



Is tank mixing site-specific premixes and multi-site fungicides effective and economic for managing soybean rust? a meta-analysis

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ABSTRACT

Soybean rust (SBR), caused by *Phakopsora pachyrhizi*, is controlled with sequential applications of commercial premixes containing two and, more recently, three site-specific fungicides. However, their efficacy has been reduced due to the development of fungicide resistance in the fungal population; hence the use of multi-site fungicides in tank mixing has been encouraged. In this work we used data from 45 uniform fungicide trials conducted across eight Brazilian states during three crop seasons (2014/15, 2015/16, and 2017/18) to identify scenarios when the practice of adding multi-site fungicides in commercial premixes was both technical- and cost-effective. Premixes of quinone outside inhibitor (QoI) + demethylation inhibitors (DMI) or succinate dehydrogenase inhibitors (SDHI) were applied alone, or tank mixed with multi-site fungicides. Three premixes (PICOxystrobin + CYPROconazole, PYRaclostrobin + FLUXapyroxad and AZOxystrobin + BENZovindiflupyr) were tank mixed with one of three multi-site fungicides (+MANCozeb, +COPpeR oxychloride, and +ChLORothalonil). The benefits from tank mixing a multi-site tended to be highest for the least effective premix. Improvements in control efficacy ($\bar{C}$, percent point; p.p.) and yield response ($\bar{D}$, kg/ha) ranged from 3 to 15 p.p.

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and 58–240 kg/ha, respectively. The improvements in $\bar{C}$ and $\bar{D}$ were affected by severity in the non-treated check; significantly higher improvements in $\bar{D}$ were determined in trials experiencing high SBR severity levels (>80%). The economic analysis for scenarios of soybean price and multi-site costs showed that the addition of +MANC, given its lower price, was more likely to be profitable compared with +CLOR and +COPR, particularly when tank mixed with the least effective commercial premix.

1. Introduction

Soybean rust (SBR) is one of the most damaging fungal diseases of soybean (*Glycine max* (L.) Merr.) caused by the obligate biotrophic pathogen *Phakopsora pachyrhizi* Syd. & P. Syd. (Goellner et al., 2010; Li et al., 2010). In Brazil, SBR is present in all soybean growing areas and where severe epidemics may develop and lead to around 80% yield losses under disease-conducive conditions (Dalla Lana et al., 2015). A couple years after the first reports of SBR epidemics in Brazil, a mandatory soybean-free period was implemented to reduce early-season inoculum. The wide adoption of early-maturing cultivars and earlier sowing dates, more recently, have greatly helped to reduce the impact of the disease (Godoy et al., 2016a). None of the current commercially grown soybean cultivars are fully resistant to all *P. pachyrhizi* races (Childs et al., 2018; Hartman et al., 2005) and hence soybean farmers should rely on routine fungicide applications for managing SBR (Beruski et al., 2020; Dalla Lana et al., 2018).

Several options of active ingredients have been made available during almost twenty years of disease management in Brazil using fungicides (Godoy et al., 2016a). Updates in fungicide programs have been frequently made based on information generated by field research to evaluate the performance of currently used and newly available products in the market. For instance, a few years after the sole use of demethylation inhibitor (DMI) fungicides, the premixes of DMIs with quinone outside inhibitors (QoI) gained attention up until the first ten years of chemical control of soybean rust. Following 2013, commercial premixes of succinate dehydrogenase inhibitors (SDHIs) and QoIs have also become available for SBR control. Recently, SDHIs have also been included in triple mixtures with QoIs and DMIs (Godoy et al., 2016a). However, a decline in control efficacy of soybean rust has been observed in the cooperative trials over the past years (Dalla Lana et al., 2018). First the DMI alone, then DMI + QoI mixtures and, lately, QoI + SDHI fungicides are no longer as effective as they were during the first years of use (Barro et al., 2021). Such decline was not only reported for single-a.i. fungicides but also for premixes after at least four years (Barro et al., 2021; Dalla Lana et al., 2018). Declines in efficacy have been linked to reports of less sensitive populations of *Phakopsora pachyrhizi* to DMI, QoI, and SDHI fungicides (Kłosowski et al., 2016; Schmitz et al., 2013; Simões et al., 2018).

FRAC (Fungicide Resistance Action Committee) published a statement about the increasing importance of multi-sites for managing fungicide resistance, including soybean rust (FRAC 2018). Since 2015, multi-site fungicides, e.g. chlorothalonil, copper oxychloride, and mancozeb, have been recently evaluated in tank mix with commercial premixes to improve SBR control efficacy and reduce the risk of resistance (Godoy et al. 2015, 2016b, 2017, 2018). Chlorothalonil, a multi-site fungicide that belongs to the chloronitriles group, was first registered in 1966 and is still in use as a protectant fungicide (Battaglin et al., 2011; Miles et al., 2007). Copper oxychloride ($3\text{Cu}(\text{OH})_2\cdot\text{CuCl}_2$) is another multi-site fungicide that has been recently evaluated against soybean rust (Chechi et al., 2020; Juliatti et al., 2017). Mancozeb, which belongs to the dithiocarbamate group (FRAC 2018), was introduced in 1962 and still has a significant importance in the fungicide market worldwide (Gullino et al., 2010; Thind and Hollomon, 2018). As a typical cost-effective multi-site protectant-only fungicide, mancozeb requires relatively high rate and frequency of application compared to modern fungicides to achieve satisfactory protection (Gullino et al., 2010; Thind and Hollomon, 2018).

In Brazil, fungicides have been evaluated annually since 2003/2004 in a network of uniform field trials (UFTs) conducted by the anti-rust consortium (CAF) with the goal of monitoring and comparing the effectiveness of a range of fungicides (Dalla Lana et al., 2018; Godoy et al., 2016a). Considerable variations in control efficacy have been observed between fungicide chemistries over the years and across regions. Meta-analysis, a statistical technique that combines results from previous studies selected by defined criteria, have become standard for summarizing and comparing fungicide performance in plant disease management (Barro et al. 2019, 2020; Edwards-Molina et al., 2019; Machado et al., 2017; Paul et al. 2008, 2018) including SBR (Barro et al., 2021; Dalla Lana et al., 2018; Delaney et al., 2018). In the present study, we used meta-analysis to: 1) estimate the improvement in both efficacy and yield return provided by tank mixing multi-site fungicides with premixes of QoI plus DMI or SDHI fungicides evaluated from 2014/15 to 2017/18 across all major soybean regions in Brazil; 2) evaluate whether the gains in the responses vary across regions; and 3) estimate the probability of breaking-even on costs for a range of scenarios of soybean prices and multi-site fungicide costs.

2. Material and methods

2.1. Data source and experimental procedures

The data used in this study were obtained from 45 UFTs, which have been published as yearly reports (Godoy et al. 2015, 2016b, 2017, 2018). The experimental design was a randomized complete block with four replications. Replicated plots were at least six rows wide and 5 m long. Three fungicide sprays were applied at label-recommended rates across crop seasons using a CO_2 backpack sprayer with a volume of 120 L ha⁻¹. Sprays initiated at around 50 days post plant emergence (before canopy closure) with subsequent applications approximately 15 days apart. Percent disease severity, which takes both percent area affected and defoliation into account (Dalla Lana et al. 2015, 2018), was assessed at the full-seed growth stage (R6) across four different points of each plot where 10 leaves were examined. The central 5 m² of each plot were harvested at the R8 stage (full maturity) and mechanically threshed. Soybean yields were calculated as kg/ha at 13% grain moisture. All weed and insect control practices followed regional recommendations.

2.2. Criteria for study inclusion and fungicide selection

To be included in the analysis, a soybean rust fungicide trial should have: 1) a non-treated plot; 2) a commercial premix applied alone or tank mixed with a multi-site in the same trial, and 3) a measure of disease severity at R6 stage (Dalla Lana et al., 2015) and/or grain yield in both fungicide-treated and non-treated plots. Among several fungicides that matched the criteria, we performed a preliminary exploratory analysis and selected three different premixes that represented a low (picoxystrobin + cyproconazole [PICO + CYPR]), intermediate (pyraclostrobin + fluxapyroxad [PYRA + FLUX]) and high (azoxystrobin + benzovindiflupyr [AZOX + BENZ]) SBR control efficacy to compare the sole application of the premix with its tank mixing with one the three multi-site fungicides: chlorothalonil (+CLOR), copper oxychloride (+COPR) and mancozeb (+MANC) (Table 1). The concentration of active ingredient (a.i.) for + CLOR and +COPR was 1080 g a.i./ha and 294 g a.i./ha, respectively, in all trials ($n = 45$), while for + MANC, the concentration varied from 1125 ($n = 24$) to 1500 ($n = 21$) g a.i./ha. The

Table 1

Fungicide treatments applied for controlling soybean rust, evaluated in 45 uniform field trials conducted during three growing seasons (2014/15, 2015/16 and 2017/18) in 25 municipalities across eight Brazilian states by the Anti-rust Consortium (CAF).

Fungicide code	Active ingredient [a.i.]	Trade name	FRAC code ^a	Rate (g a. i. ha ⁻¹)	Dose (g or ml ha ⁻¹)
PICO + CYPR	Picoxystrobin + Cyproconazole	Aproach Prima (DuPont)	11 + 3	60 + 24	300
PYRA + FLUX	Pyraclostrobin + Fluxapyroxad	Orkestra (BASF)	11 + 7	116.55 + 58.45	350
AZOX + BENZ	Azoxystrobin + Benzovindiflupyr	Elatus (Syngenta)	11 + 7	60 + 30	200
+CLOR	Chlorothalonil	Previnil (Helm)	M05	1080	1500
+COPR	Copper oxychloride	Difere (Oxiqúmica)	M01	294	500
+MANC	Mancozeb	Unizeb Gold (UPL)	M03	1125; 1500	1500; 2000

^a FRAC = Fungicide Resistance Action Committee; 11 = QoI, quinone-oxidoreductase inhibitors; 7 = SDHI, succinate dehydrogenase inhibitors; 3 = DMI, demethylase inhibitors; M = multi-site contact activity.

field experiments were conducted during three growing seasons (2014/15, 2015/16 and 2017/18) at 25 locations across eight Brazilian states (Bahia [BA], Goiás [GO], Minas Gerais [MG], Mato Grosso do Sul [MS], Mato Grosso [MT], São Paulo [SP], Paraná [PR], and Rio Grande do Sul [RS]) (Fig. 1). The trials were geographically grouped into the Northwestern (NW) region ($n = 30$, MT, MS, GO, BA, and MG states) and the Southeastern (SE) region ($n = 15$, PR, RS and SP states) (Fig. 1). MT ($n = 12$), PR ($n = 10$), MS ($n = 7$), and GO ($n = 7$) were the states with the largest number of trials, accounting for 80% of all trials.

2.3. Response variables

Two response variables were of interest in this study, similarly to a previous meta-analysis (Dalla Lana et al., 2018): control efficacy ($\bar{C}$), and yield difference ($\bar{D}$), both relative to a reference treatment (non-treated check) for the sole premix treatment or tank mixed with a multi-site fungicide (Dalla Lana et al., 2018; Madden et al., 2011; Paul et al., 2008). Given the availability of data at the plot level, the within-study or sampling variance (V) of the log mean SBR severity (L)

or non-transformed yield means (D) of treatments was estimated from the mean square error (MSE), as described previously (Paul et al., 2008, 2010). Given the statistical properties of the data (Fig. S1), mean SBR severity values were log-transformed, while no transformation was required for the mean difference in yield.

2.4. Network meta-analytic model

A network model, also called a two-way unconditional linear mixed model, was fitted directly to the treatment means (log-transformed or non-transformed) (Machado et al., 2017; Madden et al., 2016; Paul et al., 2008). The model can be written as:

$$Y_i \sim N(\mu, \Sigma + S_i) \quad (1)$$

where Y_i is the vector of L (log of the mean SBR severity) or mean yield (D) for the 12 treatments plus the non-treated check for the i th study, μ is a vector representing mean of Y_i across all studies, Σ is a 13×13 between-study variance-covariance matrix (for the 12 treatments plus the non-treated check), and S_i is within-study variance-covariance matrix for the i th study. N indicates a multivariate normal distribution. An unstructured Σ matrix was used and the models were fitted to the data with a maximum-likelihood parameter. All models were fitted to the data using the *rma.mv* function of the *metafor* package (Viechtbauer, 2010) of R (R Core Team, 2019).

The overall mean log of the response ratio ($\bar{L}_{SEV}$) for each fungicide treatment ($\hat{\mu}_{Treat}$) relative to the non-treated check ($\hat{\mu}_{Check}$) was used as effect size in the model and estimated as $\bar{L}_{SEV} = \hat{\mu}_{Treat} - \hat{\mu}_{Check}$. Overall mean percent SBR control and the respective 95% confidence intervals (CIs) were obtained by back-transforming $\bar{L}_{SEV}$ and the upper and lower limits of the confidence intervals around $\bar{L}_{SEV}$ (equation (2)).

$$\bar{C} = (1 - \exp(\bar{L}_{SEV})) \times 100 \quad (2)$$

The mean difference in yield ($\bar{D}$) was calculated by subtracting the mean yield in the non-treated check from the mean yield in the fungicide treatment (Madden et al., 2016). To test for network inconsistency, we fitted a factorial-type linear model to determine the significance of the *treatment* $\times$ *design* interaction, evaluated based on the Wald test statistic. The null hypothesis suggests that the network is consistent (Higgins et al., 2012; Madden et al., 2016; Piepho, 2014). Three and five different designs (here design refers to the set of treatments in the trial) were found in the trials reporting soybean yield and SBR severity, respectively

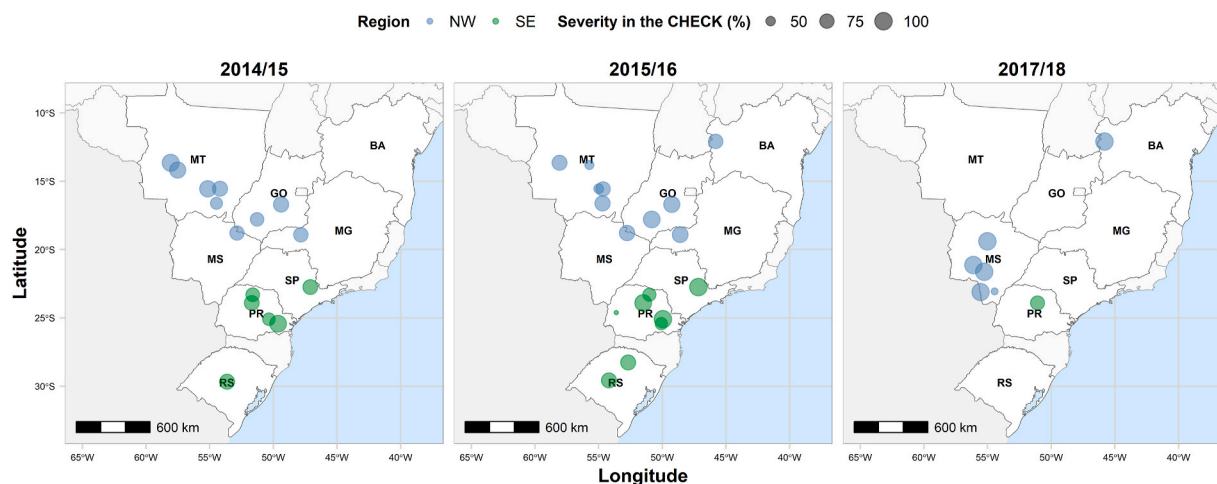


Fig. 1. Geolocation of the 25 municipalities across eight Brazilian states where 45 fungicide evaluation trials were conducted during three growing seasons (2014/15, 2015/16 and 2017/18). The size of the circle is proportional to disease severity in the non-treated CHECK in each location. The color of the circle represents two geographic regions defined in our study: Northwestern (NW) states (MT, MS, GO, BA, MG) and Southeastern (SE) states (PR, RS, SP). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

(Table S1).

2.5. Effect of moderator variable

The model was expanded to include categorical moderator variables that could explain, at least in part, the heterogeneity of the effects across trials (Madden et al., 2016). The first categorical variable was the baseline for SBR disease intensity based on the median in the non-treated check. The trials were divided into two groups representing low (<80% SBR severity) ($n = 20$) and high ($\geq 80\%$ SBR severity) ($n = 25$) disease scenarios. The second categorical variable was based on the geographical region where trials were grouped into the Northwestern (NW) region (MT, MS, GO, BA, MG) ($n = 30$) and the Southeastern (SE) region (PR, RS, SP) ($n = 15$) as mentioned previously. Linear contrasts were used to estimate the mean effect sizes and their standard errors and 95% CIs for each level of the categorical moderator (Madden et al., 2016).

2.6. Probability of breaking-even fungicide application cost

The probability (P) of breaking even on the multi-site costs (F_C) was calculated using the estimates of the mean improvement in yield from adding the multi-site fungicide ($\bar{D}_I = \bar{D}_{\text{fungicide} + \text{multi}} - \bar{D}_{\text{fungicide alone}}$), and the respective between-study variance ($\hat{\tau}$) obtained from meta-analysis. This was calculated as the cumulative standard-normal distribution function of

$$P = \Phi[\bar{D}_I - (F_C / S_P) / \sqrt{\hat{\tau}}] \quad (3)$$

where Φ is the cumulative standard-normal function and S_P is the soybean price.

Average prices of the multi-site fungicides considering: an exchange rate of \$ 5.3 BRL = 1 U\$ during May 2021; fungicide price of 2019/20 crop season; and three applications were: +CLOR: 36.00 U\$/ha, +COPR: 27.00 U\$/ha and +MANC: 24.00 U\$/ha. To obtain the national average soybean price, we gathered data from the AGROLINK database (AGROLINK, 2020) since 2014. The average soybean price used was 250 U\$/ton. Tile plots of the probability classes of breaking even on multi-site costs were produced for each premix.

3. Results

3.1. SBR severity and yield

SBR severity varied across treatments and trials. In the non-treated plots, it ranged from 40.3 to 100% and was higher than 98% in one-quarter of the studies. As expected, SBR severity was higher in the non-treated check (median 80%) compared with premixes alone or with the multi-site fungicides (Fig. 2A). Soybean yield in the non-treated check ranged from 904 to 3760 kg/ha. In general, mean yield was lower in the non-treated check plots (median 2364 kg/ha) than in the plots sprayed with either premixes alone or tank mixed with a multi-site fungicide, but there was also a considerable variation among treatments and studies. Yield in the non-treated check was higher than 2684 kg/ha

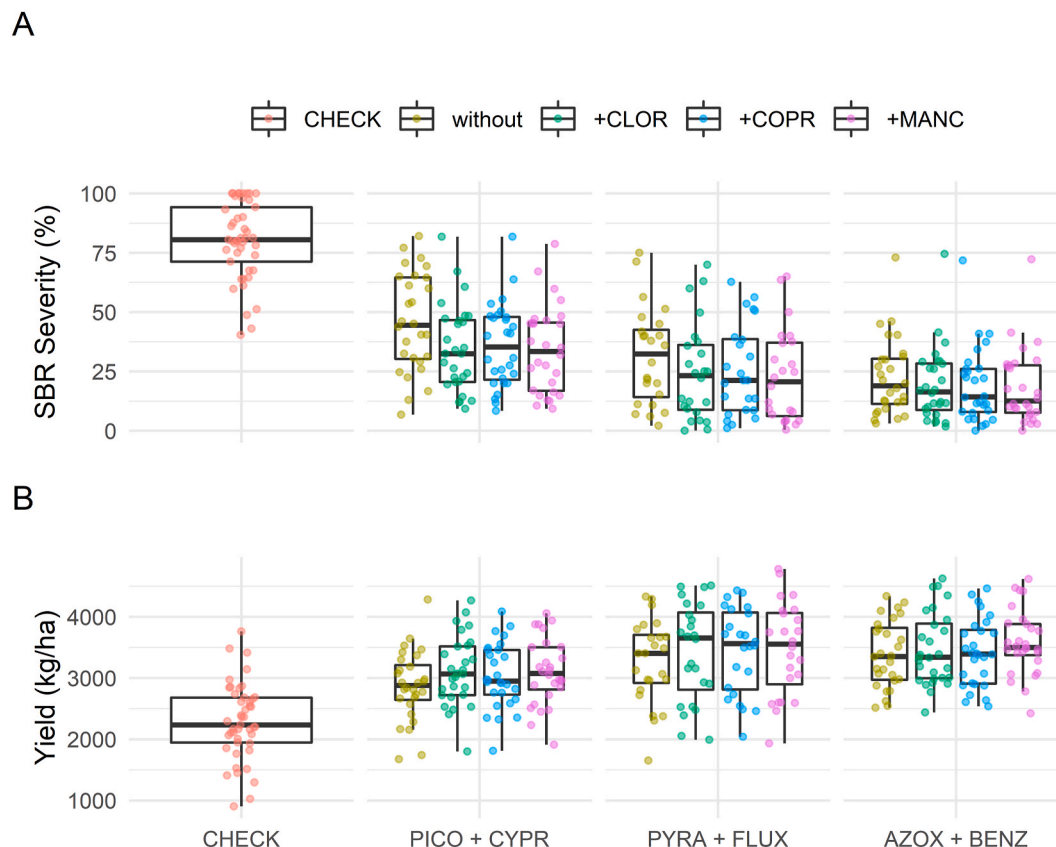


Fig. 2. Box plots and individual means of (A) soybean rust severity at R6 stage (%) and (B) soybean grain yield (kg/ha) across 45 uniform field trials conducted during three growing seasons (2014/15, 2015/16 and 2017/18) across 25 municipalities in Brazil. The treatments evaluated consisted of a non-treated (CHECK) or treated plot with 3 sprays of picoxystrobin + cyproconazole (PICO + CYPR), pyraclostrobin + fluxapyroxad (PYRA + FLUX) and azoxystrobin + benzovindiflupyr (AZOX + BENZ), applied alone (without) or amended with multi-site fungicides (chlorothalonil [+CLOR], copper oxychloride [+COPR] and mancozeb [+MANC]). The line within the box represents the median, whereas the top and bottom lines of the boxes represent the 75th and 25th percentiles of the data, respectively. The circles represent each treatment mean.

in one-quarter of all studies (Fig. 2B).

3.2. Overall improvement in control and yield using the tank mix

The percent control efficacy ($\bar{C}$) obtained from the back-transformation of the estimated differences of the log-transformed SBR severity in the fungicide-treated without multi-site and non-treated plots ranged from 48 to 78% (Table 2). Linear contrasts showed that there was a significant increase ($P < 0.05$) in $\bar{C}$ when adding any of the multi-site fungicides for all the three premixes evaluated. Among the multi-sites, efficacy for PICO + CYPR was higher when the premix was amended with +MANC (63.8%) or +CLOR (67.6%) which did not differ among them ($P = 0.2668$), but both differed ($P < 0.02$) from +COPR (59.8%). However, there was no statistical difference ($P > 0.3$) when AZOX + BENZ was amended with +MANC (82.1%), +CLOR (82.4%) or +COPR (81.6%). Finally, for PYRA + FLUX, higher $\bar{C}$ was obtained when amended with +MANC (79.3%), which differed significantly ($P < 0.01$) from +CLOR (75.1%) and +COPR (72.3%) (Table 2). The Wald test for the treatment $\times$ design interaction showed that the network was consistent ($P = 0.9987$).

The mean estimates of yield difference ($\bar{D}$) between fungicide-treated without multi-site and non-treated plots ranged from 463 to 926 kg/ha (Table 3). Similar to control efficacy, linear contrasts showed that $\bar{D}$ was significantly higher ($P < 0.05$) when mixing any of the multi-site fungicides to all three premixes evaluated. For PICO + CYPR, $\bar{D}$ was higher when the fungicide was mixed with +MANC (691.6 kg/ha), which was different ($P = 0.0042$) from +COPR (624.3 kg/ha) but not different ($P = 0.7328$) from +CLOR (681.8 kg/ha). Similarly, $\bar{D}$ was higher when AZOX + BENZ was mixed with +MANC (1110 kg/ha), which was different ($P < 0.02$) from +CLOR (1021 kg/ha) and +COPR (978 kg/ha), the latter two not differing among them ($P = 0.1172$). However, there was no statistical difference in $\bar{D}$ between multi-sites for PYRA + FLUX ($P > 0.1$), and yield difference between the premix applied alone and with multi-sites ranged from 105 to 167 kg/ha (Table 3). The Wald test for the treatment $\times$ design interaction showed that the network was consistent ($P = 0.8133$).

In general, the pattern of the relationship between the improvement in control efficacy and yield from using multi-sites compared with the premix applied alone was consistent. For PICO + CYPR, improvements in $\bar{C}$ (percent point; p.p.) and $\bar{D}$ (kg/ha) were higher for +MANC (15 p.p.; 240 kg/ha) and lower for +COPR (11 p.p.; 158 kg/ha). Similarly, for PYRA + FLUX, +MANC resulted in the highest improvement in $\bar{C}$ (12p.p.) and $\bar{D}$ (202 kg/ha). Finally, for AZOX + BENZ, improvements in $\bar{C}$

were very low (~ 3 p.p.), but in $\bar{D}$ were the highest for +MANC (190 kg/ha) and the lowest for +COPR (58 kg/ha) (Fig. 3).

3.3. Effect of moderator variable

The categorical moderator variable region did not affect control efficacy ($\bar{C}$) or yield ($\bar{D}$) estimates ($P > 0.05$). However, baseline SBR disease intensity significantly affected $\bar{C}$ and $\bar{D}$ ($P < 0.0001$). We found that $\bar{C}$ was generally lower in scenarios with high disease pressure ($\geq 80\%$). The differences in $\bar{C}$ values between low- and high-disease scenarios ranged from 1 to 20.7 percent points among the fungicide treatments. When this difference was above 10 percent points, disease baseline intensity significantly affected $\bar{C}$, as for PICO + CYPR (20.7 p.p.; $P < 0.0001$), PICO + CYPR + MANC (14.1 p.p.; $P = 0.0062$), PICO + CYPR + COPR (12.5 p.p.; $P = 0.0104$) and PICO + CYPR + CLOR (10.6 p.p.; $P = 0.0359$) (Fig. 4; Table S2). In contrast, yield response from the use of fungicides was generally greater in the high-disease than in the low-disease scenarios, with differences ranging from 83 to 486 kg/ha. Differences between low- and high-disease scenarios above 200 kg/ha significantly affected $\bar{D}$ (Fig. 4; Table S2).

3.4. Profitability of multi-site addition to the premix

The improvement in yield ($\bar{D}$) from adding the multi-site fungicide and between-study variance ($\hat{\tau}$) obtained from the meta-analysis were used to calculate the probability (P) of breaking even on multi-site costs. In general, P was affected by a range of scenarios and the variation in the multi-site cost and soybean prices. In most scenarios, probabilities were between 45 and 55%, mainly when the premixes were amended with +CLOR and +COPR (Fig. 5). A higher number of favorable scenarios ($P > 55\%$), were identified combining the premixes with +MANC (the less expensive multi-site). However, probabilities $< 45\%$ were observed in scenarios of high multi-site costs and low soybean price, especially when the premix AZOX + BENZ was combined with +CLOR and +COPR (Fig. 5).

4. Discussion

This study summarizes the benefits of tank-mixing a few selected premixes including QoI + DMI or SDHI fungicide with three different multi-site fungicides evaluated during three growing seasons (2014/15, 2015/16, and 2017/18) across a range of environments in eight Brazilian states. Most importantly, we found that the benefits tended to be

Table 2

Overall means and respective confidence intervals of log response ratio ($\bar{L}_{\text{sev}}$) and calculated percent control ($\bar{C}$) of Soybean Rust (SBR) relative to non-treated check provided by three fungicide treatments applied alone or amended with multi-site fungicides in 45 uniform field trials conducted during three growing seasons (2014/15, 2015/16 and 2017/18) in 25 municipalities across eight Brazilian states by the Anti-rust Consortium (CAF).

Premixes ^a	Multi-site ^a	k^b	Effect Size					SBR control (%)		
			$\bar{L}_{\text{sev}}$	$SE(\bar{L}_{\text{sev}})$	CI_L^c	CI_U^c	P value	$\bar{C}$	CI_L^c	CI_U^c
PICO + CYPR	–	28	–0.6586	0.0604	–0.7769	–0.5403	<0.0001	48.24	41.74	54.02
	+CLOR	28	–0.9828	0.0751	–1.1300	–0.8356	<0.0001	62.57	56.64	67.70
	+COPR	28	–0.9122	0.0686	–1.0467	–0.7777	<0.0001	59.84	54.06	64.89
	+MANC	28	–1.0171	0.0837	–1.1811	–0.8531	<0.0001	63.84	57.39	69.31
PYRA + FLUX	–	24	–1.1273	0.0903	–1.3044	–0.9502	<0.0001	67.61	61.33	72.87
	+CLOR	23	–1.3900	0.1061	–1.5981	–1.1820	<0.0001	75.09	69.33	79.77
	+COPR	24	–1.2831	0.0916	–1.4626	–1.1036	<0.0001	72.28	66.83	76.84
	+MANC	24	–1.5741	0.1330	–1.8347	–1.3134	<0.0001	79.28	73.11	84.03
AZOX + BENZ	–	28	–1.5590	0.1125	–1.7796	–1.3385	<0.0001	78.97	73.78	83.13
	+CLOR	28	–1.7410	0.1300	–1.9958	–1.4863	<0.0001	82.47	77.38	86.41
	+COPR	27	–1.6952	0.1211	–1.9324	–1.4579	<0.0001	81.64	76.73	85.52
	+MANC	27	–1.7239	0.1188	–1.9567	–1.4911	<0.0001	82.16	77.49	85.87

^a See Table 1 for complete information of the evaluated fungicides.

^b Number of trials that each fungicide was evaluated.

^c Upper (CI_U) and lower (CI_L) limits of the 95% confidence interval around $\bar{L}_{\text{sev}}$ and $\bar{C}$.

Table 3

Overall means and respective confidence intervals of difference in soybean yield ($\bar{D}$) between fungicide-treated and non-treated plots for the effect of three fungicide treatments applied alone or amended with multi-site fungicides on soybean rust severity in 45 uniform field trials conducted during three growing seasons (2014/15, 2015/16 and 2017/18) in 25 municipalities across eight Brazilian states by the Anti-rust Consortium (CAF).

Premixes ^a	Multi-site ^a	k^b	Yield response (kg/ha)				
			$\bar{D}$	SE($\bar{D}$)	CI_L^c	CI_U^c	P value
PICO + CYPR	–	28	564.52	51.54	463.49	665.55	<0.0001
	+CLOR	28	796.77	58.65	681.80	911.74	<0.0001
	+COPR	28	722.58	50.11	624.36	820.79	<0.0001
	+MANC	28	804.80	57.72	691.66	917.93	<0.0001
PYRA + FLUX	–	24	803.49	57.96	689.89	917.10	<0.0001
	+CLOR	24	926.46	67.51	794.14	1058.78	<0.0001
	+COPR	24	946.52	76.91	795.78	1097.27	<0.0001
	+MANC	24	1005.39	75.74	856.93	1153.86	<0.0001
AZOX + BENZ	–	28	1069.95	73.22	926.43	1213.47	<0.0001
	+CLOR	28	1176.46	79.22	1021.18	1331.75	<0.0001
	+COPR	28	1128.38	76.39	978.65	1278.12	<0.0001
	+MANC	28	1260.88	76.96	1110.02	1411.73	<0.0001

^a See Table 1 for complete information of the evaluated fungicides.

^b Number of trials that each fungicide was evaluated.

^c Upper (CI_U) and lower (CI_L) limits of the 95% confidence interval around $\bar{D}$.

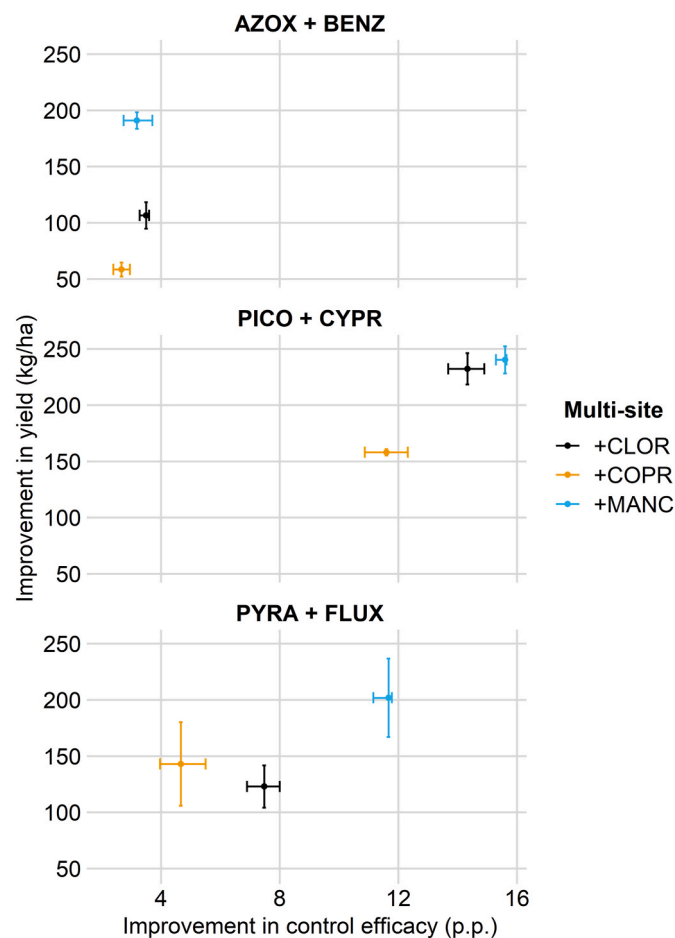


Fig. 3. Relationship between improvements in percent control efficacy (percent point; p.p.) and soybean yield (kg/ha) by active ingredient from adding multi-site fungicides (chlorothalonil [+CLOR], copper oxychloride [+COPR] and mancozeb [+MANC]) evaluated in 45 trials during three growing seasons (2014/15, 2015/16 and 2017/18) across eight Brazilian states. Vertical and horizontal error bars show the upper and lower limits of 95% confidence intervals around the overall effect for all response variables.

highest for the least effective dual premix PICO + CYPR, and the use of +MANC, given its lower price in the scenario evaluated, was more likely to be profitable compared with the other multi-sites. Finally, we found generally lower levels of SBR control and greater levels of yield response in trials with conditions conducive for severe epidemics.

The poor performance of the application of PICO + CYPR (48%) alone reported herein confirms the trend of significant decline in control efficacy determined from a previous meta-analysis (Dalla Lana et al., 2018). The previous study found a much higher efficacy (80.2%) for the same premix after summarizing the performance of fungicides using data collected from 250 UFTs conducted in a 10-year period (2004/05 to 2013/14) (Dalla Lana et al., 2018). Additionally, our previous meta-analysis (Barro et al., 2021), which summarized data from 177 UFTs conducted during six growing seasons (2014/15–2019/20) (data not included in our analysis) reported a significant decline in performance over time for the premix AZOX + BENZ, which was one of the most effective fungicides in our analysis (up to 2017/18 season), even when not tank mixed with a multi-site (78%).

Fungicide resistance in *P. pachyrhizi* populations in Brazil has been linked to declines in control efficacy over time (Barro et al., 2021; Dalla Lana et al., 2018). Indeed, the continuing use of QoIs, DMIs, and SDHIs in the past crop seasons has resulted in the selection of isolates with reduced sensitivity to those distinct chemistries (Kłosowski et al. 2016; Simões et al. 2018; Schmitz et al. 2013). Multi-site fungicides do not act systemically, as they are only surface protectants that affect different metabolic pathways of the fungus and have low resistance risk, since several mutations in target genes would be required for resistance to emerge (Thind and Hollomon, 2018). Hence, the use of premixes including single-site fungicides, such as QoI plus DMI or SDHI, tank mixed with multi-site fungicides becomes an important practice to prevent fungicide resistance (Baibakova et al., 2019; Godoy et al., 2016a; Hollomon, 2015).

In addition to being an important component in an anti-resistance strategy, this study showed that tank mixing a multi-site improved the efficacy of the site-specific premixes. However, differences in the improvement of SBR control among the multi-sites were conditioned on the premix, with +COPR performing the poorest for two premixes (PICO + CYPR and PYRA + FLUX). Moreover, previous studies summarized the sensitivity of *P. pachyrhizi* isolates to fungicides in detached leaves of soybean, and identified higher EC_{50} values (effective concentration able to reduce 50% of spore germination) for +COPR compared to +MANC and +CLOR (Chechi et al., 2020; Juliatti et al., 2017). When applied solely, Godoy et al. (2018) reported higher SBR control efficacy performed by +CLOR (52%) compared to +MANC (35%) and +COPR

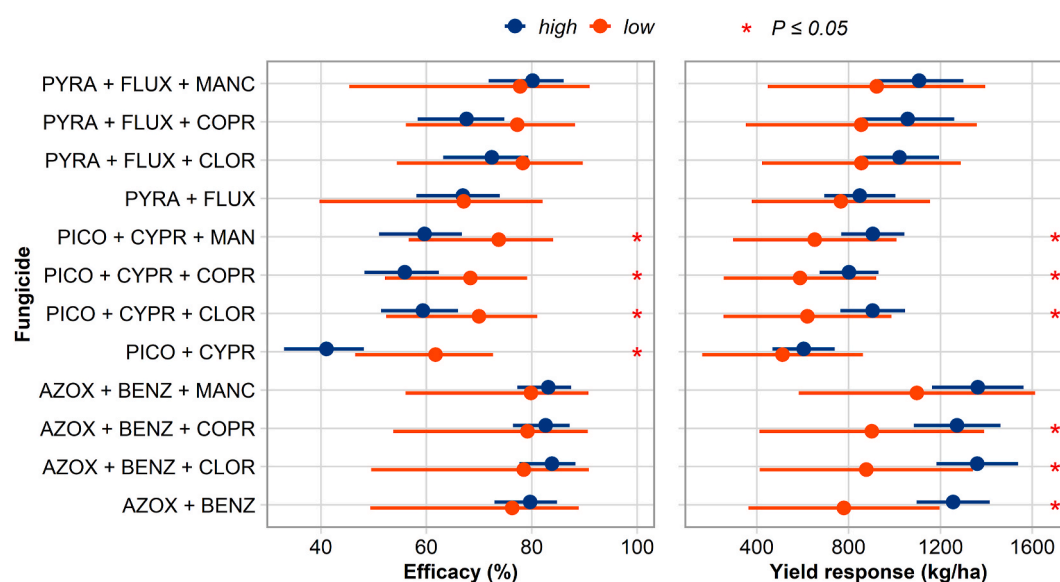


Fig. 4. Means and respective 95% confidence interval (error bars) for control efficacy (%) and soybean yield response (kg/ha) provided by fungicide treatments evaluated during three growing seasons (2014/15, 2015/16 and 2017/18) and grouped into two disease pressure classes representing low (<80% SBR severity) and high ($\geq 80\%$ SBR severity) disease scenarios. The means were calculated from back-transforming estimates by a network meta-analytic model where disease pressure was included as covariate. See Table 1 for detailed information on the fungicide treatments.

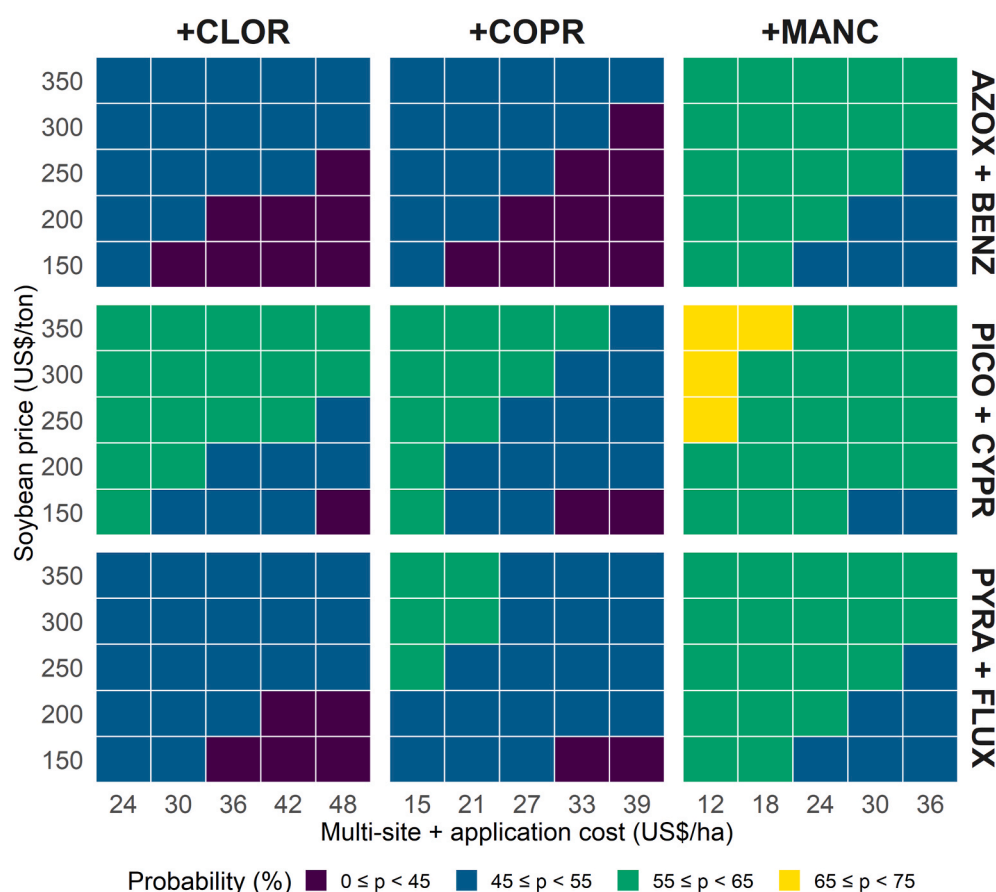


Fig. 5. Probability categories of not-offsetting on multi-site (chlorothalonil [+CLOR], copper oxychloride [+COPR] and mancozeb [+MANC]) investment for different scenarios of soybean prices and fungicide costs (multi-site product costs for three sprays [first spray at early flowering and subsequent sprays at 15 days later]) for soybean rust (SBR) control. The probability for each fungicide was calculated using the estimates of the mean yield from adding each multi-site ($\bar{D}_I = \bar{D}_{\text{fungicide} + \text{multi}} - \bar{D}_{\text{fungicide alone}}$), and the respective between-study variance ($\hat{\tau}$) obtained from a meta-analysis of 45 trials conducted over three growing seasons (2014/15, 2015/16 and 2017/18) across eight Brazilian states.

(31%) in 11 field trials during the 2017/18 growing season. However, previous studies showed + CLOR as effective as + MANC for managing SBR (Miles et al., 2007; Patil and Anahosur, 1998). For instance, Miles et al. (2007) reported similar SBR control efficacy for + CLOR (~63%) and +MANC (~67%) applied three times in field trials conducted across

three locations in Paraguay during the 2003/04 growing season.

The lowest improvement from adding + MANC was reported for the most effective premix AZOX + BENZ (3.2%; 190.9 kg/ha). However, a previous study reported enhanced benefits for AZOX + BENZ amended with +MANC (17.8%; 379/kg ha) (Enciso-Maldonado et al., 2019).

Additionally, Neto et al. (2020), during the 2016/17 growing season, reported greater improvement in SBR control efficacy for AZOX + BENZ (28%), which was applied four times and with a higher concentration (1870 g a.i.ha⁻¹) compared to the concentration applied in the trials evaluated in our analysis (1500 g a.i.ha⁻¹) for the same premix.

The expanded meta-analytic model allowed us to reduce the heterogeneity of control efficacy and yield response estimates when two classes of baseline disease were considered. As expected, higher $\bar{C}$ was found for low-disease scenarios (<80% in the non-treated check), which agrees with previous studies, where the authors also found higher SBR control efficacy in conditions of low disease pressure (Scherm et al., 2009; Delaney et al., 2018). In contrast, we found increased levels of yield response occurring under higher disease severity conditions (>80%), which agrees with the effect of fungicides on soybean diseases at increased disease levels found in previous studies (Barro et al. 2019, 2021; Delaney et al., 2018; Edwards-Molina et al., 2019).

The risk analysis showed that the probabilities of breaking even on the costs of multi-site addition depended on the premix amended, but generally were higher than 50%. The tank mix with +MANC, given its lower price, was more likely to be profitable ($P > 55\%$) compared with +CLOR and +COPR, mainly when mixed with the less effective fungicides. In case of mancozeb applied alone, six or more applications would be required to achieve a satisfactory SBR control efficacy (>80%) (Silva et al., 2015), given its moderate-to-less toxic responses to the fungus (Chechi et al., 2020) and, the fact that its residues do not persist on leaf surface due to its degradation, photolysis and wash-off (Thind and Hollomon, 2018). In this case, although mancozeb or other multi-sites are less expensive than premixes, a higher number of applications is not allowed (maximum of three sprays according to the registration) and would be less profitable considering the increase of operational costs.

In conclusion, the information provided in our study encourages the use of tank mixing commercial premix of site-specific with multi-sites, taking into account efficacy, yield response and profitability. Additionally, since fungicides with a new mode of action are not readily available, multi-sites such as mancozeb, chlorothalonil, and copper oxychloride, are options that present minimal risk for resistance, which is critical for resistance management of *P. pachyrhizi* populations, seeking to preserve the lifetime of site-specific (DMI, QoI, and SDHI) fungicides in soybean crop.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cropro.2021.105839>.

Data availability statement

The data and R scripts that support the findings of this study are openly available in the Open Science Framework project at osf.io/t34j9/. A website was generated to better visualize the scripts where all data and analyses are documented and reproducible (git.io/JZyHT).

Author's contribution

FJM and JPB contributed equally to this study. FJM, JPB and EMD conceived the idea, analyzed the data and wrote the manuscript. CVG planned and coordinated the experiments; ARD, CAF, CMU, ERAJ, FCJ, JFG, HDC, IPAJ, JMTR, JNJ, LHCP, MGC, MS, MAM, MCM, MPD, SHF, TM, VJC and WSV conducted the field trials and shared the data. All authors provided feedback and approved the final manuscript.

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