Fungicide Resistance: Threats and Management Approaches

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Ashutosh Bhaik, Mamadou Kane Mboup, and Jean-Luc Genet

Abstract

Fungal pathogens are responsible for significant reduction of crop yield globally when left untreated. The spread of fungal diseases can be controlled by crop management, rotation systems, the use of resistant cultivars, and the application of fungicides. Fungicides are often employed by farmers due to their simplicity and efficiency, thereby making it as an integral part of disease management strategies. However, resistance against these chemicals due to indiscriminate use leads to loss of efficacy. This loss of efficacy of a fungicide against a plant pathogen poses a serious problem, because of limited option of chemistries available for managing a particular set of pathogens. Also, discovery of new actives has become a key challenge due to the cost of development and stringent regulations over the past few decades. In this chapter, an attempt has been made to understand the approaches that are employed to delay or prevent the resistance development against fungicides in respect to potato crop.

Keywords

Resistance management · FRAC · Mode of action · Rotation · Fungicide mixture · Multisite fungicide · Resistance risk

A. Bhaik (✉) · M. K. Mboup · J.-L. Genet
Corteva Agriscience, Hyderabad, Telangana, India
e-mail: Ashutosh.Bhaik@corteva.com

S. Kumar Chakrabarti et al. (eds.), *Sustainable Management of Potato Pests and Diseases*, https://doi.org/10.1007/978-981-16-7695-6_3

3.1 Introduction

Ever since humans started practicing crop cultivation about 10,000 years ago, pests and diseases have been a constant threat for sustainable food supply. Fungicides are invariably being used to control plant diseases which still stand at 20% (Jørgensen et al. 2017). Historic records suggest sulfur compounds being used as early as 4500 years ago by Sumarians. Agriculture sector witnessed rapid use of pesticides after World War II with the advent of advanced chemistry. Many companies ventured into the business of pesticide manufacturing and synthesis during late twentieth century which helped farmers to produce sufficient food not only to themselves but for ever burgeoning human population.

The rapid advances in chemical disease control in agriculture lead to the following concerns:-

a) Chemical products are being phased out or restricted due to safety and environmental concerns.
b) Resistance is building up in target population due to repeated or indiscriminate use of same mode of action of chemicals.

The loss of a fungicide to agriculture through resistance is a problem that affects us all. It may lead to unexpected and costly crop losses to farmers causing local shortages and increased food prices. Manufacturers lose revenue vital to funding the enormous development costs of new products. Without reinvestment there would be no new compounds. This would cause serious disease management problems and endanger the world food supply.

3.2 History of Chemical Control and Resistance

Humans have battled plant diseases since ages by using different chemicals, with oldest report being the use of lime sulfur sprays (Forsyth 1802). Use of Bordeaux mixture by Millardet (1885) marked the beginning of use of copper compounds as fungicide for control of more dreaded diseases like grape downy mildew (*Plasmopara viticola*) and potato late blight (*Phytophthora infestans*). Later research led to the development of organic compounds especially dithiocarbamates (mancozeb), phthalimides (captafol), and chlorothalonil, which are now very widely used as non-systemic protectant fungicides. Owing to their multisite modes of action, these chemicals are still prevalent. Despite extensive use over many years, resistance has not been an issue with these fungicides.

Last few decades of twentieth century saw rapid development of new-generation fungicides which are site-specific, selective, and more systemic and had more potency against targeted pathogens. Following new set of criteria for fungicide development has been followed: (1) development of pesticides that are effective at an extremely low dosage, (2) development of pesticides that are readily degradable and less residual in the environment, and (3) development of selectively toxic

Table 3.1 Historic references of fungicide resistance in crop diseases (Adapted from Hewitt (1998) and Brent (2012))

Date	Fungicide class	Time to resistance (approx. yrs)	Disease example	References
1960	Aromatic hydrocarbons	20	Citrus storage rots, *Penicillium* spp.	Eckert (1982)
1964	Organomercury	40	Cereal leaf spot, *Pyrenophora* spp.	Noble et al. (1966)
1969	Dodine (guanidine)	10	Apple scab, *Venturia inaequalis*	Szkolnik and Gilpatrick (1969)
1970	Benzimidazoles (MBCs)	2	Many pathogens	Dekker (1986)
1971	2-Aminopyrimidines	2	Powdery mildews	Brent (1982)
1980	Phenylamides	2	Potato late blight, grape downy mildew	Staub (1994)
1982	Demethylation inhibitors (DMIs)	7	Cereal powdery mildew and other diseases	De Waard (1994)
1998	Quinone outside inhibitors (QoIs)	2	Cereal powdery mildew	Chin et al. (2001)
2007	Succinate dehydrogenase inhibitors	4–5	*Alternaria alternata* (nuts), early blight of potato (*Alternaria solani)*	Avenot and Michailides (2007) and Miles et al. (2014)

agrochemicals. Even with these development strategies, the risk of resistance to these chemistries has not come down rather the cost of product development has increased many times thereby limiting the number of new chemistries in the market. To date 50 different modes of action (FRAC 2021) are identified for fungicides.

During the first half of twentieth century, resistance against the fungicides was unknown. It was only during the 1960s when reports against performance failure started being reported from across the world. Usually, the first indications of a resistance problem came from reports from growers of failure of disease control following fungicide treatment.

During late 1980s and early 1990s, the concept of fungicide resistance was well documented and perceived by the farmers as well as the academia (Table 3.1). It was during the 1990s when Fungicide Resistance Action Committee (FRAC), an inter-company committee, was formed to manage the situation after the onset of phenylamide resistance. Phenylamide working group was established which soon after issued a set of guidelines for resistance management. The recommendations included using mixtures for foliar application, avoiding curative use, and limiting the number of sprays per season. These guidelines were implemented by all the companies involved, and this fungicide class continued in use against all target diseases (Staub 1994).

Nowadays, manufacturing companies as well as regulators are concerned about the resistance risk of new actives even before registration of the compound against a particular disease. For companies, it is about extending the product life cycle as the cost of development has increased many folds when compared to that was during last century. European regulations make it mandatory to conduct resistance risk assessment, and if appropriate, systems for risk management can be proposed, in the context of official registration of plant protection products. FRAC has also established fungicide resistance management practices, which serve as a guideline for the use and labeling of the new crop protection products. Even novel mode of action chemistries like group 49 has its own OSBPI working group which is accessing the resistance situations annually.

3.3 Resistance Defined

The loss of performance of a plant protection product because of the development of resistance in the target pest can be costly to the grower, the crop protection company, and the environment. The first reports from growers' field during the early 1960s–1970s were of failure of disease control following fungicide applications. Many other reasons than resistance could be attributed such as incorrect application (doze, time of application), use of expired or deteriorated or wrong products, wrongly identified pathogen, or application at the time of exceptionally heavy disease pressure, and at times growers and advisers attribute difficulties of disease control to fungicide resistance in the absence of evidence that resistance was the main cause. However, in many cases there was no other obvious explanation, and loss of control was soon shown to be associated with greatly decreased sensitivity of the pathogen, as revealed by laboratory or glasshouse tests on samples taken from the problem sites.

The term fungicide resistance, as used by the Fungicide Resistance Action Committee (FRAC), refers to an acquired, heritable reduction in sensitivity of a fungus to a specific anti-fungal agent (or fungicide). To manage resistance effectively, scientists study fungicide resistance on many different levels including the cellular, organismal, or population/field level. Reports of "resistance" from the field (i.e., where growers observed reduced efficacy of a product that has been effective against that particular pathogen) must be confirmed by studies at the organismal level showing a reduction in sensitivity of the fungal isolate(s) to the specific fungicide. Some scientists use the terms reduced sensitivity or tolerance when referring to smaller reductions in sensitivity which may have little or no impact on fungicide usage in the field and save the term "resistance" for large reductions in sensitivity of individual isolates which are likely to

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affect the efficacy of a specific fungicide under field conditions if the resistant isolates become widespread in the pathogen population. The term field resistance may also be used to indicate this loss of control under field conditions.

FRAC states that the term "resistance" should only be used in situations where:

- Development of resistance leads to failure of disease control under practical field conditions following proper labeled use of a fungicide.
- Demonstration that loss of control is due to the presence of pathogenic strain(s) with reduced fungicide sensitivity.

The development of fungicide resistance is a population evolutionary process. Fungi, like other organisms, are constantly changing. Occasionally, under certain conditions, these changes provide an advantage or disadvantage in terms of the progeny's ability to survive and reproduce. Advantageous changes allow the individual containing the change to survive and reproduce resulting in their progeny constituting a greater percentage of the population over subsequent generations. This can happen relatively rapidly in fungi as their *reproductive frequency* (i.e., the number of progenies produced from a single individual and the speed with which they complete their life cycle) is high. For example, a single *Phytophthora infestans* lesion can produce thousands of spores, and a spore can produce a new sporulating lesion in 3–5 days. The change may be evolutionarily neutral, or even slightly disadvantageous, under most conditions and only be advantageous when certain factors are present. This is the case with fungicide resistance. In most cases of fungicide resistance, the change leading to reduced sensitivity is evolutionarily neutral except when the specific fungicide is applied. The fungicide is exerting *selection pressure* on the pathogen population since it is killing the initial (or *wild type*) population but does not kill the changed (or *mutant*) population (Fig. 3.1). When changes are slightly disadvantageous under normal conditions (i.e., in the absence of the fungicide), the frequency of the changed population may decrease when the selection pressure is removed. This disadvantage is termed as *fitness penalty*.

Some Definitions

Qualitative resistance describes when fungicide resistance results from modification of a single major gene, and 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, e.g., is resistance developed by several pathogens to the strobilurin (FRAC code 11) fungicides.

Quantitative resistance describes when fungicide resistance results from modification of several interacting genes, and pathogen isolates exhibit a

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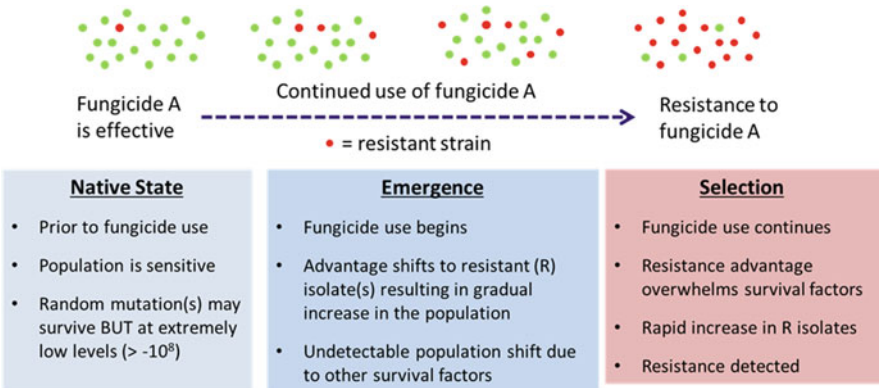

Fig. 3.1 Different stages of fungicide resistance when fungicide A is used repeatedly over several generations

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. An example is resistance in the cucurbit powdery mildew pathogen to the DMI (FRAC code 3) fungicides.

Cross resistance describes fungal isolates that are resistant to one fungicide and 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. Sometimes fungicides in the same chemical class act at a slightly different point in the biosynthetic pathway in the pathogen which sufficiently limits cross resistance.

Fungicides with **single-site mode of action** (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

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that they can safely move into the plant (fungicide is not toxic to the plant), resulting in better rain fastness than contact fungicides and better activity as they can move across 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**.

3.4 Mechanism of Resistance

Fungi have been described as "a mutable and treacherous tribe," but that even this is something of an understatement is abundantly evident.. .

E. W. Buxton, Heterokaryosis, Saltation and Adaptation (1960).

There are four main mechanisms by which fungi can become resistant to fungicides.

3.4.1 Alteration of the Target Site so that Sensitivity to the Fungicide Is Reduced

By far the most common way that fungi can become resistant to a specific fungicide is via a change at the target site. As fungi grow, their DNA is replicated when new cells are created. This process of replication is imperfect, and errors can occur. These errors are known as mutations. Since DNA is the code used to produce enzymes in the cell, some mutations result in changes to the amino acid sequence of the target site which in turn alters the shape of the lock/target site. The fungicide/key may not fit as well anymore or may not fit at all in the target site/lock. This results in a reduction in sensitivity that may range from small to very large.

3.4.2 Detoxification or Metabolism of the Fungicide

The fungal cell contains a vast array of metabolic machinery for normal cellular processes. This metabolic machinery may be able to modify the fungicide to a non-toxic form that is no longer harmful to the cell. Some fungicides are applied as inactive pro-fungicides which require further metabolism by the fungal cell to become the active form. If fungal metabolism is altered such that the activation step does not occur, the active form of the fungicide is not produced.

3.4.3 Overexpression of the Target

As discussed above, the fungicide is "competing" with the natural substrate for the target site. As more and more fungicide enter the cell, it out-competes the natural substrate for the target and as a result shuts down critical cellular processes. The production of additional target site enzyme (i.e., overexpression of the target) may increase the likelihood that enough of the fungal substrate will be able to bind with the target site enzyme such that cellular processes such as respiration can occur to some degree. Higher doses of the fungicide in in vitro experiments may restore the balance in favor of the fungicide, but higher doses may not always be practical under field conditions.

3.4.4 Exclusion or Expulsion from the Target Site

Efflux pumps exist naturally within the cell to exclude or expel foreign substances or to export endogenous substances. In fungi, the most common efflux pumps are ABC and MFS transporters. Despite these efflux pumps, most fungicides can reach effective concentrations inside the cell and inhibit cellular processes. Occasionally, these transporters are successful in expelling enough of the fungicide such that an isolate has reduced sensitivity. The fungicides expelled from the cell by a specific transporter may or may not be active at the same target site; i.e., there is not a direct relationship between the transporter that expels a specific fungicide and the target site of the fungicide. Multidrug resistance (MDR) develops when a specific transporter is able to exclude multiple fungicides from different target site groups. Application of the fungicides in question may exert enough selection pressure that isolates containing these fungicide-exporting transporters become more prevalent in the population as is the case in *Botrytis cinerea* (Kretschmer et al. 2009).

3.5 Evaluating Resistance Risk

Risk of resistance buildup and loss of efficacy to fungicide is of greater concern to all the new actives that are commercialized by crop protection companies. Resistance risk assessment therefore is a regulatory requirement in European Union. Risk is assessed by combining risk values for the fungicide, pathogen, and agronomic system under consideration, using a risk matrix (triangle) defined by Kuck and Russel (2006). The risk of resistance developing to a fungicide is driven by three components (Fig. 3.2). The first is the inherent pathogen risk. Pathogens are classified as high risk if they have a history of developing fungicide resistance, or if they would be expected to develop resistance rapidly, based on their biological characteristics. These are generally pathogens with short life cycles that have multiple generations in a single crop,and that produce spores in huge numbers. The second consideration is the risk associated with the mode of action (MoA) of the active ingredient. For example, multisite fungicides, which interfere with

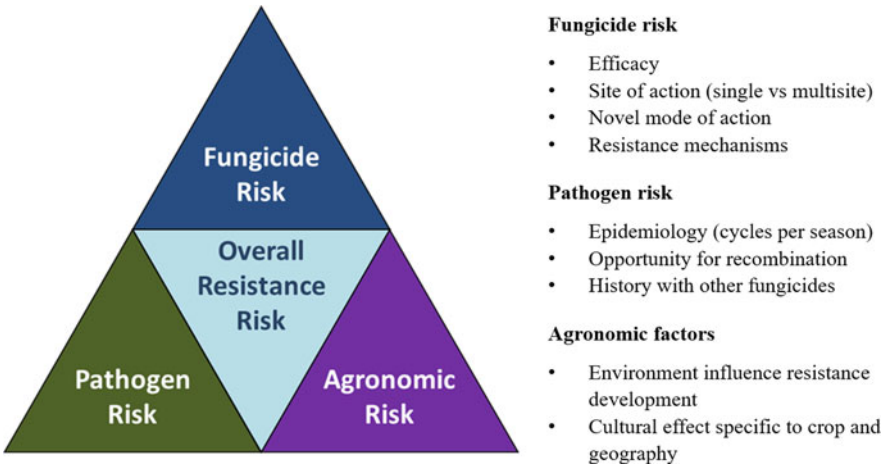

Fig. 3.2 Fungicide resistance risk triangle

multiple biochemical pathways, are considered as low risk, and resistance to these active ingredients is less likely to evolve. The final consideration is the agronomic risk, which encompasses the environment in which the fungicide is used, including farmer practices for managing disease.

The scheme has been refined lately by including numerical values for "fungicide risk" and "disease risk." These risk values are multiplied together to get the combined risk value. The resistance risk scheme was further refined by adding agronomic risk as the third factor in the matrix (Fig. 3.3). These ratings are based on the experience over the year of resistance development against the actives and published/shared data during the meetings. The agronomic risk is disproportionately high in many Asian countries. In tropical and subtropical climates, the warm and humid environment is conducive to pathogen development, and farmers may exacerbate this favorable environment through practices that allow the pathogen to survive continuously, such as planting the same crop in consecutive seasons, with limited crop rotation. Up-to-date assessments of fungicide-associated risk are presented on the FRAC website for all fungicides in current use.

3.6 Detecting and Monitoring Resistance

The first and most obvious detection of resistance is from the farmer field where he observes decline in fungicide performance, response for which is increasing dose rate and/or frequency applications of fungicides. Poor performance though can be attributed to several causes like poor application and timing, wrong dose rate, or very exceptional disease pressure. If resistance is a problem, it needs confirming trials of

Fungicide Risk	Risk	Combined Risk			Agronomic Risk
Benzimidazoles	High = 3	3	6	9	High = 1
Dicarboximides		1.5	3	4.5	Medium = 0.5
Phenylamides		0.75	1.5	2.25	Low = 0.25
Qol fungicides					
Carboxanilides	Medium = 2	2	4	6	High = 1
SBI fungicides		1	2	3	Medium = 0.5
Anilinopyrimidines		0.5	1	2.25	Low = 0.25
Phenylpyrroles					
Multi-site fungicide	Low = 1	0.5	1	1.5	High = 1
MBI-R inhibitors		0.25	0.5	0.75	Medium = 0.5
SAR inducers		0.125	0.25	0.3	Low = 0.25
		Low = 1	Medium = 2	High = 3	Pathogen Risk
		Seed borne and soil borne pathogens, Rust fungi	Eyespot, Rhynchos-porium, Septoria	Blumeria, Botrytis, Plasmopara, Magoporthe, Venturia	

Fig. 3.3 A "risk matrix" fungicide resistance risk assessment scheme (from Kuck and Russell 2006)

more than just a single season's work. So anecdotal evidence from growers must be backed up by a program of field work supported by glasshouse and laboratory assays.

3.6.1 Bioassays

Designed to reveal difference in phenotypical response to pesticide molecule. Live pest colonies, lines, populations, or isolates of interest is exposed to pesticide and then compared to those of sensitive references. A most common approach to confirm resistance is by comparing sensitivity of isolates obtained from sites where performance has eroded with the sensitivity of isolates never exposed to the at-risk fungicide. Ideally the existence of a sensitivity distribution of the target fungal population established prior to widespread use of a new fungicide will allow a meaningful confirmation of resistance. The benefit of a "baseline" sensitivity distribution in various aspects of resistance management was described in detail by Russell (2005), and its importance is recognized in many countries where a baseline sensitivity distribution is a requirement for registration of a new fungicide. The ability to confirm resistance through comparison with a baseline sensitivity will depend on the sample size from the suspected resistant population and inclusion of at least one reference isolate to check for variation between assay tests. In practice where baseline sensitivity data do not exist, comparisons can be made between isolates obtained from at-risk sites with those collected from untreated areas. Often

researchers obtain baseline data using "historic" isolates which have been maintained in culture collections, sometimes for many years, and which were isolated before the at-risk fungicide was used.

3.6.2 Molecular Assays

Molecular, nucleic acid-based assays detecting genes or mutations involved in resistance. The starting material can be living or dead population. Sufficient DNA or RNA of suitable quality should be extracted for further analysis. Literature is full of different molecular techniques used to monitor resistance, and certainly the most well documented is perhaps detection of the mutation generating the G143A amino acid change in the target b-type cytochrome of complex III of respiration, causing resistance to QoI fungicides.

3.6.3 Biochemical Assays

As most of the pesticides bind to and inactivate a vital protein (enzyme) which is responsible for some essential biochemical reaction in the pathogen, the efficiency is dependent on the pesticide reaching the binding site. Biochemical assays are usually used to situation where the mechanism of resistance has been elucidated.

3.7 Fungicide Resistance Management Approaches

Fungicide resistance management strategies aim to delay the evolution and spread of resistance in a sensitive pathogen population, while ensuring effective disease control. If fungicide resistance is confirmed or highly suspected, diverse approaches to managing resistance need to be incorporated into disease management strategies.

3.7.1 Managing the Application Dose

- FRAC recommends to strictly follow the country label for the crop-disease for effectively managing the disease and prevent the resistance development.
- The majority of the evidence suggests that an increased dose of fungicide increases selection for fungicide resistance (but note here that the primary aim of effective disease control may make it impossible to reduce fungicide dosages).
- A number of possible mechanisms by which an increased dose may reduce selection have, however, not been studied. Partial resistance and multi-gene/multi-mutation cases are the key examples of this.

3.7.2 Managing the Number of Sprays

- All current evidence suggests that increasing the number of fungicide applications increases selection for fungicide resistance.
- Most evidence suggests that splitting fungicide dosage between two or more applications increases selection.

3.7.3 The Use of Fungicide Mixtures

- The vast majority of the evidence shows that adding a mixing partner effective on the target diseases to a high resistance- risk fungicide reduces selection for fungicide resistance, even when the dose of the high-risk fungicide stays the same in the mixture.
- Adding a mixing component to a high-risk fungicide and reducing the dose of the high-risk fungicide further reduces selection for fungicide resistance.
- There is too little evidence on the use of mixtures of two at-risk fungicides, and work in this area is needed. The evidence that does exist suggest that mixing two at-risk fungicides is a valid anti-resistance strategy.

3.7.4 The Use of Fungicide Alternations

- Limited evidence suggests that alternating with a fungicide that has a different mode of action does not alter selection for the high-risk fungicide, if the number of applications of the high-risk fungicide remains constant with and without alternation.
- The evidence suggests that replacing part of the fungicide program with a fungicide with a different MOA reduces selection.

3.7.5 Alternations Versus Mixtures

- It depends on the balance between increased selection due to dose splitting and decreased selection due to mixing whether mixing reduces selection to a greater or lesser extent than alternation. The experimental and modeling evidence shows that in many cases, mixing is the better strategy, but for any single case, this needs to be established before conclusions can be reached.

3.7.6 Protective Versus Curative Use

- There is no evidence that protective or curative use consistently results in a lower rate of selection for fungicide resistance (but note that protective fungicide applications may be needed for effective disease control).

- The existing evidence suggests that the specific circumstances will determine whether a shift in spray timing will increase or decrease selection for fungicide resistance.

Resistance management should be based on evidence interpreted within a sound experimental, theoretical, and practical framework. In discussions on resistance management, it is often not explicit what the evidence is. With this chapter, we hope to contribute to evidence-based resistance management (Adopted from van den Bosch et al. 2015).

3.8 Fungicide Resentence Action Committee (FRAC)

Industry recognizes its responsibility in safeguarding new chemistries that are brought to market. Through FRAC and its Working Groups, companies are striving to establish more effective communications to alert all those involved in the research, production, marketing, registration, and use of fungicides to the problems of resistance.

With enlightened stakeholders, effective strategies can be conceived and adopted. Cooperative action is essential if we are to preserve the option of chemical disease control for our crops.

FRAC is a Specialist Technical Group of CropLife International (CLI; Formerly Global Crop Protection Federation, GCPF). As such, we work within the legal framework defined by CLI and take care to ensure that strict anti-trust guidelines are observed. In few regions Fungicide Resistance Action Group (FRAG) a are mixed groups with industry and non-industry members is also functional.

3.8.1 Purpose

The purpose of FRAC is to provide fungicide resistance management guidelines to prolong the effectiveness of "at-risk" fungicides and to limit crop losses should resistance occur.

The main aims of FRAC are to as follows:

1. Identify existing and potential fungicide resistance problems.
2. Collate information and distribute it to those involved with fungicide research, distribution, registration, and use.
3. Provide guidelines and advice on the use of fungicides to reduce the risk of resistance developing and to manage it should it occur.
4. Recommend procedures for use in fungicide resistance studies.
5. Stimulate open links and collaborations with universities, government agencies, advisors, extension workers, distributors, and farmers.

3.8.2 FRAC Guidelines

FRAC Guidelines for resistance management are produced by the individual FRAC Working Groups and Expert Fora. These Guidelines provide information on how to use specific areas of fungicide chemistry for control of plant diseases on various crops while maintaining a good anti-resistance strategy.

The Guidelines should be regarded as the minimum resistance management strategy required, and it is possible that a more stringent strategy should be used in individual cases. FRAC recommends that you seek advice from your local resistance management organization (e.g., local country FRAC or FRAG), your local crop advisor or extension agent, or the manufacturer or distributor of the product to see if a more restrictive strategy is recommended.

The FRAC Guidelines deal only with areas of fungicide chemistry. FRAC is not allowed to make recommendations for the use of individual products. If you require advice on which active ingredients to use in your disease control program, please consult your local crop advisor or extension agent, or the distributor or manufacturer of potential products.

3.9 FRAC Guidelines: Potato Diseases

FRAC guidelines with respect to use of different fungicides in potato crops and resistance management are outlined in this section. Table 3.2 enlists common fungicide groups with their mode of action and FRAC classification.

3.9.1 Oxysterol Binding Protein Homologue Inhibitor (OSBPI) Fungicides (FRAC Code 49) (Updated April 2021)

- Fungicide programs must deliver effective disease management. Apply OSBPIs at effective rates and intervals according to manufacturers' recommendations. Effective disease management throughout the season is a critical component to delay the build-up and spread of resistant pathogen populations.
- Apply OSBPIs only preventatively and in mixtures with effective fungicides from different cross-resistance groups.
- The mixture partner should give effective control of the target disease(s) at the rate and interval selected.
- Foliar exposure to OSBPI products should not exceed thirty-three percent (33%) of the total period of protection needed per crop.
- Fungicide programs must deliver effective disease management. Apply OSBPIs at effective rates and intervals according to manufacturers' recommendations. Effective disease management throughout the season is a critical component to delay the build-up and spread of resistant pathogen populations.
- Apply OSBPIs only preventatively and in mixtures with effective fungicides from different cross-resistance groups.

Table 3.2 Classification of fungicides used in potato crops based on mode of action groups, target site, and risk of resistance

FRAC code	Target site and code	Group name	Chemical group	Common name	Comments
49	F9 lipid homeostasis and transfer/storage	OSBPI oxysterol binding protein homologue inhibition	Piperidinyl thiazole isoxazolines	Oxathiapiprolin fluoxapiprolin	Resistance risk assumed to be medium to high (single site inhibitor). Resistance management required
11	C3 complex III: Cytochrome bc1 (ubiquinol oxidase) at Qo site (cyt b gene)	Complex III; cytochrome bc1 (ubiquinol oxidase) at Qo site (cyt b gene)	Methoxy-acrylates	Azoxystrobin coumoxystrobin enoxastrobin flufenoxystrobin picoxystrobin pyraoxystrobin	Resistance known in various fungal species. Target site mutations in cyt b gene (G143A, F129L) and additional mechanisms cross resistance shown between all members of the QoI group. High risk. (see FRAC QoI guidelines for resistance management)
			Methoxy-acetamide	Mandestrobin	
			Methoxy-carbamates	Pyraclostrobinpyrametostrobintriclopyricarb	
			Oximino-acetates	Kresoxim-methyl	
			Oximino-acetamides	Dimoxystrobinfenaminostrobin metominostrobin	
			Oxazolidine-dones	Famoxadone	
			Dihydro-dioxazines	Fluoxastrobin	
			Imidazolinones	Fenamidone	
			Benzyl-carbamates	Pyribencarb	

(continued)

Table 3.2 (continued)

FRAC code	Target site and code	Group name	Chemical group	Common name	Comments
40	H5 cellulose synthase	CAA-fungicides (carboxylic acid amides)	Cinnamic acid amides	Dimethomorphflumorph	Cross resistance between all members of the CAA group. Low to medium risk. See FRAC CAA guidelines for resistance management
			Valinamide carbamates	Benthiavalicarbiprovalicarb	
			Mandelic acid amides	Mandipropamid	
4	RNA polymerase I	PA-fungicides (Phenylamides)	Acyl- alanines	Benalaxyl benalaxyl-M (=kiralaxyl) furalaxyl metalaxyl metalaxyl-M (=mefenoxam)	Resistance and cross-resistance well known in various oomycetes but mechanism unknown. High risk. (see FRAC Phenylamide guidelines for resistance management)
		Oxazolidinones	Oxadixyl		
		Butyrolactones	Ofurac		
21	C4 complex III: Cytochrome bc1 (ubiquinone reductase) at qi site	QiI - fungicides (Quinone inside inhibitors)	Cyano-imidazole	Cyazofamid	Resistance risk unknown but assumed to be medium to high (mutations at target site known in model organisms). Resistance management required. No spectrum overlaps with the oomycete-fungicides cyazofamid and amisulbrom
			Sulfamoyl-triazole	Amisulbrom	

29	C5 uncouplers of oxidative phosphorylation		2,6-dinitro-anilines	Fluazinam	Low risk
27	Unknown	Cyanoacetamide-oxime	Cyanoacetamide-oxime	Cymoxanil	Resistance claims described. Low to medium risk. Resistance management required
45	C8 complex III: Cytochrome bc1 (ubiquinone reductase) at Qo site, stigmatellin binding sub-site	QoSI fungicides (Quinone outside inhibitor, stigmatellin binding type)	Triazolo-pyrimidylamine	Ametoctradin	Not cross resistant to QoI fungicides. Resistance risk assumed to be medium to high (single site inhibitor). Resistance management required

Adapted from FRAC (2021).

- The mixture partner should give effective control of the target disease(s) at the rate and interval selected.
- Foliar exposure to OSBPI products should not exceed thirty-three percent (33%) of the total period of protection needed per crop.
- In case of non-cucurbit multiple crops, do not make more than six (6) foliar applications of OSBPI product per year on the same acreage or greenhouse, targeting the same pathogen.

3.9.2 QoI Fungicides (FRAC Code 11) (Updated June 2020)

Fundamental principles that must be adhered to when applying resistance management strategies for QoI fungicides is that:

- The QoI fungicides (azoxystrobin, coumoxystrobin, dimoxystrobin, enoxastrobin, famoxadone, fenamidone, fenaminostrobin, fluoxastrobin, flufenoxystrobin, kresoxim-methyl, mandestrobin, metominostrobin, orysastrobin, pyraoxystrobin picoxystrobin, pyraclostrobin, pyrametastrobin, pyribencarb, triclopyricarb trifloxystrobin) are in the same cross-resistance group, FRAC Code 11.
- The QoI fungicide in subgroup A (metyltetraprole), Code 11A fungicide, is not cross resistant with Code 11 fungicides on the pathogens with G143A mutation.
- Fungicide programs must deliver effective disease management. Apply QoI fungicide-based products at effective rates and intervals according to manufacturers' recommendations. Effective disease management is a critical component to delay the build-up of resistant pathogen populations.
- The number of applications of QoI fungicide-based products within a total disease management program must be limited whether applied solo or in mixtures with other fungicides. This limitation is inclusive to all QoI fungicides. Limitation of QoI fungicides within a spray program provides time and space when the pathogen population is not influenced by QoI fungicide selection pressure.
- Limitation of the total number of QoI applications is detailed in the specific crop recommendations. In consideration of the cross-resistance profile of subgroups 11 and 11A, the maximum allowed number of QoI-containing sprays is increased by one, where both QoI fungicides (code 11) and QoI fungicides in subgroup A (code 11A) are included in a spray program in a given cropping season. All crop-specific recommendations will be regularly reviewed based on sensitivity monitoring.
- A consequence of limitation of QoI fungicide-based products is the need to alternate them with effective fungicides from different cross-resistance groups (refer to the specific crop recommendations).
- QoI fungicides, containing only the solo product, should be used in single or block applications in alternation with fungicides from a different cross-resistance group. Specific recommendation on size of blocks is given for specific crops.

- QoI fungicides, applied as tank mix or as a co-formulated mixture with an effective mixture partner, should be used in single or block applications in alternation with fungicides from a different cross-resistance group. Specific recommendations on size of blocks are given for specific crops.
- Mixture partners for QoI fungicides should be chosen carefully to contribute to effective control of the targeted pathogen(s). The mixture partner must have a different mode of action, and in addition it may increase spectrum of activity or provide needed curative activity. Use of mixtures containing only QoI fungicides (including two-way mixtures of code 11 fungicide and code 11A fungicide) must not be considered as an anti-resistance measure.
- Where local regulations do not allow mixtures, then strict alternations with non-cross resistant fungicides (no block applications) are necessary.
- An effective partner for a QoI fungicide is one that provides satisfactory disease control when used alone on the target disease.
- QoI fungicides are very effective at preventing spore germination and should therefore be used at the early stages of disease development (preventive treatment).

3.9.3 Late Blight (Phytophthora Infestans)

- Apply QoI fungicides according to manufacturer's recommendations for the target disease (or complex) at the specific crop growth stage indicated. Effective disease management is a critical parameter in delaying the build-up of resistant pathogen populations.
- Where QoI fungicide products are applied alone do not exceed 1 spray out of 3 with a maximum of 3 sprays per crop. Do not use more than 2 consecutive applications.
- Where QoI fungicide products are applied in mixtures (co-formulations or tank mixes) do not exceed 50% of the total number of sprays or a maximum of 6 QoI fungicide applications whichever is the lower. Do not use more than 3 consecutive QoI fungicide containing sprays.

3.9.4 Early Blight (Alternaria Solani, Alternaria Alternata)

- Where QoI fungicide products are applied solo do not exceed 33% of the total number of sprays or a maximum of 4. Where mixtures (co-formulations or tank mixes) are used do not exceed 50% of the total number of sprays or a maximum of 6 QoI fungicide applications, whichever is the lower.
- Where resistance has been confirmed, QoI fungicides must be applied only in mixture with partners contributing to the effective control of the target pathogens.

3.9.5 CAA Fungicides (FRAC Code 40) (Updated April 2020)

- Apply CAA fungicides preferably in a preventive manner.
- Alternation with fungicides having other modes of action is recommended in spray programs.
- No resistant isolates from field populations have been found since the introduction of CAA fungicides in 1993.
- Phytophthora infestans is classified by FRAC as a medium risk pathogen. Long-term experience with CAA fungicides demonstrates that the resistance risk of Phytophthora infestans to this fungicide group is low to moderate. For effective resistance management, a precautionary strategy has to be implemented.
- Apply a maximum of 50% of the total number of intended applications for late blight control.
- For more detailed product recommendations, refer to the use guidelines published by the respective CAA manufacturers.

3.9.6 Phenylamide Fungicides (FRAC Code 4) (Updated March 2020)

- The phenylamides should be used on a preventive and not curative or eradicative basis.
- For foliar applications, the phenylamides should be used in a pre-packed mixture containing an unrelated effective partner and used in a sound management program. Where residual partners are used, it is recommended to use between three quarters and full recommended rates. The phenylamide dosage in the mixture depends on its intrinsic activity and is defined by the respective company.
- The number of phenylamide applications should be limited (two to four applications per crop and year, with a maximum of two consecutive applications). The application intervals should not exceed 14 days and may be shorter in cases of high disease pressure. If rates and application intervals are reduced, the total amount of the phenylamide fungicide used per season should not exceed that of the full rate, and the total exposure time should remain the same. The rate of the mixing partners should remain the same for both intervals.
- Phenylamide sprays are recommended early season or during the period of active vegetative growth of the crop. The farmer should switch to non-phenylamide products not later than the normal standard application interval of the non-phenylamide product.

3.9.7 QiI Fungicides (FRAC Code 21) (Updated February 2021)

- Apply QiI fungicides preferably in a preventive manner.
- Apply a maximum of 50% of the total number of intended applications for late blight control during one crop cycle.

- Alternation with fungicides having other modes of action are recommended in spray programs.
- Apply QiI fungicides according to manufacturers' instructions.

3.9.8 Fluzinam Fungicides (FRAC Code 29) (Updated June 2020)

- Apply fluazinam preventatively.
- Maximum of six applications.
- In regions with reported resistance, it is recommended to limit the number of fluazinam applications to max. 50% of all applications, and use mixtures with fungicides belonging to other modes of action that provide satisfactory efficacy against Phytophthora infestans.
- No more than three sequential applications of fluazinam. In regions with resistance or reduced sensitivity, apply a maximum of two sequential applications if product is used solo.
- Refer to manufacturer's recommendations for rates and intervals.

3.9.9 Cymoxanil Fungicides (FRAC Code 27) (Updated February 2021)

- Use always in mixture with another fungicide active on the target diseases.
- Apply preventatively.
- The number of applications of cymoxanil-containing products should be restricted: Potato and Tomato: 6.
- Always follow product specific label recommendations for resistance management.

3.9.10 Ametoctradin Fungicides (FRAC Code 45) (Updated June 2021)

- Apply ametoctradin containing products in a preventative manner.
- Always follow product-specific recommendations for resistance management.

3.10 Importance of Multisite Fungicides in Managing Pathogen Resistance

One of the key recommendations of FRAC is to make use of multisite fungicides (FRAC Group M) in spray programs, especially in crops with multiple sprays such as fruits and vegetables, or certain arable crops. Due to their mode of action, multisite fungicides are considered as a low resistance risk group. Therefore, they offer the possibility for use as mixing partners or alternating with single site and

other medium- to high resistance-risk fungicides. Over the past decades, no cases of field resistance against multisite have been reported. There are clear benefits to recommending multi-site fungicides in spray programs:

- Multisite fungicides display a low risk to develop resistance and are effective mixing/alternating partners for medium- to high-risk fungicides.
- Beyond protecting and prolonging the lifespan of highly effective medium- to high resistance-risk fungicides, multisite fungicides provide added levels and spectrum of disease control. With this they can also support the single sites to be even more efficient.
- Multisite fungicides are considered a valuable tool to manage resistance by preventing or delaying its development to many pathogens in many crops.
- In some crops, multisites play an increasing role in spray programs to sustain effective disease control and resistance management, e.g., for *Zymoseptoria tritici* in wheat, *Ramularia collo-cygni* in barley, and *Phakopsora pachyrhizi* in soybeans.

Restricting the use of multisite fungicides from use in important crops could result in faster development of resistance to single site mode of action fungicides. This in turn could lead to epidemic disease development, serious crop losses, and finally the loss of highly effective fungicides for a sustainable disease management.

3.11 Conclusion and Future Outlook

To sustain ever burgeoning human population and with eminent climate change risk of invasive or lesser-known pathogens, disease management practices will play a key role in coming few decades for maintain sustainable food supply. Disease control chemicals (fungicides) will be the effective and sure shot tool in the arsenal for integrated disease management practices for minimizing crop losses. With recent advancements in advanced digital tools and predictive tools, the applications will be much more precisely targeted in a field at disease spots/patches thereby reducing the environmental loading of the active making it more sustainable. Even with newer modes of action, safer chemistries are being discovered; resistance management program still plays a pivotal role for enhancing the product life cycle. Generating baselines before launching actives, having monitoring program, and regularly reviewing the resistance management strategies will continue to play key role. The advent of new technologies and real-time detections will help organizations like FRAC not only to communicate and manage things faster but the collaboration among the stakeholders be it private corporates or public sector researchers by sharing of the data or publications will be faster and will surely help the farmers and the end consumers.

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