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OKLAHOMA COOPERATIVE EXTENSION SERVICE

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. 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 from light, irrigation, and rainfall. They also must be reapplied to protect new growth when disease threatens. This is particularly important in turfgrass following mowing which removes the treated grass.

Poor disease control with fungicides can result from several causes, including insufficient rate, inherently low fungicide effectiveness, improper timing or application method, and excessive rainfall. Resistance to fungicides is another cause of poor disease control, but it is more complex and difficult to identify. Understanding what resistance is, how it develops, and how it can be managed is crucial for insuring sustainable disease control with fungicides.

The problem of fungicide resistance became apparent following the registration and widespread use of the systemic fungicide benomyl (Benlate) in the early 1970's. Prior to the registration of benomyl, growers routinely applied protectant fungicides such as maneb and mancozeb (dithiocarbamates), or coppers to control diseases without experiencing resistance problems. A distinct advantage of benomyl was its systemic activity, which in addition to protecting plants from infection, also 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 within a few years where the fungicide was used intensively. Sudden control failures occurred with diseases such as powdery mildew, peanut leaf spot, apple scab, and dollar spot in turf.

Many of the fungicides developed and registered since the introduction of benomyl also have site-specific mode of actions and are at risk for resistance problems. While resistance risks with many of these fungicides may not be as great as with benomyl, strategies to manage the resistance risk should be developed and implemented to avoid unexpected control failures and sustain the usefulness of new products. The purpose of this fact sheet is to describe the resistance phenomenon, identify resistance risks in the different fungicide groups, and to provide guidelines for managing resistance.

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 reproductive structures), spores (small reproductive structures), or the nucleus of single cells capable of reproduction and dissemination. The resistance trait may result from single gene or multiple gene mutations. 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. Resistance often is caused by reduced fungicide uptake or detoxification by the altered fungus.

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% (EC_{50}) is then calculated for each sampled individual much in the same way an LD_{50} (50% 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 (Fig. 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 (Fig. 1A).

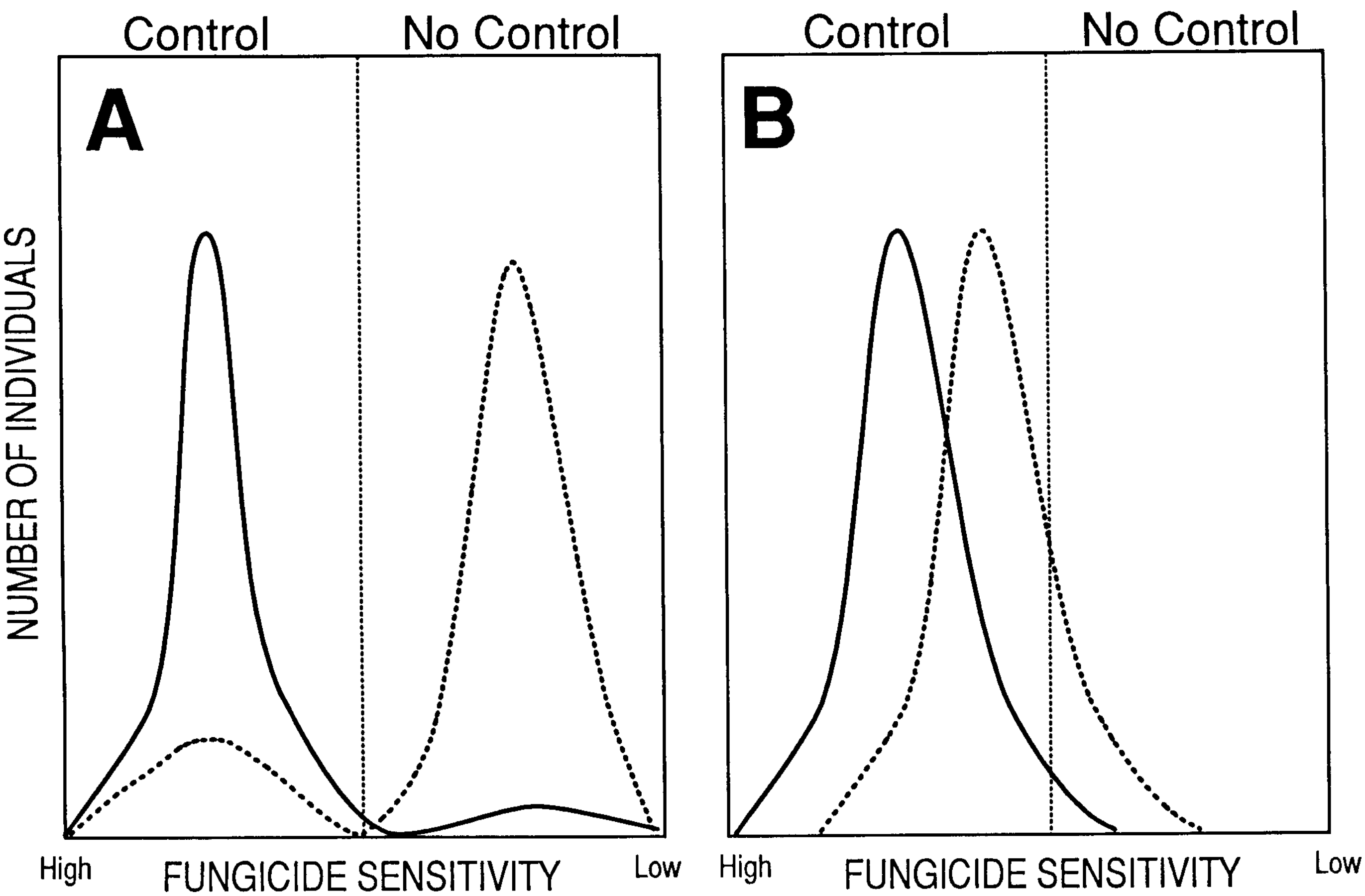

Figure 1. Depiction of the possible ways resistance develops in population of a fungal pathogen. A) Resistance development where an initially small, subpopulation of resistant strains is present before fungicide usage (solid line). Following selection pressure of fungicide use, the frequency of resistant individuals (broken line) becomes predominant and disease control is rapidly lost. B) Resistance development arising from mutations that lead 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). The shift may lead to a gradual loss of disease control.

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 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 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 genes may result in reduced fungicide activity between sprays, but the risk of sudden and complete loss of control is low. The gradual shift toward a low level of resistance where multiple genes are involved makes it difficult to clearly distinguish between sensitive and resistant sub-populations with field sampling.

Assessing Resistance Risk

Many factors affect 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 usually grouped by similarities in chemical structure and mode of action (Table 1). Site-specific fungicides disrupt single metabolic processes or structural sites of the target fungus. These include cell division, sterol synthesis, or nucleic acid synthesis. The activity of these fungicides may be reduced by single- or multiple-gene resistance. The benzimidazole and phenylamide groups are subject to single-gene resistance and carry a high risk of resistance problems. Other fungicide groups with site-specific modes of action include dicarboximides and sterol inhibitors (SI's), which are also known as demethylation inhibitors (DMI's). However, 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 activity. Systemic fungicides are taken up and distributed within plants. However, systemic activity is not a prerequisite for resistance problems. Resistance problems have developed in the dicarboximide group and with dodine, which have primarily protectant activities.

Multi-site fungicides interfere with many metabolic processes of the fungus and are usually protective in activity. 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 or absent.

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, resistant 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 15 years ago. Therefore, fungicides with resistance problems cannot be successfully reintroduced into areas where resistant strains are highly fit. More typically, resistant strains are less fit than wild-type sensitive strains. This has been true for SI 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 problem is at least partially reversible when the selection pressure of the fungicide is removed or minimized by using resistance management.

Fungicide Use Pattern

Intensive 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. The method and rate of application may also impact resistance development. Poor disease control resulting from inadequate spray coverage leads to a need for a more intensive spray program and the exposure of more individual in the fungus population 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 protective 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 often 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. Many soilborne pathogens produce fewer offspring per season than their foliar counterparts. Some soilborne diseases reproduce by forming seed-like 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 is favored by nitrogen deficiency while the severity of some foliar diseases of wheat are 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, 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.

Fungicide Resistance Management

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 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 1. Characteristics of fungicide groups and the relative risks for developing resistance problems.

Group	*Common name*	*Trade name*	*Action*[1]	*Uses*[2]	*Resistance risk*[3]	*Cross resistance*[4]
Aromatic hydrocarbons	chloroneb	Chloroneb	P	S,ST	low	yes
	dicloran	Botran	P	S,ST,PH	moderate	yes
	etridiazole	Terrazole, Koban	P	S	low	yes
	PCNB	Terraclor	P	S,ST	low	yes
Benzimidazoles	benomyl	Benlate	S	F,S,PH	high	yes
	thiabendazole	Arbortect, Mertect	S	F,S	high	yes
	thiophanate-methyl	Topsin M, Fungo 50	S	F,S,ST	high	yes
Carboximides	carboxin	Vitavax	S	ST	low	no
	flutolanil	Moncut, Prostar	S	S	low	no
Dicarboximides	iprodione	Rovral, Chipco 26019	P	F,S	moderate	yes
	vinclozalin	Ronilan, Vorlan	P	F,S	moderate	yes
Dithiocarbamates	maneb	Maneb	P	F	none	no
	mancozeb	Dithane, Fore	P	F,ST	none	no
	metiram	Polyram	P	F	none	no
Inorganics	copper hydroxide	Kocide	P	F	none	no
	copper sulfate	Basicop	P	F	none	no
	sulfur	Sulfur	P	F	none	no
Phenylamides	metalaxyl	Ridomil	S	F,S,ST	high	yes
	oxadixyl	Recoil	S	ST	low	yes
Sterol inhibitors	cyproconazole	Alto, Sentinel	S	F,S	moderate	yes
	difenconazole	Divedend	S	ST	low	yes
	fenarimol	Rubigan	S	F,S	moderate	yes
	fenbuconazole	Enable, Indar	S	F	moderate	yes
	imazalil	Nuzone	S	ST	low	yes
	myclobutanil	Eagle, Nova, Rally	S	F	moderate	yes
	propiconazole	Banner, Tilt	S	F,S	moderate	yes
	tebuconazole	Folicur, Lynx	S	F,S	moderate	yes
	triadimefon	Bayleton	S	F	moderate	yes
	triadimenol	Baytan	S	ST	low	yes
	triforine	Funginex	S	F	moderate	yes
Others	captan	Captan	P	F,ST	none	-
	chlorothalonil	Bravo, Daconil	P	F,S	none	-
	dodine	Syllit	P	F	moderate	-
	fentin hydroxide	Super Tin	P	F	low	-
	fosetyl-AL	Aliette	S	F,S	low	-
	propamocarb	Banol, Prevex	S	S,F,ST	low	-

[1] P=protectant, S=systemic.

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

[3] 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.

[4] Cross resistance is resistance to one or more of the fungicides within the same group.

(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 or blocks of sprays of the at-risk fungicide with an unrelated companion fungicide. The comparative merits of tank-mixing compared to alternating sprays has 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 much more effective when cultural practices are implemented to reduce disease pressure. The effectiveness of alternating blocks of sprays is probably less effective that the other use patterns unless an equal number of applications of the partner are made. 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 risk and for which resistance problems have arisen.

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

Benzimidazoles

Benzimidazoles (Table 1) are site-specific fungicides which interfere with cell division. Research has demonstrated that benzimidazole resistant strains are present at low frequencies in nature, even in the absence of fungicide exposure. Under selection pressure, resistance development proceeds rapidly (Fig. 1A). Resistant strains cannot be controlled by increasing the application rate or by shortening the spray interval. The resistant strains are fit and competitive in nature even without selection pressure. Therefore, a resistant population will remain resistant following substitution of a fungicide from another fungicide group. There is also strong evidence that cross-resistance exists within this fungicide group. Therefore, it is important not to substitute one benzimidazole fungicide for another.

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 these fungicides have remained effective with responsible use.

Dicarboximides

Dicarboximides (Table 1) inhibit the 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 (Fig. 1B). Dicarboximide resistant strains are less fit to survive than sensitive strains. Reducing the exposure of resistant strains to dicarboximide fungicides results in a decrease in the frequency of resistant strains and an overall shift

Table 3. Guidelines for reducing the risk of benzimidazole resistance.

1. Use all available cultural practices that reduce disease pressure.
2. Limit the seasonal number of benzimidazole applications.
3. Alternate or tank-mix benzimidazole applications with non-benzimidazole fungicide, preferably a protective fungicide with a low resistance risk.

of the population back toward sensitivity. Thus, it is possible to reintroduce dicarboximides into problem situations where resistance management has been implemented.

Resistance management strategies for dicarboximides are most important for foliar disease control programs such as for Botrytis diseases where multiple applications are required for control (Table 4). The goal is to limit selection time. Delay the first application as long as possible by using early-season applications of a protective fungicide. This allows dicarboximide deployment at a time when the population of resistant strains is potentially the lowest. The possibility of resistance problems is greatest where dicarboximides are used intensively and exclusively. The number of applications made to a particular field 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 fungicide group and replacing one dicarboximide with another where disease control is eroding is not advisable. 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.

Table 4. Guidelines for preventing and managing dicarboximide resistance in foliar disease control.

1. Use cultural practices that reduce the pathogen population.
2. Limit the number of dicarboximide applications made per season to control foliar diseases.
3. Use an effective non-dicarboximide fungicide early in the season.
4. Tank-mix or alternate dicarboximide applications with an effective non-dicarboximide fungicide having a low resistance risk.
5. Apply adequate rates as recommended on the label.
6. Use aromatic hydrocarbon fungicides cautiously where dicarboximide resistance is suspected to avoid cross-resistance problems.

Sterol Inhibitors (SI's)

SI's (Table 1) are site-specific fungicides that disrupt the synthesis of sterols. Sterols are compounds required for growth of many plant pathogenic fungi. Resistance development is similar to the dicarboximides. Typically, resistance develops slowly and is at first difficult to detect (Figure 1B). Resistant strains are thought to have reduced fitness; therefore, resistance management strategies may effectively shift the resistant populations back toward sensitivity. Because many of the newer fungicides being registered or developed are SI's, considerable attention has been paid to resistance monitoring. Baseline sensitivities (EC_{50} values) are being determined for some pathogens and crops where widespread SI usage is anticipated. Baseline sensitivities from untreated areas are used as a benchmark to detect the low-level resistance.

Resistance problems with SI's have resulted in a slow erosion in product performance, necessitating more frequent applications. Management strategies rely on the use of adequate rates and limiting exposure by tank-mixing or alternating SI applications with unrelated fungicides (Table 5). Using adequate application rates is important because mildly resistant strains can still be controlled. Avoid using SI fungicides alone all season long. Cross resistance is also a problem within this group so replacement of one SI with another is not practical. Despite the group's site specific mode of action, resistance problems have thus far been limited to powdery mildews and a few other diseases where intensive management is required. SI's should be used cautiously in these situations.

Phenylamides

Phenylamide fungicides (Table 1) are selective fungicides used to control the soilborne fungi *Pythium* and *Phytophthora* and the foliar fungi that cause late blight of potato and tomato and downy mildew diseases. Phenylamides inhibit fungal growth by disrupting RNA synthesis in these fungi. Resistance problems with phenylamides, specifically metalaxyl, were observed shortly after their introduction in situations where they were used exclusively and disease pressure was high. The origin of resistant strains and their build-up are not yet fully understood, but appears to develop rapidly from naturally occurring resistance (Fig. 1A). Unlike resistance to the benzimidazoles, resistant strains may be less fit to survive than sensitive strains because resistant populations have decreased following substitution of unrelated fungicides. Therefore, implementation of resistance management strategies may lead to a stabilized resistance situation and good fungicide performance.

Table 5. Guidelines for preventing and managing resistance to sterol inhibitor (SI) fungicides.

1. Utilize cultural practices to reduce the initial pathogen population and resistant varieties whenever possible.
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 SI fungicide per season. Extending the allowed amount of one SI fungicide with another will increase the risk of resistance development.
4. Keep the disease pressure low by using a preventive application schedule.
5. SI fungicides are not recommended for season-long use alone. Use alternate or alternating blocks of SI fungicides with non-SI fungicides, or use tank mixes of DMI fungicides with an effective protective fungicide having a low resistance risk.

Resistance management for phenylamide fungicides appears to be 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 6). The manufacturer of metalaxyl markets premixes with mancozeb and chlorothalonil for use against foliar pathogens. Selection pressure is reduced by limiting the number of sprays and extending the recommended spray interval. The marketing of pre-mixes for metalaxyl use ensures compliance with a resistance management strategy.

Table 6. Guidelines for preventing and managing resistance to phenylamide fungicides used for foliar disease control.

1. Reduce disease pressure through the use of good cultural practices.
2. Use tank or pre-packed mixtures of phenylamide with non-phenylamide fungicides.
3. Use a 3/4 to full rate of the tank-mix partner.
4. Limit the number of applications per season to 2-4 with a minimum spray interval of 14-days. Use non-phenylamide fungicides in between phenylamide sprays where shorter spray intervals are needed.
5. Use preventively and avoid curative or eradication applications.
6. Do not use soil applications for foliar disease control.

Conclusions

Fungicide resistance is one of several possible causes of poor disease control. Fungicide resistance not only threatens the usefulness of individual 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 thus 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. However, it is difficult to predict the actual risk of resistance because of many interacting factors. Experience with resistance indicates that most problems are 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. These include using cultural practices and spray schedules that help keep disease pressure low, rotating or tank mixing fungicides from different fungicide groups, and judicial use of at-risk fungicides.

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