Fungicide Resistance in Cucurbit Powdery Mildew: Experiences and Challenges

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Fungicides are an important tool for managing cucurbit powdery mildew, which is a major production problem in many areas of the world (89). Application of fungicides is presently the principal practice in most cucurbit crops for managing powdery mildew. Fungicides that are systemic or have translaminar activity are needed to obtain adequate protection of abaxial leaf surfaces, where conditions are more favorable for development of the pathogen than on adaxial surfaces (Figs. 1 and 2) (80). Unfortunately, these fungicides generally have a high risk of developing resistance because they have specific modes of action, and powdery mildew fungi have a high potential for resistance development. This has been especially true for the predominate cucurbit powdery mildew fungus, *Podosphaera (*sect. *Sphaerotheca) xanthii* (Castagne) U. Braun & N. Shishkoff (also known as *Sphaerotheca fusca* (Fr.) S. Blumer and *S. fuliginea* (Schlechtend.:Fr.) Pollacci).

Fungicide resistance is the stable, inheritable adjustment by a fungus to a fungicide, resulting in reduced sensitivity of the fungus to the fungicide. This ability is obtained through evolutionary processes. Systemic and translaminar fungicides are generally more at-risk for resistance development than contact fungicides because they typically have specific, single-site mode of action, which means they are active against only one point in one metabolic pathway in a pathogen. When resistance results from modification of a single major gene, pathogens are either resistant or sensitive to the pesticide, and disruptive selection occurs. Resistance in this case is seen as complete loss of disease control that cannot be regained by using higher rates or more frequent fungicide applications. This type of resistance is commonly referred to as "qualitative resistance" and is exemplified by resistance to benzimidazole fungicides, which results from a conformational change at the target site in various pathogens.

When resistance results from modification of several interacting genes, pathogens exhibit a range in sensitivity to the fungicide depending on the number of gene changes. Variation in sensitivity within the population is continuous or unimodal, and selection occurs in a directional manner. Resistance in this case is seen as an erosion of disease control that can be regained by using higher rates or more frequent applications. Additional selection in the pathogen may eventually result in complete loss of control. This type is commonly referred to as "quantitative resistance" and is exemplified by resistance to demethylation inhibiting (DMI) fungicides. Several mechanisms of DMI resistance seem to be operating in plant pathogens based on the broad range of phenotypic sensitivities observed (32,48). Possible mechanisms, identified mainly through work with model fungal systems, include decreased accumulation of fungicide due to increased efflux or decreased uptake, deficiency in the target site, reduced affinity for the target site, tolerance of toxic sterols, detoxifi-

Fig 1. Because powdery mildew colonies typically are larger with denser sporulation on abaxial leaf surfaces than on adaxial surfaces, control on abaxial surfaces (lower right) is very important.

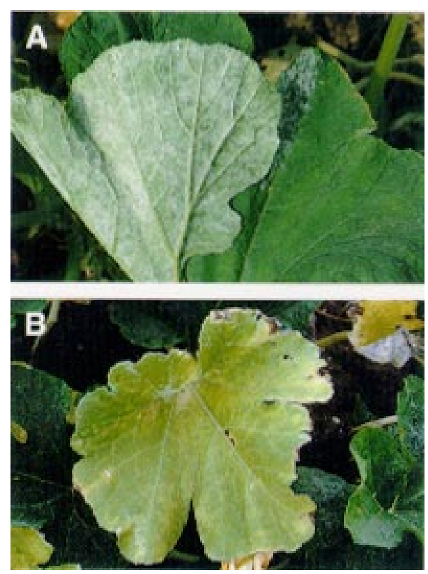

Fig 2. Leaves on pumpkin plants sprayed weekly with a contact fungicide (chlorothalonil) provided excellent control of powdery mildew only on adaxial leaf surfaces. A, Leaf is partially folded over to show that the abaxial surface is completely covered with powdery mildew, in contrast with the adaxial surface. B, Leaf is senescing prematurely due to severity of powdery mildew infection on the abaxial surface.

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cation of DMIs, detoxification of sterols, failure to activate the fungicide, deposition of fungicide in lipid droplets, and change in pH leading to protonation of fungicide (31). In addition to the major resistance genes, minor genes most likely interact with these major genes. Minor genes also account for the variation in fungicide sensitivity found in pathogen populations before exposure to fungicides. Because fungicide resistance often is not associated with complete loss of control, “field resistance” has been used for situations in which strains with reduced fungicide sensitivity are not sufficiently insensitive to affect fungicide efficacy, and “practical resistance” has been used for situations where insensitive strains are not controllable with this fungicide (11).

History of Benomyl Resistance in the United States

Benomyl, a benzimidazole fungicide, was the first fungicide with a single-site mode of action used for powdery mildew on cucurbits. Benomyl-resistant strains were detected in a greenhouse experiment in 1967 (110), the first year of field evaluations at university facilities in the United States. This was one of the first documented cases of resistance in the United States. At that time, global experiences of fungicide resistance were limited, and thus the potential impact on control and the need for management were not recognized. Benomyl was registered in February 1972 for commercial use on cucurbit crops in the United States. The first case of control failure in the field occurred the next year (Table 1). Although resistance developed quickly via disruptive selection, it apparently took years for resistant strains to become sufficiently common to have a widespread impact on efficacy (Table 1). Benomyl was effective in the midwestern United States (Indiana and Michigan) until the mid-1980s. It can only be assumed that changes in efficacy are due to resistance; fungicide sensitivity of isolates was not examined again in the United States until the early 1990s (Fig. 3), when benomyl resistance was found in several areas (88). Alternative explanations for the reduced efficacy that was observed include poor application timing and mixing errors. However, levels of control provided by other fungicides in the same experiment were not compromised, suggesting that benomyl resistance is the more likely explanation. Within one location, frequency of benomyl-resistant strains before fungicide use was found to vary from year to year (Table 2). With this yearly variation, it is difficult to predict benomyl efficacy based on frequency of resistant strains the previous year. Benomyl was not recommended for a few years following detection of resistant strains in 1991 and 1992. However, resistant strains were not detected in 1993 through 1995, indicating that benomyl would provide at least some control of powdery mildew. Since triadimefon-resistant strains were being detected before fungicide use during these years, benomyl was recommended again and suggested as the first application for powdery mildew. The situation changed greatly in 1996 through 1998 when benomyl-resistant strains were sufficiently common to prevent adequate control of powdery mildew.

History of Triadimefon Resistance in the United States

Triadimefon, a DMI fungicide, was the second single-site mode of action fungicide used for powdery mildew on cucurbits. It was registered in April 1984 for this use in the United States. Occurrence of triadimefon resistance exhibited some similarities to benomyl resistance even though resistance is quantitative for triadimefon rather

Table 1. Efficacy of the benzimidazole fungicide benomyl for controlling cucurbit powdery mildew in fungicide evaluation experiments conducted in the United States, reported by year and state where the work was done

	Efficacy of benomyl[a]			
Year	**Good**	**Moderate to poor**	**Ineffective[b]**	**Reference**
1970	NJ,VA	NY		(3,109,117)
1971	DE,MD,NJ,NY,SC			(14,45,57,105,111)
1972	NJ,KY,NC	NY		(26,36,58,103)
1973	DE,MD,NC,NJ,SC		KY	(28,37,46,59,91,115)
1974	NY	NC,NJ		(38,60,102)
1975		NJ,NY	KY	(1,27,61,116)
1976	MI	NC,NJ		(33,62,100)
1977	KS,MI			(101)
1978	FL,NY	NJ		(2,20,44)
1979		NJ,VA	FL	(4,21,22,39)
1980			NJ	(63)
1981		VA	NJ	(5,40)
1982	IN	NJ,VA		(50,51,64)
1983	MI			(118)
1984		NC		(122)
1986	MI	IN	NJ	(41,52,53,120)
1988			IN	(55)
1989		VA		(7)
1992		LA,OK,NC		(12,16,113)
1993		NC		(114)
1994	NJ	OK		(15,43)

[a] Powdery mildew severity on benomyl-treated plants was compared with severity on nontreated plants and plants treated with other fungicides. In experiments where benomyl was not tested alone, its efficacy was assessed based on whether control was improved over that obtained with the companion fungicide(s) used alone.

[b] Severity did not differ significantly between benomyl-treated and nontreated plants.

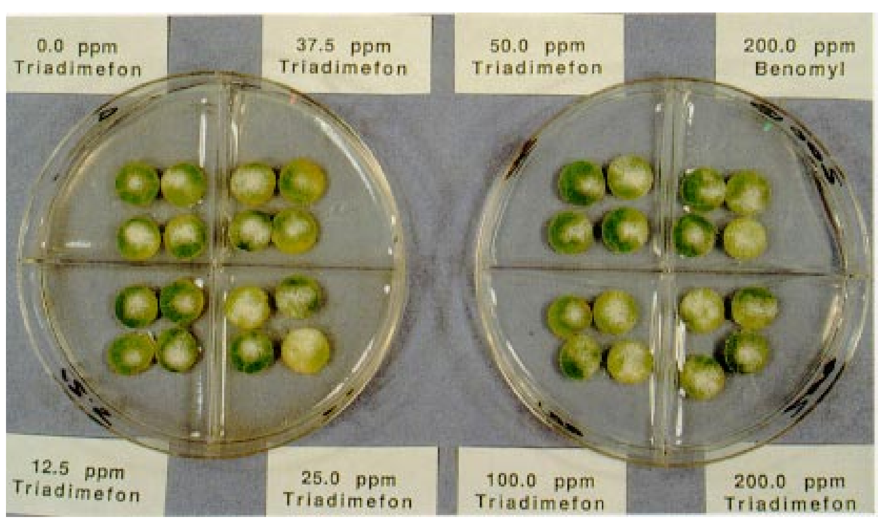

Fig. 3. Fungicide sensitivity of isolates of *Podosphaera xanthii* is determined using treated leaf disks. Squash seedlings at the cotyledon stage are sprayed with fungicide at various concentrations, air-dried, then disks are cut from cotyledons, placed in petri dishes on water agar, and inoculated by transferring conidia with a fine brush. Sensitivity is recorded as the highest concentration tolerated that does not prevent sporulation. Typically mycelial growth and sporulation are reduced at this concentration compared with lower concentrations.

Table 2. Occurrence of fungicide resistant strains at the start of powdery mildew development in research pumpkin plots on Long Island, NY, and impact of applying a demethylation inhibiting (DMI) fungicide on resistance

Year	Resistant isolates (%)[a]			
	Start of epidemic[b]		Middle of epidemic[c]	
DMI fungicide applications[d]	Triadimefon	Benomyl	Triadimefon	Benomyl
1991				
None	0	30	0	12
23 July; 7,23 Aug; 7 Sept			81	69
1992				
None	0	10	19	25
21 July; 6,21 Aug; 5 Sept			100	44
1993				
None	3	0		
16 Aug			71	
1994				
None	39	0		
2,17,30 Aug			90	
1995				
None	80	0		
31 July; 15,29 Aug			73	
1996				
None	52	48	56	31
16, 30 Aug			66	66
1997				
None	65	55		
15 Aug, 12 Sept			94	94
1998				
None	87	93		

[a] Frequency of *Podosphaera xanthii* isolates that were able to grow on leaf disks treated with triadimefon at 50 or 100 µg/ml or with benomyl at 200 µg/ml.
[b] *P. xanthii* isolates were collected from plots that had not been treated with fungicides on 15 August 1991, 14 August 1992, 11 August 1993, 6 August 1994, 1 August 1995, 20 August 1996, and 26 August 1998.
[c] *P. xanthii* isolates were collected on 19 September 1991, 17 September 1992, 1 September 1993, 19 August 1994, 18 August 1995, and 19 September 1996.
[d] Triadimefon was applied on a 14-day interval in 1991 to 1996. In 1997, the DMI fungicide myclobutanil was applied on 15 August and 12 September; benomyl was applied on 30 August. In all years, chlorothalonil was also applied on a 7-day interval.

Table 3. Efficacy of the demethylation inhibiting (DMI) fungicide triadimefon for controlling cucurbit powdery mildew in fungicide evaluation experiments conducted in the United States, reported by year and state where work was done

Year	Efficacy of triadimefon[a]			Reference
	Good	Moderate to poor	Ineffective[b]	
1982	FL			(90)
1986		NJ	NJ	(41,65,66)
1987	IN,NJ		NJ	(42,54,67)
1988	IN,KS,MI,VA	AZ		(6,55,72,121,123)
1989	KS,VA	MI		(7,119,124)
1990	IN	AZ,OH	NY	(56,73,104,127)
1991	AZ,MI[c],VA	KS,NY		(8,29,71,74,76)
1992		NC,NJ,NY,OK,TN		(10,16,68,81,113)
1993		NC		(81,114)
1994			OK	(15)
1995			NY	(78)

[a] Powdery mildew severity on triadimefon-treated plants was compared with severity on nontreated plants and plants treated with other fungicides. In experiments where triadimefon was not tested alone, its efficacy was assessed based on whether control was improved over that obtained with the companion fungicide(s) used alone. Reduced efficacy appeared to have occurred in several additional experiments conducted in the 1990s, but the treatments tested did not permit a more definitive assessment; thus they are not included in this table.
[b] Severity did not differ significantly between triadimefon-treated and nontreated plants.
[c] Resistance was associated with control failure in a commercial pumpkin field in Michigan in 1991 (82).

than qualitative as for benomyl. With both fungicides, resistance developed quickly but did not have a widespread impact on efficacy for several years. The first reported control failure with triadimefon occurred only 2 years after registration (Table 3). Frequency of resistant fungal strains prior to fungicide treatment in one location can vary substantially from year to year, as occurred in research fields at the Cornell University Long Island Horticultural Research and Extension Center (LIHREC) in New York, making it difficult to predict fungicide efficacy (Table 2). Furthermore, when resistant strains are present at an undetectable level, the pathogen population can shift to predominantly resistant strains following a single fungicide application (Table 2) (79). Thus, acceptable full-season control may not be obtainable even when only sensitive strains are detected before treatment, as occurred in 1991 and 1992 (79). While triadimefon-resistant strains of *P. xanthii* were common after applying this fungicide in 1991, 1992 (Table 2), and presumably also in 1990 when they were first detected (75), they were at an undetectable to low level (0 to 3%) before fungicide treatment in 1991 to 1993. This suggests that either selection of resistant strains was occurring more slowly in the source population, which is believed to be southern production areas, or triadimefon-resistant strains were less fit than sensitive strains. However, the situation subsequently changed. The frequency of resistant strains before treatment ranged from 39 to 87% in 1994 to 1998 (Table 2). Control failure with triadimefon occurred in 1995 when 80% of the pathogen population was resistant before the first application (85).

History of Resistance Outside the United States

The cucurbit powdery mildew fungus has also exhibited a high potential for developing resistance in other areas of the world (Table 4). It has developed resistance to several fungicide classes, including benzimidazoles, DMIs, organophosphates, hydroxypyrimidines, Qo inhibitors (QoIs), and quinoxalines (Table 4). Following resistance development, it was shown that control with DMI fungicides could be improved by decreasing spray intervals, increasing water volumes, and increasing fungicide dose (34). Resistance has developed quickly in some situations. Strains resistant to benzimidazoles, DMIs, hydroxypyrimidines, or QoIs were detected after only 1 to 2 years of intensive use (17,95) (T. Amano and Y. Nakazawa, ZEN-NOH Agricultural R&D Center, Kanagawa, Japan, *personal communication*). The high frequency of resistant strains detected in Australia in the early 1990s prompted the conclusion that there was a need for control programs less reliant on single-site mode of action fungicides (93).

Current Situation

In the United States, triadimefon is no longer registered for use on cucurbits. Two new fungicides, azoxystrobin and trifloxystrobin, that are in a new chemical group, QoIs, were registered in March and September 1999, respectively (Table 5). QoIs include strobilurins and other inhibitors of the Qo site of the cytochrome bc_1 complex. A DMI fungicide newer than triadimefon, myclobutanil, was registered on cucurbits in May 2000. Another DMI fungicide, triflumizole, is being reviewed for registration by the U.S. Environmental Protection Agency (EPA). Numerous other fungicides are available for use in other countries (Table 5). The new DMI fungicides are more active than triadimefon. There may be an upper limit to DMI resistance, reflecting the inherent limit to the biochemical changes an organism can endure to become resistant. The wheat powdery mildew fungus in northwestern Europe apparently reached its upper limit to DMI resistance as its sensitivity levels have stabilized (23). Theoretically, it should be possible to manage cucurbit powdery mildew indefinitely with a highly active DMI fungicide applied at an appropriate rate. Strains with the biologically highest level of DMI resistance will not be controllable with older DMI fungicides (practical resistance), while they will not be sufficiently insensitive to more active DMI fungicides to affect efficacy (field resistance). Triflumizole was the only DMI fungicide still effective in Japan until 2000, when inadequate control in greenhouse production was associated with resistant strains (H. Ishii, National Institute of Agro-Environmental Sciences, Ibaraki, Japan, *personal communication*). Extended efficacy of triflumizole was believed to be due to its relatively small resistance factor and high recommended dose compared with other DMIs (92).

Cross or correlated resistance among DMI fungicides presents a challenge to effectively managing powdery mildew. A consequence of cross resistance is that using one fungicide in a chemical group (e.g., triadimefon) selects for strains less sensitive to other closely related fungicides (e.g., myclobutanil). For example, the highest concentration of myclobutanil tolerated is 0.1 to 1 µg/ml for triadimefon-sensitive strains and 2 to 20 µg/ml for triadimefon-resistant strains (88). When myclobutanil was being evaluated in the United States in the early 1990s, triadimefon-resistant strains were rare before treatment, and triadimefon usually was moderately effective while myclobutanil was very effective (86). Results from these fungicide evaluation experiments were used to identify the use rate for products containing myclobutanil. By 1998, however, when myclobutanil was first available for commercial use on cucurbits in several states (through Section 18 Emergency Exemption registration), triadimefon-resistant strains were common and myclobutanil applied at the recommended label rate of 70 g a.i./ha was only moderately effective (84). The frequency of strains on Long Island, NY, that could tolerate myclobutanil at 20 µg/ml before treatment was 0% in 1993 and 53% in 1998 (84,86). Myclobutanil was not as effective in commercial fields in 1998 as expected based on previous experimental results. The use rate consequently was doubled to 140 g a.i./ha for the U.S. registration. Establishing the relationship between pathogen sensitivity to a fungicide, as determined with a laboratory assay, and fungicide efficacy in the field may provide a more logical approach than using efficacy data alone for identifying the use rate for a new fungicide in a chemical group affected by quantitative resistance. However, there are many other considerations that go into rate establishment, including production costs and regulatory constraints.

Resistance to QoI fungicides has developed quickly in some areas. In 1999, after just 2 years of commercial use, resistant strains were found in field and greenhouse crops of melon and cucumber in Japan, Taiwan, southern Spain, and southern France (30) (http://www.gcpf.org/frac/STARWG.html sponsored by Fungicide Resistance Action Committee, Global Crop Protection Federation). These are areas of high disease pressure where QoI fungicides were often applied curatively and frequently (S. P. Heaney, Syngenta Agrochemicals, Berkshire, UK, *personal communication*). Resistance arose independently at isolated locations rather than as the result of clonal spread. Resistance is widespread in Japan; it was detected in all 17 commercial locations examined in 1999 (30). Resistance developed in some crops, although growers limited the number of applications of QoI fungicides and applied them in alternation with fungicides in other chemical groups, as was recommended for managing resistance (H. Ishii, *personal communication*). Consequently, some Japanese growers are no longer using QoI fungicides for powdery mildew. Recently, highly resistant strains were still found to be widely distributed in Japan. In surprising contrast, no change in sensitivity to azoxystrobin has been detected in the United States or Mexico, where QoI fungicides have not been used as intensively as in Asia (30,97).

Proactive Approach to Resistance

Considerable effort is being made to obtain information needed to respond proactively rather than reactively to resistance. This includes determining baseline sensitivity, which is the pathogen's sensitivity to new fungicides before their registration for

Table 4. Fungicides to which the cucurbit powdery mildew fungus has developed resistance or decreased sensitivity

Chemical group Chemical name	Common name	Reference
Benzimidazole	Benomyl	(47,70,94,99,107,110)
	Carbendazim	(107)
Demethylation inhibitor		
Imidazole	Imazalil	(19,34,47,70,106)
	Triflumizole	(94)
Piperazine	Triforine	(19,34,70,94,106)
Pyrimidine	Fenarimol	(19,34,47,70,94,106)
	Nuarimol	(19,34)
Triazole	Bitertanol	(70,106)
	Myclobutanil	(88)
	Penconazole	(94)
	Propiconazole	(34,70)
	Triadimefon	(34,70,75,94)
Morpholine	Fenpropimorph	(47)
	Tridemorph	(94)
Hydroxypyrimidine		
Pyrimidinol	Bupirimate	(19,70,94)
	Dimethirimol	(47,94,107)
	Ethirimol	(34)
Phosphorothiolate		
Organophosphorous	Pyrazophos	(18,19,94)
QoI		
Strobilurin	Azoxystrobin	Pers. comm.[a]
	Kresoxim-methyl	(19)
Quinoxaline	Quinomethionate[b]	(35,69,94)
Miscellaneous	Afugan	(125)
	Dinocap	(19,35,125)
	Ditalimfos	(69)

[a] T. Amano and Y. Nakazawa, *personal communication*.
[b] Also known as oxythioquinox and chinomethionat.

use on the host. Obtaining baseline sensitivity data reveals the amount of variation in the overall pathogen population before selection from fungicide use and provides a benchmark for assessing future reports of reduced fungicide efficacy. These data are being generated by both private- and public-sector scientists. Pathogen sensitivity also is being monitored after registration. Chemical companies consider these activities to be essential components of product stewardship.

Baseline sensitivities have been examined for some of the QoI fungicides. European and North American baseline distributions for azoxystrobin were found to be similar. The mean ED_{50} value was 0.26 µg/ml, and the range was 0.056 to 0.485 µg/ml for powdery mildew isolates from these two areas (96). For isolates collected in Australia, the mean ED_{50} value was 0.23 µg/ml, the range was 0.09 to 0.33 µg/ml, and the minimal inhibitory concentration (MIC) was 0.3 to 1 µg/ml (R. G. O'Brien, Plant Protection Unit, Department of Primary Industries, Queensland, Australia, *personal communication*). In another study, the highest concentration of azoxystrobin tolerated was 0.5 to 2.5 µg/ml (MIC was 2.5 to 5 µg/ml) for most isolates collected in the United States in 1996; one isolate was able to tolerate 5 µg/ml (N. Shishkoff and M. T. McGrath, *unpublished data*). The U.S. collection was genetically diverse for other traits; it included isolates that were sensitive and resistant to triadimefon and benzimidazole, races 1 and 2, and both mating types. The highest fungicide concentration tolerated was 0.3 to 3 µg/ml for trifloxystrobin (MIC was 3 to 30 µg/ml) and 0.2 to 2 µg/ml for kresoxim-methyl (MIC was 2 to 20 µg/ml) for most isolates tested.

Table 5. Fungicides registered for controlling cucurbit powdery mildew in selected areas as of 22 November 2000

Chemical group Chemical name	Common name	Some countries where registered
Specific mode of action fungicides at risk for resistance		
Benzimidazole	Benomyl	Australia, Brazil, Canada, Czech Republic, Taiwan, USA
	Carbendazim	Australia
	Thiophanate-methyl	Brazil, Czech Republic, USA
Demethylation inhibitor		
Imidazole	Imazalil	Taiwan
	Prochloraz	Taiwan
	Triflumizole	Israel, Japan, Spain, Taiwan
Piperazine	Triforine	Brazil, Israel, Spain
Pyrimidine	Fenarimol	Australia, Brazil, Czech Republic, Israel, Spain, Taiwan
	Nuarimol	Spain
Triazole	Bromuconazole	Israel
	Cyproconazole	Spain
	Diniconazole	Taiwan
	Fenbuconazole	Israel
	Hexaconazole	Taiwan
	Myclobutanil	Canada, Israel, Japan, Spain, Taiwan, USA
	Penconazole	Israel, Spain, Taiwan
	Propiconazole	Spain
	Tebuconazole	Brazil, Israel, Taiwan
	Tetraconazole	Israel, Spain, Taiwan
	Triadimefon	Australia, Brazil, Spain, Taiwan
	Triadimenol	Australia, Germany, Israel, Spain, Taiwan
Morpholine	Tridemorph	Australia, Taiwan
Hydroxypyrimidine		
Pyrimidinol	Bupirimate	Australia, Spain, Taiwan
	Dimethirimol	Australia
	Ethirimol	Taiwan
Anilinopyrimidine	Cyprodinil	Taiwan
Phosphorothiolate		
Organophosphorous	Pyrazophos	Australia, Brazil, Israel, Spain, Taiwan
QoI		
Strobilurin		
Methoxyacrylate	Azoxystrobin	Australia, Japan, USA
Oximinoacetate	Kresoxim-methyl	Brazil, Israel, Spain, Taiwan
	Trifloxystrobin	USA
Quinoline	Quinoxyfen	Israel
Miscellaneous	Ditalimfos	Taiwan
Multi-site activity contact fungicides not at risk for resistance		
Chloronitrile	Chlorothalonil	Australia, Brazil, Canada, Japan, USA
Inorganics	Copper	USA
	Sulfur	Brazil, Canada, Czech Republic, Germany, Israel, Japan, Spain, Taiwan, USA
Quinoxaline	Quinomethionate	Brazil, Israel, Japan, Spain
Sulphamide	Dichlofluanid	Germany
Miscellaneous	Dinocap	Israel, Spain
	Oil	Czech Republic, Israel, USA
	Potassium bicarbonate	Israel, Taiwan, USA

Research is underway to obtain the necessary fundamental knowledge about new fungicides for making predictions about resistance development and for identifying appropriate application schedules (S. P. Heaney, *personal communication*). Information is needed about mode of action, resistance mechanisms, cross resistance, case histories, and pathogen biology. The focus of recent work has been the QoI fungicides. Their mode of action is to inhibit mitochondrial respiration by binding to a target site in the cytochrome bc_1 complex, thereby blocking electron transfer and ATP synthesis (126). A point mutation, consisting of alanine substituting for glycine at position 143 in the center of the Qo binding site, was found to be the mechanism of resistance to QoI fungicides for *P. xanthii* and four other fungi (30). This mechanism provides a very high level of resistance. Fitness has not been investigated yet for resistant isolates of *P. xanthii*; however, resistant isolates of *Erysiphe graminis* f. sp. *tritici* were competitive with wild-type sensitive isolates under controlled environments (30). Cross resistance among QoI fungicides has been documented with *E. graminis* f. sp. *tritici* and *Plasmopara viticola* (30). Fortunately, cross reactivity with DMI fungicides has not been detected (N. Shishkoff and M. T. McGrath, *unpublished*).

The life cycle of the cucurbit powdery mildew fungus is not completely understood. Knowledge about migration and between-crop survival is needed for a proactive response to resistance management. In most production areas, cucurbits are not grown year-round; thus, there is a period when there are no cucurbit hosts present for the obligately biotrophic cucurbit powdery mildew fungus to live on. Possible sources of initial inoculum for the reestablishment of disease include wind-borne conidia (Fig. 4) dispersed long distances from other production areas, conidia dispersed locally from reservoir hosts, and cleistothecia (Fig. 5). The relative importance of the possible inoculum sources for disease development is not known for many locations. In Australia, for example, the pathogen is assumed to survive between crops on weeds, on volunteer crop plants in tropical and nonfrosting coastal areas, and in protected home gardens (R. G. O'Brien, *personal communication*). In the northeastern United States, it has been assumed that the source is wind-borne conidia from production areas to the south. However, strains of *P. xanthii* virulent on cucurbits have been found on verbena being sold at garden centers on Long Island, NY, before powdery mildew has been observed on cucurbit crops grown in the area (112).

The sexual stage does not appear to be important in the life cycle of the cucurbit powdery mildew fungus, although sexual recombination is considered to be an important characteristic of fungal pathogens with high potential to develop resistance. Cleistothecia have been observed rarely or never on cucurbit crops in several areas of the world (77). Even where cleistothecia are formed, sexual progeny may not play a role in the life cycle because cleistothecia do not develop until near the end of the crop growing season, cucurbit crop debris typically is incorporated into the soil by plowing after harvest, and subsequent cucurbit crops are often planted in a field where cucurbit crops were not grown the previous season. Although cleistothecia have formed every year in research fields at LIHREC, the frequencies of isolates resistant to triadimefon and benomyl before fungicide treatment in 1992 and 1993 were substantially different from the resistance frequencies after treatment the previous year (Table 2), which suggests that ascospores were not important. Cleistothecia forming on perennial reservoir hosts have a greater chance of playing a role in the life cycle. Variation in fungicide efficacy results among neighboring states suggests that local inoculum is important (85). For grape powdery mildew, DMI resistance has been shown to persist in ascospores (25), which are an important source of initial inoculum (98).

Recommendations for Resistance Management

Current recommendations for managing fungicide resistance include using a diversity of fungicides within an integrated disease management program that includes nonchemical practices, such as use of resistant cultivars (11). It is critical to use an effective program in order to delay the buildup of resistant strains (http://www.gcpf.org/frac/STARWG.html). At-risk fungicides should be used at the manufacturer's recommended rate (full rate) and application interval. Using full rates is expected to minimize selection of phenotypes with intermediate fungicide sensitivity when resistance involves several genes (quantitative resistance). At-risk fungicides should be used in alternation with other at-risk fungicides with different modes of action (different cross-resistance groups), and they should be combined or alternated with multi-site fungicides that have a low resistance risk. Both types of companion fungicides are effective for managing resistance. For example, triadimefon-resistant strains were at a lower frequency when either chlorothalonil or azoxystrobin was added to a triadimefon fungicide program, and no resistant strains were detected when azoxystrobin was applied in alternation with triadimefon plus chlorothalonil (83). The current recommendation for QoI fungicides is to include a QoI in one out of three fungicide applications, with no consecutive QoI applications and a crop maximum of three QoI applications (http://www.gcpf.org/frac/STARWG.html). Limiting the number of applications of QoI fungicides to one or two per growing season is recommended by some with experience with resistance to this chemical group (Y. Nakazawa, *personal communication*). When one crop could serve as a source of inoculum for a subsequent crop, the alternation scheme among at-risk fungicides should be continued between successive crops such that the first at-risk fungicide applied to a crop belongs to a different cross-resistance group than the last at-risk fungicide applied to the previous crop. At-risk fungicides should be used only when needed most. The most critical time to use them for resistance management is early in an epidemic when the pathogen population is small. Multi-site contact fungicides should be used alone late in the growing season, where they have been shown to provide sufficient disease control to protect yield. A disease threshold approach has been recommended for initiating fungicide applications for powdery mildew (80,87). An alternative approach is to use contact fungicides during early crop growth, when better spray coverage is possible beginning before powdery mildew has started to develop, then include at-risk fungicides after fruit set when powdery mildew begins to develop. This tactic is recommended by the Australian Fungicide Resistance Action Committee.

Challenges and Future Outlook

Effectively managing resistance has been and likely will continue to be challenged by many factors. Resistance risk of a new fungicide is difficult to predict. Risk cannot always be predicted solely from the mode of action. Additionally, resistance development in model systems with yeasts or nonobligate pathogens is not always similar to that in obligate pathogens. For example, the QoI fungicides were initially thought to have a low to medium resistance risk, and resistance was predicted to be quantitative based on their mode of action (inhibition of respiration) and on results of research with yeast. However, resistance developed quickly and in a disruptive manner.

Identifying the most appropriate resistance management strategy for a fungicide is often challenged by lack of understanding of the mechanism of resistance (e.g., quantitative or qualitative) and of the mode of action (e.g., active pre- or post-symptom). Fungicide rate is important with quantitative resistance. Knowledge that QoI fungicides inhibit spore germination was an important factor leading to the decision to start with a strobilurin in the currently recommended alternation scheme with myclobutanil. This decision was also based on knowledge that triadimefon resistance occurs throughout the United States and that DMIs (e.g., myclobutanil) exhibit cross resistance. Thus, at the start of an epidemic, a strobilurin is applied when the selectable population for resistance to this fungicide group is small, since there are very few established colonies, and selection pressure for DMI resistance is delayed until the second application.

While a resistance management program for a new fungicide is needed at the time of registration, it cannot be evaluated before pathogen strains with reduced sensitivity have been found. Releasing laboratory-generated resistant strains is very risky because they cannot be contained. Furthermore, evaluation may need to be conducted over several successive crops.

At any given time, effective companion fungicides often have not been available. Registering new fungicides is a lengthy process. Typically, only one effective at-risk fungicide is available for growers to use. For example, in the United States, the first at-risk fungicide registered for cucurbit powdery mildew was the benzimidazole fungicide benomyl in 1972. When the next at-risk fungicide with a different mode of

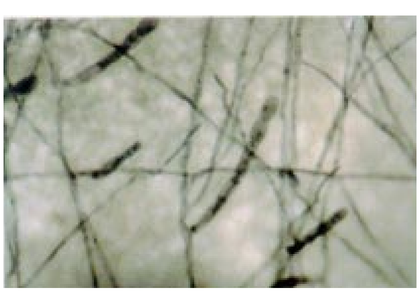

Fig 4. Conidia of *Podosphaera xanthii*.

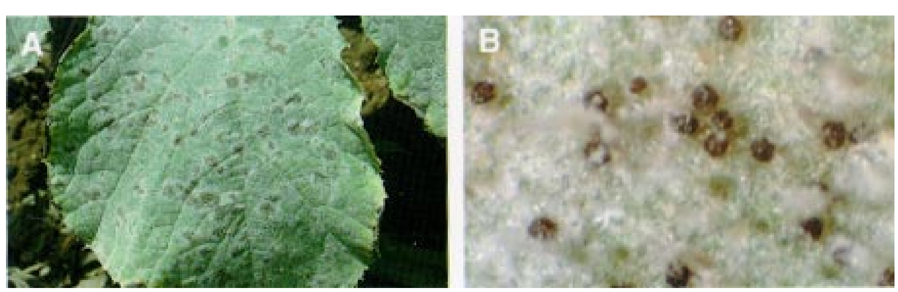

Fig 5A, Cleistothecia of *Podosphaera xanthii* on pumpkin leaf. B, Microscopic view.

action, the DMI triadimefon, was registered in 1984, resistance to benomyl was already widespread based on the reduced efficacy and control failures with benomyl that had occurred in several fungicide efficacy experiments (Table 2). Resistance to triadimefon was widespread when the first QoI fungicide, azoxystrobin, was registered in 1999. For azoxystrobin, an effective at-risk companion fungicide with a different mode of action, myclobutanil, was not widely available until 2000. In addition, registrations of some multi-site companion fungicides have been canceled or are under review in the United States through implementation of the Food Quality Protection Act (FQPA). Others have been lost because the market was too small and thus uneconomical for the manufacturer. This is the reason the main multi-site companion fungicide used previously in Australia, quinomethionate, is no longer registered (R. G. O'Brien, *personal communication*).

Product withdrawal after resistance development, followed by later reintroduction, is not a viable option for some fungicides. For this management tactic to be effective, resistant strains must be less fit than sensitive strains. However, some resistant strains have been able to persist in the absence of selection pressure from fungicide use. Benzimidazole-resistant strains have persisted for many years after use was discontinued (9,93). In addition, this tactic is unlikely to be implemented if the target fungicide is highly effective for controlling other diseases on the same crop, as is the case with azoxystrobin, which, in addition to powdery mildew, also controls anthracnose, belly rot, downy mildew, gummy stem blight, and leaf spots caused by *Alternaria* and *Cercospora*.

The labeled rate for a fungicide might not be the best rate to use for delaying resistance development with quantitative resistance. Efficacy experiments to identify rates are usually conducted before fungicides are registered for commercial use. At this time, resistant strains would likely be at too low a frequency to impact performance. The use rate selected for registration of a new fungicide typically is the lowest rate providing consistent control in the efficacy experiments. The lowest effective rate might not be the best rate to use for delaying resistance development, as it may permit strains with intermediate resistance to survive.

Cross-resistance is common among fungicides within a chemical group (47,108). Consequently, using one fungicide (e.g., triadimefon) might select for strains less sensitive to another fungicide in the same group (e.g., myclobutanil), thereby affecting its efficacy. Use rates are not based on cross-resistance data for new fungicides belonging to a fungicide group (e.g., the DMIs) to which the pathogen has already developed quantitative resistance.

Because strains have been detected with resistance to as many as four classes of fungicides, it is clear that the cucurbit powdery mildew fungus is capable of thwarting a complex fungicide program (19,93,125).

The life cycle of the cucurbit powdery mildew fungus needs to be better understood in order to manage resistance and assess resistance risk more effectively. For example, if the fungus survives between crops as cleistothecia or on a weedy reservoir host, then growers need to consider fungicides applied to the previous crop when selecting the fungicide program for the current crop. If verbena or another ornamental plant is an important source of inoculum for powdery mildew epidemics in cucurbits, then fungicides used on this other host, which could include products not yet registered on cucurbits, need to be considered when developing fungicide programs for cucurbits. A product newly registered for cucurbits could be compromised by previous selection of resistant strains on the ornamental host.

With highly mobile pathogens such as cucurbit powdery mildew, successful management may require regional implementation. Otherwise, growers using an at-risk fungicide exclusively may select resistant strains and thereby thwart efforts of growers who are using a resistance management program.

Monitoring pathogen sensitivity to fungicides is useful for documenting shifts. However, current techniques, which entail expensive sampling and laboratory screening, are limited by their inability to detect rare resistant strains.

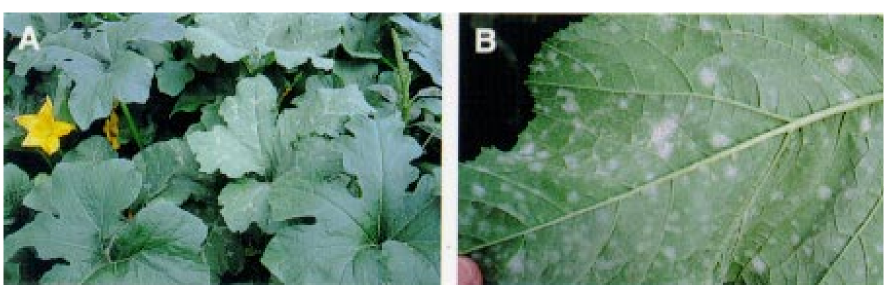

Fig 6. Pumpkin leaves in a commercial field sprayed routinely with a low rate of myclobutanil plus the contact fungicide chlorothalonil. Powdery mildew is controlled well on adaxial leaf surfaces, A, but not on abaxial surfaces, B.

Fungicide cost and efficacy are greater concerns for growers than resistance. Implementation may be difficult when the resistance management program is more expensive or less effective than using the at-risk fungicide alone full-season. Inexpensive fungicides are likely to be used intensively, whereas expensive fungicides are likely to be used at reduced rates or extended spray intervals. Growers may not be easily convinced to use a multi-site contact companion fungicide with an at-risk fungicide when current-season disease control is not improved. Although addition of a contact fungicide may manage resistance to a highly effective fungicide, it is not expected to provide a detectable increase in disease control in early stages of resistance development, because strains with reduced sensitivity to the at-risk fungicide would be at too low a frequency in the pathogen population to affect disease development.

Another risk is that development of resistance may be overlooked when a multi-site contact companion fungicide is used. This type of companion fungicide will effectively control any resistant strains on adaxial leaf surfaces, but selection of resistant strains may still progress on abaxial surfaces where spray deposit is poor. This can easily be missed because abaxial surfaces are not readily visible unless leaves are turned over (Fig. 6).

Just as many diseases and insect pests are managed after they appear, some growers become concerned about managing resistance only after it has developed. They do not recognize that the primary goal of resistance management is to delay its development rather than to manage resistant strains. Consequently, resistance management programs are not always implemented when at-risk fungicides become available for commercial agricultural use.

Resistance management programs are not enforceable. Therefore, prepacked mixtures are considered the only practical strategy for delaying development of resistance generally (13).

Managing resistance with full-rate mixtures is at odds with the public desire to reduce pesticide use. Full-rate mixtures comprise a greater quantity of fungicide than using one at-risk fungicide exclusively at a rate near the MIC for sensitive strains.

IPM tactics that delay applications until after disease detection and extend spray intervals until disease-favorable conditions have occurred may be in conflict with the accepted resistance management tactics of avoiding curative (eradicant) treatments and maintaining recommended intervals. Resistance can develop quickly when fungicides are used curatively. Each IPM tactic needs to be considered in terms of the size of the pathogen population at application and the potential impact on resistance management. Fortunately, the action threshold for cucurbit powdery mildew of one leaf with symptoms per 50 old (most susceptible) leaves is considered to be below the disease level that would correspond to a curative treatment. However, the potential problem of delayed applications needs to be kept in mind if other IPM tactics are considered in the future. For example, the threshold for initiating fungicide applications for carrot leaf blights in Canada is considerably higher, being a disease incidence of 100% for early carrots and 50% for late carrots (49). A forecasting system that times applications by predicting future occurrence of conditions favorable for infection would be compatible with resistance management, whereas a disease-warning system that alerts users to when conditions were favorable, such as TOM-CAST (24), could result in curative treatment. However, resistance is currently not a concern with either carrot leaf blights or TOM-CAST because chlorothalonil is the primary fungicide being used in these situations. Fungicide mode of action should also be considered. Applications of fungicides that inhibit spore germination, such as the QoIs, should be started earlier in disease development than fungicides with postinfection activity, such as the DMIs.

Although effectively managing resistance will continue to be challenged by biological, economic, and political factors, an understanding of these challenges and the current proactive approach to their resolution being taken ensures that we are now in a good position to address fungicide resistance in cucurbit powdery mildew.

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