General Guidelines for Managing Fungicide Resistance

Margaret Tuttle McGrath
Plant Pathology and Plant-Microbe Biology Section, SIPS, Cornell University
Long Island Horticultural Research and Extension Center
3059 Sound Avenue, Riverhead, NY 11901; mtm3@cornell.edu

Background Information and terminology. Fungicide resistance is a stable, heritable trait that imparts a reduction in sensitivity to a fungicide. This ability is obtained through evolutionary processes. The trait may be present in the pathogen population before the fungicide is used. Presence of fungicide resistant strains (biotypes) has been associated with control failure, therefore managing resistance is critical to disease control.

Fungicides with single-site mode of action (aka targeted) are generally at medium to high risk for resistance development. Single-site means the fungicide acts at a specific point in a biosynthetic pathway in the pathogen. These fungicides are at risk for resistance development because a change in the pathogen at this point can render the fungicide less effective or ineffective. A simple change of just one base pair in the DNA molecule can be sufficient to lead to full resistance (fungicide completely ineffective), as occurs with the strobilurin (FRAC code 11) fungicides. Most fungicides being developed today have a single-site mode of action because this is associated with lower potential for negative impact on the environment, including non-target organisms. Their targeted activity means that they can safely move into the plant (fungicide is not toxic to the plant), resulting in better rainfastness than contact fungicides and also better activity as they can move from where deposited on the upper leaf surface to the lower surface where pathogens often develop best. A few modern fungicides have systemic activity and can move more widely in plants, especially when applied to roots. Older fungicides, such as copper and chlorothalonil, have low potential for resistance to develop because they have multi-site mode of action.

When fungicide resistance results from modification of a single major gene, pathogen subpopulations are either sensitive or fully resistant to the pesticide. Resistance in this case is seen as complete loss of disease control that cannot be regained by using higher rates or more frequent fungicide applications. This type of resistance is commonly referred to as qualitative resistance. An example is resistance developed by several pathogens to the strobilurin (FRAC code 11) fungicides.

When fungicide resistance results from modification of several interacting genes, pathogen isolates exhibit a range in sensitivity to the fungicide depending on the number of gene changes. Variation in sensitivity within the population is continuous. Resistance in this case is seen as an erosion of disease control that can be regained by using higher rates, more frequent applications, or a fungicide in the chemical class that has inherently higher activity. Long-term selection for resistance in
the pathogen by repeated applications may eventually result in the highest labeled rates and/or shortest application intervals not being able to adequately control the disease. This type of fungicide resistance is commonly referred to as quantitative resistance. An example is resistance in the cucurbit powdery mildew pathogen to the DMI (FRAC code 3) fungicides. The pathogen is fully resistant to the first DMI fungicide, Bayleton (which is no longer registered for this use), but has continued to be sufficiently sensitive to this chemical class that DMI fungicides with inherently higher activity continue to be effective especially when used in a program with fungicides in other classes.

The term resistance sometimes is used to refer to any pathogen biotypes that are less sensitive to the fungicide than wild-type biotypes present before the fungicide was ever used. This may also be described as “shifts in sensitivity”. Practical resistance, field resistance, and often just resistance are used to refer to when failure of the fungicide to control a disease is associated with presence of resistant pathogen biotypes. Baseline sensitivity is the sensitivity of the pathogen to a fungicide (typically the first fungicide in a chemical class) determined with pathogen isolates collected before the fungicide is available for commercial use. Baseline sensitivity is a benchmark used to compare pathogen isolates obtained later, especially from fields where control achieved with the fungicide is below expectation. Laboratory resistance refers to resistance that develops under controlled selection, sometimes utilizing mutagenic compounds to promote mutations. It can provide indication of potential for resistance to develop, but sometimes the mutation that occurs is not the one(s) that occur through selection from fungicide use under field conditions.

Using fungicides, or other management practices, exerts selection pressure on the pathogen population to adapt and survive. Ability to adapt is greater with targeted fungicides (and also resistant varieties) than with multi-site fungicides and other practices. There might be just one resistant individual when the trait first appears in a pathogen population. Repeated use of the fungicide alone can rapidly shift the population to predominately resistant biotypes potentially during just one growing season with pathogens like those causing powdery mildews and downy mildews because they produce an abundance of asexually-produced spores and have short cycles (about 1 week from infection to spore production). Consequently while the first application provides excellent control, by the end of the season there may be failure.

Resistant biotypes can persist in the pathogen population when the fungicide is not used if the resistant trait does not have a fitness cost, which is often the case with fungicides. Selection can continue to occur unintentionally because the fungicide is used for other pathogens or is in a combination product.

Fungal isolates that are resistant to one fungicide are often also resistant to other closely-related fungicides, even when they have not been exposed to these other fungicides, because these fungicides all have similar mode of action. This is called cross
resistance. Sometimes fungicides in the same chemical class act at a slightly different point in the biosynthetic pathway in the pathogen which is sufficient that cross resistance does not occur. Rarely negative cross resistance occurs between unrelated fungicides because the genetic change that confers resistance to one fungicide makes the resistant isolate more sensitive to another fungicide. Correlated resistance is used to describe when a pathogen strain is resistant to chemically unrelated fungicides. This can occur when mutation for resistance occurs in a biotype already resistant to a different fungicide, or when the same mechanism of resistance functions with both fungicides, which can occur when the mechanism is reduced influx or rapid efflux of the fungicides (these are uncommon resistance mechanisms).

**Fungicide Group Codes** designating chemical groups were developed to facilitate managing resistance by the Fungicide Resistance Action Committee (FRAC). These codes are usually on the front of labels or in the resistance management section. Fungicides with the same Group Code have similar mode of action and therefore likely will exhibit cross resistance. Thus it is critically important for managing resistance to know the group code for the fungicides being used for a particular disease to avoid alternating among chemically similar fungicides. Presently there are 47 numbered FRAC Group Codes plus NC (not classified), 5 numbered with a ‘P’ (for host plant defense), 8 numbered with a ‘U’ (for unknown mode of action), and 11 numbered with an ‘M’ (for multi-site contact activity). A list of the codes for all fungicide active ingredients (e.g. common names) can be downloaded from www.frac.info. Select ‘publications’ in the list on the left of the page to get to where there is a pdf file with the current ‘FRAC Code List’. The resistance risk for each fungicide group is in the ‘comments’ column. It is a global list with fungicides not registered in the USA.

It is important to realize that resistance risk for a new fungicide can be difficult to predict. Risk cannot always be predicted solely from the mode of action. Additionally, resistance development in model systems with yeasts or non-obligate pathogens is not always similar to that in obligate pathogens. For example, the Qol fungicides were initially thought to have a low to medium resistance risk and resistance was predicted to be quantitative based on their mode of action (inhibition of respiration) and on results from research with yeast. However, resistance developed quickly and in a disruptive manner. Furthermore, it developed first in the USA in a pathogen not considered highly prone to developing resistance (gummy stem blight fungus) rather than in the cucurbit powdery mildew fungus.

**Managing fungicide resistance** is critically important to extend the period of time that an at-risk fungicide is effective, and these management practices can prevent control failure. The primary goal of resistance management is to delay its development rather than to manage resistant fungal strains after they have been detected. Therefore, resistance management programs need to be implemented when at-risk fungicides first become available for commercial use. The overall strategy to managing resistance is to minimize use of the at-risk fungicide without sacrificing disease control. This is
accomplished by using the at-risk fungicide with other fungicides and with non-chemical control measures, such as disease resistant varieties, in an integrated disease management program. It is critical to use an effective disease management program to delay the build-up of resistant strains. The larger the pathogen population exposed to an at-risk fungicide, the greater the chance a resistant strain will develop. When an integrated program is used to manage resistance and resistance develops to one of the fungicides, the other practices and fungicides used may provide enough control that the inefficacy of the one fungicide can be difficult to detect, especially in a commercial field.

**Specific Guidelines.** The first step in effectively managing fungicide resistance is to obtain information on current occurrence of resistance and on fungicide risk for the target disease as well as fungicides to be used. Just as some fungicides are more prone to resistance developing, some pathogens are more prone to developing resistance. Information about a fungicide’s risk can be found in the FRAC Code List (see paragraph on codes above). Fungi that cause powdery mildew diseases are the pathogens most prone to developing resistance. Cucurbit powdery mildew is a good example. The pathogen has developed resistance to almost every chemical class at risk for resistance following repeated use somewhere in the world. Other pathogens attacking vegetable crops grown in the Northeast that have developed resistance include those causing late blight of potato and tomato, downy mildew of cucurbits, early blight of potato and tomato, Phytophthora blight, and gummy stem blight of cucurbits. There is a Pathogen Risk List at the FRAC web site. Tables with resistance risk for specific combinations of fungicide and vegetable pathogen are posted at http://vegetablemdonline.ppath.cornell.edu/NewsArticles/NewsList.htm. While it is critical to use resistance management practices when the combination has high risk, it is prudent due to the challenge of predicting resistance to use these practices with most fungicides except those with multi-site contact activity. State guidelines on pest management contain information on known occurrence of pesticide resistance in the area.

Reduce the need for fungicides at-risk for resistance development by using disease-resistant varieties and other cultural management practices.

Start fungicide applications very early in disease development or before symptoms are seen. It is more difficult, often impossible, to control the pathogen in an established lesion, as opposed to a germinating spore, thus the potential is greater for resistance to develop.

Reduce the use of specific at-risk fungicides by using them only when needed most and by using other fungicides with different FRAC codes in alternation. The most critical time to start using at-risk fungicides for both disease control and resistance management is early in development of a disease that is expected to reduce yield if not managed. When the pathogen population is small, selection pressure is low because there are few individuals exposed to the selection force (fungicide in this situation). Alternating
among fungicides in the same chemical group (FRAC code) is not really an alternation because they share the same mode of action (there are rare exceptions when mode of action is slightly but sufficiently different among related fungicides that they do not exhibit cross resistance). It is not known whether a strict alternation (apply fungicide once and then switch, which is the usual recommendation) is better than a block alternation (apply twice in a row and then switch). With a block alternation there is selection pressure over a longer period; however, the dose remains high and the fungicide will control any pathogen biotypes present able to survive a low dose. With single applications the fungicide dose will more quickly decline to this low dose, which could be a concern if the fungicide used in alternation is not as effective.

At-risk fungicides should be used at the manufacturer’s recommended rate and application interval. Using highest label rates is expected to minimize selection of strains with intermediate fungicide sensitivity when resistance involves several genes (quantitative resistance).

When one crop could serve as a source of inoculum for a nearby crop planted later (wind-dispersed inoculum) or a successive crop (soil-borne inoculum), the alternation scheme among at-risk fungicides should be continued between successive crops such that the first at-risk fungicide applied to the second crop belongs to a different FRAC group than the last at-risk fungicide applied to the first crop.

Multi-site mode of action fungicides have low resistance risk and thus play an important role in resistance management for the single-site mode of action fungicides. Multi-site fungicides (those with a FRAC code that includes ‘M’) will control any resistant strains they contact. They are recommended used in a tank mix with single-site fungicides. Check the label: some single-site fungicides are formulated as premix products with multi-site fungicides to manage resistance (e.g. Gavel). Multi-site fungicides typically are not recommended used in alternation with single-site fungicides because they are not as effective as the single-site fungicides. Multi-site fungicides can be used alone before symptoms are detected when the pathogen is expected to be present soon to provide initial, preventive disease control. They should be used alone late in the growing season, where they have been shown to provide sufficient disease control to protect yield. Maximize spray coverage by adjusting application methods (nozzles, spray volume, pressure, ground speed) and spraying when calm. The better the coverage, especially on the underside of leaves, the greater the contribution of the multi-site fungicides to control and the lower the selection pressure for resistance development. Use water sensitive paper to assess coverage.

Follow any additional resistance management guidelines specified on the label. These will be in a section on resistance management and/or in the use directions for specific diseases. Remember that the label is a legal document. In addition to manufacturer restrictions pertaining to alternations and tank-mixtures, there are often limits on the total amount to be applied and the number of allowable applications per season.
Another important component of resistance management is assessing disease control and reporting any loss of efficacy potentially due to resistance to local extension specialists. Report promptly so that samples of the pest can be collected if testing is warranted. Also consider whether there are other possible causes for poor control such as poor timing (e.g. application missed when rain occurred).

**Useful websites with information about fungicide resistance:**

**Fungicide Resistance Management Guide for the Northeastern USA.** Covers pathogens affecting vegetable crops in the region.
http://vegetablemdonline.ppath.cornell.edu/NewsArticles/2015%20FRAC%20Guide%20for%20the%20Mid-Atlantic.pdf

**Fungicide Resistance Action Committee.** Resources at this site include the Pathogen Risk List, List of Resistant Plant Pathogens, bulletins on managing and assessing resistance, and FRAC Code List which includes mode of action and resistance risk of fungicides.
http://www.frac.info/

**Pesticide Environmental Stewardship.** Content includes fungicide resistance terms, mechanisms, management, etc. Sections on insecticides and herbicides as well.
http://pesticidestewardship.org/resistance/FungicideResistance/Pages/FungicideResistance.aspx

*Updated November 2015*