University of Idaho
College of Agricultural and Life Sciences

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Managing Fungicide Resistance

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INTRODUCTION—
All Idaho crops are at risk

Resistance to fungicides in plant pathogen populations is one of the most significant problems in chemical disease management. Fungicide resistance may be defined as the stable, inheritable adjustment by a pathogen to a fungicide, resulting in reduced sensitivity of the pathogen to the fungicide.

The use of fungicides will continue to play a major role in disease management for the foreseeable future, so development of strategies to manage fungicide resistance is necessary to maintain a useful arsenal of the most effective fungicides. Such strategies are required if we are to prolong the useful life of these disease control agents.

Resistance to formerly effective fungicides has been reported from almost all crops where fungicides are used. All major crops in Idaho are at risk. Although this publication will focus on fungicide resistance management in sugarbeet and potato production, the principles are applicable to all crops.

The rate of resistance evolution in the fungi can be attributed to several factors that can act separately or together. The fastest response is expected when a highly effective systemic and persistent fungicide is applied sequentially on the major part of a crop area to control a pathogen that is efficiently dispersed with an effective sexual state and a high infection rate in a highly susceptible variety. The reassortment of genes where a fungus has a sexual stage facilitates combinations of fungicide resistance and survival fitness.

However, not all these factors are present in systems where resistance has developed. Resistance can occur in the absence of a sexual stage. For example, fungi with several asexual spore generations and infection cycles per year generally develop resistance more rapidly than those with one generation per year.

EDITOR'S NOTE

Most new fungicides used in sugarbeets and potatoes have single-site modes of action, making it likely for resistance in the pathogen to develop and the fungicide to become ineffective.

This publication addresses methods to manage the application of fungicides to prolong their useful lives. It specifically targets sugarbeet and potato crops that have the highest use of fungicides in Idaho, but the principles apply to all crops.

Intended audience is primarily growers, field workers, consultants, and chemical dealers. Other audiences are the public and legislators.

Late blight of potato caused by *Phytophthora infestans* shows severely diseased plants with no fungicide treatment compared with an effective fungicide treatment. It's not hard to guess which is which.

Sugarbeet powdery mildew

Although some plant diseases may be managed through altering cultural practices, many diseases are only managed acceptably with the application of a fungicide.

For example, cultural practices have little or no effect on sugarbeet powdery mildew. The one exception is that the disease is less severe with sprinkler irrigation than with furrow irrigation, but at least one fungicide application is still required in most cases to prevent economic loss.

Sensitivity to powdery mildew differs among sugarbeet cultivars, but resistance in current cultivars is not great enough to forego fungicide treatment. Therefore, the application of fungicides is, and likely will remain, the principle practice for managing this disease. The powdery mildews are among the pathogens with the greatest potential for fungicide resistance development.

Potato early and late blight

For other diseases, environmental factors such as favorable moisture conditions due to rainfall or excessive irrigation, favorable temperatures, and wind make major contributions to disease pressure.

These factors are especially important for foliar diseases such as potato early blight and late blight. While early blight can also be managed with proper plant fertility and is less severe with certain cultivars, fungicide applications are usually necessary to prevent early vine death and tuber infections.

Any cultural measures that slow down the development of an epidemic and reduce disease pressure will provide the additional benefit of delaying loss of effectiveness of valuable fungicides.

Sugarbeet example of fungicide resistance

A good example of the impact of fungicide resistance occurred only a few years back in the sugarbeet industry. Triadimefon (Bayleton) was extensively used in Idaho for powdery mildew control on sugarbeet beginning in 1982.

Rates as low as 2 to 4 oz/acre would give near season long control, but by 1987, increased rates were necessary to maintain control for only about three weeks. Reduced control was initially blamed on low application rates and poor fungicide coverage within the crop canopy, but the manufacturer withdrew the Bayleton label on annual crops because of developing fungicide resistance.

There were no alternatives other than sulfur for control when a severe powdery mildew epidemic hit in 2000.

Potato resistance examples

More recent resistance problems have been encountered with strobilurin and metalaxyl/mefenoxam chemistries in potatoes. Metalaxyl (Ridomil) was first introduced in the 1970s as an effective tool for controlling diseases caused by Oomycetes, such as late blight and pink rot of potato.

Metalaxyl could be applied after potato plants showed symptoms of late blight, and the disease could be almost completely arrested. The development of resistance to metalaxyl in the late blight pathogen population was rapid.

In many European countries, resistance was observed after a single year of metalaxyl use. Withdrawing metalaxyl use in some European countries resulted in an increase of pathogen isolates sensitive to metalaxyl.

However, this did not happen in the United States. Pathogen isolates resistant to metalaxyl increased in frequency, even in the absence of metalaxyl use. Mefenoxam, an enantiomer (molecular mirror image) of metalaxyl, was released in 1997 under the trade name Ridomil Gold.

Mefenoxam was more active than metalaxyl against Oomycete pathogens, and many anticipated that it would be effective against metalaxyl-resistant isolates of the late blight pathogen. Unfortunately, it was not. All isolates of the late blight pathogen collected in Idaho in 2001 were resistant to mefenoxam, even though it had not been previously used in any of the fields reported to have late blight.

DYNAMICS OF RESISTANCE

Resistance development is most likely the result of a genetic mutation that gives the pathogen the ability to counteract or circumvent the activity of the fungicide. Such mutations may not contribute to the pathogen's ability to survive under natural conditions, but allow the organism to survive when the selective pressure of the fungicide application is present.

It is believed that a small, stable portion of a pathogen population contains a mutation that confers resistance to a fungicide. With intensive and repeated use of a single fungicide, the sensitive portion of the population can be destroyed, leaving only the resistant portion of the population to survive, multiply, and become dominant (see Figure 1).

TYPES OF RESISTANCE

Worldwide, resistance in pathogen populations has been reported to more than 135 different active ingredients. However, failure of a fungicide application to control a particular disease is not necessarily due to fungicide resistance. Poor or poorly-timed application, use of expired product, or extremely heavy disease pressure can all be responsible for ineffective control.

The most effective fungicides are those with systemic or translaminar (ability to move from top to bottom of leaf) activity. Fungicides with this type of activity are somewhat mobile within the plant and can provide protection from the target pathogens even on portions of the plant surface that did not receive direct treatment. These are the fungicides, unfortunately, that have the highest risk of resistance development because they have very specific modes of action.

Qualitative—extremely rapid—resistance

Resistance to some fungicides may be seen as complete loss of disease control resulting from a modification of a single major gene in the pathogen. In this scenario, pathogens are either resistant or sensitive to the fungicide, but none are intermediate.

Increasing the rate or frequency of fungicide application does not change disease control in the resistant population. This type of resistance is referred to as "qualitative resistance."

Fungicides associated with qualitative resistance are often referred to as "single site" fungicides, because they interfere with a single metabolic pathway in the pathogen. In this case, only a single mutation in the pathogen population is needed for resistance to develop. The development of resistance to this type of fungicide can be extremely rapid. Metalaxyl resistance in the late blight pathogen cited earlier in this publication is an example of qualitative resistance.

Quantitative resistance develops over time

A continuous variation in sensitivity to a fungicide within a pathogen population is known as polygenic or "quantitative resistance." This resistance results from the modification of several genes in the pathogen population, and develops

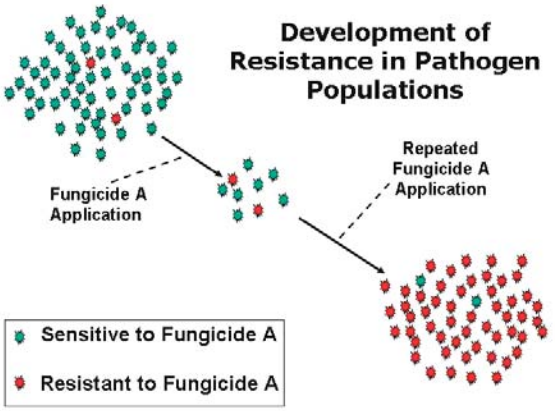


Figure 1. Illustration shows how resistance develops in a pathogen population.

This sugarbeet field did not have a fungicide applied. It shows how severe the disease can become without treatment. This field had nearly a 25 percent loss in yield due to powdery mildew.

somewhat gradually over time.

Increasing the fungicide application rate or the frequency of application improves fungicide performance, but continued use could eventually result in complete loss of control.

As resistance develops, the lack of control is often attributed to poor coverage, too low a rate, poor timing of application, or improper calibration. Fungicides of this type are often referred to as "multisite" fungicides because they interfere with multiple metabolic sites in the pathogen.

In this case, several mutations must occur simultaneously before resistance can develop. While some chemistries with multisite activity are considered at risk, there are several classes of multisite fungicides, such as the dithiocarbamate fungicides, that have been in continuous use since the 1940s with no cases of resistance having been reported to date.

FUNGICIDE GROUPS

Fungicides have been classified into groups according to their mode of action (Table 1) by a scientific working group called the Fungicide Resistance Action Committee (FRAC). The number of each group was assigned based on the relative time that each product was introduced for use. Fungicides from the same group have the same mode of action and should be treated as the same fungicide, even though the common name and formulation may be different.

Most effective = most at risk

The most effective fungicides for plant disease control that are also the most at risk for development of pathogen resistance are found in five of the major FRAC chemical groups or classes (Table 1): methyl benzimidazole carbamates (Group 1), dicarboxamides (Group 2), demethylation inhibitors (DMI, Group 3), phenylamides (Group 4), and Qo inhibitors (QoI, primarily strobilurins, Group 11).

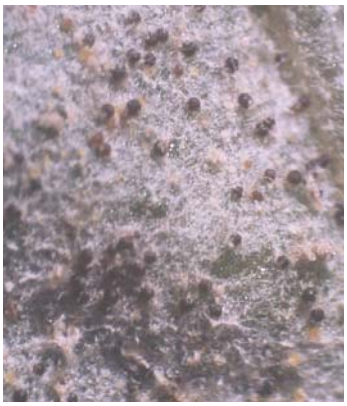
Fungicides that induce plant defenses, have multisite activ-

Table 1. Selected chemical groups, common fungicide names, and registered product names for fungicides used in Idaho.

FRAC Group Code	Group name	Common name	Product/trade name examples
1	Methyl Benzimidazole Carbamates	thiabendazole thiophanate-methyl	Mertect Tops, Topsin M
2	Dicarboxamides	iprodione vinclozolin	Rovral, Iprodione Ronilan
3	Demethylation inhibitors (DMI)	myclobutanil propiconazole triadimefon	Laredo Orbit, Propimax, Quilt, Stratego, Tilt Bayleton
4	Phenylamides	metalaxyl mefenoxam	Ridomil, Allegiance FL Apron XL, Dividend XL, Helix, Ridomil Gold EC, Ridomil Gold Bravo, Ultra Flourish
11	QoI (Quinone outside inhibitors)	azoxystrobin pyraclostrobin trifloxystrobin famoxadone fenamidone	Amistar, Heritage, Quadris, Quilt Cabrio, Headline, Pristine Flint, Gem, Stratego Tanos Reason
[1]M	M3 – dithiocarbamates	mancozeb maneb	Dithane, Manzate, Penncozeb, Maneb, Manex, Seed Treatment for Potatoes
[1]M	M5 – phthalonitriles	chlorothalonil	Bravo, Daconil, Echo, Equus

Table adapted from FRAC (Fungicide Resistance Action Committee) web site www.frac.info/frac/index.htm.

[1] M = Multisite contact activity. Generally considered a low-risk group for the development of fungicide resistance in pathogen populations, and cross resistance does not occur among different M groups.



Left: Photo shows sugarbeet powdery mildew in its early stages. A fungicide should be applied when the disease is first detected in the field at this stage. **Center: Closeup shows sexual stage** of sugarbeet powdery mildew. The sexual stage was first detected in Idaho in 2001—only the second time it was detected in the U.S. The implication of the sexual stage is that it allows for genetic recombination and the fungus to more rapidly develop a fungicide resistant population. **Right: Potato early blight,** another fungus with the ability to develop resistance to fungicides, is caused by *Alternaria solani*.

ity, or whose mode of action is unknown were assigned to letter categories (Groups P, M or U, respectively). Fungicides currently available or being considered for registration for sugarbeet powdery mildew control fall into the benzimidazoles, DMIs and QoIs. Fungicide labels will now indicate the class to which each fungicide belongs.

The benzimidazoles (Group 1) include Mertect, Tops and Topsin M (Table 1). Resistance to the benzimidazoles is of the qualitative type, and some of the most serious cases of fungicide resistance have occurred in this chemical group.

The problem started in the late 1960s with resistance in the powdery mildew pathogen on curcurbits (pumpkins, winter squash) reported in greenhouse plantings after only one year of use. Resistance to the benzimidazoles develops quickly, is stable, and sensitivity will usually not be restored by cessation of their use. Among the first cases of resistance in *Cercospora beticola* (causing Cercospora leaf spot) to the benzimidazoles was on sugarbeet in Greece in 1971.

Sugarbeet resistance in the mid-1980s

In the United States, resistance in Cercospora on sugarbeet developed in the Red River Valley in the mid-1980s after only three years of benzimidazole use.

After nearly 20 years of non-use in this production area, there is some evidence that there is limited Cercospora sensitivity returning to this group of fungicides in the southern Minnesota Beet Sugar Cooperative Factory District when used in combination with other fungicides.

Because of resistance, fungicides in this group are not effective if used alone.

1990s resistance in potato dry rot fungi

In the early 1990s, a similar problem occurred in the potato dry rot fungi, *Fusarium sambucinum* and *Fusarium coeruleum*, and with the silver scurf fungus, *Helminthosporium solani*.

Benzimidazole fungicides were used to manage dry rot both on cut seed (TBZ and Tops formulations) and on whole potatoes as they were placed into storage (Mertect). According to a survey of benzimidazole resistance performed by the University of Idaho from 1993 to 1995, nearly 85 percent of all *F. sambucinum* isolates examined were resistant.

As a result, the storage formulation of benzimidazole (Thiabendazole, Mertect 340F) is used by fewer and fewer growers and seed piece treatments such as thiophanate-methyl (Tops 2.5D) have now been combined with an EBDC fungicide (mancozeb) to produce the product known as Tops MZ.

Benzimidazole resistance in *H. solani* occurred during the same time period. As a result, options for managing silver scurf in potato storages are very limited.

QoI group—resistance develops rapidly

The strobilurins are the primary fungicides in the QoI group (Group 11, Table 1). Two fungicides that recently gained registration for powdery mildew control on sugarbeet are pyraclostrobin and trifloxystrobin, sold under the trade names of Headline and Gem. Both fall into this category.

Resistance in this category is qualitative, develops rapidly, and is stable once it develops. For example, in 1999, after only two years of commercial use, resistant strains of the powdery mildew pathogen were found in field and greenhouse crops of melon and cucumber in Japan, Taiwan, southern Spain, and southern France.

Resistance arose independently at isolated locations rather than as the result of spread of a single resistant strain originating from a single location. This resistance resulted from a single mutation substitution of one amino acid, and resistant isolates were competitive with wild-type sensitive isolates.

In potatoes, the strobilurin fungicide azoxystrobin (Quadris) was introduced with an emergency use permit in 1998. A survey of isolates of the early blight fungus (*Alternaria solani*) from North Dakota, Nebraska, and Wisconsin showed a 10-fold decrease in sensitivity to Quadris in 2002. Early blight control with Quadris in research plots at North Dakota State University and the University of Wisconsin was similar to disease control obtained using standard protectant fungicides, none of which were satisfactory in these trials.

Resistance to DMI inhibitors develops slowly

The demethylation inhibitors (DMI, Group 3, Table 1)

include triadimefon (Bayleton), myclobutanil (Laredo) and propiconazole (Orbit and others), and are examples of quantitative resistance. Resistance to the DMIs develops slowly, is relatively unstable, and sensitivity may be restored with non-use of this group. The use of DMIs in resistance management strategies is very valuable.

Low risk for resistance development

Of inestimable value to any fungicide resistance management strategy is the availability of effective fungicides that have a very low risk for resistance development.

Compounds such as the ethylenebis dithiocarbamates (M3 compounds, Table 1) and phthalonitriles (M5 compounds) have been in use for more than 50 years without a single case of resistance developing. Because of the widespread activity of these types of fungicides, there are limits on how many pounds of active ingredient can be applied on a given crop in any one year. In addition, they are not approved for management of disease in all crops.

In contrast, the single site types of fungicides tend to be more "silver bullet" in their activity and often target a narrow spectrum of fungi, having little or no effect on other organisms including non-pathogens and beneficials. They also tend to work very effectively even when applied at very low concentrations of active ingredient. The trade-off is that they are vulnerable to resistance development.

CROSS RESISTANCE AND MULTIPLE RESISTANCE

Cross resistance—resist one, resist all

The modes of action of the various fungicides within each of the FRAC code groups are very similar or the same.

Therefore, any pathogen population that is resistant to one fungicide within a group will almost certainly be resistant to other members of that same group—known as cross resistance. Thus most or all fungicides within the group will be less effective or useless against that pathogen population.

This limits the flexibility for managing resistance. An example of this was demonstrated recently for the silver scurf pathogen on potatoes in California. Isolates from a population of *H. solani* that had been frequently exposed to thiophanate-methyl, a thiophanate fungicide (Group 1), were found also to be resistant to benomyl (thiabendazole), a benzimidazole (also Group 1). Benomyl had never been used on potatoes in this area.

Multiple resistance—more than one chemical group

In contrast to cross resistance, pathogen populations have been shown to develop resistance to fungicides from more than one chemical group. This type of resistance is called multiple resistance.

The intensive use of at-risk fungicides without following resistance management principles can result in the development of multiple resistance. For example, curcurbit powdery mildew strains have been detected with resistance to as many as three groups of fungicides, including the QoIs, benzimidazoles and DMIs, after only two years of intensive use in Japan.

Cercospora beticola on sugarbeet in the Red River Valley has shown resistance to fungicides in at least two groups. Multiple resistance across groups coupled with cross resistance within groups creates the possibility for the loss of efficacy of a large number of fungicides.

Because of the ease of resistance developing to the benzimidazole and QoI fungicides, resistance in the same pathogen to these two classes of fungicides is highly possible with sugarbeet powdery mildew.

FUNGICIDE RESISTANCE MANAGEMENT PRINCIPLES

It is essential to use a management program to prevent or delay the buildup of resistant strains, since attempting to manage resistance after it has developed will likely be ineffective. Although not all of these principles are applicable to every system, most can be implemented generally.

Alternate fungicides. The most important of these principles is that at-risk fungicides should be alternated with fungicides with different modes of action (from different groups), and they should be combined or alternated with fungicides with low resistance risk (e.g. M group fungicides in Table 1).

Use manufactrer's full rate. Also, at-risk fungicides should be used at the manufacturer's recommended full rate and application interval. Use of full rates is expected to minimize selection of strains with intermediate sensitivity when resistance is polygenic (quantitative resistance).

Unfortunately, the use rate that companies select for registration of a new fungicide is often the lowest rate providing consistent control. Therefore, the lowest effective rate may allow strains with intermediate resistance to survive.

Use early in an epidemic. At-risk-fungicides should only be used when absolutely necessary. The most critical time to use at-risk fungicides for resistance management is early in the epidemic when the pathogen population is low.

The tactic of delaying application and using an at-risk fungicide as a curative (eradicant) is inconsistent with good

Sugarbeet plants with severe powdery mildew show some leaves almost totally covered with disease while others appear not as severe. Photo documents contrast between the two.

resistance management. Resistance can develop quickly when fungicides are used curatively because far greater numbers of the pathogen are available for selection and survival, and intermediate resistance can more easily be selected.

Understand mode of action. Understanding the mode of action of available fungicides is important. The risk of resistance developing and remaining stable for long periods is greatest with the qualitative resistance groups such as benzimidazoles (Group 1) and QoI's (Group 11).

For some fungicide/pathogen management situations, there may be only a limited number of options for tank mixing or alternation of fungicides, such as with powdery mildew of sugarbeet.

Because there has never been a case of resistance developing to sulfur, tank mixing sulfur with any at-risk fungicide as a standard practice will give good control of sugarbeet powdery mildew and can be very helpful in resistance prevention. The cost of adding sulfur as a tank mix is very small.

In potatoes, tank mixing QoI fungicides with broad spectrum protectants such as chlorothalonil (Group M5) or EBDC's (Group M3) will prolong the efficacy of QoI fungicides. In these situations, it is of utmost importance that resistance management guidelines be carefully followed.

PESTICIDES DISCLAIMER
ALWAYS read and follow the instructions printed on the pesticide label. The pesticide recommendations in this UI publication do not substitute for instructions on the label. Due to constantly changing pesticide laws and labels, some pesticides may have been cancelled or had certain uses prohibited. Use pesticides with care. Do not use a pesticide unless both the pest and the plant, animal, or other application site are specifically listed on the label. Store pesticides in their original containers and keep them out of the reach of children, pets, and livestock. Trade names are used to simplify the information; no endorsement or discrimination is intended.

SUMMARY

- Target pathogens are more likely to develop resistance against fungicides with specific modes of action (qualitative resistance). Failure to follow resistance management guidelines carefully will likely result in the loss of these new fungicides as effective control measures
- It is essential to use a management program to prevent or delay the buildup of fungicide resistant pathogen strains. Attempting to manage resistance after it has developed is far more difficult than prevention.
- At-risk fungicides should be mixed with a companion fungicide from a different class or, if available, with a multisite material such as an EBDC.
- Alternate applications should be made using fungicides with different modes of action.
- It is best to limit at-risk fungicides to just a few applications per year. The same fungicide, or fungicides with the same mode of action, should never be used consecutively. Examples: For sugarbeet powdery mildew, avoid using benzimidazoles and QoI's in the same growing season. In potatoes, if a QoI fungicide is used in furrow, do not use a QoI as the first foliar fungicide application.
- At-risk fungicides should be used early in the epidemic when the pathogen population is low. Curative (eradicant) treatments should be avoided because they select for intermediate resistance.
- At-risk fungicides should be used at the manufacturer's recommended full rate and application interval. Reduced rates will likely select for populations of intermediate resistance.
- Continuing the alternation practice into the following year may be advantageous.

FURTHER READING

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NOTES

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