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Minimizing the Selection Pressure of Site-Specific Fungicides Towards *Phakopsora pachyrhizi* in Mato Grosso State: A Review

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Abstract

The determining cause of selection pression that has resulted in the increased development of resistance of *Phakopsora pachyrhizi* to fungicides used in Mato Grosso, Brazil, is the use of site-specific fungicides (DMIs, QoIs and SDHIs) solo or in double and triple mixtures. These fungicides have selected mutants resulting in cross and multiple resistance to *P. pachyrhizi*. The other secundary selection factors are: (a) fungus with high reproductive potential; (b) three sprayingns/area/season; (c) annually sprayed area of more than 10 million hectares; (d) fungus under site-specific selection during 20 years totaling 200 applications/area. Reports indicate that resistance develops only for site-specific, having resulted in eight mutations in Brazil involved with sensitivity reduction to *P. pachyrhizi*. In contrast, for multisites (chlorothalonil, mancozeb, copper oxychloride) there was found no report on the resistance development in rust-causing fungi and for general fungi to copper fungicides. It is not necessary to withdraw site-specifics from the market, nor the synthesis of molecules with new mode of action, but to avoid their use alone or in their mixtures. In this sense, it is more efficient to market them only in combination with multissites. An example is the worlwide success achieved in the control of oomycetes in potatoes, tomatoes and vines with metalaxyl + mancozebe. This review clearly shows the problem, site-specific mode of action fungicides solo, on resistance development to *P. pachyrhizi* and the solution, site-specific + mode of action multissites, sprayed in all soybean grown area and in all applications. Preventing and delaying adaptation to fungicide resistance in the pathogen is the main objective of disease management.

Keywords: Asian sobean rust, fungi resistance, multisite fungicides

1. Introduction

In the 2020/21 season, the cultivated area with soybean [*Glycine max* (L.) Merr.] in Mato Grosso (MT) state, Brazil, reached 10.9 million hectares and producing 37.4 million tons of grain (IMEA, 2021).

Asian soybean rust (ASR), caused by the biotrophic basidiomycete fungus *Phakopsora pachyrhizi* (H. Sydow & P. Sydow, 1914), was detected in the South American continent in 2001 (Morel, 2001; Yorinori et al., 2005) and is now present where soybeans are cultivated in MT.

Damage has been estimated and reported without mentioning the methodology for their quantification (Nutter et al., 1993). However, they can be appraised in fields with mathematical models (Danelli et al., 2012). Therefore, as a disease causing economic damage, like ASR, it must be controlled.

2. ARS Control Measures Implemented in MT

To minimize the damage, the control measures implemented in MT were: (a) soybean free period from June 15th to Septebmer 15th (Seixas & Godoy, 2007; Godoy et al., 2016); (b) Use early cycle cultivars seeded at the beginning of the recommended seeding time; (c) limitation of the sowing time to reduce the number of fungicide sprayings; (d) and the use of fungidides: (i) Use QoIs preventatively or as early as possible in the disease cycle, preferably in mixtures (co-formulations or, where permitted, tank mixes) with fungicides from a different cross-resistance group, and limiting the number of sprays; (ii) Apply DMIs always in mixtures with effective non-cross-resistant, consider partially resistant soybean varieties, reduce the planting window, give preference to early-cycle varieties and endorse soybean free-period; (iii) Apply SDHI always in mixtures. The mixture partner should provide satisfactory disease control when used alone on the target disease, apply a maximum of two sprays per soybean crop, and preventively or as early as possible in the disease cycle (FRAC, 2020; FRAC, 2021; IMEA, 2021).

Nonetheless, chemical control has been the main management measure. Early on, private and the sanitary state agencies did not warn that the use of site-specific fungicides had the potential to select resistant mutants leading to resistance in a short period of time.

Despite the availability of a wide variety of fungicides, the ASR control relies on only three mode of action (MOA) chemicals (DMI, QoI, ISDHI) leading to a high pressure for resistance selection.

Two groups of fungicides under discussion are: (i) Site-specific MOA, monosite or unisite fungicide that of the millions of biochemical reactions that take place in the fungus cell, they interfere with only one biochemical site generally an enzyme. This is a vital enzyme for the fngus physiology, so if it is blocked, the fungus will die. Fungicides with a site-specific MOA are at high risk for the development of resistance compared to multiple-site fungicides (Mueller et al., 2013); (ii) Multisite MOA fungicides paralyzes at least five metabolic processes of the fungus (FRAC-UK., 2020; Mueller et al., 2013). For this reason, the resistance development to them has not been frequently reported and, for MT, chlorothalonil, mancozeb or copper oxychloride with potential to stop *P. pachyrhizi* selection pressure has been few times mention.

Concerned with the raise of fungicide resistance, private and state agencies have recommed to mix fungicides with different mechams of action (MOA), however, all site-specific, without clearly stressing the need to mix them with multi-sites (Godoy et al., 2016; Godoy et al., 2017; FRAC-UK, 2018).

Moreover, little has been warned about the time of the first fungicide spray that may result in increasing the number of sprayings and so accelerating resistance development. In most cases in MT the first spray is made empirically at (i) Growth stage '0', (ii) at pre-closing soybean rows, or (iii) at flowering, increasing the number of unnecessary applications.

3. The Emergence of Site-Specific Sensitivity Reduction

To mitigate the damage, ASR control began in the 2002/03 season with isolated use of site-specific demethylation inhibitors (DMI) fungicides chemically named triazoles (difenoconaol, flutriafol, miclobutanil and tebuconazole). This non-recommended practice, use of isolated site-specific fungicides, resulted in the rapid evolution of reduced fungus sensitivity to all three MOA (DMI, QoI, SDHI) (Reis et al., 2017) confirming the reports on the risk of their solo use**.**

As expected, the fungicide effective life may be considered short. Thus the reduced sensitivity of *P. pachyrhizi* to IDMs was reported in the 2006 season (Silva et al., 2008), to QoIs in the 2012 and to SDHIs in the 2015 (Godoy et al., 2016). Today, they present cross and multiple resistance to the three MOA and with less than 50% control. Site-specific double or triple mixtures (DMI + QoI, DMI + DMI; DMI + SDHI, DMI + QoI + SDHI) are no longer effective as the individual components are not due to the cross and multiple resistance presence (EMPPO, 1988; FRAC, 2020).

4. The ASR Control Decline by Fungicides

The discussed facts reflex is seen in the current situation of ASR control by commercial fungicides. Therefore, the situation that has persisted during 20 years in which few effective measures supported by science have been implemented is alarming (Figure 1). Although the maximum soybean yield is obtained with control more than 80%, the greatest profit depends on the effectiveness and the application cost (Reis et al., 2017a).

The reducing ASR control evolution has resulted in some fungicides mixtures with so low control that they were no longer used by growers (Figure 1). As the selection pressure did not stop the control decline progresses season after season.

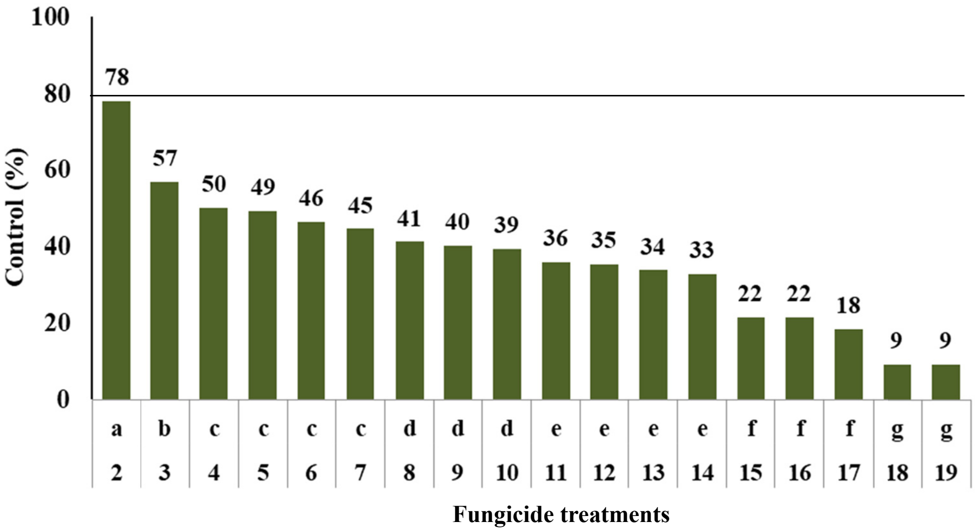

Figure 1. Fungicide treatments effect on ASR final leaflet severity control at R6 GS. Means (letters at columns base) compared by Scott & Knott test. (2) pico + tebu + mcz; (3) pico + benz; (4) azox + cypr + mcz; (5) chlo + tebu; (6) pyra + flux: (7) pyra + epox + flux; (8) trifl + prot: (9) pico + tebu; (10) azox + benz; (11) pico + cypr; (12) meto + tebu; (13) trifl + prot + bixa; (14) trifl + tebu; (15) trifl + cypr; (16) carb + tebu + kres; (17) femp; (18) dife + cypr; (19) azox + cypr.The black line represents the control corresponding to the maximum soybean yield

Source: Reis et al. (2021c).

Seeking a solution for the constant rust control reduction, the Ministry of Agriculture and Livestock and Supply (MAPA) published the Act 71, December 2016, in which a decision was taken to eliminate fungicides for ASR control, from the package insert, with less than 80% control. However, five years have passed and no control improvement has been reported (Figure 1).

5. Reducing Control Efficacy and Yield

Considering these facts, how much soybeans grain does MT fail to harvest annually due to reduced ASR control by site-specific fungicides?

Soybean grain yield (kg/ha) is linearly related to the ASR control. The amount of yield reduction, in the 10.9 million hectares cultivated in MT, in the 2020/21 season (IMEA, 2021) was calculated with the function $y = 1{,}927.9 + 31.633\ C$ (where y = grain yield and C = ASR control (%) taken from Reis et al. (2021c). In this example, based on unsprayead plots (1,927.9 kg/ha), each control percentage point increased 31.633 kg/ha of soybean grains (Table 1).

Table 1. Soybean grain yield reduction simulation as a function of Asian soybean rust control effectiveness in different extensions of cultivated areas

Control (%)	Area (ha)			
	1.0		10,000,000	
	Yield^{y} kg/ha	Damage^{z} kg/ha	Yield (t)	Damage (t)
80	4,458.54	0	4,458,540,000	0
70	4,142.21	316.33	4,142,210,000	3,166
60	3,825.88	632.66	3,825,880,000	6,326.6
50	3,509.55	948.99	3,509,550,000	9,489.0
40	3,193.22	1,265.32	3,193,220,000	12,653.2
30	2,876.89	1,581.65	2,836,890,000	15,816.65

Note. $y = 1927.9 + 31.633 \times 80 = 4{,}458.5$ and so on substituting the different (80 to 30%) control values in the equation; z = damage, the highest yield 4,458.5 minus the yield of each treatment: $4458.5 - 4142.2 = 316.33$.

6. The Identification of Mutations in *Phakopsora pachyhrizi*

The evolution of *P. pachyrhizi* sensitivity reduction to date has not stopped. Site-specific fungicides are not mutagenic, but selection agents. Decreased sensitivity is caused by its repeated use that exerts selection on the target fungus population. In each fungicide application, sensitive individuals are eliminated, leaving the resistant ones that finally dominate the population. As it is a dynamic process, without stopping the cause, the use of a site-specific, the control reduction is also not paralyzed.

Eigth mutations have been detected over the years in the *P. pachyrhizi* population, first for the QoIs: F129 L, later on the DMI: F120L, Y131F/H, K142R, I145F, I475T and recently on the SDHI: C-I86F and C-N88S (Corteva/FRAC, verbal information; Klosowski et al., 2015; Schmitiz et al., 2014; Simões et al., 2018).

Therefore, it is evident that the measures implemented so far did not prevent the evolution of the sensitivity reduction of *P. pachyrhizi* towards site-specific fungicides, because they continue to be widely sprayed.

7. Identifying the Cause

The problem is the incessant selection pressure, for 20 years, imposed by the use of site-specific fungicides (double or triple co-formulations), leading to the sensitivity evolution of *P. pachyrhizi*, reducing the control effectiveness and the grower's profit.

8. Proposed Solutions

In face of *P. pachyrhizi* sensitivity reduction evolution to site-specific fungicides, which intensifies season after season (Figure 1), solutions have been proposed to reduce the imposed selection pression.

The soybean free period and soybean sowing calendar were established to minimize the risks of *P. pachyrhizi* resistance development, without however mentioning that the main cause was and is the use of site-specifics (Godoy et al, 2016; MAPA, 2021). The term soybean free-perid was used for the first time in 2005 and its implementation aimed at preventing the soybean cultivation under irrigation. At that time, it was thougth that, regardless of irrigation, there were green bridges even with the water deficit occurring in June, July and August. In reality, green bridges were and are being eliminated by winter fallow in MT (Haas et al., 1974).

These measures may be considered at risk if the main cause will not be eliminated, the site-specific fungicides used solo. Only seeding time regulation is not the most effective strategy with the greatest impact to reduce *P. pachyrhizi* selection to site-specific fungicides, especially limited to December 31th. Later sowing, February, evoking the escape principle, may be more effective as demonstrated in MT (Reis et al., 2021c). In other similar cases of resistance management, similar citations of legislation limiting the sowing period were not found in the literature (Gisi & Siertotzki, 2015; Schepers & Cooke, 2015).

9. The Main Cause of Reduced Sensitivity of *P. pachyrhizi* to Fungicides

The resistance develpment is direct linked to the use of site-specific fungicides. Rapid resistance devlopment has been reported mainly with site-specific fungicides (Brent & Hollomon, 2007; EMPPO, 1988; Hollomon, 2015). Therefore, similar to other pathosystems, the control failure is due to the isolated use of site-specific fungicides that select resistant mutants, such as those used to fight *P. pachyrhizi*, starting with DMI (difenoconazole, flutriafol, miclobtanoill and tebuconazole), later, with QoI and SDHIs used in double or triple mixtures and with the presence of cross and multiple resistance, since the 2002/03 season.

Knowing now the cause of the reduced sensitivity of the target fungus, it is clear where the the solution should be focused. In personal information, via internet, Dr. Hedeo Ishii wrote: "*If you still need to use DMI fungicides for some reasons, the best way will be mix them with multisite inhibitors. To mix DMIs with QoIs or SDHIs will not be good choise anymore because of resistance to QoIs and SDHs already developed in P. pachyrhizi*".

10. Secondary Causes

10.1 The Target Fungus

Pathogenic fungi, such as *P. pachyrhizi*, with high reproductive potential are the most vulnerable to the resistance development. The proportion is one mutant for one million spores for the targe fungus: (i) in MT the cultivated area more than 10 million hectares; (ii) a soybean plant with high severity can produce 400 million spores (Reis et al., 2021); (iii) soybeans weed plants amid cotton crop attacked by rust, although ignored, also accelerate selection pressure (Reis et al., 2021c).

10.2 Frequency of Spraying

Selection pressure is also a function of the number of site-specific applications per area (van den Bosch et al., 2014). The average in the MT state, in soybean, is three sprayings, but considering the soybean plants as weed amid the cotton crop (Reis et al., 2021b) and attacked by rust, it is six-seven, totaling 10 per season/area; certainly this is another problem to be solved.

10.3 Time of Fungicide Exposition

The time of the fungus exposure to the fungicide also contributes to the increase the seletion pressure (Dekker, 1986). The use of site-specific solo (in double or triple mixtures) for 20 years has totaled 200 applications per area! Selection pressure is proportional to the number of applications only for site-specific (DMI, QoI, SDHI) and not for multi-sites (Hahm & Leroch, 2015).

As the main cause is still working in MT, the reduction in sensitivity is reaching other pathogenic fungi to soybean and cotton crops. For example, in addition to *P. pachyrhizi*, the fungus *Corynespora cassiicola* (Berk. & Curt.) Wei., which causes target spot both on soybeans and cotton, became also resistant to QoIs, SDHIs and TSIs (tubulin synthesis inhibitors), *Cercospora kikuchii* (Matsumoto & Tomoyasu) Gardner, causal agent , to QoIs, SDHIs, and TSI and *Ramulariopsis gossypii* (Speg.) Braun (sin. = *Ramularia areola* Atk) to QoI (FRAC, 2012).

For these reasons, only legislative decisions taken in MT have not been the most effective in reducing selection pressure by not focusing on the main cause, the use site-specific fungicides solo without multissites.The process is dynamic and new cases of resistance development will be reported not only in the soybean crop.

11. Minimizing Selection Pressure

Therefore, even against a fungus with a high sporulation potential, receiving many sprayings per season, large area treated for many years, the problem become limited to the primary cause, the use of site-specific fungicides.

The literature points out the factors involved in the cause and management of resistance development (Delp & Dekker, 1985; EMPPO, 1988; FRAC, 2020; Gisi & Siertotzki, 2015; Hahm & Leroch, 2015; Ishii & Hollomon, 2015; Schepers & Cooke, 2015; Reis et al., 2017b; Van den Bosch, 2014). If the strategies reported by these and other authors had been considered and implemented, the problem would have been avoided or delayed by the use of site-specific fungicides in combination with multisites.

A lesson from the past on how efficiently the solution of oomycetes (*Plasmopara, Peronospora* and *Phytophthora*) resistance to the highly potent site-specific, metalaxyl was found and implemented. The resistance development, was only solved when metalaxyl was mixed with multisites (Corio-Costet, 2012; Schepers & Cooke, 2015; Gisi & Sierotzki, 2015; FRAC, 2020).

It is likely that in MT, the cause continues due to the use of site-specific solo, large treated area (population of the fungus), high sprayings number/area/season and it is still unknown how long it will persist.

Mutations at the fungus target site and conferring resistance only occur against site-specific fungicides (Hahm & Leroch, 2015). On the other hand, multisite fungicides (*e.g.*, chlorothalonil, mancozeb and copper oxychloride) are not prone to mutations (Hahm & Leroch, 2015), as they act at different points in the fungus metabolism and, therefore, play a key role in anti-resistance strategy (McGrath, 2004).

Therefore, the solution is clear, to stop the use of site-specific solo and to start using them in mixtures with multisites, as pointed out in the literature.

It is important to review the ASR control measures implemented in MT, such the sowing limitation to 12/31th, and compare them to what science points out as the cause of the fungi sensitivity reduction to fungicides and how to minimize it:

(a) From the time when control failure to site-specific IDMs was detected, 2006 season, they should have further been used in combination with multi-sites (Dr. Hideo Ishii, personal information).

(b) The components of the mixtures must contain multisites that present a low risk of resistance development (*e.g.*, chlorothalonil, mancozeb, copper oxychloride, etc.) (Corio-Costet, 2012; Gisi & Sierotzki, 2015; Schepers & Cooke, 2015; FRAC, 2018; FRAC, 2020). Prefabricated double or triple mixtures containing only site-specific are not efficient in the control of *P. pachyrhizi*.

(c) Mixtures of site-specific + multi-site fungicides must be sprayed over the entire soybean area and in all sprayings; as in the control of the mentioned oomycetes, these ready-made mixtures formulated should dominate the market; multisite fungicides do not select for resistant mutants; therefore, it is not necessary to develop new molecules with a site-specific mode of action; however, in the 2020/21 season, site-specific + multi-site mixtures have been applied in only 10% of the treated area.

(d) As in the control of downy mildews on potatoes, tomatoes and vines, the ideal is not to make isolated site-specific formulations available on the market, but rather pre-fabricated ones containing site-specific + multi-site (Gisi & Sierotzki, 2015; Schepers & Cooke, 2012); and

(e) Similarly to our proposal, Ishii et al. (1955) reported that successive applications of thiophanate-methyl and benomyl (site-specifics) rapidly increased the level of resistance in the populations *Venturia nashicola* Tanaka & Yamamoto in pear orchards. When the application of benzimidazoles was stopped and other multisite fungicides alone (captafol, dithianon, captan, milneb, captafol, oxinecopper) were applied in orchards where highly resistant isolates predominated, the proportion of highly resistant isolates gradually decreased and that of intermediately resistant, weakly resistant, and sensitive isolates increased. This phenomenon was thought to be an example of genetic homeostasis within plant pahtogenici fungi. Similarly, tebuconazole (DMI), the first fungicide used in MT for ASR management, its initial control was more than 80%, six seasons of isolated use reached 18% (Godoy et al., 2016), and after stopping its solo use, control reached 45% (unpublished data).

(f) Intensify the diffusion of technology regarding the need for the use of multi-sites to fight the site-specific fungicides resistance towards *P. pachyrhizi.*

12. Final Remarks

The main cause of selection pression that has resulted in the increased development of resistance of *Phakopsora pachyrhizi* to fungicides used in Mato Grosso, Brazil, is the use of site-specific fungicides (DMIs, QoIs and SDHIs) solo or in double and triple mixtures. It is not necessary to withdraw site-specifics from the market, nor the synthesis of molecules with new mode of action, but to avoid their use alone or in their mixtures. This review points out the problem, site-specific mode of action fungicides solo on resistance development to *P. pachyrhizi,* and the solution, site-specific + mode of action multissites, sprayed in all soybean grown area and in all applications.

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