A Quantitative Review of Fungicide Efficacy for Managing Downy Mildew in Cucurbits

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ABSTRACT

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A meta-analysis of the effect of fungicides on cucurbit downy mildew was conducted using data previously published in *Fungicide & Nematicide Tests* and *Plant Disease Management Reports* from 2000 to 2008. Standardized mean effect size (the difference in disease intensity expressed in standard deviation units between the fungicide treatment and its corresponding untreated control) was calculated for each of the 105 field studies evaluating the effects of fungicides on cucurbit downy mildew. Fixed- and random-effects meta-analyses were performed on the log-transformed standardized mean effect sizes to estimate the overall mean effect size ($\bar{L}_+$), and to determine the variability in the effect size among studies. Fungicides led to a significant ($P < 0.001$) reduction in disease with an $\bar{L}_+$ value of 1.198, indicating that, overall, fungicides were highly effective against cucurbit downy mildew. Fixed- and random-effects meta-analyses were then conducted to determine the effects of moderator variables on $\bar{L}_+$. The fixed-effects model resulted in narrower 95% confidence intervals and generally lower estimates of moderator subgroup mean effect size ($\bar{L}$) than the random-effects models.

Fungicide efficacy was significantly ($P < 0.001$) greater in cucumber, with $\bar{L}$ being 26.5% higher in cucumber than in other cucurbits. Year of study, number of sprays, and disease pressure in the control significantly ($P < 0.001$) affected $\bar{L}$. Fungicide efficacy was significantly lower during the 2004–05 season than prior to or after the 2004–05 season. Studies in which disease pressure was moderate had a significantly higher $\bar{L}$ than studies with either low or high disease pressure. Fungicide efficacy was $\geq 22\%$ in studies that received 5 to 6 sprays than in studies that received 1 to 4 or >6 sprays. Fungicide products led to a significant ($P < 0.001$) reduction in disease, although there was substantial between-study variability. The pyridinylmethyl-benzamide group of fungicides (fluopicolide) was the most effective, followed by the carbamate (propamocarb) and quinone inside inhibitors (cyazofamid) group of fungicides, while the carboxylic acid amide group (mandipropamid and dimethomorph) was the least effective. A combination of protectant and systemic fungicides resulted in a proportional increase in $\bar{L}$ compared with sole application of either protectant or systemic fungicides.

Additional keywords: fixed- and random-effects models, *Pseudoperonospora cubensis*.

Cucurbit downy mildew is one of the most damaging diseases of cucurbitaceous crops worldwide. The disease is caused by the oomycete pathogen *Pseudoperonospora cubensis* (Berk. & M. A. Curtis) Rostovzev, which was first documented in Cuba in 1868 (3). Downy mildew on cucurbits can be found in temperate areas, such as the Americas, Europe, Japan, and Australia; in tropical areas in South Africa; and in some semiarid regions in the Middle East. Within these regions, the disease is especially damaging in areas characterized by warm and humid weather that favors disease development (31), such as in the southeastern United States.

At least 50 cucurbit species are known hosts of *P. cubensis* but the most economically important host crops are *Cucumis sativus* (cucumber), *Cucumis melo* (cantaloupe and muskmelon), *Cucurbita pepo* (zucchini, pumpkin, and winter and summer squash), and *Citrullus lanatus* (watermelon) (26). Among these crop host species, cucumber (*Cucumis sativus*) is relatively the most susceptible to *P. cubensis*. In the eastern United States and California, cucurbit downy mildew is an annual problem on cucurbits in late summer and fall. Since the 1960s, resistance in *Cucumis sativus* had adequately controlled the disease with minimal use of fungicides (17). However, in 2004, the cucumber crop in North Carolina, Virginia, Delaware, Maryland, and New Jersey was devastated by downy mildew, resulting in a 40%

region-wide loss of the crop. For cucumber alone, the average yield loss for the entire region in 2004 was estimated at \$20 million (17). In cucurbits, host plant resistance alone is no longer sufficient to control downy mildew (25,26). Thus, fungicides are now routinely applied in commercial cucurbit fields throughout the eastern United States and elsewhere to adequately control the disease.

In 1996, the sales value of the global fungicide market for controlling cucurbit downy mildew was \$120 million (11). Phenylamides, strobilurins, carboxylic acid amides (CAAs), benzamides, cyanoacetamide-oxime, and carbamates are among the fungicide chemistries commonly used to control this disease. Since their discovery in 1977 (44), phenylamide fungicides such as metalaxyl contributed to effective control of diseases caused by members of the order Peronosporales (12). However, 2 years after introduction, the first metalaxyl-resistant isolates of *P. cubensis* were reported in Israel (35). Strobilurin fungicides, such as azoxystrobin and trifloxystrobin, were launched in 1996 (39) and represented a new and important class of chemicals that provided control of fungal diseases caused by oomycete, ascomycete, and basidiomycete pathogens. However, reduced efficacy of strobilurins was also reported in *P. cubensis* in Japan in 1999 (19). The systemic carboxylic acid amide fungicides were developed primarily to control downy mildew and were effective in controlling cucurbit downy mildew until resistance in *P. cubensis* was reported in 2004 in China (49). In the late 1990s, the pyridinylmethyl-benzamide fungicide, fluopicolide, the first of a new generation of fungicides with a novel mode of action, was developed

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by Bayer CropScience to control a wide spectrum of oomycete diseases (4). Launched in the United States in 2007, fluopicolide has now become a new standard for oomycete disease control and, to date, there are no reports that document reduced sensitivity of *P. cubensis* or other oomycetes to this fungicide.

Mixtures of single-site (systemic) and multi-site (protectant) fungicides have been recommended for disease control programs in an effort to prolong the efficacy of systemic fungicides by delaying build up of resistant strains in pathogen populations (41). When compared with treatments using a protectant fungicide alone, mixtures of systemic and protectant fungicides are expected to provide superior efficacy and have the advantage of permitting longer spray intervals. However, a number of factors, including the type of fungicide and the existing pathogen population, influence the effectiveness of mixtures of systemic and protectant fungicides. For example, mixtures of metalaxyl with mancozeb were less effective in reducing cucurbit downy mildew on cucumber compared with the mancozeb treatment alone (38) whereas, in an earlier study (37), a mixture of these two fungicides was more effective than sole applications of either fungicide. This latter case most likely illustrates the influence of the pathogen population on the effectiveness of fungicide mixtures in disease control.

When downy mildew occurs early in the cucumber growing season, up to 11 sprays may be necessary to adequately control the disease. More than 30 different fungicide products are labeled for managing cucurbit downy mildew in the United States. Many of these labeled products, including new products under trial, are evaluated annually in fungicide efficacy tests. Results of these efficacy tests are submitted by individual investigators and published by the Plant Management Network as short reports (typically one page), with an emphasis on the table of results. In these reports, the magnitude of disease reduction is variable among studies evaluating the same fungicide products. This variability in fungicide efficacy results leads to different interpretations and, hence, different recommendations to growers within the state or region where the study was conducted. Furthermore, due to the large number of products and product combinations, no single study can make all the appropriate comparisons. Thus, there is a need to summarize efficacy data from many studies in order to draw the most robust conclusions.

Here, we use a meta-analytical approach (29,32) to quantitatively review the results of fungicide efficacy trials for controlling cucurbit downy mildew in the eastern United States from 2000 to 2008. Meta-analysis is an objective approach for integrating and interpreting results and drawing conclusions from multiple studies. This analytic approach also allows for the evaluation of study-specific characteristics that are likely to influence treatment effects (27). The objectives of the quantitative research synthesis reported herein were to (i) quantify the overall efficacy of fungicide treatments in reducing downy mildew intensity in cucurbits; (ii) determine to what extent fungicide efficacy is influenced by cucurbit type, overall disease pressure, and the number of spray applications; and (iii) evaluate differences in efficacy among fungicide classes used to control cucurbit downy mildew.

MATERIALS AND METHODS

Data source. Data were obtained from reports published in *Fungicide and Nematicide Tests* from 2000 to 2006 and *Plant Disease Management Reports* from 2007 to 2008. These sources were chosen primarily because they publish a diverse range of fungicide efficacy studies regardless of whether their results are positive (i.e., with significant differences) or negative. A set of criteria was applied to determine whether or not a particular report could be included in this analysis. First, the report had to provide at least one measure of disease intensity such as disease

incidence, disease severity, area under the disease progress curve, or disease intensity expressed as an index or on an arbitrary scale. In cases where both incidence and severity were available, the latter was used in the analysis. Second, an estimate of the pooled sample variance (s^2_{pooled}) from the analysis of variance had to be provided for the report to be included in the database. The parameter s^2_{pooled} was used to calculate the population variance (σ^2) using the equation $\sigma^2 = s^2_{pooled}[(n - 1)/n]$, where n = total sample size (treatments $\times$ replications). In a number of cases, s^2_{pooled} was calculated from Fisher's least significant difference (LSD) values presented in the reports. Where the LSD value was not provided and the reports had at least three means that were significantly different, the LSD was estimated as the mean of the largest nonsignificant difference and the lowest significant difference between two means (H. K. Ngugi, *personal communication*). Of the 142 fungicide efficacy reports on cucurbit downy mildew published from 2000 to 2008, 105 reports (studies) with 1,072 entries (fungicide treatment–study combinations) met the criteria outlined above. The remaining studies that were omitted from the database lacked sufficient statistical information to calculate s^2_{pooled} or estimate the LSD value.

Quantitative synthesis of fungicide effects across studies.

The standardized mean difference, commonly referred to as Cohen's d , was used to evaluate the efficacy of fungicide treatments in each study. Cohen's d is one of the most commonly used estimates of effect size with the best statistical properties (23). Values of $d > 0.2$, 0.5, 0.8, and 1.0 represent nominally small, medium, large, and very large effects, respectively (13). For each entry, the effect size was calculated as

$$d = \frac{\bar{X}_C - \bar{X}_T}{\sigma_{pooled} J}$$

where $\bar{X}_T$ and $\bar{X}_C$ are the disease intensity means of the treated and control groups, respectively, and σ^2_{pooled} is the pooled population variance for the corresponding study, calculated from s^2_{pooled} (36). The term J corrects for bias due to small sample size (15) and is calculated as $J = 1 - 3/[4(n_T + n_C - 2) - 1]$, where n_T and n_C are the numbers of replications for the treated and control groups, respectively. The variance of d is given by $\sigma^2(d) = [(n_T + n_C)/(n_T n_C)] + [d^2/2(n_T + n_C)]$, in which n_T and n_C are defined as above. In meta-analysis, each effect size d_i (where $i = 1$ to k denotes the number of a given entry) is weighted by its corresponding variance, $\sigma^2(d_i)$, whereby the weight, w_i , assigned to each effect size estimate is inversely proportional to its variance, $w_i = 1/\sigma^2(d_i)$. The combined estimate of the effect size across all studies, d_+ , was calculated as

$$d_+ = \frac{\sum_{i=1}^k w_i d_i}{\sum_{i=1}^k w_i}$$

and its variance,

$$\sigma^2(d_+) = \frac{1}{\sum_{i=1}^k [1/\sigma^2(d_i)]}$$

was used to compute a 95% confidence interval around d_+ . The total heterogeneity Q_T across all entries is given by

$$Q_T = \sum_{i=1}^k w_i (d_i - d_+)^2$$

(15). A value of Q_T greater than the theoretical χ^2 value (with $k - 1$ degrees of freedom) indicates that the variance is greater than expected due to sampling error, warranting a test for moderator variables. The natural log of d , $\ln(d)$ ($= L$), had a normal distribution as opposed to d and, thus, the meta-analysis was performed on L .

Fixed- and random-effects meta-analyses were performed to estimate the overall mean effect ($\bar{L}$) and to determine the variability in the effect size among studies. This was prompted by the need to reexamine recommendations in literature where random-effects models have been proposed for routine use in meta-analysis in preference to fixed-effects models. If $L_1, \dots, L_k$ are k independent effect-size parameters, and $\hat{L}_1, \dots, \hat{L}_k$ are the corresponding effect-size estimates with estimated variances $\text{var}(\hat{L}_1), \dots, \text{var}(\hat{L}_k)$, the fixed-effect model can be written as $L_i = \beta_0 + \beta_1 X_{i1} + \dots + \beta_p X_{ip}$, while the random-effects model can be written as $L_i = \beta_0 + \beta_1 X_{i1} + \dots + \beta_p X_{ip} + u_i$, where $X_{i1}, \dots, X_{ip}$ are the p study characteristics for the i th study, β_0 is the intercept, $\beta_1, \dots, \beta_p$ are regression coefficients for the p study characteristics, and u_i is the deviation between the true and effect predicted size. The random effect u_i is assumed to be independent with mean zero and variance σ^2_L . The fixed-effect model above can be estimated using $\hat{L}_i = \beta_0 + \beta_1 X_{i1} + \dots + \beta_p X_{ip} + \varepsilon_i$. The estimation errors, $\varepsilon_i = \hat{L}_i - L_i$, are assumed to be independent with a mean zero and variance $\text{var}(\hat{L}_i)$. Similarly, the random-effects model can be estimated using $\hat{L}_i = \beta_0 + \beta_1 X_{i1} + \dots + \beta_p X_{ip} + \varepsilon_i + u_i$ and the estimation errors $\varepsilon_i + u_i = \hat{L}_i - L_i$ are assumed to be independent with a mean zero and variance $\text{var}(\hat{L}_i) + \sigma^2_L$. The fixed-effects model was fitted using PROC MIXED of SAS (version 9.1, SAS Institute, Cary, NC) in which study was considered as a fixed effect and L_i was weighted by $1/\text{var}(\hat{L}_i)$. The random-effects model, in which study was considered as a random effect and L_i was weighted by $1/\text{var}(\hat{L}_i) + \sigma^2_L$, was fitted using PROC MIXED of SAS based on the maximum likelihood method (27).

Estimation of the between-studies variance component. An estimate of the between-study variance component ($\hat{\sigma}^2_L$) was obtained when the homogeneity test resulted in a value of Q_T greater than the theoretical χ^2 value. The normal procedure in estimating $\hat{\sigma}^2_L$ is by maximum likelihood using PROC MIXED of SAS (27), where a random-effects model is fitted in which L_i is weighted by $1/\text{var}(\hat{L}_i) + \hat{\sigma}^2_L$. The maximum likelihood estimation is more efficient if the distributional assumptions about the study-specific random effects are correct; however, these assumptions are often difficult to either justify theoretically or verify empirically (14) and, thus, distribution-free estimates of the between-studies variance component ($\hat{\tau}_L^2$) are often attractive. A simple estimate of $\hat{\tau}_L^2$ is given by

$$\hat{\tau}_L^2 = \begin{cases} \frac{Q_T - (k-1)}{a} & \text{if } Q_T \geq (k-1) \\ 0 & \text{if } Q_T < (k-1) \end{cases} \quad (1)$$

where a is given by

$$a = \sum_{i=1}^k w_i - \frac{\sum_{i=1}^k w_i^2}{\sum_{i=1}^k w_i} \quad (2)$$

In both equations 1 and 2, Q_T , k , w_i , and w_i^2 are defined as above. Estimates of τ^2 are set to 0 when $Q_T - (k-1)$ yields a negative value because, by definition, τ^2 cannot be negative. If the within-study sampling-error variances, $\sigma^2(d_i)$, used to construct w_i are known exactly and the estimate is not set to 0 when $Q_T - (k-1) < 0$, then w_i are constants and the estimate is unbiased, a result which does not depend on assumptions about the distribution of the random effects (or the conditional distribution of the effect sizes themselves). Inaccuracies in the estimation of $\sigma^2(d_i)$ (and, hence, w_i) may lead to biases, although they are usually not substantial. The truncation of $\hat{\tau}_L^2$ at zero can be a source of bias when k is small but this bias becomes insignificant when $k > 20$ (16).

Analysis of moderator variables. Fixed- and random-effects meta-analyses were expanded to evaluate the effect of dichoto-

mous or ordinal moderator variables on the overall mean effect size, $\bar{L}_+$. First, entries were grouped based on whether the cucurbit crop used in the study was cucumber (*Cucumis sativus*) or other cucurbit species (*Cucumis melo*, *Cucurbita pepo*, or *Citrullus lanatus*). Second, entries were then grouped based on whether the other cucurbit species in the study was *Cucurbita pepo* (squash), *Cucumis melo* (cantaloupe), or *Citrullus lanatus* (watermelon). A disease pressure variable (DP) was defined based on the disease intensity in the untreated control (DP_C) and the expected maximum disease intensity (DP_{MX}) for the study as $DP = (DP_C/DP_{MX}) \times 100$. The corresponding disease pressure classes were (i) low ($DP < 30\%$), (ii) moderate ($DP = 30$ to 50%), and (iii) high ($DP > 50\%$). Based on the severe outbreak of the disease in the eastern United States in 2004, entries were grouped into three categories: (i) before the 2004–05 season, for studies conducted between 1999 and 2003; (ii) the 2004–05 season, for studies conducted between 2004 and 2005; and (iii) after the 2004–05 season, where studies were conducted from 2006 to 2007.

Treatment-oriented moderator variables included (i) the number of spray applications, whereby entries were grouped into three categories based on whether 1 to 4, 5 to 6, or >6 sprays were applied for disease control, and (ii) fungicide grouping based on the Fungicide Resistance Action Committee code list (1). Depending on the subgroup name of fungicide product (Table 1), fungicide classes were defined for each entry: (i) a single systemic group applied alone or in combination with another systemic group, (ii) a single systemic group applied in combination with a protectant group, and (iii) two systemic groups applied in combination with a protectant group. Entries with three or more systemic groups applied in combination with or without a protectant group were too infrequent to warrant further analysis. Based on this definition, 23 fungicide subgroups were defined.

The moderator variables (crop type, other cucurbit type, year of study, disease pressure, number of sprays, and fungicide group) were considered to be fixed effects. Thus, the overall meta-analytical model was a fixed-effect model for the fixed-effects meta-analysis but a mixed-effects model for the random-effects meta-analysis. An independent meta-analysis was performed for L and for each moderator variable. To determine whether moderator variables significantly affected overall mean log-transformed standardized mean effect size ($\bar{L}_+$) and to estimate separate mean effect sizes for sub-groups of a moderator variable ($\bar{L}$), models were fitted using PROC MIXED of SAS using the same weights described above. These models were identical to those described for models fitted without moderator variables, except that the mean effect size was composed of terms for each level of the moderator variable. The use of weights is analytically much easier to implement in PROC MIXED than approaches commonly presented in meta-analytical articles (46) that use sampling variance data sets. The significance of moderator variables on the effect sizes was based on a χ^2 test (27). Two levels of a moderator variable were considered significantly different if the 95% confidence interval around the difference of their $\bar{L}$ values did not include zero (13).

RESULTS

Percent control and standardized mean effect size. Percent control based on the difference in mean disease intensity between the untreated check ($\bar{DI}_C$) and the corresponding fungicide treatment ($\bar{DI}_T$) expressed as percentage of the untreated check, $(1 - \bar{DI}_T/\bar{DI}_C) \times 100$, varied from 7 to 85% across all the studies. In all, $\approx 60\%$ of the studies had a percent disease control $\leq 50\%$, while 40% of all the studies had a percent control $> 50\%$ (Fig. 1A). The standardized mean effect size, d , varied from 0.74 to 15.3 (Fig. 1B). Out of 105 studies in the database, 99% had a large magnitude of disease suppression ($d > 0.8$). The mean effect

size across studies (d_+) was 3.3, indicating that fungicides had, on average, a very large effect on disease suppression. Further, the 95% confidence interval of d_+ was 2.9 to 3.7, implying that d_+ was significantly >0.

The plot of the distribution of d values revealed a significant deviation from normality ($P < 0.0001$, based on the Shapiro Wilk test). However, a frequency plot of the natural log of d , $\ln d = L$ (Fig. 1C), was normally distributed ($P = 0.2678$, based on the Shapiro Wilk test). The null hypothesis of homogeneity across studies based on L was rejected ($Q_T = 417.1$, $n = 105$, $P < 0.001$), indicating that variability in L was greater than would be expected due to random sampling error. Thus, a fixed- and random-effects meta-analysis was performed to determine the influence of selected moderator variables on natural-log of combined estimate across studies, L_+ .

Influence of moderator variables on fungicide efficacy. The overall log-transformed standardized mean effect size ($\bar{L}_+$) was significantly ($P < 0.001$) different from zero, based on the standard normal meta-analysis test. Based on the fixed- and random-effects models, the estimated $\bar{L}_+$ was 1.151 and 1.198, respectively (Table 2). The corresponding untransformed standardized effect size, d_+ , was 3.2 and 3.3, respectively. The 95% confidence interval for $\bar{L}_+$ was narrower for the fixed-effects model (1.031 to 1.270) but wider for the random-effects model (1.1047 to 1.348). The estimated random-effects variance component for $\bar{L}_+$ based on maximum likelihood was 0.317 (Table 2) and was significantly ($P < 0.0001$) different from zero based on a standard normal test, with a 95% confidence interval of 0.210 to 0.425. The calculated distribution-free random-effects variance component was 0.195.

Based on the χ^2 tests, $\bar{L}_+$ was significantly affected by all the moderator variables evaluated in this study (Table 3). The between-groups heterogeneity (Q_b) was equally significant ($P < 0.001$) for the fixed- and random-effects models. The within-groups heterogeneity (Q_w) was highly significant ($P < 0.0025$) based on the fixed-effects model except for the fungicide variable, where Q_w was not significant ($P = 0.5128$). None of the Q_w heterogeneities were significant based on the random-effect model (Table 3). The random-effects model resulted in slightly higher estimates for $\bar{L}_+$, larger variance for $\bar{L}_+$ and, thus, wider 95% confidence intervals for $\bar{L}_+$ than the fixed-effects model, except for fungicide products. For this latter subgroup, the random effects model resulted in larger variances and wider 95% confidence intervals for $\bar{L}_+$ than the fixed-effects model but $\bar{L}_+$

values were not consistently higher for the random-effects than the fixed effects model (Table 4).

When studies were categorized based on the cucurbit species, studies in which fungicides were used on cucumber had significantly higher ($P < 0.001$) subgroup mean effect size ($\bar{L}$) than studies in which fungicides were evaluated on other cucurbit species (Fig. 2A). Disease response to fungicides was $\approx 27\%$ higher in cucumber than in other cucurbit types (Table 4). Based on the significant Q_w for the fixed-effects model for all host types, other cucurbit type grouping was broken down and analyzed as a separate moderator variable, and studies that had *Cucumis melo* as the host crop had significantly higher $\bar{L}$ than studies in which either *Citrullus lanatus* or *Cucurbita pepo* was the host plant (Fig. 2B). Disease response to fungicide application on *Cucumis melo* was ≈ 35 and 60% higher than that observed on *Cucurbita pepo* and *Citrullus lanatus*, respectively. The width of the 95% confidence interval around $\bar{L}$ was narrowest for studies with *Cucurbita pepo* and widest for studies with *Cucumis melo*, regardless of whether the analysis was based on a fixed- or random-effects model. The wider interval for the latter group of studies reflected the relatively small number of study–fungicide combinations considered in this category ($n = 46$) and the large sampling variance (Table 4). Year of study relative to a severe outbreak of cucurbit downy mildew in 2004 had a significant effect on $\bar{L}_+$ ($P < 0.0001$). Studies conducted in the 2004–05 season had a significantly ($P < 0.001$) lower $\bar{L}$ compared with studies conducted prior to or after 2004–05 (Fig. 3). The estimate of $\bar{L}$ was highest for studies conducted after 2004–05 season and this estimate was ≈ 19 and 13% higher than that of studies conducted in 2004–05 and prior to 2004–05 season, respectively (Table 4).

All disease- and treatment-oriented moderator variables (disease pressure, number of spray applications, and fungicide products) significantly ($P < 0.001$) affected $\bar{L}_+$ (Table 3). Studies with moderate disease pressure (30 to 50% disease intensity in the control) had a higher estimate of $\bar{L}$ than studies in which the disease pressure was low (<30%) or high (>50%) (Fig. 4). The lowest estimate of $\bar{L}$ was observed in studies with the lowest disease pressure and this estimate was 40% lower than that of studies for which disease pressure was moderate (Table 4). The width of the 95% confidence interval around $\bar{L}$ was widest for low disease pressure, which reflected the relatively small number of entries ($n = 87$) for this category and the large sampling variance (Table 4). When categorizing studies based on number of spray applications, studies that received 5 to 6 sprays had signi-

TABLE 1. Chemical products and cucurbit host types included in a meta-analysis to determine the efficacy of fungicides in suppression of cucurbit downy mildew caused by *Pseudoperonospora cubensis* based on reports published in *Fungicide and Nematicides Tests* and *Plant Disease Management Reports* from 2000 to 2008

Group name	FRAC code ^a	Fungicide products	Cucurbit type ^b	No. of studies ^c
Benzamides (pyridinylmethyl-benzamides)	43	Fluopicolide	<i>Cucurbita pepo</i> , <i>Cucumis melo</i> , <i>Cucumis sativus</i>	24
Benzamides (toluamides)	22	Zoxamide	<i>Cucurbita pepo</i> , <i>Cucumis sativus</i> , <i>C. melo</i>	29
Carboxylic acid amides (CAA)	40	Dimethomorph, mandipropamid	<i>Cucurbita pepo</i> , <i>Cucumis melo</i> , <i>C. sativus</i> , <i>Citrullus lanatus</i>	49
Carbamates	28	Propamocarb	<i>Cucurbita pepo</i> , <i>Cucumis melo</i> , <i>C. sativus</i>	65
Cyanoacetamide-oxime (oximes)	27	Cymoxanil	<i>Cucurbita pepo</i> , <i>Cucumis melo</i> , <i>C. sativus</i> , <i>Citrullus lanatus</i>	52
Demethylation inhibitors (DMI)	3	Difenoconazole, myclobutanil, tebuconazole, triflumizole	<i>Cucurbita pepo</i> , <i>Cucumis sativus</i>	31
Methyl benzimidazole carbamates	1	Thiophanate-methyl	<i>Cucurbita pepo</i> , <i>Cucumis sativus</i> , <i>Citrullus lanatus</i>	10
Multi-site inhibitors (protectants)	M	Copper salts, mancozeb, maneb, chlorothalonil	<i>Cucurbita pepo</i> , <i>Cucumis melo</i> , <i>C. sativus</i> , <i>Citrullus lanatus</i>	100
Phenylamides (PA)	4	Metalaxyl	<i>Cucurbita pepo</i> , <i>Cucumis melo</i> , <i>C. sativus</i>	38
Quinone inside inhibitors (QiI)	21	Cyazofamid	<i>Cucurbita pepo</i> , <i>Cucumis melo</i> , <i>C. sativus</i> , <i>Citrullus lanatus</i>	52
Quinone outside inhibitors (QoI)	11	Azoxystrobin, pyraclostrobin, trifloxystrobin, famoxadone, fenamidone	<i>Cucurbita pepo</i> , <i>Cucumis melo</i> , <i>C. sativus</i> , <i>Citrullus lanatus</i>	88

^a Fungicide Resistance Action Committee (FRAC) codes are based on the updated listed published in 2009.

^b *Cucurbita pepo* refers to pumpkin and zucchini, winter, summer, and butternut squash; *Cucumis melo* refers to cantaloupe and muskmelon; *Cucumis sativus* refers to cucumber; and *Citrullus lanatus* refers to watermelon.

^c Number of fungicide treatments in a single study ranged from 4 to 26 entries.

Fig. 1. **A**, Frequency distribution for the difference between fungicide-treated and untreated plots expressed as a percentage of the disease in the untreated control averaged across treatments in each study; **B**, standardized mean difference between fungicide-treated and untreated plots; and **C**, log-transformed standardized mean difference between fungicide-treated and untreated plots, $\log_e d = L$, based on synthesis of reports published in *Fungicide and Nematicides Tests* and *Plant Disease Management Reports* from 2000 to 2008 ($k = 105$); values of $d > 1$ or $L > 0.05$ represent very large effects.

ificantly higher $\bar{L}$ than studies that received 1 to 4 or >6 sprays (Fig. 5). The estimate of $\bar{L}$ in studies with 1 to 4 or >6 sprays was ≈ 20 to 25% lower than in studies that received 5 to 6 sprays (Table 4).

The effect of fungicide product on $\bar{L}_+$ was also statistically significant ($P < 0.001$). Among fungicide groups where sole applications of their respective fungicides was used, studies in which fluopicolide was used to control downy mildew had significantly the largest $\bar{L}$, while the smallest estimate of $\bar{L}$ was in studies that received a CAA fungicide (Fig. 6). The estimate of $\bar{L}$ in studies that received a sole application of fluopicolide was 18% higher than in studies that received sole applications of carbamates or Qil fungicides but >200 and $>300\%$ higher than in studies with sole applications of phenylamide and CAA fungicides, respectively (Table 4). In addition, studies that received both a systemic and protectant fungicide had a correspondingly larger $\bar{L}$ than studies that received separate applications of either a systemic or a contact fungicide (Fig. 6). In this latter category, the estimate for $\bar{L}$ was highest in studies that received fluopicolide and a protectant fungicide. Further, in this latter group, studies that received a demethylation inhibitors and a protectant fungicide had the widest confidence interval around $\bar{L}$, reflecting the larger sampling error and smaller number of entries ($n = 11$ and 12, respectively) (Table 4).

Compared with fixed- and random-effects models fitted without moderator variables, models fitted after the inclusion of moderator variables resulted in only marginally smaller between-study variances for $\bar{L}_+$ (data not shown). The above moderator variables accounted for 5 to 9% of the between-study variance for $\bar{L}_+$ and, thus, up to 90% of variation among studies was not accounted for in our meta-analysis models, although all the moderator variables significantly affected $\bar{L}_+$.

DISCUSSION

Fungicide efficacy trials are routinely conducted to determine the effectiveness of different fungicides in controlling cucurbit downy mildew. Results from these individual studies vary widely and range from no reduction to considerable reduction in disease intensity (10,22,47). This variation can be attributed to, among other factors, (i) inherent differences among fungicides in their effect against *P. cubensis* (37), (ii) differences in fungicide application rates, (iii) timing of first application in relation to disease onset, (iv) differences in the aggressiveness of local pathogen populations (35), (v) differential susceptibility of cultivars to cucurbit downy mildew (48), and (vi) differences in weather conditions prevailing at the test locations which result in variable levels of disease intensity or a variable response of host to infection. The wide range in efficacy of fungicides in individual studies and the inability to evaluate all available products in a single study demands the need for an objective approach to integrate and interpret results so that conclusions can be drawn from multiple studies conducted in several locations and years. Meta-analysis allows for the evaluation of study-specific characteristics that are likely to influence efficacy of fungicides in controlling cucurbit downy mildew.

TABLE 2. Effect size summary statistics and estimates of between-study variance component in the meta-analysis of cucurbit downy mildew response to fungicides based on reports published in *Fungicide and Nematicides Tests* and *Plant Disease Management Reports* from 2000 to 2008

Model	k^a	Effect size ^b				Variance component ^c	
		$\bar{L}_+$	$se(\bar{L}_+)$	CI_L	CI_U	$\hat{\sigma}^2_{L^+}$	$\hat{\tau}^2_{L^+}$
Fixed effects	105	1.151	0.061	1.031	1.270	...	...
Random effects	105	1.198	0.077	1.047	1.348	0.317	0.195

^a Total number of studies used in the meta-analysis.

^b $\bar{L}_+$ = Log-transformed overall standardized mean difference; $se(\bar{L}_+)$ = standard error of $\bar{L}_+$; CI_L and CI_U = lower and upper limits of the 95% confidence interval around $\bar{L}_+$, and P = probability value (or significance level).

^c Between-study variance component of $\bar{L}_+$ estimated by maximum likelihood ($\hat{\sigma}^2_{L^+}$) or distribution-free approaches ($\hat{\tau}^2_{L^+}$).

Fixed- and random-effects meta-analyses showed that the efficacy of fungicides on cucurbit downy mildew is very high on average but variable among studies. The random-effects model generated larger estimates of $\bar{L}_+$ or $\bar{L}$ than the fixed-effects model. The corresponding 95% confidence interval bands for estimates were narrower for the fixed-effect model than for the random-effect model. Thus, this would indicate that estimates from the fixed-effects model are more precise than those from the random-effects model (13). However, Hunter and Schmidt (18) argue that, unlike random-effects models, the confidence intervals of fixed-effects models overstate the precision of the estimates of the difference between subgroups of moderator variables. The basis of the argument by Hunter and Schmidt (18) is that fixed-effects models fail to account for true between-studies variance that random-effects models include as a defining parameter which, in this study, was 0.3 or 0.2 (based on a distribution-free model). Thus, random-effects models have been recommended (18) for routine use in meta-analysis in preference to fixed-effects models.

Application of fixed-effects significance tests and confidence intervals is based on the assumption that the studies being analyzed are homogeneous at the level of study population effect sizes. For example, for the effect size, L , the fixed-effects model assumes that the population value of L is the same in all studies included in the meta-analysis. The random-effects model does not make this assumption (14,15) and allows for the possibility that

the population parameter values vary from study to study (2,14). However, because the random-effects model assumes that effect sizes (L s) are randomly sampled from a $\sigma^2_L > 0$ population, the validity of this model is integrally tied to the procedures that are followed in selecting the meta-analysis studies and to the purported generalizability of the inferences to be drawn from the results (30). For example, suppose that every effort is made to retrieve all of the relevant studies of the efficacy of a particular fungicide. If the effort is successful, the entire population of L s will have been selected, under the assumption that the population has not been hypothesized to also include all future relevant studies. More realistically, there will be studies that will not be reported, and these studies arguably could differ in some systematic way from those that are selected and included in the analysis. Because the studies have not been randomly selected from the population, the random-effects model will tend to overestimate σ^2_L , resulting in biased confidence intervals and hypothesis tests. Even if σ^2_L is large, nonrandom sampling of the studies may yield very similar collections of studies from one meta-analysis to the next, hence limiting the actual variability in L s. As such, the random-effects model does not hold true, at least according to a strict view of randomization in statistical inference. It is also true that fixed- and random-effects models give similar answers when there is, in fact, a common population effect size and there are situations in which the fixed-effects model is appropriate even when there is substantial heterogeneity of results

TABLE 3. Between-group (Q_b) and within-group (Q_w) heterogeneity for moderator variables from fixed- and random-effects analyses of the response of cucurbit downy mildew to fungicide treatments based on reports published in *Fungicide and Nematicides Tests* and *Plant Disease Management Reports* between 1999 and 2008

Variable	Group	df	Fixed-effects model		Random-effects model	
			Q_b	Q_w	Q_b	Q_w
Host type ^a	<i>Cucumis sativus</i>	519	<0.0001	0.0005	<0.0001	0.4217
	Other cucurbits	552	...	...	...	...
Other cucurbits ^a	<i>Cucurbita pepo</i>	424	<0.0001	0.0025	<0.0001	0.4137
	<i>Cucumis melo</i>	45	...	...	...	...
	<i>Citrullus lanatus</i>	81	...	...	...	...
	Before 2004–05 season	364	<0.0001	0.0001	<0.0001	0.4129
Year	2004–05 season	360	...	...	...	...
	After 2004–05 season	346	...	...	...	...
	Low	86	<0.0001	0.0002	<0.0001	0.4100
Disease pressure	Moderate	178	...	...	...	...
	High	806	...	...	...	...
No. of sprays	1–4 sprays	190	<0.0001	0.0003	<0.0001	0.4160
	5–6 sprays	591	...	...	...	...
	>6 sprays	289	...	...	...	...
	Carboxylic acid amides (CAA)	17	<0.0001	0.9912	<0.0001	0.9912
Fungicides ^b	Carbamates	26	...	...	...	...
	Demethylation inhibitors (DMI)	21	...	...	...	...
	Pyridinylmethyl-benzamides (fluopicolide)	14	...	...	...	...
	Phenylamides	14	...	...	...	...
	Quinone inside inhibitors (QiI)	39	...	...	...	...
	Quinone outside inhibitors (QoI)	35	...	...	...	...
	Multi-site inhibitors (protectants)	202	...	...	...	...
	CAA + protectants	20	...	...	...	...
	Carbamates + protectants	43	...	...	...	...
	DMI + protectants	11	...	...	...	...
	Fluopicolide + protectants	10	...	...	...	...
	MBC + protectants	9	...	...	...	...
	Cyanoacetamide-oxime (oximes) + protectants	18	...	...	...	...
	Phenylamides + protectants	10	...	...	...	...
	QiI + protectants	48	...	...	...	...
	QoI + protectants	78	...	...	...	...
	Toluamides + protectants	17	...	...	...	...
	CAA + QoI + protectants	21	...	...	...	...
	Carbamate + CAA + protectants	11	...	...	...	...
	DMI + QoI	19	...	...	...	...
	Oximes + QoI + protectants	51	...	...	...	...
	QiI + QoI + protectants	11	...	...	...	...

^a *Cucurbita pepo* refers to pumpkin and zucchini, winter, summer, and butternut squash; *Cucumis melo* refers to cantaloupe and muskmelon; *Cucumis sativus* refers to cucumber; and *Citrullus lanatus* refers to watermelon.

^b Fungicides are grouped based on the Fungicide Resistance Action Committee (FRAC) listed published in 2009.

(16). The choice of which meta-analytic model to use should be based on contextual conditions (i.e., factors associated with the heterogeneity of *Ls*) in which the studies were conducted and the domain over which the effect of interest is to be generalized (30). Fixed-effects models should be preferred when the contextual conditions are sufficiently defined and the sample domain closely matches the population domain, whereas random-effects models should be used if the contextual conditions are not well defined or the sample domain notably underrepresents the population domain.

In a variety of *ceteris paribus* conditions, cucumber is more susceptible to cucurbit downy mildew than other cucurbitaceous host crops (43). In this study, fungicide efficacy was greater for the susceptible cucumber than the relatively less susceptible cucurbit host types such as muskmelon, pumpkin, and watermelon. The efficacy of fungicides has also been reported to be higher in susceptible than resistant genotypes in the control of *Fusarium* head blight in wheat (20) and late blight in potato (24) while, in some studies (28,33), fungicide efficacy has been reported to be lower in susceptible than in resistant genotypes. Thus, although yield response to fungicides and cost of reduced yield were not evaluated in this study, fungicide use in cucurbit downy mildew is likely to be more cost-effective for cucumber than other cucurbitaceous crops. When other cucurbit types were

analyzed separately, fungicide efficacy overall was greater for *Cucumis melo* (cantaloupe and muskmelon) than *Cucurbita pepo* (squash) or *Citrullus lanatus* (watermelon). However, the possible beneficial effect of fungicide use on cantaloupe and muskmelon is clouded by the considerable variation in the fungicide efficacy results associated with this subgroup.

Prior to 2004, downy mildew was primarily a problem on squash, pumpkin, and melon and less of a problem on cucumber, where it was inconspicuous in North Carolina (34). Downy mildew had been successfully controlled on cucumber through the use of resistant cultivars since the 1950s (40). However, in 2004, severe outbreaks caused considerable losses in the eastern U.S. cucumber crop (17). This severe outbreak may explain the significantly lower efficacy of fungicides in the 2004–05 season reported in this study. The use of less effective fungicides and the high disease pressure early in the season could also have contributed to the lower efficacy of fungicide observed in 2004–05 season. It was suggested that a new population of *P. cubensis* had appeared in the United States, and subsequent studies showed that these new strains were more aggressive on cucumber than those collected prior to 2004 (7). Around this 2004–05 growing season, a new pathotype of *P. cubensis* able to attack squash and pumpkin was also reported for the first time in Israel (5). However, no data exists to suggest that this emergence of aggressive populations of

TABLE 4. Summary statistics from fixed- and random-effects analyses for moderator variables in of the response of cucurbit downy mildew to fungicide treatments based on reports published in *Fungicide and Nematicides Tests* and *Plant Disease Management Reports* from 2000 to 2008

Group	Subgroup	Fixed-effects model				Random-effects model			
		Estimate	Variance	95% CI ^a		Estimate	Variance	95% CI ^a	
				Lower	Upper			Lower	Upper
All hosts ^b	<i>Cucumis sativus</i>	1.292	0.0013	1.223	1.362	1.377	0.0079	1.202	1.552
	Other cucurbits	1.021	0.0011	0.955	1.086	1.053	0.0064	0.895	1.210
Other cucurbits ^b	<i>Cucurbita pepo</i>	1.147	0.0007	1.096	1.198	1.167	0.0043	1.038	1.296
	<i>Cucumis melo</i>	1.543	0.0147	1.305	1.781	1.573	0.0703	1.053	2.093
	<i>Citrullus lanatus</i>	0.963	0.0074	0.794	1.132	1.281	0.0416	0.881	1.681
	Before 2004–05 season	1.118	0.0017	1.037	1.199	1.132	0.0020	1.043	1.220
Year	2004–05 season	1.068	0.0017	0.986	1.149	1.078	0.0020	0.989	1.167
	After 2004–05 season	1.268	0.0019	1.183	1.353	1.283	0.0022	1.191	1.374
	Low	0.979	0.0074	0.809	1.148	1.142	0.0399	0.750	1.533
Disease pressure	Moderate	1.379	0.0038	1.258	1.500	1.480	0.0242	1.175	1.785
	High	1.119	0.0008	1.065	1.174	1.196	0.0048	1.126	1.332
No. of sprays	1–4 sprays	1.017	0.0021	0.926	1.107	0.921	0.0132	0.695	1.146
	5–6 sprays	1.255	0.0011	1.190	1.319	1.298	0.0057	1.149	1.448
	>6 sprays	1.031	0.0033	0.919	1.144	1.216	0.0099	1.021	1.411
	Fungicide group ^c	0.379	0.0296	0.041	0.716	0.451	0.0370	0.074	0.828
Fungicide group ^c	Carboxylic acid amides (CAA)	1.352	0.0236	1.050	1.653	1.285	0.0301	0.945	1.625
	Demethylation inhibitors (DMI)	0.652	0.0271	0.329	0.974	0.614	0.0362	0.241	0.804
	Pyridinylmethyl-benzamides (fluopicolide)	1.537	0.0448	1.122	1.952	1.495	0.0625	1.005	1.985
	Phenylamides	0.728	0.0403	0.334	1.121	0.873	0.0470	0.447	1.297
	Quinone inside inhibitors (QiI)	1.284	0.0064	1.127	1.441	1.264	0.0287	0.932	1.596
	Quinone outside inhibitors (QoI)	0.775	0.0168	0.521	1.029	0.732	0.0221	0.440	1.024
	DMI + QoI	1.131	0.0319	0.781	1.481	1.242	0.0429	0.836	1.648
	Multi-site inhibitors (protectants)	0.912	0.0026	0.832	0.992	0.891	0.0064	0.734	1.047
	CAA + protectants	1.376	0.0317	1.026	1.725	1.378	0.0374	0.998	1.756
	Carbamates + protectants	1.432	0.0149	1.192	1.672	1.559	0.0198	1.283	1.835
	DMI + protectants	1.229	0.0700	0.710	1.747	0.913	0.0823	0.351	1.475
	Fluopicolide + protectants	1.706	0.0640	1.210	2.202	1.697	0.0784	1.147	2.246
	MBC + protectants	0.953	0.0683	0.441	1.465	1.169	0.0896	0.5823	1.756
	Cyanoacetamide-oxime (oximes) + protectants	1.632	0.0367	1.256	2.007	1.546	0.0434	1.137	1.955
	Phenylamides + protectants	1.244	0.0558	0.781	1.706	1.226	0.0676	0.716	1.736
	QiI + protectants	1.367	0.0132	1.140	1.594	1.458	0.0198	1.182	1.734
	QoI + protectants	1.233	0.0081	1.057	1.409	1.239	0.0126	1.019	1.459
	Toluamides + protectants	1.336	0.0367	0.960	1.711	1.341	0.0427	0.935	1.746
	CAA + QoI + protectants	1.379	0.0291	1.045	1.714	1.341	0.0362	0.968	1.713
	Carbamates + CAA + protectants	0.906	0.0491	0.471	1.341	1.262	0.0665	0.746	1.758
	DMI + QoI + protectants	1.230	0.0381	0.847	1.613	1.427	0.0532	0.975	1.879
	Oximes + QoI + protectants	1.450	0.0132	1.225	1.675	1.335	0.0185	1.068	1.602
	QiI + QoI + protectants	1.507	0.0563	1.042	1.972	1.423	0.0698	0.905	1.941

^a CI = confidence interval limit.

^b *Cucurbita pepo* refers to pumpkin and zucchini, winter, summer, and butternut squash; *Cucumis melo* refers to cantaloupe and muskmelon; *Cucumis sativus* refers to cucumber; and *Citrullus lanatus* refers to watermelon.

^c Fungicide grouping is based on the Fungicide Resistance Action Committee (FRAC) listed published in 2009.

Fig. 2. Comparative response for cucurbit downy mildew on **A**, cucumber (*Cucumis sativus*) versus other cucurbits and **B**, other cucurbit species, *Cucurbita pepo* (pumpkin and butternut, summer, winter, and zucchini squash) versus *Cucumis melo* (cantaloupe and muskmelon) versus *Citrullus lanatus* (watermelon), to fungicide treatments based on synthesis of reports published in *Fungicide and Nematicides Tests* and *Plant Disease Management Reports* from 2000 to 2008 ($k = 105$); L = the log-transformed standardized mean difference ($= \log_e d$) between fungicide-treated and untreated plots, with values of $L > 0.05$ representing very large effects. Depicted responses are based on a random-effects model for which error bars indicate the 95% confidence interval, while the dotted vertical line is the sample weighted mean effect size across all entries. CI(ΔL) is the 95% confidence interval around the difference in L between respective cucurbit types.

Fig. 3. Fungicide efficacy on cucurbit downy mildew prior to 2004–05, during 2004–05, and after 2004–05 seasons, based on synthesis of reports published in *Fungicide and Nematicides Tests* and *Plant Disease Management Reports* from 2000 to 2008 ($k = 105$); L = the log-transformed standardized mean difference ($= \log_e d$) between fungicide-treated and untreated plots, with values of $L > 0.05$ representing very large effects. Depicted responses are based on a random-effects model for which error bars indicate the 95% confidence interval, while the dotted vertical line is the sample weighted mean effect size across all entries. CI(ΔL) is the 95% confidence interval around the difference in L between two levels of disease pressure.

P. cubensis in Israel and the United States was a linked event. In 2007, highly effective fungicides such as fluopicolide (4) were introduced in the United States market for the control of cucurbit downy mildew. The introduction of newer and more effective fungicide products is reflected by the higher efficacy in the control of downy mildew after 2004–05 compared with before or during the 2004–05 season.

The presented $\bar{L}_+$ is the expected efficacy when a fungicide is applied to control any amount of disease intensity on any cucurbit host. However, in some cases, fungicides may have been applied when there was no disease or the disease intensity was very low; or, sometimes, fungicides were applied when disease intensity was moderate or very high. This study showed that disease pressure affected fungicide efficacy. The lowest $\bar{L}$ was observed in studies where the disease pressure was low and variability was also highest for this category of disease pressure. For example, the standard error of $\bar{L}$ was higher and the 95% confidence interval was wider for studies with low disease pressure than for

studies with higher disease pressure. This high variability could be due, in part, to less precise measurements of low disease levels. A similar response of low disease intensity to fungicide applications has been reported for a synthesis of the efficacy of tebuconazole on *Fusarium* head blight of wheat (32). When disease pressure is low, a lack of benefit from fungicides is not surprising because there would be little or no disease present. The highest $\bar{L}$ was found in studies that had a moderate amount of disease pressure. In studies where disease pressure was high, the decrease in $\bar{L}$ was relative to fungicide efficacy observed in studies with moderate disease pressure. The low $\bar{L}$ at high disease pressure is probably due to the inability of fungicides to prevent all infections under conditions that were presumably very conducive for disease development. It is also possible that sprays were initiated too late to result in any meaningful level of disease control. Assuming that disease pressure influenced the need to spray, it is plausible that this would explain the low $\bar{L}$ in studies in which a few (1 to 4 sprays) or a very large number of appli-

Fig. 4. Effect of cucurbit downy mildew disease pressure on the log-transformed standardized effect size, L ($= \log_e d$), of disease suppression by fungicide treatments based on synthesis of reports published in *Fungicide and Nematicides Tests* and *Plant Disease Management Reports* from 2000 to 2008 ($k = 105$). Values of $L > 0.05$ represent very large effects. Low = <30 , moderate = ≥ 30 to ≤ 50 , and high = $>50\%$ of disease intensity in the untreated control. Depicted responses are based on a random-effects model for which error bars indicate the 95% confidence interval, while the dotted vertical line is the sample weighted mean effect size across all entries. $CI(\Delta L)$ is the 95% confidence interval around the difference in L between two levels of disease pressure.

Fig. 5. Standardized response of cucurbit downy mildew to different number of fungicide applications based on synthesis of reports published in *Fungicide and Nematicides Tests* and *Plant Disease Management Reports* from 2000 to 2008 ($k = 105$); L = the log-transformed standardized mean difference ($= \log_e d$) between fungicide-treated and untreated plots, with values of $L > 0.05$ representing very large effects. Depicted responses are based on a random-effects model for which error bars indicate the 95% confidence interval, while the dotted vertical line is the sample weighted mean effect size across all entries. $CI(\Delta L)$ is the 95% confidence interval around the difference in L between two categories of number of sprays applied.

cations (>6 sprays) were used to control the disease. For example, in studies that received fewer sprays, disease intensity was very low or no disease was present, resulting in reduced control. The corresponding $\bar{L}$ associated with this latter group also had the widest bands for the 95% confidence interval.

Among the chemical products evaluated in this study, the pyridinylmethyl-benzamide (fluopicolide), carbamate (e.g., propamocarb), and quinone inside inhibitor (QiI) (e.g., cyazofamid) groups of fungicides were the most effective, whereas the CAA (dimethomorph and mandipropamid) group was the least effective. The phenylamide (metalaxyl) group of fungicides (45) has been used as a reference group when establishing the effectiveness of other fungicides in downy mildew control (12). In this study, the efficacy of phenylamides was less than the overall average efficacy of chemical products used to control cucurbit downy mildew. The reduced efficacy of phenylamides is most likely due to insensitivity of *P. cubensis* (6) to this group of fungicides. Fluopicolide is the first derivative of the new acylpicolide class of chemicals, whose mode of action is interference with the delocalization of spectrin-like proteins during mitosis (42). This fungicide is also highly effective against other oomycetes such as *Phytophthora infestans*, for which consistent control has been reported (9). The reduced efficacy of CAA fungicides observed here may be due to increased insensitivity of *Pseudoperonospora cubensis* to this group of fungicides. Zhu et al. (49) reported a high risk for the occurrence of resistance to flumorph in *P. cubensis* in a cucumber crop in China. In the latter study (49), flumorph also showed cross-resistance with dimethomorph and iprovalicarb. Mandipropamid was ineffective when first tested in several field studies in the United States in 2005 (8), which provides further evidence of cross resistance among the CAA fungicides.

One strategy that is recommended to prolong the efficacy of systemic fungicides is their use with compounds with different active ingredients (45) and, preferably, protectant fungicides. Mathematical models and experimental studies indicate that such mixtures reduce selection of resistant subpopulations compared with sensitive subpopulations (21,41). In *P. cubensis*, a mixture of flumorph and mancozeb was reported to provide significantly better control of cucurbit downy mildew than flumorph alone and resulted in a delay in resistance development (49). In another study, the relative increase in control of metalaxyl-sensitive strains of *P. cubensis* obtained from a metalaxyl-mancozeb mixture, compared with metalaxyl alone, was in the order of 3 to 24 (37). Although the actual mechanism governing synergy between fungicides with different modes of action is not known, it has been speculated that exposure of fungal propagules to sublethal concentrations of one fungicide weakens them to an extent that sublethal concentrations of the second fungicide will be detrimental (37). This may partly explain the higher $\bar{L}$ observed in this study for a mixture of protectant and systemic fungicides compared with systemic fungicides alone. In the present study, a mixture of a protectant (e.g., mancozeb and chlorothalonil) and metalaxyl resulted in an improved efficacy compared with metalaxyl alone. Generally, mixtures of systemic fungicides also had greater efficacy against downy mildew than did individual systemic fungicides.

In summary, fungicide groups provided a significant reduction in cucurbit downy mildew, although there was considerable unexplained variability in their efficacy. Further, fungicide efficacy was greater in cucumber than in all other cucurbit crops, with a moderate number of applications resulting in the most effective control. Due to lack of published data on disease-related yield losses associated with specific levels of disease intensity, it is not clear whether the estimated degree of control reported in this study economically justifies routine fungicide application for cucurbit downy mildew control. Given that disease pressure will vary yearly, a more rational management approach should consider economic factors and local and regional disease risk to

improve fungicide decision making. Due to the nature of the available data, this meta-analysis did not consider other factors that would influence fungicide efficacy, such as timing of first application (i.e., disease severity at first application), different types of surfactants and adjuvants, and amount of active ingredients. Disease severity at first application can be used to determine whether a threshold effect operates in the cucurbit downy mildew system (i.e., whether applying the first fungicide after some severity threshold is exceeded would result in reduced disease control or reduced yield response and how this varies for different cucurbit crops). Nonetheless, our results show a clear difference in

Fig. 6. Comparative response of cucurbit downy mildew on cucurbit to different fungicide groups based on synthesis of reports published in *Fungicide and Nematicides Tests* and *Plant Disease Management Reports* from 2000 to 2008 ($k = 105$). **A**, Fungicide groups applied singly or in combination but with no protectant fungicides; **B**, fungicide groups applied in combination with protectant fungicides; and **C**, fungicide groups applied in combinations with other groups and protectant fungicides. $\bar{L}$ the log-transformed standardized mean difference ($= \log_e d$) between fungicide-treated and untreated plots, with values of $\bar{L} > 0.05$ representing very large effects. Depicted responses are based on a random-effects model for which error bars indicate the 95% confidence interval, while the dotted vertical line is the sample weighted mean effect size across all entries. $CI(\Delta L)$ is the 95% confidence interval around the difference in $\bar{L}$ between two categories of fungicide products. Fungicide groups: CAA = carboxylic acid amides, DMI = demethylation inhibitors, PA = phenylamides, QiI = quinone inside inhibitors, and QoI = quinone outside inhibitors.

efficacy among several fungicide groups alone or in combination, and provide critical information that should be taken into account when using fungicides for cucurbit downy mildew control.

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