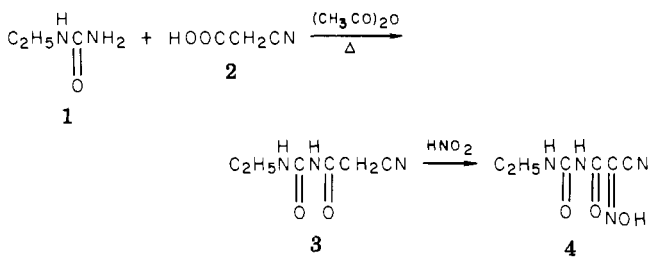
2-Cyano-*N*-[(ethylamino)carbonyl]-2-(methoxyimino)acetamide, a New Fungicide

2-Cyano-*N*-[(ethylamino)carbonyl]-2-(methoxyimino)acetamide (DPX-3217; active ingredient in Dupont Curzate fungicide) is a new chemical compound with systemic properties. It provides excellent post-infection curative as well as protectant activity at 80 mg of active ingredient/L for the control of late blight of tomato and potato (*Phytophthora infestans*) and grape downy mildew (*Plasmopora viticola*). The material has a low acute mammalian toxicity pattern with an oral LD_{50} for male rats of 1425 mg/kg for an 80% active formulation and shows no evidence of cumulative toxicity. It has a residual life of a few days and a high degree of safety to many grape, potato, and tomato varieties.

The potent systemic plant disease control agents discovered and developed in the early 1970's lacked effectiveness against Phycomycete fungal pathogens. Therefore, there was a need for improved control of downy mildews and late blight of potato/tomato. This communication presents chemical, toxicological, and biological information on DPX-3217, a new disease control agent with unique properties for the control of certain Phycomycetes.

CHEMICAL METHODS

2-Cyano-*N*-[(ethylamino)carbonyl]-2-(methoxyimino)-acetamide (DPX-3217), a new chemical compound, was synthesized as follows: Heating the commercially available materials ethylurea (**1**) and cyanoacetic acid (**2**) together in acetic anhydride resulted in the formation of 1-(1-cyanoacetyl)-3-ethylurea (**3**), mp 169–170 °C. This intermediate was treated with sodium nitrite and hydrochloric acid in aqueous medium to give 2-cyano-*N*-[(ethylamino)carbonyl]-2-(hydroxyimino)acetamide (**4**), mp 208–209 °C. This oxime was methylated by refluxing with dimethyl sulfate and powdered anhydrous potassium carbonate in acetone to give the final product, which has a melting point of 160–161 °C. Nuclear magnetic resonance and infrared spectra and microanalysis data support the structure of DPX-3217 below [IR (KBr) 3340 (free N–H), 3230 and 3160 (bonded N–H), 3000 (C–H), 2240 (C≡N), 1700 cm^{-1} region (C=O); ^1H NMR (Me_2SO) δ 1.1 (t, 3 H, CH_3), 3.25 (doublet of quartets, 2 H, CH_2), 4.32 (s, 3 H, CH_3O), 7.71 (broad t, H, NH) 10.2 (broad s, NH); ^{13}C NMR (Me_2SO) δ 14.75 (NCH_2–CH_3), 34.3 (N–CH_2–), 66.16 (C–CH_3), 107.69 (CN), 126.6 (CH_3O–N=*C*–CN), 151.4 (HN–C(=O)–NH), 158.3 (N–*C*(=O)–C=N). Anal. Calcd for $C_7H_{10}N_4O_3$: C, 42.40; H, 5.09; N, 28.28. Found: C, 42.40; H, 5.24; N, 20.30.] The solubility of DPX-3217 in water is 1000 ppm.



TOXICOLOGY

Experimental methods used in the toxicity studies have been described by Sherman and Kaplan (1975). DPX-3217 has a favorable mammalian toxicity pattern. It has low acute toxicity, with an oral LD_{50} for male rats of 1425 mg/kg for an 80% active formulation. The acute dermal LD_{50} for the active ingredient for male rabbits is greater than 3000 mg/kg. No mortality occurred at this maximum feasible dose.

When administered orally to male rats at an active ingredient dosage of 200 mg kg^{-1} day^{-1} for a total of ten doses over a 2-week period, there is no mortality and no evidence of cumulative toxicity.

DPX-3217 is neither a skin irritant nor a skin sensitizer when tested on guinea pigs as a 50% aqueous suspension. It is a very slight eye irritant in rabbits, resulting in temporary conjunctival irritation.

The dietary 8-day LC_{50} is 2847 ppm (active ingredient) for bobwhite quail and >10000 ppm for mallard ducks. DPX-3217 is slightly toxic for bluegill sunfish and rainbow trout, the LC_{50} values (96 h) being 13.5 and 18.7 ppm, respectively, based on active ingredient.

DPX-3217 was not mutagenic in the *Salmonella*/microsome assay in strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 either in the presence or absence of an activation system using the methods of Ames (1975).

RESIDUES AND ENVIRONMENT

DPX-3217 decomposes rapidly in treated crops and the residues in plants are always very low. For example, after eight applications of 15 g/hL, residues found in grapes 7 days after the last application were 0.1 ppm or less (Holt, 1979; Belasco et al., unpublished). No trace of DPX-3217 has been found in the tubers of sprayed potatoes. Metabolism studies in grapes and potatoes using 2-^{14}C-labeled DPX-3217 have demonstrated rapid and complete breakdown accompanied by incorporation of ^{14}C into natural plant constituents such as sugars and proteins (Belasco et al., unpublished). Field soil disappearance studies with 2-^{14}C-labeled DPX-3217 (Baude, unpublished) of the type described by Rhodes (1977) were carried out in four locations in the United States using 30-cm sections of stainless steel tubing (diameter 10 cm) driven into the soil. These studies showed rapid breakdown of DPX-3217, the half-life being less than 2 weeks whatever the type of soil. After 4 weeks of exposure (up to 10 cm of rain), more than 90% of the residual radioactivity remained in the upper 5 cm of the soil columns, indicating that leaching is not a problem with DPX-3217.

BIOLOGICAL ACTIVITY

In field and greenhouse tests DPX-3217 preparations have demonstrated excellent control of grape downy mildew (*Plasmopora viticola*) and late blight of tomato and potato (*Phytophthora infestans*) (Denis, 1976; Douchet et al., 1977; (Richards and Delp, 1976; Serres and Carraro, 1976). Control was obtained from foliar application or soil drench treatment applied before or after infection.

Limited evaluations against several soil-borne *Phytophthora* have not shown promise. The lack of effect is due in part to rapid decomposition but in some cases to inactivity on the fungus. DPX-3217 preparations are rela-

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Table I

treatment applied 18 h after inoculation	foliar spray concn, mg of AI/L	% tomato late blight control
DPX-3217	80	100
	16	79
Maneb	2000	0
untreated	0	0

Table II

treatment in Delaware vineyard replicated 5 times	no. of days from inoculation to treatment	foliar spray concn, mg of AI/L	% grape downy mildew control
DPX-3217	1	112	100
	3	112	99
	4	112	100
	7	112	84
mancozeb	1	1000	16
untreated		0	(1-2 infected leaves/ shoot)

tively ineffective against other pathogens such as *Alternaria* spp., *Botrytis* spp., and *Erysiphe* ssp. Some in vitro evaluations have been misleading because of fungistatic and volatile side effects. Therefore, most studies were conducted on host plants under natural growth conditions.

POSTINFECTION EFFECT

Successful disease control is obtained in greenhouse tests when DPX-3217 is applied after artificial inoculation with *P. infestans* to healthy tomato plants and incubated at 20 °C and 100% relative humidity. Plants treated with traditional fungicides or untreated plants kept in the greenhouse have typical disease symptoms and are killed within 5 days by the late blight disease under these test conditions.

Under less favorable conditions for disease development in potato field tests, foliar spray applications of 75 ppm active ingredient stop infection 2–3 days after artificial inoculation.

Postinfection control of grape downy mildew is possible in the greenhouse with foliar applications of 100 mg of active ingredient (AI) DPX-3217/L up to 3 days after artificial inoculation when incubated under optimum conditions for disease development (20 °C and 100% RH). Successful disease control is obtained in the field with longer elapsed times between inoculation and DPX-3217 application. The longer incubation time required for grape downy mildew disease development as compared with late blight probably accounts for the greater latitude in postinfection control. The postinfection control by low rates of DPX-3217 provides a significant new dimension to chemical plant disease control strategies for these diseases.

Some established sporulating late blight and downy mildew lesions are inactivated by treatment with DPX-3217. This is evidenced by the failure of the lesion to expand and absence or reduction of sporulation. In Delaware vineyard tests, sporangial production was reduced over 70% for up to 4 days following a foliar spray with DPX-3217 at a concentration of 150 mg AI/L. In some cases, treated lesions look normal but sporangia from them either fail to develop or to germinate. Germination of zoospores released from grape downy mildew sporangia is reduced by 85% in concentrations above 10 mg of AI DPX-3217/L. The remaining 15% have malformed germ tubes.

SYSTEMIC ACTION

Systemic movement is acropetal, apparently in the xylem tissue, and little or no downward movement is noted. As would be expected with woody plants, the penetration and local systemic movement in grapes are much less effective than in succulent tomatoes. Application of DPX-3217 to the ventral side of tomato leaflets stops disease development from inoculations on the dorsal side. This across-leaf effect is not always possible in grapes. With the tomato leaves covered to avoid treatment, DPX-3217 applications at concentrations of 2000 ppm active ingredient to the tomato plant stems also provides excellent disease control on untreated foliage. Concentrations of 80 ppm active ingredient when applied as a foliar spray to run-off, or 5 kg of AI/ha applied as a soil drench to tomatoes growing in pots results in effective systemic disease control.

PREVENTIVE DISEASE CONTROL

DPX-3217 has protectant action, but its residual life may be limited to a few days, expecially under hot weather conditions. Therefore, mixtures of DPX-3217 plus half rates of more residual fungicides such as zineb, mancozeb, fixed coppers, folpet, etc., provide maximum disease control. This is a result of combining the postinfection curative action of DPX-3217 with longer protection from another fungicide. A regular protectant schedule with dilute spray concentrations of 12 g of active ingredient/hL mixed with one-half the recommended concentration of a protectant fungicide such as mancozeb are more effective for grape downy mildew control than full concentrations of the protectant fungicide alone. This is especially true under heavy disease pressure.

CROP SAFETY

As a foliar spray, DPX-3217 has shown a high degree of safety to many grape, potato, and tomato varieties and other crops when used in a series of applications alone or in combination with other fungicides at dosages several times the effective rate.

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LITERATURE CITED

Ames, B. N., McCann, J., Yamasoki, E., *Mutat. Res.* 31, 347 (1975).
Denis, S. J., *Proc. Am. Phytopath. Soc.* 3, 324 (1976); Abstract.
Douchet, J. P., Absi, M., Hay, S. J. B., Mutan, L., Villani, A., Proceedings of the 1977 British Crop Protection Conference, 1977, p 535.
Holt, R. F., *Pestic. Sci.*, in press (1979).
Rhodes, R. C., *J. Agric. Food Chem.* 25, 528 (1977).
Richards, B. L., Jr., Delp, C. J., *Proc. Am. Phytopath. Soc.* 3, 288 (1976); Abstract.
Serres, J. M., Carraro, G. A., *Med. Fac. Landbouwwet., Rijksuniv. Gent.* 41, 645 (1976).
Sherman, H., Kaplan, A. M., *Toxicol. Appl. Pharmacol.* 34, 189 (1975).

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