) of various rodenticidal baits causing 50% mortality

Species	Body weight (kg)	Zinc phosphide 2.5%	Sodium fluoroacetate 0.25%	Pyrinuron 2%	Warfarin 0.1%	EL-614 0.005%
Rat	0.25	0.45	0.25	0.15	58	10
Mouse	0.025	-	0.17	0.12	37	2.5
Pig	50	40-80	60-80	> 125	200-1000	1000
Dog	5	4-8	0.12-0.4	> 250	400-5000	500
Cat	2	1.6-3.2	0.24-0.4	< 10	8-320	90
Chicken	1	0.8-1.2	4-12	36	4000	1000

FENARIMOL - A NEW FUNGICIDE FOR THE CONTROL OF POWDERY MILDEWS AND APPLE SCAB

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Summary Fenarimol, 2,4'-dichloro-α-(pyrimidin - 5-yl)benzhydryl alcohol, evaluated under research code number EL-222, is a new, foliar applied fungicide which has shown excellent activity at low application rates against many plant pathogenic fungi. It is particularly active in controlling powdery mildews and apple scab. As well as apple scab, powdery mildews of apples, cucurbits and grapes will be considered with respect to their control by fenarimol.

Results from acute and sub-acute toxicological studies indicate that fenarimol has a low order of toxicity.

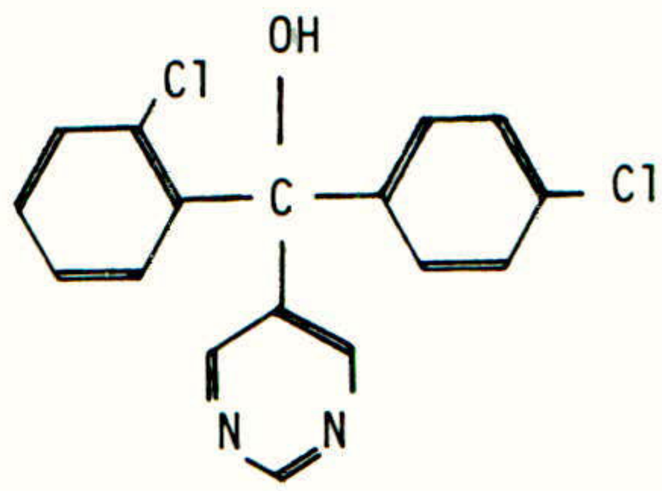
Résumé Fenarimol, 2,4'-dichloro-α-(pyrimidin - 5-yl)benzhydryl alcohol, evalué sous le No de code EL-222 est un nouveau fungicide foliaire qui appliqué à de doses relativement basses a demontré une excellente activité sur un grand nombre de champignons parasites. Le produit est particulierement actif contre la travelure et l'oïdium du pommier. Outre les resultats sur pommier, des données sur l'efficacité du produit contre l'oïdium de la vigne et l'oïdium des cucurbitacées sont présentes dans cette communication. Les resultats des études de toxicité aiguë et sub-aiguë indiquent que le produit est d'une toxicité relativement basse.

INTRODUCTION

Fenarimol is a broad-spectrum, locally-systemic, fungicide discovered and developed by Eli Lilly and Company. It was first described by Brown, Taylor and Hall (1975).

The compound has been widely tested in Europe and elsewhere and the purpose of this paper is to summarise its physical and chemical characteristics and its fungitoxic properties.

Physical and Chemical Properties



$C_{17}H_{12}Cl_2N_2O$

Molecular weight 331.2

2,4'-dichloro-α-(pyrimidin-5-yl)benzhydryl alcohol (IUPAC)

α-(2-chlorophenyl)-α-(4-chlorophenyl)-5-pyrimidinemethanol (Chemical Abstracts)

The pure compound is a white crystalline solid, m.p. 117-119 ^{0}C. It is soluble in acetone, acetonitrile, benzene, chloroform and methanol but only slightly so in hexane. Its solubility at 25 ^{0}C is 13.7 mg/l water at pH7. Its vapour pressure is $< 1 \times 10^{-7}$ mmHg at 25 ^{0}C. The chemical is unstable in ultraviolet light.

Toxicology Results from acute toxicological studies indicate that fenarimol has a low order of toxicity.

Table 1

Summary of acute oral toxicological data for technical fenarimol a/

Species	Toxicity (mg/kg bodyweight)
Rat	LD_{50} = 2 500
Dog	LD_0 b/ > 200
Mouse	LD_{50} = 4 500

a/ The technical material used in these studies was 100% pure fenarimol.

b/ Dose rate which caused no mortality among test animals.

Table 2

Control of primary and secondary apple powdery mildew in England with fenarimol and reference products

Treatment	Formulation	Rate (ppm a.i.) Up to petal fall	Rate (ppm a.i.) After petal fall	Primary powdery mildew control (%) a/	Secondary powdery mildew control (%) b/
Fenarimol	12% e.c.	15	30	95	94
Fenarimol	12% e.c.	20	40	97	95
Fenarimol	12% e.c.	30	60	98	96
Binapacryl	50% e.c.	375		80	81
Bupirimate	25% e.c.	125		91	86
Dinocap	50% e.c.	250		47	94
Pyrazophos + binapacryl	30% e.c., 50% a.c.	83 + 190		85	94
Triforine	20% e.c.	250		86	89
Untreated	-	-		0 (92) c/	0 (83) c/
S.E.				4.0	2.2

a/ Assessed 21st June and 24th June after nine or ten applications.

b/ Assessed 13th August and 20th August after 15 or 16 applications.

c/ The figure in parentheses represents the incidence or severity of infection in the untreated control at the time of assessment.

Numerous long-term tests in laboratory animals, including reproduction and life-time carcinogenicity studies, have shown that fenarimol is safe for use as an agricultural fungicide when used according to label precautions.

Formulations Fenarimol is formulated as either a 4% or 12% e.c. or as a 6% w.p.

FUNGICIDAL PROPERTIES

Apple powdery mildew *(Podosphaera leucotricha)* The eradicant effect of fenarimol in controlling primary apple powdery mildew is shown in Table 2. The three fenarimol treatment regimes used were 15, 20 or 30 ppm at 10-14 d intervals up to petal fall and 30, 40 and 60 ppm at 7 d intervals from petal fall to late July. The results are the means of two experiments carried out in Herefordshire and Somerset, England.

The data presented in Table 2 also show the protective properties of fenarimol in controlling secondary apple powdery mildew demonstrated in the same two trials.

Apple scab *(Venturia inaequalis)* Slightly higher rates of fenarimol are required to provide acceptable control of fruit scab compared with those required for satisfactory control of powdery mildew and foliar scab. In circumstances of light to moderate disease pressure over a wide range of climatic conditions (e.g. West Germany, Austria, Hungary, Yugoslavia, Lebanon, Syria) the application of fenarimol at 54 g/ha and 10-14 d intervals provides excellent disease control. Results of a trial carried out in Hartmannsdorf, Austria are shown in Table 3.

Table 3

Control of fruit scab of apple cv. Golden Delicious in Austria following 9 applications of fenarimol [a/]

Treatment	Formulation	Rate (ppm a.i.)	Control (%) fruit scab
Fenarimol	12% e.c.	42	94
Captan	50% w.p.	1 500	87
Mancozeb	80% w.p.	1 600	80
Untreated	-	-	0(26) [b/]
S.E.			12.6

a/ All treatments were applied at 10-14 d intervals in 1 250 l. water/ha.

b/ The figure in parentheses represents the mean percentage of diseased fruits in the untreated control at the time of assessment.

In areas with extreme scab pressure, for example in Northern Ireland and northern *Italy*, combination with reduced rates of other products is necessary to obtain the *high* levels of control demanded. Table 4 contains the results of one such large scale, non-replicated experiment conducted in Ferrara, Italy on apple cv. Imperatore.

Table 4

Control of fruit scab of apple in Italy following applications of fenarimol alone and in combination with reduced rates of captan, dodine or mancozeb

Treatment [a]	Formulation	Rate (ppm a.i.)		Control (%) of fruit scab
		Up to one third fruit size	After one third fruit size	
Fenarimol	6% w.p.	42	42	84
Fenarimol + captan	6% w.p., 50% w.p.	42 + 750	42 + 600	99
Fenarimol + dodine	6% w.p., 65% w.p.	42 + 390	42 + 325	99
Fenarimol + mancozeb	6% w.p., 80% w.p.	42 + 1 440	42 + 800	97
Dodine + thiophanate-methyl	35% w.p., 35% w.p.	350 + 350	350 + 350	90
Untreated	-	-	-	0(96) [b]

[a] All treatments were applied at 7-8 d intervals up to one-third fruit size, then at 9-12 d intervals in 1 500 l. water/ha increasing to 2 000 l/ha.

[b] The figure in parentheses represents the mean percentage of diseased fruit in the untreated control at the time of assessment.

The excellent preventive and curative/eradicative properties of fenarimol against *V. inaequalis* were demonstrated in an experiment carried out at the Gorsem Research Station, Belgium. Using fenarimol spray concentrations of 40 and 53 ppm, applications were made 96 h after scab infection period was recorded and trees were only subsequently re-sprayed when another infection period was recorded after a further lapse of not less than 96 h. Thus, the minimum possible interval between sprays was 8 d; the actual periods between the sprays were 15, 13, 10, 18 and 10 d. Results are summarised in Table 5.

Emulsifiable concentrate formulations of fenarimol are neutral with respect to russetting on apples while wettable powder formulations are slightly cosmetic.

Grape powdery mildew *(Uncinula necator)* Against grape powdery mildew fenarimol allows much flexibility in determining the optimum rate and spray schedule according to individual circumstances and level of disease control desired. It may be applied at high (∿ 1000 l/ha), or low (∿ 300 l/ha) volume at either relatively low rates, 12-18 g/ha, and short spray intervals, or at higher rates, 24-36 g/ha, and extended

spray intervals.

Table 5

Control of leaf scab of apple when an eradicant treatment was delayed for 96 h after detection of an infection period and further eradicant/protectant treatment was delayed for at least 96 h

Treatment	Formulation	Rate (ppm a.i.)	Control (%) of leaf scab
Captan	80% w.p.	1 200	54
Dodine	65% w.p.	500	72
Fenarimol	6% w.p.	40	93
Fenarimol	6% w.p.	53	100

The range of control of *U. necator* provided by fenarimol, compared with that of sulphur, is shown in Table 6. Two experiments were conducted in Egerci, Turkey with the grape cv. Sultanina in which the compounds were applied at 7 d intervals in 800-1 000 l. water/ha.

Table 6

Mean percentage control of *Uncinula necator* on grape berries in two experiments following 10 or 11 applications of fenarimol or wettable sulphur

Treatment	Formulation	Rate (a.i.)	Disease control (%) on berries
Fenarimol	12% e.c.	9 ppm	93
Fenarimol	12% e.c.	12 ppm	98
Fenarimol	12% e.c.	18 ppm	98
Sulphur	80% w.p.	2.5 kg/ha	82
Untreated	-	-	0(76) a/
S.E.			2.2

a/ The figure in parentheses represents the mean incidence of infection in the untreated control at the time of assessment.

The level of disease control provided by higher rates of fenarimol is shown in Table 7 which summarizes the results from an experiment conducted in Murcia, Spain on the table grape cv. Ohanes. The compounds were applied according to a downy mildew fungicide spray schedule in 800-1 000 l. water/ha.

Table 7

Mean percentage control of *Uncinula necator* on grape berries after 6 and 7 applications according to a downy mildew fungicide spray schedule

Treatment	Formulation	Rate (a.i.)	Disease control (%) on berries 12.7.76	3.9.76
Fenarimol	12% e.c.	24 ppm	98	100
Fenarimol	12% e.c.	30 ppm	100	100
Fenarimol	12% e.c.	36 ppm	100	100
Fenarimol	12% e.c.	42 ppm	100	100
Sulphur	98% dust	49 kg/ha	98	91
Untreated	-	-	0(7) a/	0(25) a/
S.E.			25.6	16.0

a/ Figures in parentheses represent the mean percentage surface area of berries infected in the untreated control at the time of assessment.

The eradicative effect of fenarimol against *U. necator* is seen in Table 8 which shows the result of an experiment conducted in Bologna, Italy using grape cv. Müller-Thurgau in which 20% berry surface infection was allowed to develop before three applications of fungicide were made at 7 d intervals in 1 000 l. water/ha.

Table 8

Mean percentage control of *Uncinula necator* on grape berries 7 d after 3 eradicative applications of fenarimol

Treatment	Formulation	Rate (ppm a.i.)	Disease control (%) on berries
Fenarimol	6% w.p.	18	79
Fenarimol	6% w.p.	24	83
Fenarimol	6% w.p.	30	88
Fenarimol	6% w.p.	36	93
Untreated	-	-	0(52) [a/]

[a/] The figure in parentheses represents the mean percentage surface areas of berries infected in the untreated control at the time of of assessment.

Some grape varieties have been found to be sensitive to emulsifiable concentrate formulations of fenarimol during cool weather and at early stages of growth, but wettable powder formulations have been safe under all conditions and on all varieties tested.

Cucurbit powdery mildew *(Erysiphe cichoracearum, E. polygoni, Sphaerotheca fuliginea)*
Powdery mildews of a wide range of cucurbits are equally well controlled by fenarimol and typical examples are summarised in Table 9.

Table 9

Control of cucurbit powdery mildews on a range of crops

Crop	Treatment	Rate (ppm a.i.)	Control (%) of powdery mildew
Honeydew melon	fenarimol	30	99.5
Squash	fenarimol	30	94.0
Cantaloupe	fenarimol	30	100.1
Cucumber	fenarimol	30	97.5
Watermelon	fenarimol	30	100.0

In experiments, the results of which are not presented here, fenarimol has been shown to be highly effective in controlling powdery mildews of a number of other crops including gooseberry, hop, mango, okra, peach, pepper, rose, strawberry and tomato. The fungicide has also shown activity against a number of other plant pathogenic fungi.

References

BROWN, I.F.; TAYLOR, H.M.; HALL, H.R. (1975) EL-222, a new fungicide with eradicative activity. *Proceedings American Phytopathological Society*, 2, 31.