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Fungicide Resistance Management

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Fungicides are important tools for managing diseases in many crops. Unlike insecticides and some herbicides which kill established insects or weeds, fungicides are most commonly applied to protect healthy plants from infection by fungal plant pathogens. To be effective, fungicides must be applied before infections become established and in a sufficient spray volume to achieve thorough coverage of the plant or treated area. Protection from fungicides is temporary because they are subject to weathering and breakdown over time. They also must be reapplied to protect new growth when disease threatens. Poor disease control with fungicides can result from several causes including insufficient application rate, inherently low effectiveness of the fungicide on the target pathogen, improper timing or application method, and excessive rainfall. Resistance (lack of sensitivity) to fungicides in fungal pathogens is another cause of poor disease control. The development of fungicide resistance is influenced by complex interactions of factors such as the mode of action of the fungicide (how the active ingredient inhibits the fungus), the biology of the pathogen, fungicide use pattern, and the cropping system. Understanding the biology of fungicide resistance, how it develops, and how it can be managed is crucial for ensuring sustainable disease control with fungicides.

The problem of fungicide resistance became apparent following the registration and widespread use of the systemic fungicide (see fungicide mobility below) benomyl (Benlate) in the early 1970s. Prior to the registration of benomyl, growers routinely applied a protectant fungicide (see fungicide mobility below) such as maneb, mancozeb, or copper to control diseases without experiencing resistance problems. A distinct advantage of benomyl over the protectant fungicides was its systemic activity. In addition to protecting plants from infection, systemic activity conferred rainfastness and provided disease control when applied after the early stages of infection. Superior disease control was often achieved with benomyl compared to the protective dithiocarbamates. However, benomyl differed from the dithiocarbamates in its site-specific mode of action (see Fungicide Groups and Mode of Action below) which was readily overcome by several fungal pathogens. Resistance problems appeared a few years after benomyl was introduced where the fungicide was used intensively. Sudden control failures occurred with diseases such as powdery mildew, peanut leaf spot, and apple scab.

Many of the fungicides developed and registered since the introduction of benomyl also are systemic, have a site-specific mode of action, and are at increased risk for resistance problems. Fungicide resistance is now a widespread problem in global agriculture. Fungicide resistance problems in the field have been documented for more than 100 diseases (crop - pathogen combinations), and within about half of the known fungicide groups. Many more cases of resistance are suspected but have not been documented. While resistance risks with many of fungicides may not be as great as with benomyl, strategies to manage the resistance risk have been developed and implemented to avoid unexpected control failures and sustain the usefulness of new products. As a result of resistance management strategies, fungicides within all mode of action groups remain useful disease management tools in at least some cropping systems. The purpose of this bulletin is to describe the resistance phenomenon, identify resistance risks in the different fungicide groups, and to provide general guidelines for managing resistance. Since this fact sheet was first written, many new fungicides have been registered, and mode of action groups and specific resistance management strategies are now specified on fungicide labels. The listing of fungicides by mode of action group here is useful for identifying appropriate fungicides for use in tank mixtures and application schedules as part of the recommended resistance management programs.

Fungicide Mobility

Understanding the mobility of fungicides on and in treated plants, and how various fungicides are classified based on mobility is important when making decisions pertaining to the selection of the best fungicide for a particular disease and its optimal application timing. Fungicides can be classified into two basic mobility groups: protectant or penetrant. Regardless of its mobility characteristics, no fungicide will be highly effective after the development of disease symptoms and pathogen reproduction (spore production). Fungicides can slow or stop the development of new symptoms if applied in a timely fashion, but fungicides will not cure existing disease symptoms. Therefore, understanding fungicide mobility, fungicide mode of action, and the biology of the target pathogen are important so fungicide applications are made before the disease becomes established and more difficult to control.

Protectant fungicides are active on the plant surfaces where they remain after application. There is no movement of the fungicide into the plant. Because they remain on the plant surface, protectant fungicides loose activity after being washed off the plant and must be re-applied to new growth that develops after application. Protectant fungicides typically prevent spore germination, therefore they must be applied prior to infection and have no effect once the fungus grows into the plant resulting in infection.

Penetrant fungicides are absorbed into plants following application. Because these fungicides are absorbed into plants, they are generally considered systemic fungicides. However, penetrant fungicides have different degrees of systemic movement once inside the plant. Some fungicides are 'locally systemic,' only moving a short distance such as through a few layers of plant cells. Fungicides that move from one side of a leaf to other have 'translaminar' movement. Translaminar and locally systemic fungicides are not transported throughout the

plant. Highly mobile fungicides are either 'xylem-mobile' or 'true systemics.' Xylem-mobile fungicides move upward in plants and outward to the periphery of leaves with water through the xylem, the water conducting tissue of the plant. True systemic fungicides move both upward through the xylem, and downward through the phloem, the food conducting tissue of the plant. Few if any fungicides are fully systemic. Unlike protectant fungicides, penetrant fungicides are rain fast within a few hours of application and may require a less thorough application coverage to be effective. In addition, many penetrant fungicides inhibit fungal growth and sporulation and can be effective when applied after the early stages of infection. Regardless of the level of systemic movement, penetrant fungicides have limited 'curative' ability. Generally they only stop or slow infections within the first 24- to 72-hour period following fungal penetration into the plant. Therefore, penetrant fungicides must be applied before or shortly after infection, and are ineffective on existing symptoms. Both protectant and penetrant fungicides provide good disease control when applied before infection and are best applied on a preventive schedule.

Development of Fungicide Resistance

Resistance is a genetic adjustment by a fungus that results in reduced sensitivity to a fungicide. Reduced sensitivity is thought to be a result of genetic mutations which occur at low frequencies (one in a million or less) or of naturally occurring sub-populations of resistant individuals. Individuals in a fungal population may consist of the mycelium (the body of a fungus), sclerotia (large survival structures), spores (small reproductive structures), or the nucleus of single cells capable of reproduction and spread. The resistance trait may result from single gene or multiple gene mutations (see build-up of resistance below). Single-gene mutations that confer resistance to site-specific fungicides are more likely to develop than the simultaneous occurrence of mutations in multiple genes needed to confer resistance to multi-site inhibiting fungicides. Mechanisms of resistance differ depending on the mode of action, but include alteration of the target site, reduced fungicide uptake, active export of the fungicide outside fungal cells, and detoxification or breakdown of the fungicide.

The level of resistance to a fungicide can be measured in the laboratory by exposing a collection of members of a field population to the fungicide and measuring toxicity response. Toxicity responses are usually measured as inhibition of fungus growth, spore germination, or actual plant infection in cases where the fungus cannot be cultured. The effective concentration which inhibits growth, germination, or infection by 50 percent (EC_{50}) is then calculated for each sampled individual much in the same way an LD_{50} (50 percent lethal dose) is calculated for assessing the acute toxicity of a pesticide to rats or mice. Where many members of a population are sampled and screened, a range of sensitivity (or resistance) to the fungicide is usually observed. The frequency distribution of the sensitivity of individuals in the population is usually normal or bell-shaped, typical of many biological responses in nature (Figure 1). Where the fungicide is newly introduced or where the risk of resistance is low, the population is distributed over a sensitive range. However, a distribution consisting of two distinct sub-populations also may occur where a small sub-population of resistant strains is present along with a larger sub-population of sensitive strains (Figure 1A).

Build-up of Resistance

Resistance in a population becomes important when the frequency of resistant strains builds up to dominate the population. The build-up of resistant strains is caused by repeated use of the fungicide which exerts selection pressure on the population. The fungicide selectively inhibits sensitive strains, but allows the increase of resistant strains. This shift toward resistance occurs at different rates, depending on the number of genes conferring resistance. When single gene mutations confer resistance, a rapid shift toward resistance may occur, leading to a population that is predominantly resistant and where control is abruptly lost (Fig. 1A). When multiple genes are involved, the shift toward resistance progresses slowly, leading to a reduced sensitivity of the entire population (Fig. 1B). The gradual shift with the multiple gene effect may result in reduced fungicide activity between sprays, but the risk of sudden and complete loss of control is low. It is difficult to clearly distinguish between sensitive and resistant sub-populations with field sampling during the early shifts towards reduced sensitivity because sensitivity responses overlap. Large numbers of individuals must be tested to identify the gradual type of resistance.

Assessing Resistance Risk

Many factors effect the development of resistance and its build-up in the field, which makes it difficult to predict the resistance risk for new fungicides. Despite resistance problems that have been identified following the introduction of some new fungicides, many examples can be cited where their use continues to be effective. Factors that must all be considered in assessing resistance risk include the properties of the fungicide, the biology of the pathogen, and the crop production system where the fungicide is used.

Fungicide Groups and Mode of Action

Fungicides are grouped by similarities in chemical structure and mode of action. Site-specific fungicides disrupt single metabolic processes or structural sites of the target fungus. These include cell division, sterol synthesis, or nucleic acid (DNA and or RNA) synthesis. The activity of site-specific fungicides may be reduced by single or multiple-gene mutations. The benzimidazole, phenylamide, and strobilurin groups are subject to single-gene resistance and carry a high risk of resistance problems. Other

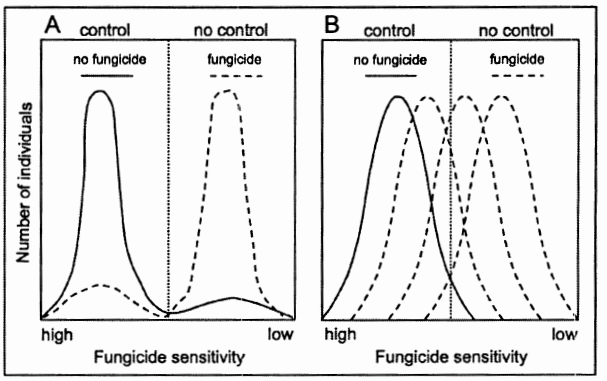

Figure 1. Depiction of the possible ways fungicide resistance develops in population of a fungal pathogen. A) Abrupt (qualitative) resistance development where an initially small, subpopulation of resistant strains is present before fungicide usage or develops as a result of a single gene mutation occurring at low frequency (solid line). Following selection pressure of fungicide use, the frequency of resistant individuals (broken line) becomes predominant and disease control is rapidly lost. B) Gradual (quantitative) resistance development arising from an accumulation of mutations in multiple genes that leads to reduced sensitivity. The initial population (solid line) is sensitive, but gradually shifts towards reduced sensitivity under the selection pressure of fungicide use (broken line).

fungicide groups with site-specific modes of action include dicarboximides and sterol demethylation inhibitors (DMIs), but resistance to these fungicides appears to involve slower shifts toward insensitivity because of multiple-gene involvement. Many of the site-specific fungicides also have systemic mobility. However, systemic mobility is not necessary for resistance development. Resistance problems have developed in the dicarboximide group and with dodine, which are protectant fungicides.

Multi-site fungicides interfere with many metabolic processes of the fungus and are usually protectant fungicides. Once taken up by fungal cells, multisite inhibitors act on processes such as general enzyme activity that disrupt numerous cell functions. Numerous mutations affecting many sites in the fungus would be necessary for resistance to develop. Typically, these fungicides inhibit spore germination and must be applied before infection occurs. Multi-site fungicides form a chemical barrier between the plant and fungus. The risk of resistance to these fungicides is low.

There are two codes currently used to classify fungicides by mode of action (Table 1). The mode of action group (A, B, etc.) refers to the general target site such as nucleic acid synthesis, cell wall synthesis, respiration, etc. Sub-groups (A1, A2, etc.) within a mode of action group refer to specific biochemical target sites of fungicide activity. The FRAC (Fungicide Resistance Action Committee) code is used on the fungicide label. The FRAC code refers to fungicides that have same site-specific mode of action and share the same resistance problems across members of the group (cross-resistance). FRAC groups are currently numbered from 1 to 43 in order of their introduction to the marketplace. FRAC groups and mode of action subgroups are mostly the same.

Fitness of Resistant Strains

Fitness is the ability to compete and survive in nature. Strains of pathogens resistant to some fungicides compete equally well with sensitive strains and are still present after the fungicide in question is no longer in use. For example, strains of *Cercospora arachidicola* which causes early leaf spot of peanut are still established in the southeastern U.S. where benomyl resistance was a problem more than 20 years ago. Therefore, fungicides with resistance problems cannot be successfully reintroduced into areas where resistant strains are highly fit. Fortunately, resistant strains are sometimes less fit than wild-type sensitive strains. This has been true for DMI resistance in powdery mildews and for dicarboximide resistance in Botrytis diseases. Unfit strains only compete well under the selection pressure of the fungicide. Thus, the resistance is at least partially reversible when the selection pressure of the fungicide is removed or minimized by using resistance management.

Fungicide Use Pattern

Frequent and exclusive usage of at-risk fungicides increases the risk of resistance problems. Selection pressure is increased where repeated applications are required for disease control as with many foliar diseases. Selection pressure and the risk of resistance are low for seed treatments and for many soilborne diseases which require only one or two applications per season. The method and rate of application may also impact resistance development. Poor disease control resulting from causes such as improper application timing or inadequate spray coverage may result in a need for a more intensive spray program and the exposure of more individuals to the fungicide. Using adequate rates in a manner that produces good disease control reduces the reproductive capacity of fungal pathogens, thus reducing selection pressure. Similarly, a preventive spray program is less risky than a rescue program because selection pressure is applied to fewer individuals. Finally, an increase in selection pressure results from an excessive number of applications where a real need is not justified.

Pathogen Biology

Fungal pathogens with high rates of reproduction are most prone to develop fungicide resistance. Because many individuals (usually spores) are produced by these fungi, more individuals are exposed to selection pressure and there is a greater probability of mutations that lead to reduced fungicide sensitivity. Foliar diseases produce thousands of spores on the surface of an individual leaf spot. Furthermore, these diseases typically have several reproductive cycles per season. Under selection pressure of a fungicide, resistant individuals may increase rapidly and dominate the population after several cycles of infection and reproduction.

Diseases with low reproduction rates generally complete only one life cycle per season. Soilborne pathogens produce fewer offspring per season than their foliar counterparts. Some soilborne diseases reproduce by forming seed-like survival structures called sclerotia. There may be fewer than a hundred sclerotia formed per plant. Where an at-risk fungicide is used for soilborne disease control, resistance development is likely to be slow because comparatively few individuals are exposed to selection pressure.

Crop Production Practices

Production practices that favor increased disease pressure also promote resistance development by increasing the number of individuals exposed to selection pressure. Pathogens reproduce at higher rates on susceptible varieties compared to resistant or partially resistant varieties. Selection pressure also may be reduced for resistant varieties because fewer applications should be needed for effective disease control. Inadequate or excessive fertilization with nitrogen may increase disease incidence in some crops. For example, early blight of potato and tomato and dollar spot of turfgrass are favored by nitrogen deficiency. Alternatively, the severity of spring dead spot of bermudagrass and some foliar diseases of wheat is increased with intensive nitrogen fertilization. Excessive irrigation or frequent irrigation with small amounts of water increases the incidence of many diseases by promoting disease spread, extended periods of leaf wetness, and high soil moisture.

Continuous cropping and poor sanitation practices promote severe early-season disease development. Closed cropping systems such as greenhouses are particularly prone to resistance problems because plants are grown in crowded conditions that may favor severe disease development, rapid spread, and high selection pressure. Permanently established plantings of perennial crops such as orchards, nurseries, and vineyards are particularly prone to resistance problems. Unlike annual crops where crop rotation can be practiced, many pathogens survive from year to year on plants and crop debris within permanent plantings resulting in a local pathogen population exposed to yearly selection pressures.

Resistance Management Strategies

Strategies for managing fungicide resistance are aimed at delaying its development. Therefore, a management strategy should be implemented before resistance becomes a problem. The only way to absolutely prevent resistance is to not use an at-risk fungicide. This is not a practical solution because many of the modern fungicides that are at risk for resistance problems provide highly effective, broad-spectrum disease control. By delaying resistance and keeping its level under control, resistance can be prevented from becoming economically important. Because practical research in the area of fungicide resistance management has been limited, many of the strategies devised are based in the theory of expected responses of a pathogen population to selection pressure. For the most part, evaluations of the effectiveness of these strategies have not been based on

Table 1. Fungicides registered in the United States grouped by mode of action and relative risk for developing resistance problems.

Mode of action	*Group*[1]	*Group name*	*Common name*	*Trade names*	*Mobility*[2]	*Uses*[3]	*Risk*[4]
Nucleic acid synthesis	A1 (4)	Phenylamide	metalaxyl	Allegiance, MetaStar, Apron	S	ST, F, S	H
			mefenoxam or metalaxyl-M	Ridomil Gold, Apron XL, Subdue, Ultra Flourish, Quali Pro	S	ST, F, S	H
Mitosis and cell division	B1 (1)	Benzimidazole	thiabendazole	Mertect	S	ST, PH	H
			thiophanate-methyl	Topsin M, Cleary's 3336, T-Methyl, OHP 6672, Thiophanate Methyl	S	ST, F, S	H
	B3 (22)	Benzamide	zoxamide	Gavel (+ mancozeb)	S	F	M
	B5 (43)	Acylpicolide	fluopicolide	Presidio	S	F,S	M
Respiration	C2 (7)	Carboxamide	carboxin	Vitavax	S	ST	L
			flutolanil	Contrast, Moncut, ProStar, Artisan (+ propiconazole)	S	ST, F, S	M
			boscalid	Endura, Emerald, Pristine (+ pyraclostrobin)	S	F, S	M
	C3 (11)	Strobilurin (Quinone outside Inhibitor (QoI))	azoxystrobin	Abound, Amistar, Heritage, Quadris, Protege, Dynasty, Quilt (+ propiconazole)	S	F, S, ST	H
			famoxidone	Tanos (+ curzate)	S	F	H
			fenamidone	Reason	S	F	H
			fluoxastrobin	Evito, Disarm	S	F, S	H
			kresoxim-methyl	Cygnus, Sovran	S	F	H
			pyraclostrobin	Cabrio, Insignia, Headline, Pristine (+ boscalid)	S	F, S	H
			trifloxystrobin	Flint, Compass, Gem, Trilex, Absolute (+ tebuconazole), Stratego (+ propiconazole)	S	F, S, ST	H
	C4 (21)	Quinone inside Inhibitor (QiI)	cyazofamid	Ranman	S	F	M
	C5 (29)	Dinitroaniline	fluazinam	Omega	P	F, S	L
	C6 (30)	Organo tin	triphenyl tin hydroxide	Super Tin, Agri Tin	P	F	L
Amino acids and proteins	D1 (9)	Anilino-Pyrimidine	cyprodinil	Vanguard, Switch (+ fludioxanil)	S	F	M
			pyrimethanil	Scala	S	F	M
	D4 (25)	Antibiotic (bactericide)	streptomycin	Agri-Mycin, Streptomycin, Firewall	P	ST, F	H
	D5 (41)	Antibiotic (bactericide)	oxytetracycline	Mycoshield, Flameout	P	F	H
Signaling	E1 (13)	Quinoline	quinoxyfen	Quintec	P	F	M
	E2 (12)	PhenylPyrrole	fludioxonil	Maxim, Scholar, Medallion, Switch (+ cyprodinil)	P	ST, F, PH	L-M
Lipids and membranes	F1 (2)	Dicarboximide	iprodione	Rovral, Chipco 26019, Iprodione, Chipco 26GT	P	F, S	M-H
			vinclozolin	Ronilan, Curalan	P	F, S	M-H
	F3 (14)	Aromatic Hydrocarbon	chloroneb	Nu-Flow D, Nu-Flow ND	P	ST	L
			dichloran	Botran	P	F, S, PH, ST	L-M
			PCNB	Terraclor, Turfcide	P	ST, S	L
			etridiazole	Terrazole, Terramaster	P	S	L-M
	F4 (28)	Carbamate	propamocarb HCl	Previcur Flex, Banol	S	F, S	L-M
	F5 (40)	Carboxylic Acid Amide	dimethomorph	Acrobat, Forum	S	F	L-M
			mandipropamid	Revus			
Sterol synthesis	G1 (3)	Demethylation Inhibitor (DMI)	cyproconazole	Alto, Quadris Xtra (+azoxystrobin)	S	F	
			fenarimol	Rubigan	S	F, S	M
			imazalil	Flo-Pro IMZ, Nu-Zone, Fecundal	S	ST, PH	L
			difenconazole	Dividend, Revus Top (+ mandipropamid)	S	ST, F	L-M

Table 1. continued.

Mode of action	*Group*[1]	*Group name*	*Common name*	*Trade names*	*Mobility*[2]	*Uses*[3]	*Risk*[4]
	G1 (3)	DMI (cont'd)	fenbuconazole	Enable, Indar	S	F	M
			myclobutanil	Nova, Rally, Eagle, Systhane, Laredo	S	F, S	M
			metconazole	Caramba, Quash	S	F,S	M
			propiconazole	Tilt, Orbit, Banner Maxx, Propiconazole, Propimax, Bumper, Propensity, Quilt (+ azoxystrobin), Stratego (+ trifloxystrobin)	S	F, S	M
			prothioconazole	Proline, Provost (+ tebuconazole)	S	F,S	M
			tebuconazole	Folicur, Raxil, Muscle, Trisum, Tebuzol, Orius, Elite, Absolute (+ trifloxystrobin)	S	F, S, ST	M
			tetraconazole	Domark, Eminent	S	F	M
			triadimefon	Bayleton	S	F, S	M
			triadimenol	Baytan	S	ST	L
			triflumizole	Procure, Terraguard	S	F, S	M
	G3 (17)	Hydroxyanilide	fenhexamid	Elevate, Captevate (+ captan)	P	F	L-M
Cell wall synthesis	H4 (19)	Polyoxins	polyoxin	Endorse	S	F, S	M
Plant defense activator	P1 (P)	Benzo-thiadiazole	acibenzolar-S-methyl	Actigard, Blockade	S	F	L
Unknown	U1 (27)	Cyanoacetamideoxime	cymoxanil	Curzate, Tanos (+ famoxadone)	S	F	M
	U2 (33)	Phosphonate	fosetyl-AL	Aliette, Legion, Chipco Signature	S	F	L
			phosphorous acid	Phostrol, AgriFos	S	F	L
			potassium phosphite	Fosphite, Prophyt	S	F	L
Multi-site activity	M1 (M1)	Inorganic	copper salts	Kocide, Cuprofix, Tenn-Cop, Basic Copper, Champ, Champion, Nu-Cop, Copper-Count-N	P	F	L
	M2 (M2)	Inorganic	sulfur	Microthiol, Sulfur, Super Six, Thiolux, Thiosperse	P	F	L
	M3 (M3)	Dithiocarbamate	ferbam	Ferbam	P	F	L
			mancozeb	Dithane, Penncozeb, Manzate, Fore, Mankocide (+ copper)	P	F, ST	L
			maneb	Maneb, Manex, Pentathlon	P	F, ST	L
			metiram	Polyram	P	F	L
			thiram	Thiram, Defiant	P	F, ST	L
			ziram	Ziram	P	F	L
	M4 (M4)	Phthalimide	captan	Captan, Captec	P	F, ST	L
	M5 (M5)	Chloronitrile	chlorothalonil	Bravo, Equus, Echo, Daconil, Chloronil, Chlorothalonil, Initiate, Concord, Spectro	P	F, S	L
	M7 (M7)	Guanadine	dodine	Syllit, Dodine	P	F	M

[1] Subgroups represent specific target sites within a mode of action, cross-resistance may occur within subgroups, FRAC group is in parenthesis. FRAC code is based on time of product registration and potential for cross-resistance within subgroups.

[2] P=protectant, S=systemic or penetrant.

[3] S=soilborne diseases, F=foliar diseases, ST=seed treatment, PH=post-harvest treatment.

[4] The resistance risk is assigned based on the worst case-scenario. For example, dicarboximide resistance is serious for some Botrytis diseases, but resistance problems have not developed with other uses. Seed treatment uses are considered low-risk regardless of the fungicide's properties.

research, but rather on observations made where the fungicides have been used commercially on a large scale.

Specific strategies for resistance management vary for the different fungicide groups, the target pathogen(s), and the crop. However, some strategies are generally effective (Table 2). Resistance management should integrate cultural practices and optimum fungicide use patterns. The desired result is to minimize selection pressure through a reduction in time of exposure or the size of the population exposed to the at-risk fungicide. Probably the most important aspect of optimizing use patterns is the deployment of tank mixtures and alternating sprays of the at-risk fungicide with a fungicide from a different mode of action group. The comparative merits of tank-mixing compared to alternating sprays have been debated. Some theorize that tank-mixing reduces selection pressure only when the partner fungicide is highly effective and good coverage is achieved. Alternating fungicides is thought to act by reducing the time of exposure. In practice, examples can be cited for the effectiveness of both approaches. Both practices are more effective when cultural practices are implemented to reduce disease pressure. The alternation of blocks of more than one spray is probably less effective in resistance management than the other use patterns. For example, a block of four continuous sprays of the DMI fungicide tebuconazole is recommended at mid-season for peanut disease control. Despite the use of at least one application of a non-DMI fungicide before and after the 4-spray block, resistance to tebuconazole in both early and late leaf spot diseases became a widespread problem in less than 10 years.

Table 2. Cultural practices and fungicide use patterns that reduce disease pressure and selection for fungicide resistance.

Strategy	*Result*
Cultural practices	
use resistant varieties	lower disease incidence and rate of increase
maintain proper soil fertility	reduces disease incidence
avoid sites with high disease pressure	avoids high selection
crop rotation	reduces initial pathogen population
sanitation	reduces initial pathogen population
Fungicide use patterns	
use only when justified	avoids unnecessary selection
use protectively	hits small populations
achieve good spray coverage	reduces populations exposed to selection
use tank mixes with protectants	reduces populations exposed to selection
alternate fungicides from different fungicide groups	reduces selection time
do not use soil applications against foliar diseases	reduces selection time

The proper choice of a partner fungicide in a resistance management program is critical. Generally, good partner fungicides are multi-site inhibitors that have a low resistance risk (e.g. chlorothalonil, mancozeb, etc.) and are highly effective against the target pathogen. However, the use of an unrelated at-risk fungicide with no potential for cross-resistance problems also may be effective. Specific resistance management strategies will be discussed for fungicide groups with the greatest history and/or risk for resistance problems.

Benzimidazoles (FRAC Group 1; Mode of Action Sub-Group B1)

Benzimidazoles are site-specific fungicides which interfere with cell division. They have systemic mobility and have activity on many pathogens except water molds (e.g. Pythium and Phytophthora) and darkly pigmented fungi (e.g. Alternaria). Research has demonstrated that benzimidazole resistant strains may be present at low frequencies in nature, even in the absence of fungicide exposure. Under selection pressure, resistance development is abrupt and rapid (Figure 1A). Resistant strains cannot be controlled by increasing the application rate or by shortening the spray interval. Resistant strains are often fit and competitive in nature even without selection pressure. Therefore, some populations have remained resistant where benzimidazole use has been discontinued for 10 years. Resistance to benzimidazoles has been documented for more than 60 diseases and cross-resistance exists within this fungicide group. Benzimidazole resistance has received less recent attention because the fungicide benomyl is no longer registered in the U.S. However, resistance management remains important for thiophanate-methyl, the other widely used benzimidazole fungicide.

Management of benzimidazole resistance relies on reducing the selection pressure by limiting fungicide exposure and using tank mixtures or alternating sprays with a fungicide with a low resistance risk (Table 3). Where multiple sprays are required for disease control, avoid using benzimidazoles alone for an extended period of time. In spite of the numerous resistance problems with benzimidazoles, there are also many examples where benzimidazoles have remained effective for more than 30 years with judicial use.

Strobilurins (FRAC Group 11; Mode of Action Sub-Group C3)

Strobilurin fungicides, also know as quinine-outside inhibitor (QoI) fungicides, are synthetic analogues of a naturally occurring compound produced by a wood rotting fungus. Strobilurins inhibit

Table 3. Guidelines for reducing the risk of resistance to benzimidazole fungicides (FRAC Group 1, Mode of Action Group B1).

1. Use cultural practices and pest management strategies that reduce disease pressure.
2. Do not exceed the allowable number of benzimidazole applications on the label.
3. Alternate or tank-mix benzimidazole applications with a fungicide from a different mode of action group. In tank-mixtures, both the benzimidazole and tank mix partner must be applied at their labeled rate.
4. Benzimidazoles should be use in preventive programs that keep disease pressure low.

respiration in fungal cells by targeting a protein (cytochrome bc-1) that is encoded by a gene in the mitochondria. The fungicides are broad-spectrum with activity against all the major types of fungal pathogens. Strobillurin fungicides penetrate plant leaves and move from one side of the leaf to the other. This translaminar mobility makes them rain-fast, but they lack true systemic movement in the plant compared to some other systemic fungicides. Strobilurins act on a broad range of fungal processes including spore germination, fungal growth, and reproduction (sporulation). Strobilurin fungicides have been registered on numerous crops because of their broad-spectrum activity and excellent human and environmental safety profiles. However, like the benzmidazoles, resistance developed shortly after their introduction in the late 1990s. Three different single-gene mutations have been identified that abruptly confer resistance (Figure 1A) that has been documented for more than 20 diseases. Resistant isolates are cross-resistant to all other strobilurin fungicides, but not to other mode of action groups including the closely related QiI (Group C4 or 21) fungicides.

Resistance management programs rely on reducing selection pressure by keeping disease pressure low, applying strobilurins in mixtures or alternation with fungicide from a different mode of action group, and limiting the number of applications per crop season (Table 4). Several strobilurin fungicides are marketed in pre-mixtures with non-strobilurin fungicides for use on certain crops.

Dicarboximides (FRAC Group 2; Mode of Action Sub-Group E3)

Dicarboximides inhibit both spore germination and fungal growth. Resistance is thought to arise by mutations. The frequency of resistant individuals and their level of resistance increase gradually with prolonged selection pressure (Figure 1B). Resistance to dicarboximide fungicides has been identified for more than 15 diseases including brown rot of stone fruits, gray mold (Botrytis) on several crops, and important turf grass diseases. Dicarboximide resistant strains of some pathogens are less fit to survive than sensitive strains. Reduced exposure of resistant strains to dicarboximide fungicides result in a decrease in the frequency of resistant strains and possibly an overall shift of the population back toward sensitivity. Thus, it has been possible to reintroduce dicarboximides into problem situations where resistance management has been implemented.

Table 4. Guidelines for reducing the risk of resistance to strobilurin fungicides (FRAC Group 11; Mode of Action Group C3).

1. Use integrated pest management and cultural practices known to reduce disease pressure. Strobilurin fungicides may be used in extension-sponsored disease advisory (disease forecasting) programs, which recommend application timing based on weather or risk factors favorable for disease development.
2. Limit the number of strobilurin applications to two to four per season depending on the crop as specified on the label.
3. Limit the number of sequential applications of strobilurin fungicide to one or two, depending on the crop and or region as specified on the label, before alternating with a fungicide from a different mode of action group.
4. Make preventative applications to keep disease pressure low.
5. Use pre-mixtures or tank mixtures of strobilurin fungicides with fungicides from a different mode of action group. The minimum labeled rates of each fungicide in the tank mix should be used.

Table 5. Guidelines for preventing and managing resistance to dicarboximide fungicides (FRAC Group 2, Mode of Action Group E3).

1. Use cultural practices that reduce the pathogen population.
2. Limit the number of dicarboximide applications to a maximum of 2-3 per season and maintain regular prolonged times without exposure to dicarboximides.
3. Tank-mix or alternate dicarboximide applications with an effective non-dicarboximide fungicide having a low resistance risk. Dicarboximide fungicides applied in tank mixtures count toward season totals.
4. Apply adequate rates as recommended on the label.

The primary goal of resistance management strategies for dicarboximides is to limit selection time (Table 5). Delay the first application as long as possible by using early-season applications of a protectant fungicide. This allows the deployment of dicarboximides at a time when the population of resistant strains is potentially the lowest. The possibility of resistance problems is greatest where dicarboximides are used frequently and exclusively. The number of applications made to a particular site should not exceed three per season. This applies to multiple crops grown in the same field. Resistance problems are likely to be manifested by a partial loss of control and a need for a closer spray interval. There is evidence that cross-resistance exists between members of this group and one dicarboximide should not be replaced with another where resistance is a problem. Dicarboximide resistance appears to be a manageable problem. These fungicides have remained useful for control of soilborne diseases and have been successfully reintroduced into cropping systems where resistance problems have arisen.

Demethylation Inhibitors (FRAC Group 3; Mode of Action Sub-Group G1)

Demethylation inhibitor (DMI) fungicides (Table 1) are site-specific fungicides that disrupt the synthesis of sterols. Sterols are compounds required for growth of many plant pathogenic fungi. DMIs are a large group of systemic fungicides that have a broad range of activity against many types of foliar and soilborne diseases except for those caused by the water molds. Resistance development is similar to the dicarboximides. Typically, resistance develops gradually and is at first difficult to detect (Figure 1B). Resistant strains are thought to have reduced fitness; therefore, reduced selection pressure through the use resistance management strategies may partially shift the resistant populations back toward sensitivity. DMI resistance has been documented for more than 20 diseases including apple scab, powdery mildews, gray mold, and brown rot of stone fruit.

Management strategies rely on the use of adequate rates and limiting exposure by tank-mixing or alternating DMI applications with unrelated fungicides (Table 6). Using adequate application rates is important because mildly resistant strains can still be controlled. Avoid using DMI fungicides alone all season long. Cross resistance is also a problem within this group so replacement of one DMI with another is not practical. Premixtures of DMI fungicides with strobilurin or protectant fungicides are being marketed for many crops to improve the spectrum of diseases controlled and to comply with resistance management guidelines.

Phenylamides (FRAC Group 4; Mode of Action Sub-Group A1)

Phenylamides are highly systemic fungicides specifically used to control diseases caused by water molds. Such dis-

Table 6. Guidelines for preventing and managing resistance to demithylation inhibitor (DMI) fungicides (FRAC Code 3; Mode of Action Group G1).

1. Use available cultural practices and resistant varieties to reduce disease pressure.
2. Apply according to label directions and do not use less than the minimum label rate alone or in tank mixtures.
3. Do not exceed the maximum allowed amount of a single DMI fungicide per season. Extending the allowed amount of one DMI fungicide with another will increase the risk of resistance development.
4. Keep the disease pressure low by using a preventive application schedule.
5. DMI fungicides are not recommended for season-long use alone. Alternate sprays or blocks of sprays a fungicide from a different mode of action group, use tank mixes of DMI fungicides with an effective protective fungicide having a low resistance risk.

Table 7. Guidelines for preventing and managing resistance to phenylamide fungicides (FRAC Group 4; Mode of Action Group A1).

1. The phenylamides should be used in a preventive program to keep disease pressure low.
2. For foliar applications, phenylamides should be used in premixtures with an unrelated (non-phenylamide) fungicide.
3. Solo formulations for soil use should not be used for foliar diseases and mixtures rather than straight phenylamides should be used for seed treatments whenever possible.
4. Soil treatments of phenylamides should not be used against foliar diseases.
5. The number of phenylamide applications should not exceed two to four per crop and year.
6. Phenylamide sprays are recommended early in season or during the period of active vegetative growth of the crop prior to switching to a non-phenylamide product later in the season.

eases include damping off and root and lower stem rots caused Pythium and Phytophthora, and foliar diseases such as late blight, downy mildew, and white rust. Phenylamides inhibit fungal growth by disrupting RNA synthesis. Resistance problems with phenylamides, specifically metalaxyl, were observed shortly after their introduction where they were used exclusively and disease pressure was high. Resistance is governed by one or two genes and a low frequency of resistant individuals may exist in wild populations prior to use of these fungicides. Resistance can increase rapidly through selection of the naturally occurring strains (Figure 1A). Cross resistance occurs with other phenylamide fungicides, but not with fungicides from other mode of action groups. Both resistant and sensitive strains survive in the absence of phenylamide fungicide use and their levels tend to equilibrate over time. Resistance management is critical to limit the proportion of resistant strains in a population.

Resistance management for phenylamide fungicides is most important for foliar diseases such as late blights and downy mildews for which multiple sprays are required. Management relies heavily on the use of premixes of phenylamides with protectant fungicides and limiting selection pressure (Table 7). The manufacturer of metalaxyl-M markets premixes with mancozeb, copper, and chlorothalonil for use against foliar pathogens. Selection pressure is reduced by limiting the number of sprays per crop and year. The marketing of pre-mixes of metalaxyl-M with non-related protectant fungicides ensures compliance with a resistance management strategy.

Conclusions

Fungicide resistance is one of several possible causes of poor disease control. Fungicide resistance not only threatens the usefulness of individual of fungicides, but also the farm economy because of potential yield losses from poor disease control. Unfortunately, registrations are being lost for older broad-spectrum fungicides that have a low resistance risk. Many of the newer replacement fungicides are more selective in the number and types of diseases controlled and have site-specific modes of action making them more prone to resistance problems. Maintaining an array of effective fungicides is critical. Resistance management strategies should be recommended by crop advisors and implemented by growers to prolong the active life of at-risk fungicides. Fungicide groups have different levels of resistance risk. Risk assessment is critical for newly developed fungicides. Mode of action group and resistance management strategies are now clearly included on the registration labels of most site-specific fungicides. However, it is difficult to predict the actual risk of resistance because of many interacting factors. Experience with resistance indicates that resistance problems are often manageable. Monitoring resistance levels in pathogen populations is essential for assessing risk and evaluating management practices. Unfortunately, there is no coordinated monitoring effort in place and growers will generally have to rely on proven methods of resistance management.

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