Performance and profitability of fungicides for managing soybean white mold: a 10-year summary of cooperative trials

Jhonatan P Barro[1], Maurício C Meyer[2], Claúdia V Godoy[2], Alfredo R Dias[3], Carlos M Utiamada[4], David de S Jaccoud Filho[5], Dulândula S M Wruck[6], Edson P Borges[7], Fabiano Siqueri[8], Fernando C Juliatti[9], Hércules D Campos[10], José N Junior[11], Luciana C Carneiro[12], Luis H C P da Silva[13], Mônica C Martins[14], Ricardo S Balardin[15], Roberto K Zito[2], Silvânia H Furlan[16], Wilson S Venancio[17], Emerson M Del Ponte[1]

[1] Departamento de Fitopatologia, Universidade Federal de Viçosa, 36570-000 Viçosa, MG, Brazil, [2] Embrapa Soja, 86001-970 Londrina, PR, Brazil, [3] Fundação Chapadão, 79560-000 Chapadão do Sul, MS, Brazil, [4] TAGRO, 86070-460 Londrina, PR, Brazil, [5] Departamento de Fitotecnia e Fitossanidade, Universidade Estadual de Ponta Grossa, 84030-900 Ponta Grossa, PR, Brazil, [6] Embrapa Agrossilvipastoril, 78550-970, Sinop, MT Brazil, [7] Fundação Chapadão, 79560-000 Chapadão do Sul, MS, Brazil, [8] Fundação Mato Grosso, 78750-000 Rondonópolis, MT, Brazil, [9] Universidade Federal de Uberlândia, 38400-902 Uberlândia, MG, Brazil, [10] Universidade de Rio Verde, 75901-970, Rio Verde, GO, Brazil, [11] Centro Tecnológico para Pesquisas Agropecuárias, 74130-010 Goiânia, GO, Brazil, [12] Universidade Federal de Goiás, 75801-615 Jataí, GO, Brazil, [13] AgroCarregal, 75900-000 Rio Verde, GO, Brazil, [14] Círculo Verde Assessoria Agronômica e Pesquisa, 47850-000 Luís Eduardo Magalhães, BA, Brazil, [15] Universidade Federal de Santa Maria, 97111-970 Santa Maria, RS, Brazil, [16] Instituto Biológico, 04014-900 São Paulo, SP, Brazil, [17] CWR Pesquisa Agrícola, 84035-130 *Ponta Grossa, PR, Brazil.*

*Corresponding author: delponte@ufv.br

Abstract

White mold, caused by *Sclerotinia sclerotiorum*, is a yield-limiting disease of soybean in Brazil. Uniform fungicide trials have been conducted annually since 2009. Data from 74 cooperative field trials conducted over a 10-year period were assembled. We selected five fungicides applied two times around flowering: dimoxistrobin + boscalid (DIMO+BOSC), carbendazim + procymidone (CARB+PROC), fluazinam (FLUZ), fluopyram (FLUO) and procymidone (PROC). In addition, thiophanate-methyl (TMET) applied four times was included as a low-cost treatment, for comparison. Network models were fitted to the log of white mold incidence (%) and sclerotia mass (g/ha) data and to the non-transformed yield (kg/ha) data for each treatment, including untreated check. Lowest and highest mean (95%CI) percent reduction in incidence and sclerotia mass, from back-transforming the meta-analytic estimates, was 54.2 (49.3-58.7) and 51.6 (43.7-58.3) (TMET) and 83.8 (79.1-87.5) and 87 (81.9-91.6) (CARB+PROC), respectively. The overall mean (95%CI) yield responses ranged from 323 (247.4 - 400.3) kg/ha (TMET) to 626 (521.7-731.7) kg/ha (DIMO+BOSC), but the variance was significantly explained by a binary variable (30% threshold) describing disease incidence in untreated check. On average, an increment of 352 kg/ha was estimated for trials where incidence was >30% compared to low-disease scenario. Hence, the probability of breaking even on fungicide costs for high-disease scenario was greater than 65% for the more effective, but more expensive (FLUZ) fungicide than TMET. For the low-disease scenario, profitability was less likely and depended more on variations in fungicide cost and soybean price.

White mold, also known as Sclerotinia stem rot, is a damaging disease of worldwide importance for several crops including common bean (*Phaseolus vulgaris* L.), canola (*Brassica napus* L.), cotton (*Gossypium hirsutum* L.), potato (*Solanum tuberosum* L.), soybean (*Glycine max* L.), and sunflower (*Helianthus annuus* L.) (Boland and Hall 1994). Symptoms of the disease include water-soaked stem lesions that acquire light brown coloration resulting in the appearance of dense white mycelium; severely affected plants may wilt and die prematurely (Peltier et al. 2012). In Brazil, soybean yield losses due to white mold may reach 50 to 70%, especially at high elevation regions (> 600 m) where cooler weather conditions favors the disease (Lehner et al. 2016). White mold is considered endemic to approximately 23% (≈7.7 million ha) of the soybean production area in Brazil (Meyer et al. 2016a). In the United States, estimates of cumulative economic losses as a result of white mold were 2.8 million metric tons between 2010 and 2014, with an estimated cost of $1.2 billion USD (Allen et al. 2017; Willbur et al. 2018b).

White mold is caused by *Sclerotinia sclerotiorum* (Lib.) de Bary*,* an ascomycete fungus that is capable of surviving and remaining viable for several years in soil in the form of sclerotia, a hard dark resting body consisting of a mass of hyphal threads (Adams and Ayers 1979). During moist periods and cooler temperatures (10 to 21°C), sclerotia germinate and produce multiple apothecia that release ascospores, the primary inoculum (Adams and Ayers 1979; Clarkson et al. 2014; Schwartz and Steadman 1978). Ascospores are easily dispersed throughout the canopy and escape to the atmosphere by air currents. When flowering stages are reached, the ascospores are capable of infecting the petals during disease-inducing environmental conditions: temperature between 15 to 25°C and leaf wetness of minimum 2 to 4 hours (Young et al. 2004). The infected senescing flowers provide a nutrient source and means for the fungus to disperse throughout the

canopy (petal-borne inoculum) and infect the stem and leaves. White-cottony mycelia is then formed, which eventually produces dark sclerotia of variable size (Abawi and Grogan 1975; Boland and Hall 1994; Fall et al. 2018; Lehner et al. 2016).

The disease is best managed by integrating multiple management practices including host resistance, use of healthy/treated seed, rotation with non-host species (grasses), shifting planting dates, modifying row spacing and seed density to avoid a dense canopy, and application of biological agents and fungicides (Meyer et al. 2014; Mueller et al. 2002; Peltier et al. 2012; Vieira et al. 2010; Willbur et al. 2018b; Wutzki et al. 2016). Among all tactics, the use of chemical fungicides remains the most effective tool for protecting soybean plants during flowering when the primary infection takes place (Meyer et al. 2016a; Mueller et al. 2002; Sumida et al. 2015; Wutzki et al. 2016).

In Brazil, several active ingredients from different chemical groups and mode of action have been suggested for white mold management including fluazinam (inhibitor of phosphorylation oxidative, acting on the respiration of the pathogen), procymidone (acts on osmoregulation of the fungal membranes), thiophanate-methyl (inhibits mitotic division by disturbing the assemblage of microtubules), and boscalid (inhibitor of succinate dehydrogenase, which acts on stage II of fungus respiration) (Brent and Hollomon 2007; Lehner et al. 2017; Meyer et al. 2014; Meyer et al. 2017).

A cooperative trial network was established in Brazil in 2008 to evaluate the efficacy of fungicides against white mold, and results have been reported for individual seasons (Meyer et al. 2014). As expected, the chemistries performed differently and variations, or inconsistencies, when comparing treatments, or when comparing the same treatment at different site-years are due to variation in formulation, dose, number of fungicide sprays, inoculum concentrations and

seasonal environment affecting disease and fungicide performance. A previous study in Brazil summarized performance, yield benefits and economics of one fungicide (fluazinam) evaluated in several trials conducted in the state of Paraná, south of Brazil (Tupich et al. 2017).

In the current study, we used a meta-analytical approach to summarize the effect-size (e.g., percent control and yield response) of fungicide treatments (Madden et al. 2016). Meta-analysis has gained popularity to summarize fungicide performance in plant disease management (Belova et al. 2013; Machado et al. 2017; Ojiambo et al. 2010; Paul et al. 2008; Paul et al. 2011). When multiple comparisons among treatments are of interest, network meta-analysis (NMA) has been recommended as a more powerful approach that provides more precise estimates and overcomes the limitations of the traditional pairwise meta-analysis, which compares only two treatments at a time, thus not taking the within-study correlations into account (Madden et al. 2016).

Originally developed to use data generated from trials with two arms (link between two treatments) and with a common comparator, thus allowing the indirect comparison of three treatments (A vs. B; B vs. C), NMA involves more than one common comparator (the linking treatment) that allows simultaneously both direct and indirect results from all study's arms into a single pooled effect (Salanti et al. 2008). The most common approach to NMA in plant pathology is the arm-based modeling, also known as the unconditional model, where treatment means, and not the contrasts, are used as effect-sizes (Madden et al. 2016). Several recent studies have fitted network models to fungicide trial data to obtain estimates of control efficacy and crop yield response (Machado et al. 2017; Madden et al. 2016; Ngugi et al. 2011; Paul et al. 2008).

Our main objective was to summarize the yield response, but also the relative reduction (percent control efficacy) of white mold disease incidence and sclerotia production, to selected

fungicide treatments evaluated during ten growing seasons across several locations in Brazil. In addition, the economic benefits were explored using the mean and respective variances of the meta-analytic estimates of yield response to calculate the probability of breaking-even on costs considering a range of scenarios including multiple soybean prices as well as varying fungicide costs.

Material and Methods

Data source and experimental procedures. The database of soybean yield and disease (white mold incidence and sclerotia mass) were obtained from the national cooperative white mold trial network ("Ensaios Cooperativos da Rede de Mofo Branco"). These trials were firstly established in 2008 for evaluating the performance of both registered and non-registered fungicides against soybean white mold. Most of the data used in our study have been published as yearly summaries where a combined analysis approach was used for comparing means (multiple comparison) of white mold incidence (%), sclerotia mass (g) and soybean yield (kg/ha) across all evaluated fungicide treatments within a same year. These reports were produced for yearly uniform trials conducted in 2013/14 (Meyer et al. 2015a), 2014/15 (Meyer et al. 2015b), 2015/16 (Meyer et al. 2016b), 2016/17 (Meyer et al. 2017) and 2107/18 (Meyer et al. 2018) growing seasons. The data from 2012/13 have not been published (Meyer et al. personal communication) and data from the 2008/09 to 2011/12 seasons were available at the trial level (multiple comparison made within a trial) in an earlier four-season summary report (Meyer et al. 2014). Data from the latter study have been used in a previous meta-analysis of the disease incidence-soybean yield relationship (Lehner et al. 2016).

The cooperative trials were conducted following a standard protocol as described elsewhere (Lehner et al., 2016). Briefly, the fungicides were applied two, three or four times using a backpack sprayer pressurized by CO_2 with a spray volume of 150 to 200 liter ha^{-1}. The first application was made between the beginning flowering (R1) and full flowering (R2) growth stages with subsequent applications at a fixed 10-day interval. The experiments were conducted in a randomized complete block design with four replications for each treatment, including the nontreated check. Plots were 6 m long with six rows spaced at 0.45 or 0.5 m (16.5 or 18 m^2).

White mold and yield variables. White mold intensity was assessed either at beginning seed (R5) or full seed (R6) growth stage across trials. Incidence, or the percent of diseased plants in the sample, was calculated based on the visual binary scores (0 – healthy or 1 - symptomatic) assigned to each plant of the center two rows of the plot. The center four rows of the plot were harvested either by hand or using a small-plot combiner. To prevent sclerotia from being blown out of the back of the plot combiner, the fan speed was decreased compared to normal operation so that they remain associated with the grain sample. When hand-harvested, plants were passed through a thresher to obtain the grain + sclerotia sample. In both cases, the sclerotia were manually separated from the grain. Grain weight and moisture were obtained after removing the sclerotia, and crop yield was expressed as kg/ha at 13% moisture. Sclerotia weight data were transformed to g/ha.

Criteria for treatment selection. To be included in the analysis, a fungicide treatment should have been present in at least 20 trials and over a period of four years. All but one fungicide treatment that matched the criteria were applied two times: early flowering [R1/R2]

and 10 days later, including: dimoxistrobin+boscalid (DIMO+BOSC), carbendazim+procymidone (CARB+PROC), fluazinam (FLUZ), fluopyram (FLUO), and procymidone (PROC). The only fungicide treatment applied four times on a 10-day interval starting at R1/R2 was the benzimidazole, thiophanate-methyl (TMET). This four-spray treatment (evaluated in 48 trials conducted during nine growing seasons) was included in our analysis due to being a more cost-effective fungicide. Complete information for the selected fungicide treatments are presented in Table 1.

After treatment selection, the database, with raw data at the plot (block) level (four replicates), contained data from 74 independent trials conducted at 22 locations across eight Brazilian states (Table S1). The states were grouped into Northern (n = 46 trials, MS, MT, MG, GO, and BA states) and Southern region (n = 28 trials, SP, PR, and RS states) (Fig. 1). In the Northern region, most of the trials were conducted in the state of Goiás (n = 29 trials). In the South, most trials were conducted in the state of Paraná (n = 24 trials). Together with Goiás, these trials accounted for 71.6% of all trials. During the 10-year period, the season with the greatest number of trials (n = 12) was 2011/12, followed by 2015/16 (n = 10).

The number of trials was not the same for the two response variables because some measurements were not obtained in all trials, such as sclerotia production, which was not evaluated in 16 trials, and soybean yield not evaluated in one trial. Therefore, data from all 74 trials were available for disease incidence; 58 trials for sclerotia production and 73 trials for yield.

Within the network meta-analysis context, the number of study designs (or study types), where design describes the unique combination of fungicide treatments in a study (trial in our

case) (e.g. design 1 = TMET, PROC and FLUZ; design 2 = TMET, PROC and FLUO, etc.) (Piepho 2014; Madden et al. 2016; Machado et al. 2017), was five for yield and disease incidence and eight for sclerotia production.

These study designs composed a network of treatments where both direct and indirect evidence of comparison are used in the network meta-analyses (Madden et al. 2016). A network graph is composed of nodes (fungicide treatments) and edges or links between two treatments directly compared in the same trial. The corresponding graph allows the visualization of the number of direct comparisons between two fungicide treatments as depicted by the thickness of the edges and the numbers presented at the top of the links. An example of such a network graph is presented for the treatments evaluated with regards to yield response (Fig. 2).

Meta-analytic models. Although data were available at the plot level for most trials, an aggregated measure (means of the treatment for each variable of interest) was obtained at the trial level, which is a typical approach used in meta-analysis (Madden et al. 2016). For this approach, a measure of within-study variability (inverse of the sampling variance) is required to weight studies based on sampling variance. Given the availability of data at the plot (block) level, the required within-study sampling variance was obtained from the standard deviation of the four replicates, as an alterative to the mean square error of an analysis of variance model fitted to the trial data as used elsewhere (Machado et al. 2017; Paul et al. 2008).

The main variable of interest in the current study was the yield response measured as the difference (mostly positive) between yield in the fungicide-treated plots and the nontreated plots (Machado et al. 2017; Paul et al. 2011). Since yield is related to white mold intensity (Fall et al. 2018; Lehner et al. 2016), which is known to be reduced by fungicide applications, we obtained

estimates of the mean percent reduction of incidence and sclerotia mass by the selected fungicides.

The mean absolute difference in yield was used as effect size; no transformation or standardization was required given the statistical properties of the data (Fig. S1). The yield difference was calculated directly after model fitting by subtracting estimated means for the treatments under comparison (fungicide minus nontreated) (Machado et al. 2017). For the two disease ratio variables (relative reduction of incidence and sclerotia mass) the log of the means (L_{INC} and L_{SCL})was used as effect size in the model given its better statistical properties than the ratio (Madden et al. 2016) (Fig. S1). The percent control was obtained by taking the difference of the estimated means of the logs ($\overline{L}_{INC}$or $\overline{L}_{SCL}$), which equals the ratio of the two means (Paul et al. 2008). The mean ratio was used to obtain the control efficacy ($\overline{C}$, percent reduction in the incidence or sclerotia mass) and their 95% confidence intervals (95%CI) by back-transforming mean estimates of the ratio (difference in the logs) and the respective upper and lower limits of their 95%CIs as $\overline{C}$= (1 - (exp($\overline{L}_{INC/SCL}$)) × 100) (Machado et al. 2017; Paul et al. 2009). The model can be written as Equation 1:

$$\boldsymbol{Y_i \sim N(\mu, \sum + S_i)} \quad (1)$$

Where Y_i is the vector of *L* (log of the means of incidence or sclerotia mass) or mean yield for the six treatments plus the nontreated for the *i*th study, $\boldsymbol{\mu}$ is a vector representing the mean of Y_i across all trials, $\sum$ is a 7 × 7 between-study variance-covariance matrix (for the seven treatments, including the nontreated), and $\boldsymbol{S_i}$ is within-study variance-covariance matrix for the *i*th study. An unstructured $\sum$ matrix ($\boldsymbol{N}$) was used, given its better fit to the data when comparing to simplex structures such as compound symmetry and heterogeneous compound symmetry (data not

presented). ***N*** indicates a multivariate normal distribution. A maximum likelihood estimation models were fitted to the data using the *rma.mv* function of the *metafor* package of R (Viechtbauer 2010).

Effect of moderators on yield response. The model was expanded to include moderator variables that could explain, at least in part, the heterogeneity of the effects across trials. First, we created a moderator variable for the incidence level in the check treatment (the baseline incidence). The crop yield response from using fungicides usually varies with baseline incidence: the greater the baseline disease, the greater the response, as reported for foliar diseases of maize and target leaf spot of soybean (Edwards-Molina et al. 2018; Paul et al. 2011). For white mold, incidence was reported to be strongly associated with yield losses (Lehner et al. 2016). For simplified scenarios representing a low-disease and high-disease baseline, we separated the data into two sets of epidemics, greater and equal or lower than 30% incidence, which was the median value of the nontreated plots. Second, we tested whether white mold incidence and sclerotia mass treated as continuous variables (without grouping) significantly affected estimated yield for each fungicide treatment. The moderator variables were included and tested in the model as described elsewhere (Machado et al 2017; Paul et al. 2008).

Effect of study design on network results. To test for the inconsistency of the network due to the influence of the study design, a factorial-type of anova model was used to test for the significance of the treatment × design interaction, evaluated based on the Wald test statistic. The null hypothesis suggested that the network is consistent (Madden et al. 2016; Piepho et al. 2014).

Probability of breaking-even on fungicide cost. The probability of breaking-even on the fungicide plus application cost (F_C) was calculated using the meta-analytic estimates of mean yield difference ($\overline{D}$), and respective between-study variance ($\hat{\tau}$), between fungicide-treated and nontreated means for each class of disease scenario (high or low disease in the nontreated) (Table 3). Two representative treatments were selected: FLUZ, representing a high-cost/more-effective fungicide and TMET, the low-cost/least-effective option. The probability was calculated as $p = \phi\ [(\overline{D} - F_C/S_P)/\sqrt{\hat{\tau}}]$, where ϕ is the cumulative standard-normal function (Machado et al. 2017; Paul et al. 2011); S_P is the soybean price and F_C is the fungicide costs (product + application). For each fungicide-baseline incidence, 48 scenarios were simulated (six S_P × eight F_C), totaling 192 scenarios. Average prices of the fungicides considering an exchange rate of $4.10 BRL = 1 US$ during September 2018 and fungicide price of 2017/18 crop season were: FLUZ: 40.00 US$/ha and TMET: 7.5 US$/ha. The operational costs were fixed at 10.00 US$/ha and the average soybean price used was 378 US$/ton. The cost of TMET ranged from 36 to 92 US$/ha (for four applications) and the cost of FLUZ ranged from 64 to 120 US$/ha (two applications). Tile plots of the probability classes of breaking even on fungicide costs were produced for each fungicide and disease level.

Data processing and availability. All data processing and analyses, as well as graphical work, were performed with R version 3.5.0. Texts and scripts were prepared as R Markdown documents rendered as a website for facilitating understanding of the anlaysis. All data and the analyses are documented, reproducible, and openly available for download at the Open Science Framework data repository (osf.io/v7y2e)

Results

White mold and yield variables. Disease incidence and sclerotia mass in the nontreated plots ranged from 3.6 to 100% (median = 31.8%) and from 40.1 to 17,856.3 g/ha (median = 3,294.5 g/ha). There was a large variation in white mold incidence in the nontreated plots among the years and within a year, the latter reflecting field-specific differences in initial inoculum and weather conditions (data not available). Across seasons, the greatest median incidence (65%) was recorded in the 2008/09 and the lowest median incidence (14.7%) in the 2012/13 season (Fig. 3A). Sclerotia mass was less variable than incidence among the years, with the highest amounts in 2012/13 (median = 6,730 g/ha) season and the lowest amounts in 2015/16 (median = 1,147 g/ha) season (Fig. 3B). As expected, the use of any of the fungicides resulted in reduced white mold incidence and sclerotia production compared to the nontreated. Median values for incidence and sclerotia mass were mostly below 12% and 1,000 g/ha, respectively when using the fungicides (Fig. 4).

Baseline yield ranged from 1,438 to 4,813 kg/ha (median = 2,989 kg/ha) across the trials. As expected, yield was greater in the fungicide-treated plots than in the nontreated ($P < 0.0001$) (Fig 5B). Similar to disease variables, there was a considerable variation in yield among the seasons and locations/trials within a season (each dot in Fig. 5A represents a location). The greatest median yield (3,964 kg/ha) was observed in the 2014/15 season and the lowest (2,265.0 kg/ha) during the 2008/09 crop season (Fig. 5).

Meta-analytic models. The percent control efficacy for incidence ($\overline{C}_{INC}$), obtained from back-transforming the estimated differences of the log-transformed incidence in the fungicide-

treated and nontreated ranged from 54 to 83%. Three fungicides, CARB+PROC, DIMO+BOSC and FLUO reduced incidence by at least 80%, not differing significantly among them ($P > 0.30$). These were followed by FLUZ with efficacy above 75% and differing significantly from PROC ($P = 0.0001$). The lowest control efficacy was obtained for TMET (54%), differing significantly from all other fungicides ($P < 0.0001$). The difference in percent control efficacy between the most and the least effective fungicide was 29.6 percentage points (Table 2). The Wald test for the treatment × design interaction showed that the network was consistent ($P = 0.70$).

For sclerotia mass reduction, the estimated mean control efficacy relative to the nontreated ($\overline{C}_{SCL}$), obtained from back-transforming the differences in the log-transformed original values, ranged from 51 to 87%. Again, three fungicides, which were best for reducing incidence (CARB+PROC, DIMO+BOSC and FLUO), showed the greatest percent reduction of levels greater than 80%, followed by FLUZ and PROC with reduced efficacy, but above 75%. The lowest reduction in sclerotia mass was estimated for TMET (51%), differing significantly from all other fungicides ($P < 0.0001$). The greatest efficacy was estimated for CARB+PROC, differed significantly from the three fungicides with efficacies estimated below 80% ($P < 0.05$), but not from the other two ($P > 0.3$). The difference between the most and the least effective fungicide to reduce sclerotia mass was 36.2 percentage points (Table 2). The Wald test determined that the consistency of the network was affected significantly by the study design ($P < 0.0001$).

There was a positive association between the estimated efficacies for the two disease variables, although differences between some of them are not too large. In general, the pattern was similar between the two variables with CARB+PROC and TMET being the most and least effective for reducing both white mold incidence and sclerotia mass (Fig. 6).

The mean estimates of yield difference ($\overline{D}$) between fungicide treatments and the nontreated plots ranged from 323 to 626 kg/ha among them. Yield gains as great as 600 kg/ha were estimated for three fungicides: DIMO+BOSC, FLUZ and FLUO ($P > 0.3$). These were followed by CARB+PROC (579 kg/ha), PROC (529 kg/ha) and TMET (323 kg/ha). The latter differed significantly from all other fungicides ($P < 0.0001$). The difference between the estimated means for the most and least effective fungicide was 303 kg/ha (Table 3). The Wald test for the treatment × design interaction showed that the network was consistent ($P = 0.99$).

In general, the pattern of the relationship between control efficacy for each disease variable (incidence or sclerotia) and yield differences was consistent. The fungicide treatment leading to the greatest mean disease control, CARB+PROC, was less effective than three other fungicides with regards to yield gain and similar to PROC alone, with mean efficacy estimated in 10 percentage points lower than CARB+PROC. TMET consistently provided the least yield difference and least reduction of white mold incidence (Fig. 7).

Effect of moderators on yield response. The expanded model including the categorical interaction term (baseline incidence) differed significantly from the simpler model based on the likelihood ratio test (LRT) test ($P = 0.0018$), meaning that incidence in the check explained portion of the variability in yield difference. We determined that $\overline{D}$ was generally greater in the high-disease scenario (Table 3). The differences in $\overline{D}$between the low-disease and high-disease scenario ranged from 232 kg/ha (TMET) to as high as 422 kg/ha (DIMO+BOSC) among the fungicide treatments. When these two disease variables were treated as continuous (white mold incidence and sclerotia production), they did not affect $\overline{D}$ ($P > 0.05$).

Probability of breaking-even on fungicide cost. The estimates of $\overline{D}$ and between-study variance ($\hat{\tau}$) for each baseline disease (Table 3) were then used to calculate the probability of breaking even on fungicide costs. As expected, lower probability values were in general calculated for the low-disease than high-disease scenarios, and for the fungicide that were least effective to protect yield (Fig. 8). For instance, four applications of TMET were more likely to be profitable (> 50% probability) for the high-disease scenario only. The same was found for FLUZ where probabilities ranged from 65 to 80% of breaking even on costs for the high-disease scenario. For the low-disease scenario, the higher chances of profitability (around 60%) were calculated only for the more effective/expensive fungicide.

Discussion

In this study, network meta-analytic models allowed us to compare fungicides and provide quantitative estimates of effect sizes and their uncertainty using all available evidence in a unified modeling framework (Machado et al. 2017; Paul et al. 2008). The statistical analyses of the raw data, published in the annual reports, compared treatment means (using multiple comparison tests) at the trial level or combining all trials within a season, thus failing to properly provide an overall quantitative estimate (and its uncertainty) of yield benefits from using fungicides, a variable of greater importance for decision-making and economic analysis. Other known advantages of such analysis include increased statistical power, weighting of the estimates, and treating studies as random effects, thus allowing to make inferences to all possible trials that could be conducted (Madden et al. 2016).

The expansion of the meta-analytic model allowed us to explain, at least a portion of the heterogeneity of the estimate of yield response through moderator analysis. The heterogeneity in

yield responses was reduced when considering two classes of baseline disease, which represent two production situations influenced by environment, inoculum levels and specific agronomic practices. This was expected given the strong association between white mold and soybean yield (Lehner et al. 2016) and the more limited benefit of fungicides when baseline disease is relatively low or nearly absent (Edwards-Molina et al. 2018; Paul et al. 2011). Indeed, a three-location study conducted in central Paraná, Brazil, could not detect evidence of yield benefits from using 17 treatments (combinations of fungicides and number of applications) evaluated for the control of white mold in soybean, compared with the nontreated plots (Wutzki et al. 2016). The incidence levels in those trials were below 32%, which corroborates our conclusions of reduced yield benefit from using fungicides when conditions are not overly favorable for epidemics. Interestingly, in most cases, the fungicides evaluated in that study effectively reduced disease incidence and sclerotia mass compared to the nontreated, but failed to reduce disease severity (Wutzki et al. 2016). The appraisal of the means depicted in the bar graphs for each of the three trials of the Wutzki et al. (2016) study, suggests a numerical increase in yield relative to the nontreated, for several fungicides, at levels that fall within our estimated yield gain for the low-disease scenario. The failure to detect such differences, contrary to our study, may be due to the known low power of single experiments and the focus on the means rather than effect-sizes, as in meta-analysis (Madden and Paul 2001).

Our analysis showed that three fungicides, DIMO+BOSC, FLUZ and FLUO, performed best and similarly with regards to maximizing yield: Mean estimates of yield response ranged from +765 to +821 kg/ha for the high-disease scenario. Intriguingly, CARB+PROC was ranked first with regards to disease control (both incidence and scleroria mass), but the estimated mean yield response was significantly lower than those three fungicides. In the previous meta-analysis

of the fluazinam effect on soybean yield, data from 18 experiments conducted in the central (Campos Gerais) region of PR state, Brazil, were used and an overall positive response of 413.9 kg/ha (CI95% 344.6 to 483.1) was estimated using a random-effects model (Tupich et al. 2017). That mean estimate is lower than what we obtained in the current study (523 to 723 kg/ha) for FLUZ applied twice. The authors also tested the effect of two disease categories as moderator of the yield responses (15% threshold for severity and 35% threshold for incidence). However, contrary to our findings, the moderator did not affect yield gain. In that work, the number of entries (21 and 24) was much lower than in our study (73 entries) and evaluated treatments with one, two or three applications of FLUZ. Such differences may explain incongruence in the findings likely due to lower power of the study and trial-specific conditions. One noteworthy outcome, when the disease variables were treated as continuous in our expanded models, they did not significantly affect yield response. We believe that obtaining estimates of the two categories of disease, for which a significant difference was determined, is more important. Although it throws away the detail information about the variation in the values of the predictors when the variable is continuous (e.g. all range of incidence), comparing the two groups (low-disaese and high-disase) is of more practical value for decision making, especially for cases when an epidemic risk information is available, such as how likely an epidemic of concern will occur (De Wolf et al. 2003). Finally, the relationship between the disease incidence/sclerotia mass did not appear linear (data not presented) and so the categorization was a more straightforward approach to learn about the relationship than fitting more complicated non-linear models.

In a previous two-year study in southern Brazil, FLUZ and PROC applied twice during flowering produced similar control efficacy when considering incidence or severity values.

However, PROC led to greater reduction of sclerotia mass than FLUZ, which is in agreement with our results (Berger Neto et al. 2017). The authors suggested that this difference is likely due to to the systemicity of PROC that extends the effect of the fungicide, preventing mycelium formation.

Our results showed that TMET, although applied four times, was the least effective for white mold control. In the midwestern United States, Mueller et al. (2002) reported 63% efficacy of TMET applied twice during soybean flowering, which is above our estimated confidence interval for this benzimidazole fungicide. Such difference may be partially explained by location-specific factors and different doses, 0.84 to 1.12 kg/a.i./ha, which were greater than the doses applied in the Brazilian trials (0.5 kg/a.i./ha). Although least effective as determined by yield, our risk analysis showed that yield response from applying four sprays of TMET may likely result in break-even costs under more favorable conditions for epidemics, given its lower cost compared to the most effective (but more expensive) fungicides. However, greater probabilities were estimated for FLUZ, which is less prone to the development of fungicide resistance compared with TMET (Koenraadt et al. 1992; Lehner et al. 2015). Studies on fungicide resistance in Brazilian *S. sclerotiorum* populations are scarce and a recent work has reported the presence of a TMET-resistant strain isolated from common bean (*Phaseolus vulgaris* L.) plants in a production region where this fungicide is regularly used (Lehner et al. 2015). Additional studies are needed to investigate whether TMET-resistant populations are present in soybean regions where application of this fungicide targeting white mold is frequent. Given the availability of more profitable fungicides and the risk of resistance, the use of TMET should not be encouraged in favor of the most effective yet profitable ones. Whether one or two sequential sprays of TMET or FLUZ are needed, our results determined that probability of

breaking-even on direct costs, (fungicide plus application) was lower and the estimated mean yield response more uncertain (wider confidence interval) under the low-disease rather than the high-disease risk scenario.

The information provided in our study may be of greater value should it be incorporated into a decision support system that takes not only economic scenarios (soybean price and application costs), but also disease risk into account, using white mold forecasting models such as the one recently developed in the U.S. for soybean (Willbur et al. 2018a). We are not aware of warning systems being used for predicting white mold on Brazilian soybean. The current database of the cooperative trials provides important resource for validating existing models or developing new ones specific to Brazilian conditions.

Acknowledgements

The authors are thankful to the Programa de Pós-graduação em Fitopatologia (UFV) and CNPq - Conselho Nacional de Desenvolvimento Científico e Tecnológico for providing a graduate scholarship to J. P. Barro and the CNPq for a research fellowship for E. M. Del Ponte. The authors are thankful to Dr. Eduardo S. G. Mizubuti and Dr. Sarah J. Pethybridge for their useful comments in an earlier draft of the manuscript.

LITERATURE CITED

Abawi, G. S., and Grogan, R. G. 1979. Epidemiology of diseases caused by *Sclerotinia* species. Phytopathology 69:899-904.

Adams, P., and Ayers, W. A. 1979. Ecology of *Sclerotinia* species. Phytopathology 69:896-898.

Allen, T. W., Bradley, C. A., Sisson, A. J., Byamukama, E., Chilvers, M. I., Coker, C. M., Collins, A. A., Damicone, J. P., Dorrance, A. E., Dufault, N. S., Esker, P. D., Faske, T. R., Giesler, L. J., Grybauskas, P., Hershman, D. E., Hollier, C. A., Isakeit, T., Jardine, D. J., Kemerait, R. C., Kleczewski, N. M., Koenning, S. R., Kurle, J. E., Malvick, D. K., Markell, S. G., Mehl, H. L., Mueller, D. S., Mueller, J. D., Mulrooney, R. P., Nelson, B. D., Newman, M. A., Osborne, L., Overstreet, C., Padgett, G. B., Phipps, P. M., Price, P. P., Sikora, E. J., Smith, D. L., Spurlock, T. N., Tande, C. A., Tenuta, A. U., Wise, K., Wrather, J. A., Young-Kelly, H. 2017. Soybean yield loss estimates due to diseases in the United States and Ontario, Canada from 2010 to 2014. Plant Health Progress 18:19-27.

Belova, A., Narayan, T., and Olkin, I. 2013. Methyl bromide alternatives for strawberry and tomato pre-plant uses: A meta-analysis. Crop Prot. 54:1-14.

Berger-Neto, A., Jaccoud-Filho, D. S., Wutzki, C. R., Tullio, H. E., Pierre, M. L. C., Manfron, and F., Justino, J. 2017. Effect of spray droplet size, spray volume and fungicide on the control of white mold in soybeans. Crop Prot. 92:190-197.

Boland, G. J., and Hall, R. 1994. Index of plant hosts of *Sclerotinia sclerotiorum*. Can. J. Plant Pathol. 16:93-108.

Brent, K. J., and Hollomon, D. W. 2007. Fungicide resistance in crop pathogens: how can it be managed? FRAC Monograph No. 1 (second, revised edition). Fungicide Resistance Action Committee.

Clarkson, J. P., Fawcett, L., Anthony, S. G., and Young, C. 2014. A model for *Sclerotinia sclerotiorum* infection and disease development in lettuce, based on the effects of temperature, relative humidity and ascospore density. PLoS One 9:15-25.

De Wolf, E. D., Madden, L. V., and Lipps, P. E. 2003. Risk assessment models for wheat Fusarium head blight epidemics based on whithin-season weather data. Phytopathology 93:428-435.

Edwards-Molina, J. P., Paul, P. A., Amorim, L., da Silva, L. H. C. P., Siqueri, F. V., Borges, E. P., Campos, H. D., Nunes Junior, J., Meyer, M. C., and Martins, M. C. 2019. Meta-analysis of fungicides efficacy on soybean target spot and cost-benefit assessment. Plant Pathol. 68:94-106.

Fall, M. L., Boyse, J. F., Wang, D., Willbur, J. F., Smith, D. L., and Chilvers, M. I. 2018. Case study of an epidemiological approach dissecting historical soybean Sclerotinia stem rot observations and identifying environmental predictors of epidemics and yield loss. Phytopathology 108:469-478.

Lehner, M. S., Paula Júnior, T. J., Silva, R. A., Vieira, R. F., Carneiro, J. E. S., Schnabel, G., and Mizubuti, E. S. G. 2015. Fungicide sensitivity of *Sclerotinia sclerotiorum*: A thorough assessment using discriminatory dose, EC_{50}, high resolution melting analysis and description of new point mutation associated with tiophanate-methyl resistance. Plant Dis. 99:1537-1543.

Koenraadt, H., Somerville, S. C., and Jones, A. L. 1992. Characterization of mutations in the beta-tubulin gene of benomyl-resistant field strains of *Venturia inaequalis* and other plant pathogenic fungi. Phytopathology 82: 1348-1354.

Lehner, M. S., Pethybridge, S. J., Meyer, M. C., and Del Ponte, E. M. 2016. Meta-analytic modelling of the incidence–yield and incidence–sclerotial production relationships in soybean white mould epidemics. Plant Pathol. 66:460-468.

Lehner, M. S., Del Ponte, E. M., Gugino, B. K., Kikkert, J. R., and Pethybridge, S. J. 2017 Sensitivity and efficacy of boscalid, fluazinam, and thiophanate-methyl for white mold control in snap bean in New York. Plant Dis. 101:1253-1258.

Machado, F. J., Santana, F. M., Lau, D., and Del Ponte, E. M. 2017. Quantitative review of the effects of triazole and benzimidazole fungicides on Fusarium head blight and wheat yield in Brazil. Plant Dis. 101:1633-1641.

Madden, L. V., and Paul, P. A. 2011. Meta-analysis for evidence synthesis in plant pathology: An overview. Phytopathology 101:16-30.

Madden, L. V., Piepho, H. P., and Paul, P. A. 2016. Statistical models and methods for network meta-analysis. Phytopathology 106:792-806.

Meyer, M. C., Campos, H. D., Godoy, C. V., and Utiamada, C. M., 2014. Ensaios cooperativos de controle químico de mofo branco na cultura da soja: safras 2009 a 2012. Documentos 345. Embrapa Soja, Londrina, Brazil.

Meyer, M. C., Campos, H. D., Godoy, C. V., and Utiamada, C. M. 2016a. Ensaios cooperativos de controle biológico de mofo-branco na cultura da soja - safras 2012 a 2015. Documento 368. Embrapa Soja, Londrina, Brazil.

Meyer, M. C., Campos, H. D., Godoy, C. V., Utiamada, C. M., Pimenta, C. B., Machado, A. Q. Neto, D. C., Jaccoud Filho, D. S. D. S., Borges, E. P., Siqueri, F. V., Juliatti, F. C., Nunes Junior, J., Carneiro, L. C., Silva, L. H. C. P., Madalosso, M., and Balardin, R. S. 2015a. Eficiência de fungicidas para controle de mofo-branco (*Sclerotinia sclerotiorum)* em soja, na safra 2013/2014: Resultados sumarizados dos ensaios cooperativos. Circular Técnica 109. Embrapa Soja, Londrina, Brazil.

Meyer, M. C., Campos, H. D., Godoy, C. V., Utiamada, C. M., Pimenta, C. B., Jaccoud Filho, D. S., Borges, E. P., Siqueri, F. V., Juliatti, F. C., Nunes Junior, J., Carneiro, L. C., Silva, L. H. C.

P., Sato, L. N., Madalosso, M., Martins, M. C., Balardin, R. S., Silva, S. A., and Venancio, W. S. 2015b. Eficiência de fungicidas para controle de mofo-branco (*Sclerotinia sclerotiorum)* em soja, na safra 2014/2015: Resultados sumarizados dos ensaios cooperativos. Circular Técnica 114. Embrapa Soja, Londrina, Brazil.

Meyer, M. C., Campos, H. D., Godoy, C. V., Utiamada, C. M., Pimenta, C. B., Jaccoud Filho, D. S., Borges, E. P., Juliatti, F. C., Nunes Junior, J., Carneiro, L. C., Silva, L. H. C. P., Sato, L. N., Madalosso, M., Goussain, M., Martins, M. C., Debortoli, M. P., Balardin, R. S., and Venancio, W. S. 2016b. Eficiência de fungicidas para controle de mofo-branco (*Sclerotinia sclerotiorum*) em soja, na safra 2015/2016: Resultados sumarizados dos ensaios cooperativos. Circular Técnica 122. Embrapa Soja, Londrina, Brazil.

Meyer, M. C., Campos, H. D., Godoy, C. V., Utiamada, C. M., Pimenta, C. B., Jaccoud Filho, D. S. D. S., Borges, E. P., Juliatti, F. C., Nunes Junior, J., Carneiro, L. C., Silva, L. H. C. P., Sato, L. N., Goussain, M., Martins, M. C., Tormen, N. R., Balardin, S. A., and Venancio, W. S. 2017. Eficiência de fungicidas para controle de mofo-branco (*Sclerotinia sclerotiorum)* em soja, na safra 2016/17: Resultados sumarizados dos ensaios cooperativos. Circular Técnica 133. Embrapa Soja, Londrina, Brazil.

Meyer, M. C., Campos H. D., Godoy, C. V., Utiamada, C. M., Seii, A. H., Dias, A. R., Jaccoud Filho, D. S., Borges, E. P., Juliatti, F. C., Nunes Junior, J., Silva, L. H. C. P., Sato, L. N., Martins, M. C., and Venancio, W. S. 2018. Eficiência de fungicidas para controle de mofo-branco (*Sclerotinia sclerotiorum*) em soja, na safra 2017/18: Resultados sumarizados dos ensaios cooperativos. Circular Técnica 140. Embrapa Soja, Londrina, Brazil.

Mueller, D. S., Dorrance, A. E., Derksen, R. C., Ozkan, E., Kurle, J. E., Grau, C. R., Gaska, J. M., Hartman, G. L., Bradley, C. A., and Pedersen, W. L. 2002. Efficacy of fungicides on *Sclerotinia sclerotiorum* and their potential for control of Sclerotinia stem rot on soybean. Plant Dis. 86:26-31.

Ngugi, H. K., Lehman, B. L., and Madden, L. V. 2011. Multiple treatment meta-analysis of products evaluated for control of fire blight in the eastern United States. Phytopathology 101:512-522.

Ojiambo, P. S., Paul, P. A., and Holmes, G. J. 2010. A quantitative review of fungicide efficacy for managing downy mildew in cucurbits. Phytopathology 100:1066-1076.

Paul, P. A., Madden, L. V., Bradley, C. A., Robertson, A. E., Munkvold, G. P., Shaner, G., Malvick, D. K., Allen, T. W., Grybauskas, A., Vincelli, P., and Esker P. 2011. Meta-analysis of yield response of hybrid field corn to foliar fungicides in the U.S. Corn belt. Phytopathology 101:1122-1132.

Paul, P. A., Lipps, P. E., Hershman, D. E., McMullen, M. P., Draper, M. A., and Madden, L. V. 2008. Efficacy of triazole-based fungicides for Fusarium head blight and deoxynivalenol control in wheat: A multivariate meta-analysis. Phytopathology 98:999-1011.

Peltier, A. J., Bradley, C. A., Chilvers, M. I., Malvick, D. K., Mueller, D. S., and Wise, K. A. 2012. Biology, yield loss and control of sclerotinia stem rot of soybean. J. Integr. Pest Manag. 3:1-7.

Piepho, H. P. 2014. Network meta-analysis made easy: Detection of inconsistency using factorial analysis-of-variance models. BMC Med. Res. Methodol. 14:61.

Salanti, G., Higgins, J. P. T., Ades, A. E., and Ioannidis, J. P. A. 2008. Evaluation of networks of randomized trials. Stat. Methods Med. Res. 17:279-301.

Schwartz, H. F., and Steadman, J. R. 1978. Factors affecting sclerotium populations of, and apothecium production by, *Sclerotinia sclerotiorum*. Phytopathology 68:383-388.

Sumida, C. H., Canteri, M. G., Peitl, D. C., Tibolla, F., Orsini, I. P., and Araújo, F. A. 2015. Chemical and biological control of sclerotinia stem rot in the soybean crop. Ciência Rural:760-766.

Tupich, F. L. B., Fantin, L. H., Silva, A. L. da, and Canteri, M. G. 2017. Impacto do controle do mofo-branco com fluazinam na produtividade da soja no Sul do Paraná: metanálise. Summa Phytopathol. 43:145-150.

Vieira, R. F., Paula Júnior, T. J., Teixeira, H., and de S. Carneiro, J. E. 2010. White mold management in common bean by increasing within-row distance between plants. Plant Dis. 94:361-367.

Viechtbauer, W. 2010. Conducting Meta-analyses in R with the metafor Package. J. Stat. Softw. 36:1-48.

Willbur, J.F., Fall, M.L., Bloomingdale, C., Byrne, A.M., Chapman, S.A., Isard, S.A., Magarey, R.D., McCaghey, M., Mueller, B.D., Russo, J.M., Schlegel, J., Chilvers, M.I., Mueller, D.S., Kabbage, M., and Smith, D.L. 2018a. Weather-based models for assessing the risk of *Sclerotinia sclerotiorum* apothecial presence in soybean (*Glycine max*) fields. Plant Dis. 102:73-84.

Willbur, J. F., McCaghey, M., Kabbage, M., and Smith, D. L. 2018b. An overview of the *Sclerotinia sclerotiorum* pathosystem in soybean: impact, fungal biology, and current management strategies. Trop. Plant Pathol. https://doi.org/10.1007/s40858-018-0250-0

Wutzki, C. R., Jaccoud Filho, D. S., Berger Neto, A., Tullio, H. E., Juliatti, F. C., and Nascimento, A. J. 2016. Redução do nível de mofo-branco na soja pelo manejo de fungicidas. Biosci. J. 32:642-651.

Young, C. S., Clarkson, J. P., Smith, J. A., Watling, M., Phelps, K., and Whipps, J. M. 2004. Environmental conditions influencing *Sclerotinia sclerotiorum* infection and disease development in lettuce. Plant Pathol. 53:387-397.

Table 1: Information of fungicide treatments applied for controlling white mold (*Sclerotinia sclerotiorum*) on soybean which were evaluated in 74 cooperative fungicide trials conducted yearly from 2008/9 to 2017/18 in Brazil

Fungicide a.i.	Study code	Commercial name	Sprays[a]	FRAC[b]	Dose (g/ha)
Dimoxystrobin+Boscalid	DIMO+BOSC	Spot	2	11 + 7	0.4
Fluazinam	FLUZ	Frowncide	2	29	0.5
Fluopyram	FLUO	PNR[c] + Aureo[d]	2	7	0.2
Procymidone	PROC	Sumilex	2	2	0.5
Carbendazim+Procymidone	CARB+PROC	Carbomax + Sialex	2	1 + 2	0.5 + 0.5
Thiophanate-methyl	TMET	Cercobin	4	1	0.5

[a] Number of applications: first spray at flowering and the following 10 days apart.
[b] Fungicide Resistance Action Committee (FRAC) code.
[c] PNR = Product Not Registered.
[d] Adjuvant.

Table 2: Overall means[a] and respective lower and upper 95% confidence intervals (CI_L and CI_U) of control efficacy (percent reduction) of white mold incidence ($\overline{C}_{INC}$) and sclerotia mass ($\overline{C}_{SCL}$) for selected fungicide treatments evaluated during ten years (2008/9 to 2017/18) across 74 field trials

	Incidence control (%)				Sclerotia mass control (%)			
Fungicide[a]	***K*[b]**	$\overline{C}_{INC}$	CI_L	CI_U	***k***	$\overline{C}_{SCL}$	CI_L	CI_U
CARB+PROC	27	83.8	79.1	87.5	22	87.7	81.9	91.6
DIMO+BOSC	72	82.2	78.8	84.9	54	85.7	81.9	88.8
FLUO	73	81.7	78.1	84.8	54	83.3	79.6	86.3
FLUZ	74	78.1	74.6	81.1	56	76.1	70.1	80.9
PROC	74	74.4	70.5	77.8	58	78.2	71.9	83.0
TMET	62	54.2	49.3	58.7	48	51.6	43.7	58.3

[a] An arm-based network meta-analysis was fitted to the log of the original treatment means weighted by the inverse of the sampling variance prior to obtain the reported control efficacy.

CARB+PROC = Carbendazim (0.5 g/ha) + Procymidone (0.5 g/ha), DIMO+BOSC = Dimoxystrobin + Boscalid (0.4 g/ha), FLUO = Fluopyram (0.2 g/ha), FLUZ = Fluazinam (0.5 g/ha), PROC = Procymidone (0.5 g/ha), TMET = Thiophanate-methyl (0.5 g/ha).

[b] Number of trials that each fungicide was evaluated.

Table 3. Statistics for the estimates of the mean and respective lower and upper 95% confidence intervals (CI_L and CI_U) yield response or difference ($\overline{D}$) between fungicide-treated and non-treated plots not conditioned (overall estimate) and conditioned (moderator analysis) to categorized white mold incidence on soybean representing a low (incidence in the non-treated check < 30%) or high disease (incidence > 30%) scenario, which significantly reduced heterogeneity of the estimates using data from 74 field trials conducted in Brazil from 2008/2009 to 2017/2018

Fungicide[a]	*k*[b]	Condition	$\overline{D}$	CI_L	CI_U	*P-value*[c]	*tau* ($\hat{\tau}$)[d]
DIMO+BOSC	72	Overall	626.7	521.7	731.7		
	38	High disease	821.1	694.3	947.9	<0.0001	651,600.53
	34	Low disease	398.9	85.1	712.6		
FLUZ	73	Overall	623.4	523.5	723.3		
	38	High disease	801.8	677.9	925.8	<0.0001	622,757.23
	35	Low disease	419.0	114.0	724.0		
FLUO	73	Overall	602.6	513.1	692.0		
	39	High disease	765.9	657.1	874.7	<0.0001	630,246.18
	34	Low disease	413.4	143.7	683.1		
CARB+PROC	27	Overall	579.7	463.2	696.3		
	10	High disease	763.2	604.1	922.4	0.0006	663,656.94
	17	Low disease	375.8	-3.6	755.3		
PROC	72	Overall	529.6	440.7	618.6		
	38	High disease	685.6	575.9	795.2	<0.0001	596,457.08
	34	Low disease	346.2	73.1	619.3		
TMET	62	Overall	323.8	247.4	400.3		
	34	High disease	431.2	333.0	529.5	0.0015	495,396.05
	28	Low	198.8	-43.2	440.8		

[a] CARB+PROC = Carbendazim (0.5 g/ha) +Procymidone (0.5 g/ha), DIMO+BOSC = Dimoxystrobin + Boscalid (0.4 g/ha), FLUO = Fluopyram (0.2 g/ha), FLUZ = Fluazinam (0.5 g/ha), PROC = Procymidone (0.5 g/ha), TMET = Thiophanate-methyl (0.5 g/ha).

[b] Number of trials that each fungicide was evaluated.

[c] Probability value (significance level) for the effect of fungicide on yield gain (at the selected baseline disease).

[d] Between-study variance.

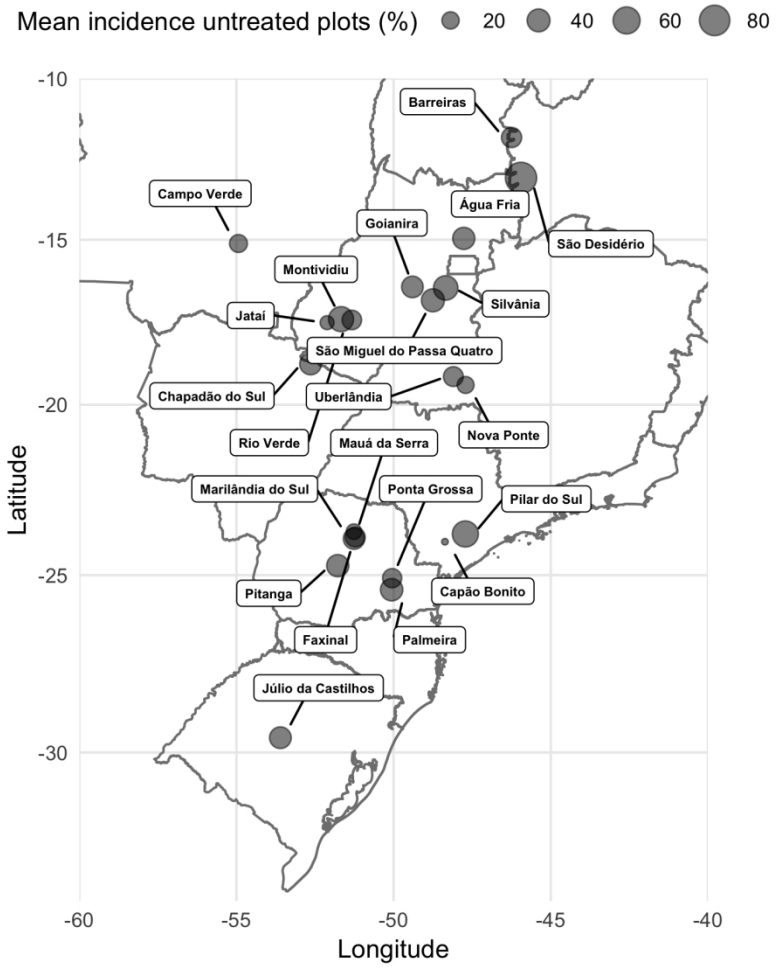

Figure 1. Geolocation and names of the 22 municipalities from eight states of Brazil where uniform fungicide trials (n = 74) were conducted and white mold incidence, sclerotia mass production and soybean yield were recorded. The size of the circle is proportional to the mean of white mold incidence in the nontreated check plot across trials and years.

635x635mm (72 x 72 DPI)

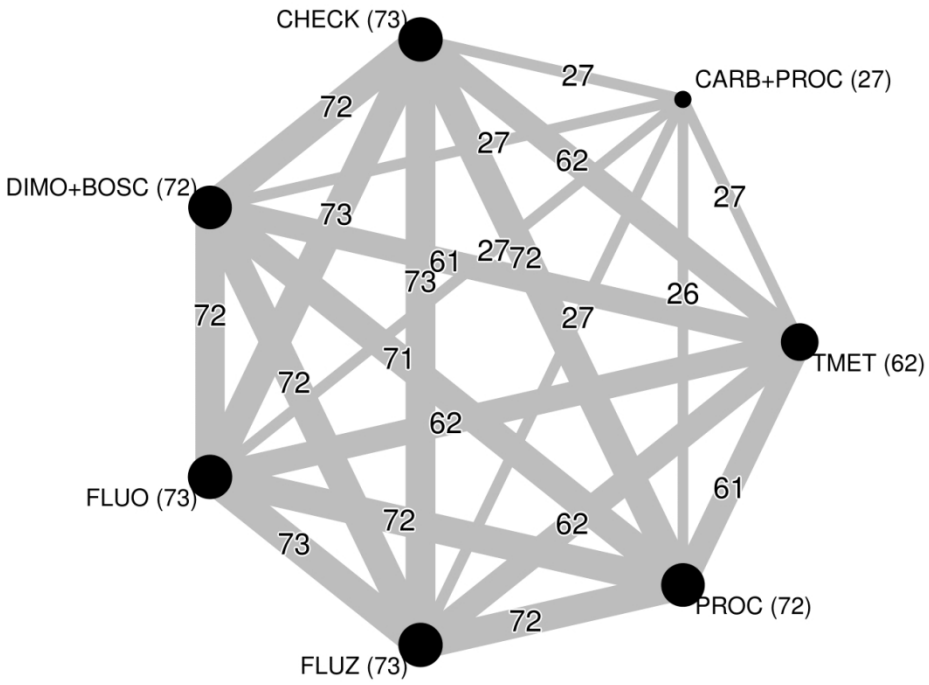

Figure 2. Network of pairwise treatment comparisons in 73 trials for estimating differences in soybean yield conducted in Brazil from 2008/9 to 2017/18. Five fungicides (FLUO = fluopyran; FLUZ = fluazinam; PROC = procymidone; DIMO + BOSC = dimoxistrobin + boscalid and CARB + PROC = carbendazim + procymidone) were applied twice (flowering and ten days later) and one applied four times (TMET: thiophanate-methyl). Line width is proportional to the number of pairwise comparison of two fungicides in the same trial. Circle size is proportional to the number of trials (within parenthesis).

493x493mm (72 x 72 DPI)

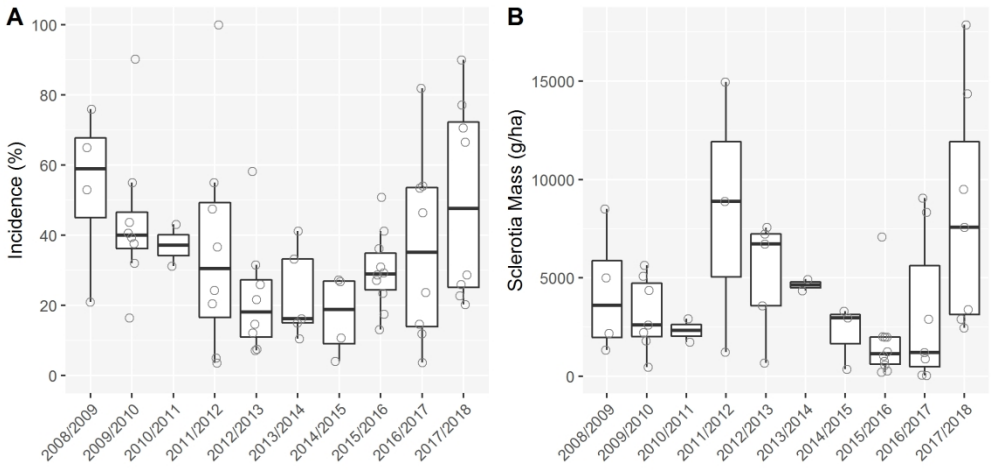

Figure 3: Boxplots for the within-season variation (across trials) of mean white mold incidence (A) and sclerotia mass (B) in the untreated check of 72 fungicide trials conducted in Brazil from 2008/9 to 2016/17. The thick horizontal line inside the box represents the median, the limits of the box represent the lower and upper quartiles, and the circles represents yearly means of each fungicide treatment (See Table 1).

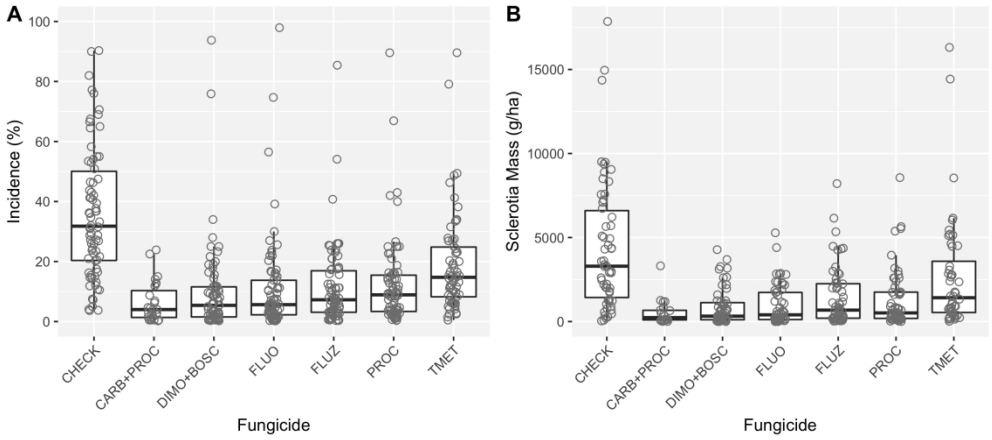

Figure 4: Box plots and individual means of white mold incidence (%) (A) and sclerotia mass production (g/ha) (B). The treatments consisted of a nontreated check (CHECK) or treated with two sprays of dimoxystrobin+boscalid (DIMO+BOSC), fluazinam (FLUZ), fluopyram (FLUO), procymidone (PROC), carbendazim + procymidone (CARB+PROC), and thiophanate-methyl (TMET) applied four times. The line inside the box represents the median and the circles represents each treatment mean.

952x423mm (72 x 72 DPI)

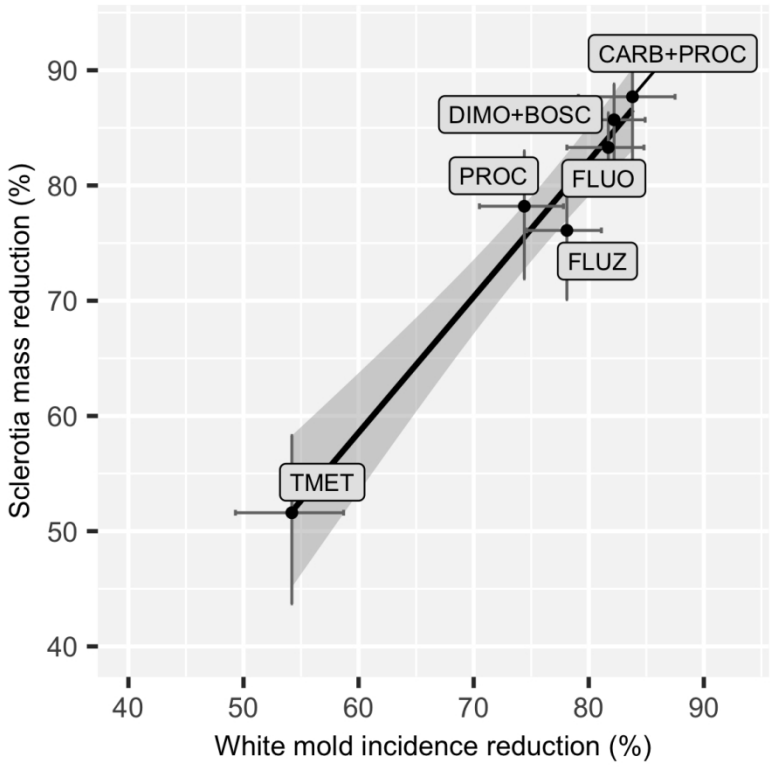

Figure 5: Relationship between percent reduction of white mold incidence (%) and percent reduction of sclerotia mass (%) for five fungicides applied twice (flowering and 10 days later) and one applied four times (TMET) evaluated in a network meta-analysis of 74 trials from 2008/9 to 2017/18 in Brazil. Vertical and horizontal error bars represent the upper and lower limits of 95% confidence intervals around mean estimates for both response variables. FLUO = fluopyran; FLUZ = fluazinam, PROC = procymidone, DIMO + BOSC = dimoxistrobin + boscalid, CARB + PROC = carbendazim + procymidone, TMET: thiophanate-methyl.

529x423mm (72 x 72 DPI)

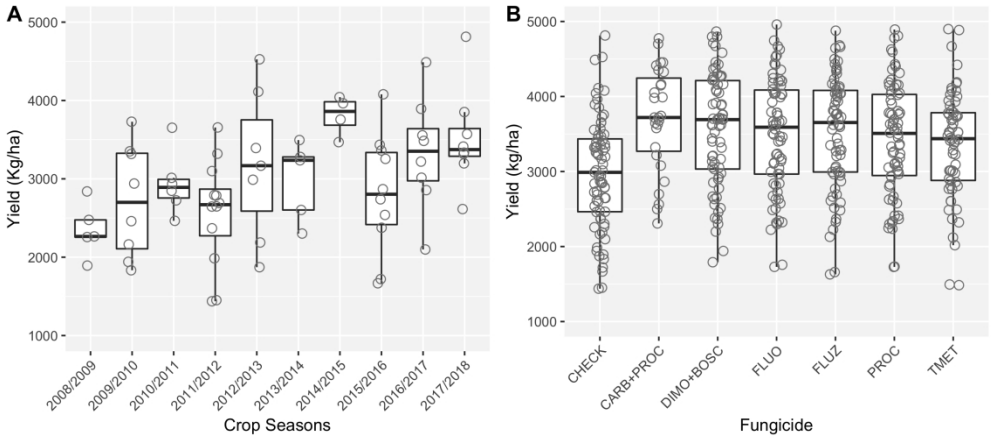

Figure 6: Box plots for the means of grain yield (kg/ha) in the non-treated check (CHECK) plots of trials conducted during ten years (A) and means for a set of fungicide treatments evaluated in 74 trials (B). Fungicides evaluated were applied twice at flowering and 10 days later: dimoxystrobin+boscalid (DIMO+BOSC), fluazinam (FLUZ), fluopyram (FLUO), procymidone (PROC) and carbendazim + procymidone (CARB+PROC). Thiophanate-methyl (TMET) was applied four times.

952x423mm (72 x 72 DPI)

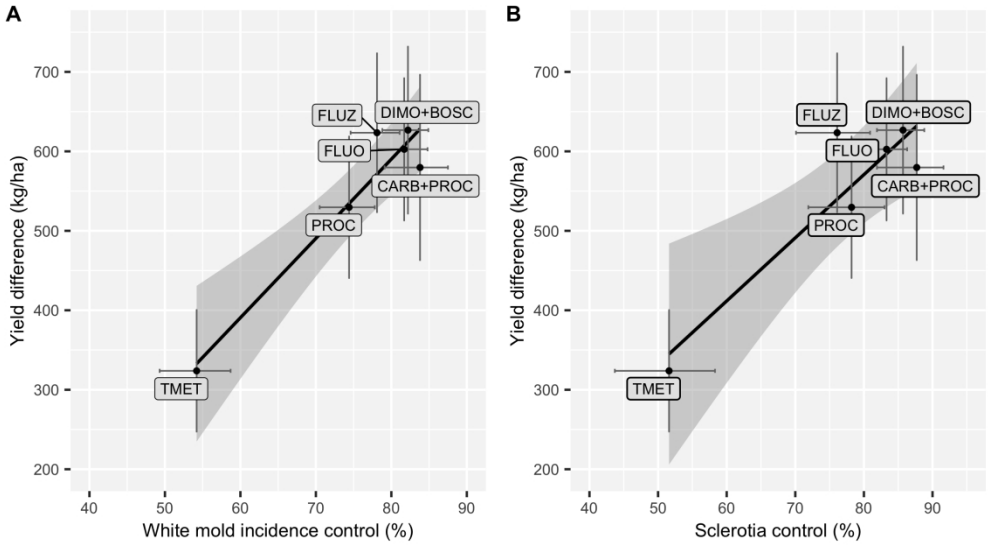

Figure 7: Relationship between percent reduction of white mold incidence (A) or sclerotia amount (B) and yield increase relative to non-treated plots, for five fungicides applied twice (flowering and 10 days later) and one applied four times (TMET: thiofanate-methyl). Data were obtained from a cooperative network of 74 independent fungicide trials in Brazil from 2008/9 to 2017/18. Bars show the upper and lower limits of 95% confidence intervals around black point estimates for both responses. FLUO = fluopyran; FLUZ = fluazinam, PROC = procymidone, DIMO + BOSC = dimoxistrobin + boscalid, CARB + PROC = carbendazim + procymidone, TMET: thiophanate-methyl.

952x529mm (72 x 72 DPI)

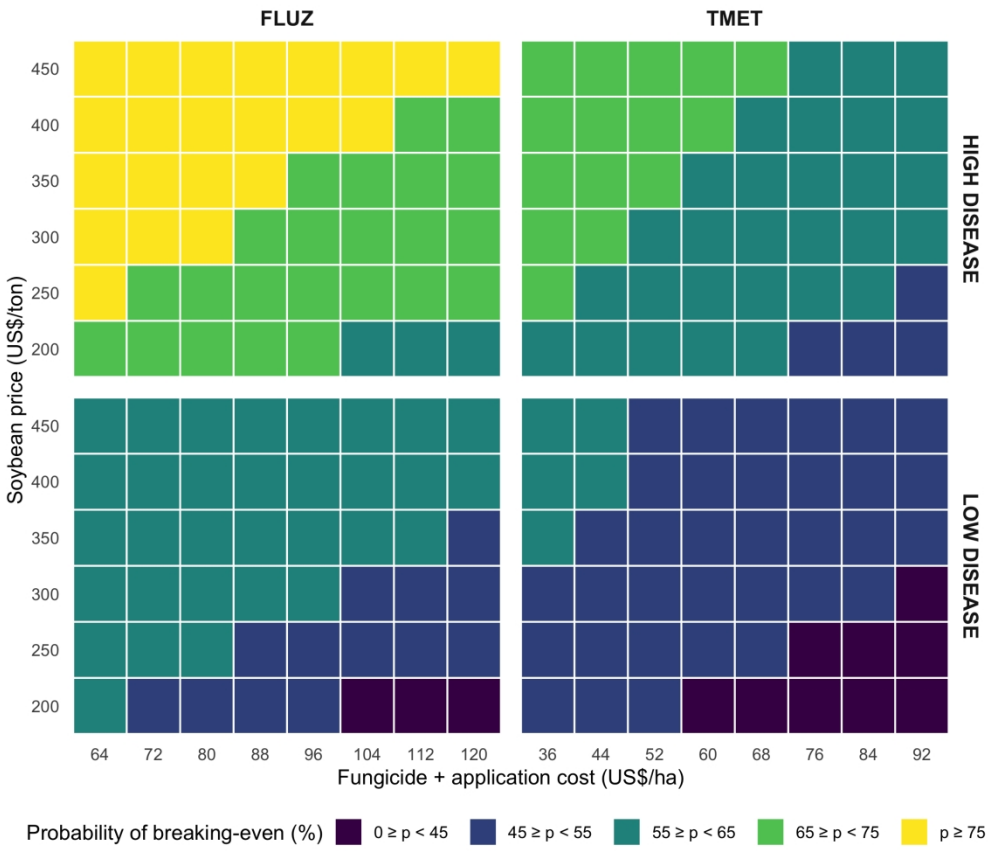

Figure 8: Probability categories of breaking even on fungicide investment for different scenarios of soybean prices and fungicide costs (product price + operational costs [fixed at $10.00 U.S./]) for fluazinam (FLUZ) applied twice (flowering and 10 days later), and thiophanate-methyl (TMET) applied four times (flowering and 10-day intervals) for white mold control. Probability for each fungicide treatment was calculated using the estimates of the mean difference (D), and respective between-study variance (), conditioned to disease class representing a low-disease (incidence < 30%) or a high-disease (incidence ≥ 30%) scenario (Table 3), obtained from meta-analysis of data from 74 trials conducted over ten growing seasons in Brazil.

846x740mm (72 x 72 DPI)

Supplemental material

Table S1: Summary information for 72 trials where it was tested the effect of dimoxystrobin+boscalid (DIMO+BOSC), fluazinam (FLUZ), fluopyram (FLUO), procymidone (PROC), thiophanate-methyl (TIOF) and carbendazim + procymidone (CARB+PROC) applied twice (flowering and 10 days later) and thiophanate-methyl (TMET) applied four times (flowering and 10-day intervals) on white mold control in Brazil from 2008/9 to 2016/17.

Trial	Season	Location	Long	Lat	State	Elevation	Region	Cultivar
1	2008/09	Montividiu	51°40’05”	17°25’17”	GO	921	Northern	P98Y11
2	2008/09	São Miguel do Passa Quatro	48°45'13"	16°51'46"	GO	1031	Northern	M 7908 RR
3	2008/09	Silvânia	47°46'08"	14°57'54"	GO	1050	Northern	CD 219 RR
4	2008/09	Mauá da Serra	51°13’07”	23°53’57”	PR	1029	Southern	BRS 282
5	2008/09	Nova Ponte	47°42'42"	19°24'24"	MG	999	Northern	AN-8500
6	2009/10	Montividiu	51°40’05”	17°25’17”	GO	921	Northern	P98Y11
7	2009/10	São Miguel do Passa Quatro	48°45'13"	16°51'46"	GO	1027	Northern	M 7908 RR
8	2009/10	Água Fria	47°46'08"	14°57'54"	GO	891	Northern	M 7908 RR
9	2009/10	Campo Verde	54°56'17"	15°06'55"	MT	985	Northern	M 8230 RR
10	2009/10	Nova Ponte	47°42'42"	19°24'24"	MG	1005	Northern	M 8200
11	2009/10	Uberlândia	47°56'58"	19°12'54"	MG	947	Northern	BRS Valiosa RR
12	2009/10	Pilar do Sul	47°42'59"	23°48'47"	SP	800	Southern	BRS 231
13	2009/10	Mauá da Serra	51°13’07”	23°53’57”	PR	909	Southern	BRS 232
14	2010/11	Montividiu	51°40’05”	17°25’17”	GO	921	Northern	P98Y11
15	2010/11	São Miguel do Passa Quatro	48°45'13"	16°51'46"	GO	1027	Northern	M 7908 RR
16	2010/11	Silvânia	47°46'08"	14°57'54"	GO	1050	Northern	BRS 8160 RR
17	2010/11	Água Fria	47°46'08"	14°57'54"	GO	891	Northern	M 7639 RR
18	2010/11	Ponta Grossa	50°03'09"	25°05'42"	PR	1021	Southern	BMX Ativa RR
19	2010/11	Marilândia do Sul	51°15’30”	23°44’51”	PR	868	Southern	BMX Potência RR
20	2011/12	São Miguel do Passa Quatro	48°45'13"	16°51'46"	GO	1027	Northern	M 7908 RR
21	2011/12	Goianira	49°24'2,7"	16°26'6,3"	GO	737	Northern	M 7908 RR
22	2011/12	Uberlândia	47°56'58"	19°12'54"	MG	947	Northern	P98Y11
23	2011/12	Chapadão do Sul	52°38'38”	18°46'47”	MS	813	Northern	ST 810 RR
24	2011/12	Ponta Grossa	50°03'09"	25°05'42"	PR	1021	Southern	BMX Turbo RR
25	2011/12	Palmeira	50°03'19"	25°25'45"	PR	820	Southern	BMX Apolo RR

26	2011/12	Palmeira	50°03'19"	25°25'45"	PR	820	Southern	BMX Potencia rr
27	2011/12	São Desiderio	45°57'03"	13°05'33"	BA	844	Northern	M9144
28	2011/12	Montividiu	51°40’05”	17°25’17”	GO	921	Northern	P 98Y11
29	2011/12	Campo Verde	54°56'17"	15°06'55"	MT	736	Northern	TMG 1174 RR
30	2011/12	Faxinal	51°15'50"	23°56'53"	PR	998	Southern	BMX TURBO RR
31	2011/12	Capão Bonito	48°22'	24°02'	SP	730	Southern	5909 RR
32	2012/13	Chapadão do Sul	52°38'38”	18°46'47”	MS	813	Northern	P98Y11 RR
33	2012/13	Rio Verde	51°19'30"	17°27'25"	GO	748	Northern	TMG 1179
34	2012/13	Ponta Grossa	50°03'09"	25°05'42"	PR	1021	Southern	BMX Potencia RR
35	2012/13	Jataí	52°07'23"	5°59'16''	GO	749	Northern	Anta 82 RR
36	2012/13	São Miguel do Passa Quatro	48°45'13"	16°51'46"	GO	1027	Northern	Emgopa 313 RR
37	2012/13	Faxinal	51°15'50"	23°56'53"	PR	820	Southern	BRS 284
38	2012/13	Uberlandia	47°56'58"	19°12'54"	MG	947	Northern	P98Y11
39	2012/13	Ponta Grossa	50°03'09"	25°05'42"	PR	1021	Southern	-
40	2013/14	Chapadão do Sul	52°38'38”	18°46'47”	MS	813	Northern	P98Y30 RR
41	2013/14	Montividiu	51°40’05”	17°25’17”	GO	921	Northern	P 98Y11 RR
42	2013/14	Mauá da Serra	51°13’07”	23°53’57”	PR	909	Southern	MONSOY M 5917 IPRO
43	2013/14	Ponta Grossa	50°03'09"	25°05'42"	PR	1021	Southern	FTS Ibyara RR
44	2013/14	Ponta Grossa	50°03'09"	25°05'42"	PR	1021	Southern	V-top
45	2014/15	Rio Verde	51°19’30”	17°27’25”	GO	921	Northern	NA 5909 RR
46	2014/15	Ponta Grossa	50°03'09"	25°05'42"	PR	1021	Southern	NA 5909 RG
47	2014/15	Montividiu	51°40’05”	17°25’17”	GO	921	Northern	Monsoy 8210 IPRO
48	2014/15	Mauá da Serra	51°13’07”	23°53’57”	PR	909	Southern	M Soy 5917
49	2015/16	Montividiu	51°40’05”	17°25’17”	GO	921	Northern	MSOY 6972
50	2015/16	Montividiu	51°40’05”	17°25’17”	GO	921	Northern	M 8210 IPRO
51	2015/16	Silvânia	47°46'08"	14°57'54"	GO	1050	Northern	M 8210 IPRO
52	2015/16	Silvânia	47°46'08"	14°57'54"	GO	1050	Northern	M 8210 IPRO
53	2015/16	Uberlândia	47°56'58"	19°12'54"	MG	863	Northern	BG41801RR
54	2015/16	Barreiras	46° 15’ 15”	11° 50’ 12”	BA	454	Northern	M 8349 IPRO
55	2015/16	Júlio de Castilhos	53° 36’ 01”	29° 35’ 13”	RS	513	Southern	NS 5151 IPRO
56	2015/16	Júlio de Castilhos	53° 36’ 01”	29° 35’ 13”	RS	513	Southern	BMX Alvo RR
57	2015/16	Mauá da Serra	51°13’07”	23°53’57”	PR	909	Southern	BMX Garra IPRO
58	2015/16	Faxinal	51°15'50"	23°56'53"	PR	820	Southern	BRS 284

59	2016/17	Ponta Grossa	50°03'09"	25°05'42"	PR	1021	Southern	NA 5909
60	2016/17	Pitanga	51° 46' 58"	24° 43' 15"	PR	952	Southern	BMX Ativa RR
61	2016/17	Silvânia	47°46'08"	14°57'54"	GO	1050	Northern	BRS 8170IPRO
62	2016/17	Uberlândia	47°56'58"	19°12'54"	MG	863	Northern	BMX Deafio RR
63	2016/17	Montividiu	51°40'05"	17°25'17"	GO	921	Northern	M8372 Ipro
64	2016/17	Chapadão do Sul	52°38'38"	18°46'47"	MS	813	Northern	5G8015 IPRO
65	2016/17	Palmeira	50°03'19"	25°25'45"	PR	865	Southern	TMG 7062 IPRO
66	2016/17	Mauá da Serra	51°13'07"	23°53'57"	PR	909	Southern	BRS 284
67	2017/18	Mauá da Serra	51°13'07"	23°53'57"	PR	909	Southern	BRS 284
68	2017/18	Chapadão do Sul	52°38'38"	18°46'47"	MS	813	Northern	5G8015 IPRO
69	2017/18	Rio Verde	51°19'30"	17°27'25"	GO	921	Northern	M7110 IPRO
70	2017/18	Montividiu	51°40'05"	17°25'17"	GO	921	Northern	TMG 2182 IPRO
71	2017/18	Silvânia	47°46'08"	14°57'54"	GO	1050	Northern	NS 7707 IPRO
72	2017/18	Pitanga	51° 46' 58"	24° 43' 15"	PR	952	Southern	NA 5909 RG
73	2017/18	São Desiderio	45°57'03"	13°05'33"	BA	844	Northern	CD 2851 IPRO
74	2017/18	São Miguel do Passa Quatro	48°45'13"	16°51'46"	GO	1027	Northern	M8210 IPRO

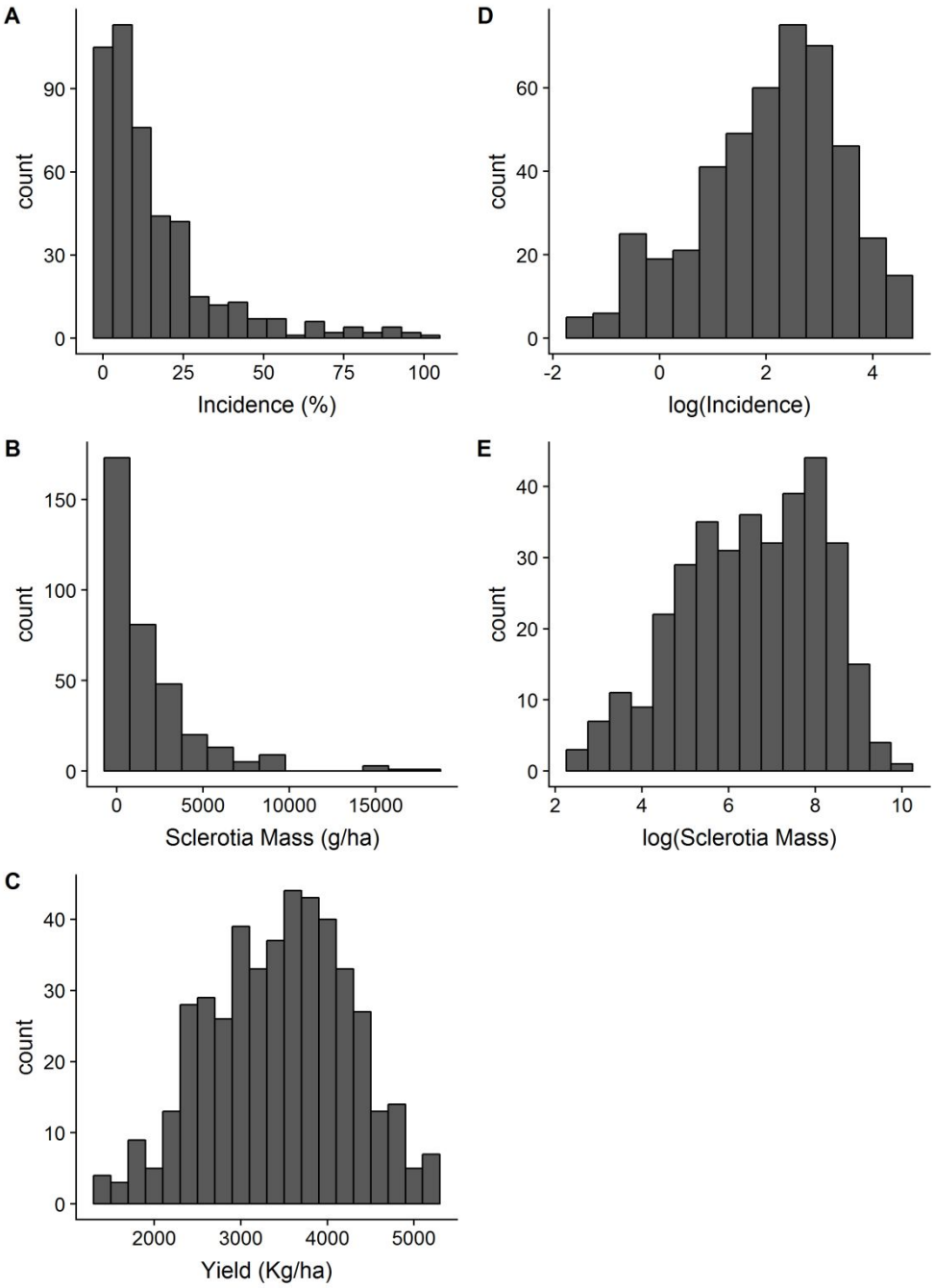

Figure S1: **A** - **C**: Histograms for the distribution of white mold incidence, sclerotia mass and yield to check normality; **D** - **E**: log-transformed incidence and sclerotia mass data for normalizing the distribution and use in the meta-analysis.