Chapter 5
Evidence-Based Resistance Management: A Review of Existing Evidence

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Abstract The control of fungal plant pathogens has been characterised by repeated cycles of introduction of new fungicides and for many of them a subsequent loss of efficacy due to the emergence and selection of resistant pathogen strains. Several strategies have been proposed to prevent, or at least delay, resistance problems. Such resistance management strategies should be based on evidence interpreted within a sound experimental and theoretical framework. Industry and regulatory decisions about fungicide resistance management often cannot wait for the accumulation of new evidence, so decisions should be taken by weighing the existing evidence. In discussions on resistance management, it is often not explicit what the evidence is. In this chapter, we review experimental and modelling evidence on (1) the choice of application dose, (2) the number of applications, (3) the use of fungicide mixtures, (4) the use of fungicide alternation and (5) protectant versus curative fungicide application. At several places in the text, we stress that resistance management should not compromise effective disease control.

Keywords Evidence • Resistance management • Fungicides • Mixture • Alternation • Dose • Spray timing • Protective • Curative

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5.1 Introduction

The use of fungicides as crop protection agents is characterised by a cycle of introduction of a fungicide mode of action followed, in many cases, by the build-up of pathogen strains that are resistant or less sensitive to the fungicide and growers eventually abandoning use of the fungicide because it no longer provides effective disease control. Resistance management methods have been suggested ranging from (1) the management of application dose, (2) the management of the number of sprays, (3) the use of fungicide mixtures, (4) the use of fungicide alternation and (5) the avoidance of curative use of fungicides.

The choice of fungicide resistance management methods should be based on evidence. Ideally, the evidence should be used to develop a framework within which each resistance management method can be assessed for its ability to reduce the selection for resistance posed by the fungicide. The authors of this chapter have developed such a framework and have, in a series of reviews, shown that the framework makes predictions that are consistently in close agreement with published evidence (van den Bosch and Gilligan 2008; van den Bosch et al. 2011, 2014a, b).

In this chapter, we summarise the findings in the reviews. We will structure the chapter around the key resistance management methods listed above. For definitions of any unfamiliar words used in this chapter, we refer to the Chap. 4. We will use the "governing principle" discussed in that chapter, so we suggest reading that section first. Instead of repeating the extensive reference lists from the reviews, we refer the reader to these reviews for details on the references in several places.

Important Note Resistance management is only one of the aspects to be considered when developing a fungicide application programme. Fungicides are used to control plant disease, so any resistance management strategy of practical relevance needs to provide effective disease control. It is easy to find ineffective fungicide programmes that minimise selection, but such programmes are of no practical use.

5.2 Practical Use of the Existing Evidence

In advocating evidence-based resistance management, the authors recognise that commercial and regulatory decisions about product development and registration cannot wait for the accumulation of all the evidence that might be desirable. Decisions need to be made on basis of the existing evidence. The review of existing evidence presented in this chapter does, however, lead to a set of conclusions (see Sect. 5.9) that is well underpinned by the existing evidence. These conclusions are underpinned by experimental as well as modelling research on a wide range of very contrasting modes of action and patho-systems. The upshot of this is that these conclusions can thus be used to underpin the development of resistance management plans.

This issue is most acute where a new mode of action fungicide is being introduced, and the manufacturer, regulatory authorities and advisory bodies have to

decide on appropriate resistance management strategies. At that point, there is no history of the resistance behaviour, usually no resistant isolates available from the field to help judge how resistance might evolve and no evidence of the effectiveness of different strategies for that specific mode of action. The only relevant guidance at this point thus is the set of conclusions derived from a review of existing evidence and the knowledge gained by the company during the development of the fungicide. For example, we find overwhelming evidence that adding a mixing partner reduces selection for fungicide resistance. Given a new MOA about which nothing is known, the only sensible assumption thus is that for this MOA, mixing will be a useful resistance management strategy. The same holds for the other conclusions on resistance management.

We thus advocate that the set of conclusions reached in this chapter provides the strongest available basis for decisions on resistance management of new modes of action. The strategies can then be refined by specific information on the new mode of action, as it becomes available – for example, from laboratory mutation studies, from specific modelling of resistance evolution based on the known efficacy of the new compounds and their potential mixture partners and then from experience of resistance development on the first patho-systems on which the new mode of action is used.

5.3 Managing the Application Dose

In discussions on fungicide resistance, claims are sometimes made that it is important to use the maximum dose permitted on the product label (labelled dose), in order to prevent, or at least slow down, the development of resistance. The evidence about the effect of dose on selection for fungicide resistance, however, tells a different story.

Van den Bosch et al. (2011, 2014a, b) summarise the available evidence on the effect of dose. Of the experiments on 19 pathogen-fungicide combinations, published in 15 papers, 16 show that an increased dose increases selection for fungicide resistance, and only two show a decreased selection for resistance. In eight of the eight published modelling studies, it was found that an increasing dose increases selection for resistance. How can this be?

Before answering this question, we need to stress that reducing the dose of a fungicide may compromise effective disease control. We are thus not advocating here that dosages should be reduced without careful consideration of the circumstances. But where dose can be reduced appropriately (Paveley et al. 2001), it should be considered as a resistance management option.

The idea that using the maximum permitted dose is a good anti-resistance measure may have originated from insecticide resistance. Consider a diploid sexually reproducing insect and the effect of an insecticide on mortality of the homozygous SS, heterozygous SR and homozygous RR genotypes (S is the sensitive allele and R the resistant allele, Fig. 5.1), where we discuss here a case where the heterozy-

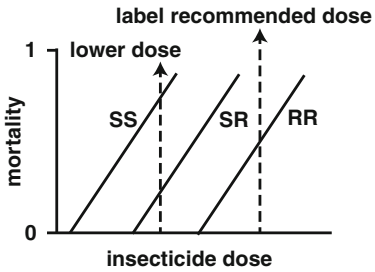

Fig. 5.1 An illustration of the mortality rate of an insect species as a function of the dose of the insecticide applied. The line marked SS is the dose response curve of homozygous sensitive individuals, the line marked SR is the curve for heterozygotes and the line marked RR is the curve for homozygous resistant individual

gous is intermediately sensitive to the fungicide. Applying the maximum permitted dose will cause high mortality of the heterozygous individuals.

When the resistance frequency is small, almost all resistance alleles will be present in heterozygous individuals, because virtually all individuals carrying one or more resistance alleles (SR and RR) will mate with a homozygous sensitive individual, SS. This results in heterozygous individuals and homozygous sensitive individuals. The maximum permitted dose may then delay (or prevent) the development and increase of homozygous resistant, RR, individuals by a high kill rate of the heterozygotes.

In contrast to insects, most of the economically important fungal plant pathogens are haploid when fungicide sprays are applied; many functionally diploid fungi reproduce in a purely clonal manner. The use of the maximum permitted dose tactic can then not be expected to work as it does in diploid sexual species, and the published evidence clearly shows that to be the case.

The available evidence suggesting that, in most cases, a lower dose decreases the selection for resistance may not however tell the whole story. We have determined four hypothetical mechanisms that may lead to the contrary case of a lower dose increasing the rate of resistance selection (see van den Bosch et al. 2011, 2014a, b for more details). These are however hypothetical possibilities, and none of these have yet been proven to operate in reality.

The most likely cases where a reduced dose increases selection for resistance, or where the effect of dose on selection might be broadly neutral, involve partial resistance and/or the involvement of several genes, or mutations within a gene, each with a small effect on the level of resistance. Space restrictions prevent us from discussing this subject in more detail here, and we refer to the papers by van den Bosch et al. (2011, 2014a, b) for more details.

Note: The maximum permitted dose is proposed by the manufacturer and approved by the regulator, taking into account the disease control efficacy, exposure and toxicology to nontarget organisms. The reasoning above about the effect of dose on resistance selection is however not dependent on the permitted dose that is set, because the logic concerns relative, rather than absolute dosages.

5.4 Managing the Number of Applications

There are two cases to consider when discussing the number of applications: firstly, simply increasing or reducing the number of applications, whilst keeping the dose constant and, secondly, splitting dose, for example, by halving the dose of the spray but applying the fungicide twice as often.

Reducing the number of applications is expected to reduce the selection for fungicide resistance because the pathogen is exposed to the selective pressure over a shorter period. The existing evidence, both experimental and modelling, supports this expectation although the number of studies is small. Six publications study the effect of changing the number of applications on selection, and all find that increasing number of applications increases selection. Two modelling studies come to the same conclusion. See van den Bosch et al. (2014a) for references.

Van den Bosch et al. (2014a) show, from the selection coefficient and exposure time governing principle (see the Chap. 4), that splitting dose is expected to increase selection for resistance, because the increase in exposure time outweighs the effect of decreasing dose. There are 11 pathogen-fungicide combinations studied and published (see van den Bosch et al. 2014a for references). Of these, ten cases show increased selection for split dose applications. Only one case shows a reduced selection for resistance with split dose applications. The two existing modelling studies also find that splitting application dose increases the rate of selection for fungicide resistance.

5.5 The Use of Fungicide Mixtures

There is a long standing debate about the usefulness of fungicide mixtures as a resistance management strategy. The evidence accumulated over the last two decades has made it possible to answer some of the unanswered questions about mixtures (van den Bosch et al. 2014a, b).

5.5.1 Adding a Mixing Partner to an At-Risk Fungicide (Not Reducing the Dose of the At-Risk Fungicide)

One of the key discussions on the use of mixtures has been whether adding a mixing partner to an at-risk fungicide and not reducing the dose of the at-risk fungicide has any effect on the rate of selection for resistance. Some authors suggest that ‘mixing only reduces the build-up of pesticide resistance by reducing the required dose of the pesticides that are mixed’ (Birch and Shaw 1997). Others suggested that adding a mixing component without lowering the dose of the at-risk fungicide is a valid resistance management method (FRAC 2010).

When resistance is developing against a fungicide A and we add a mixing partner B with a different mode of action, the mixing partner affects both the pathogen strains which are sensitive and the strains which are resistant to the fungicide A. Hence, the population growth rates of the sensitive and the resistant strains are reduced to the same extent by the mixing partner. The governing principle (see the Chap. 4) then tells us that we can expect the selection for resistance to A to decrease. This prediction has been tested against published evidence.

We have found a total of 51 pathogen-fungicide mixing partner combinations tested. In 44 of these combinations, the mixture treatment programme showed a lower rate of selection for fungicide resistance. This holds for multi-site and single-site mixing partners. Only in two cases was greater selection measured. These cases could subsequently be related to cross-resistance to the fungicides (van den Bosch et al. 2014b for further detail). Of the nine modelling studies, seven show that mixing without reducing the dose of the at-risk fungicide decreases selection. In the two remaining studies, other parameters, such as spray coverage and fitness costs, play a role.

A detailed modelling study by Hobbelen et al. (2011a) shows that the effective life of an at-risk fungicide (defined as the time between introduction of the fungicide and the moment the fungicide can no longer provide effective disease control due to the build-up of resistance) is increased by adding a fungicide with a different mode of action to an at-risk fungicide. The model was parameterised to represent the use of QoI fungicides against infections of wheat with *Zemoseptoria tritici* (formerly known as *Mycosphaerella graminicola*) using a multi-site acting, chlorothalonil-type mixing partner. With a full dose of the mixing partner, the effective life of the QoI fungicide was doubled (see Table 1 in the Chap. 4).

5.5.2 Adding a Mixing Partner as well as Reducing the Dose of the At-Risk Fungicide

All current evidence suggests that adding a mixing partner to an at-risk fungicide and lowering the dose of the at-risk fungicide is a valid resistance management tactic. Of the 13 papers with, in total, 20 pathogen-fungicide combinations tested, 15 cases show a reduced selection for resistance of the at-risk fungicide when used as a mixture. The modelling study by Hobbelen et al. (2011) shows that the effective life of an at-risk fungicide is increased by adding a mixing partner and reducing the dose of the at-risk fungicide.

5.5.3 What to Mix with?

Companies need to select an appropriate partner fungicide for the mixture. Analysing the existing evidence from both experimental and modelling studies (van den Bosch et al. 2014b), we have found two pieces of clear-cut evidence:

1. Both the existing experimental evidence (Bolton and Smith 1988; English and van Halsema 1954; Genet et al. 2006; Lalancette et al. 1987) and the modelling evidence (Hobbelen et al. 2011b) show that the larger the dose of the mixing partner, the smaller the selection for fungicide resistance and the longer the effective life of at-risk fungicide (see Table 1 in the Chap. 4).
2. A mixing partner fungicide with a lower efficacy will give a smaller reduction in selection rate. Considering two possible mixing partners, to which no resistance has (yet) developed, the best choice would thus be to use the fungicide with the highest efficacy. The existing evidence also implies that a fungicide to which resistance has developed to high levels is not an appropriate mixing partner.

In practice, fungicide manufacturers may be constrained to use their own active substances in the choice of mixing partners, rather than optimal combinations, due to commercial considerations. But agreements to access active substances from other manufacturers may enable a stronger choice in some cases.

5.5.4 Mixing Two At-Risk Fungicides

The number of multi-site fungicides is limited, and environmental policy may reduce their number further. This leads to the development of fungicides mixtures where two at-risk fungicides are mixed, to both of which resistance can develop. Such mixtures present two opposing forces:

1. By mixing with fungicide B, as we have seen before, the selection for resistance to fungicide A is reduced and vice versa.
2. But adding an at-risk mixing partner creates a selection pressure for resistance against that mixing partner.

The question thus is whether the gain, in terms of slowing down selection, from adding an at-risk fungicide to the spray programme outweighs the loss of putting an additional fungicide at risk of resistance.

There is very little evidence available to come to a general conclusion on this matter. Only three papers have been published comparing the selection for resistance to two fungicides of a mixture (Brent et al. 1989; Lorenz et al. 1992; Thygesen et al. 2009). All these show that the rate of development of resistance is slowed down for both fungicides in the mixture. Hobbelen et al. (2013) developed a model parameterised for *Zemoseptoria tritici* and two fungicides to which high levels of resistance develop. Key conclusions from this modelling study were that mixing two at-risk fungicides always gave an equal or higher effective fungicide life compared to either concurrent (i.e. applying the two modes of action solo to different fields within the same seasons) or sequential use (i.e. using one mode of action for several seasons until it became ineffective and then using the other mode of action) of the solo products.

Milgroom and Fry (1988) were the first to show that the initial frequency of resistance has a major effect on the success of resistance management strategies. Van den Bosch et al. (2014a) cite various modelling studies corroborating that

strategies (including the use of mixtures) are substantially more effective if implemented at the moment a new mode of action is introduced. Waiting until resistance has emerged and is detected in field populations and then putting a resistance management programme in place is unlikely to be effective, unless the resistance is of a slow-shifting type. We are not the first to make this important point, yet discussions about resistance management often start at the moment resistance is found in field.

5.6 The Use of Fungicide Alternation

Alternation is frequently considered as a resistance management tactic. However, there are two different types of alternation that are not always clearly separated in discussions on resistance management:

1. Given a spray programme with fungicide A, we *add* sprays with fungicide B with a different mode of action, between the sprays with A (Fig. 5.2).
2. Given a spray programme with applications of fungicide A, we *replace* part of the applications with sprays with fungicide B (Fig. 5.2).

In the case that an application with fungicide B is added in between applications of A, it is important to recognise that selection for resistance to A will only take place when fungicide A is present. In the figure, we made the decay rate of fungicide A fast enough so that the effect of A has vanished when B is applied. In such cases, fungicide B has no effect on the selection for resistance to fungicide A simply because fungicide A is not operating when B is present. This leads us to predict that

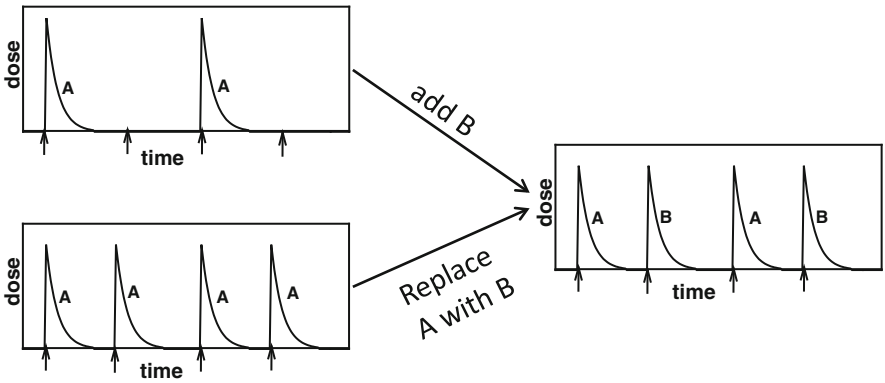

Fig. 5.2 Two different ways to alternate: (1) *add* an application with fungicide *B* in between two applications of fungicide *A* and (2) *replace* applications with fungicide *A* by applications with fungicide *B*. For each panel, time is on the *x*-axis. The time points where fungicide treatments may be applied are marked with arrows pointing to the *x*-axis in all the panels. Dose is plotted on the *y*-axis. For ease of representation, the fungicide dose decays rapidly, so that the time windows in which the fungicide is active do not overlap. There are two fungicides of differing modes of action that can be used in the treatment programme: fungicide *A* and fungicide *B*

adding B has no effect on selection. This prediction is supported by the existing evidence, although the evidence is limited. Of the five pathogen-fungicide combinations that have been tested experimentally (see van den Bosch et al. 2014a for the references), four show no change in selection when B is added to the application programme. In one case, a larger selection for resistance is measured when B is applied, which can be explained by the cross-resistance to the specific fungicides involved (van den Bosch et al. 2014a).

In the case where applications with fungicide A are replaced by applications with B, Fig. 5.2, we expect the selection for resistance to be reduced because the fungal population is exposed to selection pressure for resistance to A only half the time. There are 15 pathogen-fungicide combination cases published (see van den Bosch et al. 2014a for the references) that study this situation. In 12 cases, a reduced selection for resistance was measured when using the alternation; in three cases, no difference was measured.

5.7 Mixture Versus Alternation

Are mixtures better resistance management tactics than alternations? Several authors have studied this question resulting in different answers. To understand the key issues, let's consider a mixture and an alternation using equal amounts of the two fungicides A, an at-risk fungicide to which resistance is developing, and fungicide B with a different mode of action to which no resistance is developing. The alternation consists of an application with fungicide A at dose D_A (which can be a full dose or anything lower than a full dose) followed by an application with fungicide B at dose D_B (again at or below a full dose). To transform this alternation into a mixture, we split the dose of both fungicide A and fungicide B and mix the half doses of A and B and apply this mixture at each spray event. See Fig. 5.3 for an illustration. Which of these two treatment plans selects the least for resistance to fungicide A?

There are two opposing forces:

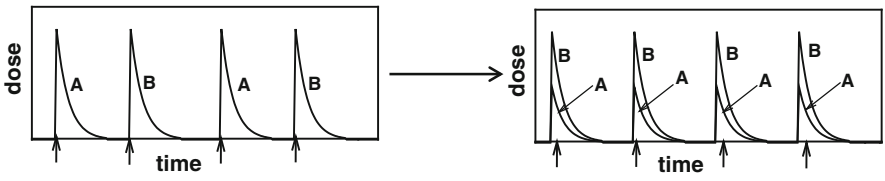

Fig. 5.3 Alternations versus mixtures. For each panel, time is on the *x*-axis. The time points where fungicide treatments may be applied are marked with *arrows* pointing to the *x*-axis in all the panels. Dose is plotted on the *y*-axis. For ease of representation, the fungicide dose decays rapidly, so that the time windows in which the fungicide is active do not overlap. There are two fungicides of differing modes of action that can be used in the treatment programme: fungicide A and fungicide B

1. The dose of at-risk fungicide A is split into two half doses. As discussed, splitting a dose increases the selection for resistance.
2. The half dose of A is mixed with fungicide B. Mixing decreases selection, as discussed previously.

It is thus a question of the balance between the increased selection due to dose splitting and the decreased selection due to mixing that determines whether alternation is a more effective resistance management strategy than mixing or vice versa. This reasoning results in the prediction that whether mixtures or alternations are most effective in reducing selection depends on the particular characteristics of the pathogen-fungicide combination being considered. This finding is reflected in the published evidence. There are eight publications (see van den Bosch et al. 2014a for the references) studying 12 pathogen-fungicide mixing partner combinations. Of these, six show a smaller selection for resistance in the mixture treatment than in the alternation treatment. In two cases, alternation has a smaller selection for resistance than mixtures. In the remaining four cases, no difference was measured between the two tactics.

The modelling evidence (see van den Bosch et al. 2014a, b for the references) leans towards mixtures being the tactic that reduces selection the most. Four papers show this, at least when spray coverage is incomplete, which is always the case in practice. The remaining one study gives a mixed picture with particular circumstances affecting which one is the best anti-resistance tactic.

From a practical perspective, the limited number of spray applications to cereal crops constrains the extent to which alternation can be implemented. In contrast, the multiple-spray programmes applied to control potato late blight (*Phytophthora infestans*), and the wide range of modes of action available, offer many possible options for alternation, mixtures or combinations of the two approaches. These options have not been adequately explored.

5.8 Protective Versus Curative Use

The strict definition of protective use of a fungicide refers to an application timed prior to infection, so that infections are prevented. Curative use refers to the fungicide affecting the pathogen, by increasing the duration of the latent period, constraining lesion size or reducing spore production by an application after infection has occurred. Most resistance management guidance, such as from the Fungicide Resistance Action Committee, advises to use fungicides as protective and avoid curative use because curative use would promote selection for resistant/insensitive strains.

Surprisingly, there is no evidence on the effects of protectant and curative use of fungicides on selection for fungicide resistance. Milgroom and Fry (1988) commented on the absence of studies on protective and curative use. Twenty years later,

Brent and Hollomon (2007) reiterated this and stated that 'to the authors knowledge there is no experimental evidence comparing the resistance risks of prophylactic versus threshold-based schedules, and research on this would be useful'.

We note here again that the primary aim of using fungicides is effective disease control, and the choice of protective and curative sprays or a combination thereof can have major influence on disease control efficacy. To maintain effective disease control, it may, depending on the patho-system and fungicide, be necessary to prevent the epidemic from developing early in the season, making protective fungicide use important. For example, for yellow rust (*Puccinia striiformis*), protective treatment is essential to obtain effective control, and in such cases, curative use may compromise disease control. So, we are not advocating here to use fungicides curatively, but we are saying that using fungicides protectively may be necessary for effective disease control, not for resistance management. There is no evidence that a protective spray is good for fungicide resistance management.

In practice, 'protective' and 'curative' use of fungicides are often loosely translated into use earlier or later in the growing season, respectively. If we compare earlier and later use of fungicides, there are, in total, six pathogen-fungicide resistance cases which have been studied and reported in the literature. In two cases, earlier sprays were found to increase selection for resistance. In three cases, the selection for resistance for earlier sprays was smaller than for later sprays. In one case, no difference was measured (see van den Bosch et al. 2014a for the references). There are two published modelling studies comparing early and later spray applications. One reports an increased selection from earlier sprays and another one reports an increased selection from later sprays.

A factor that may further complicate the issue is that infections in a crop are not synchronised, and the pathogen population is usually a mixture of the various life cycle stages of the pathogen. This makes it difficult to determine whether a spray is (mostly) protective or (mostly) curative.

In conclusion, current evidence does not support early or protective treatment being a resistance management tactic, as it is not possible to conclude whether protective or curative use has the lowest rate or selection for fungicide resistance. Depending on the patho-system-fungicide combination, protective treatment may be essential for effective disease control, however.

Where a mixture is being applied which comprises systemic and nonsystemic components, there is an argument for using the mixture under circumstances where the nonsystemic components will be an effective part of the mixture. In the case of potato late blight, for example, this would imply use early in the season, when initial inoculum is arriving in the crop. However, more generally, there is a resistance downside to early treatment, because prophylactic treatment decisions are more prone to uncertainty about whether treatment is necessary (the disease may fail to develop to damaging levels in the absence of treatment). It is clear that any unnecessary treatments add to selection, even though disease severity is low. Hence, we should avoid anti-resistance guidance which might result in fungicides being applied earlier than the optimum timing for efficacy and economic response.

5.9 Discussion

We have presented the evidence on the effectiveness of a range of resistance management tactics. This chapter combines the information gathered in three recent reviews by van den Bosch and Gilligan (2008) and van den Bosch et al. (2011, 2014a, b). From the evidence discussed, a set of clear conclusions can be derived. These are:

Managing the Application Dose

- 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.

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.

The Use of Fungicide Mixtures

- The vast majority of the evidence shows that adding a mixing partner 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 suggests that mixing two at-risk fungicides is a valid anti-resistance strategy.

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 programme with a fungicide with a different MOA reduces selection.

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 modelling 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.

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.

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