UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460
OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

April 22, 2004

MEMORANDUM

SUBJECT: Technical review of Monsanto's submission: "Impact of Effective Refuge Size and Typical Insecticide Use Practices on Model Predictions of Years to Resistance of Tobacco Budworm and Cotton Bollworm to Bollgard® Cotton"
EPA Reg. No. 524-478 and EPA Reg. No. 524-522; Submission dated March 13, 2004 (MRID 462224-03)

TO: Leonard Cole (PM-90)
Regulatory Action Leader
Microbial Pesticides Branch, Biopesticides and
Pollution Prevention Division (7511C)

FROM: Sharlene R. Matten, Ph.D., Biologist
Microbial Pesticides Branch, Biopesticides and
Pollution Prevention Division (7511C)

PEER REVIEW: Alan H. Reynolds, M.S., Entomologist
Microbial Pesticides Branch, Biopesticides and
Pollution Prevention Division (7511C)

ACTION REQUESTED: Provide a technical review of Monsanto's submission: "Impact of Effective Refuge Size and Typical Insecticide Use Practices on Model Predictions of Years to Resistance of Tobacco Budworm and Cotton Bollworm to Bollgard®[1] Cotton" submitted as part of the terms and conditions of EPA Reg. No. 524-478 (September 29, 2001) and EPA Reg. No. 524-522 (December 23, 2002).

[1]Bollgard® and Bollgard II® are registered trademarks of Monsanto Company.

CONCLUSIONS

1. EPA agrees with Gustafson et al.'s (2004) analysis that the model output is very sensitive to effective refuge size and use of insecticide sprays on Bollgard cotton for cotton bollworm (*Helicoverpa zea*, CBW) control. With this understanding, the 5% external, unsprayed structured refuge option is adequately protective to delay tobacco budworm (*Heliothis virescens*, TBW) and CBW resistance if effective refuge size and typical use practices (i.e., pyrethroid oversprays of Bollgard fields) are included as parameters in the model. Empirical data are needed to validate the model. The Agency mandated that Monsanto collect data regarding the utilization of alternate hosts for CBW resistance management and pyrethroid overspray efficacy against CBW in Bollgard (and Bollgard II) cotton fields as terms and conditions of the Bollgard and Bollgard II registrations (EPA Reg. Nos. 524-478 and 524-522, respectively). The alternate host studies (Head and Voth, 2004) and pyrethroid overspray studies (Greenplate, 2004) are reviewed separately.

2. The Gustafson et al. (2004) model is limited and cannot appropriately consider the spatial and temporal dynamics of CBW utilization of alternative hosts by generation. EPA disagrees with the way "effective refuge size" is calculated. Effective refuge is not the sum of the total acres of conventional cotton, soybean, and other alternate hosts (assumed to be 10%) per county. This assumes that every possible host is equal in its ability to produce moths and that these moths will be equally fit and produced in synchrony to mate with any putative resistant moths from the Bollgard (or Bollgard II) cotton fields. Rather, effective refuge must be the sum total of the acres of each alternate host weighted by its production ability, fitness, and generation contribution (synchrony). Corn should also be included in the effective refuge size calculation.

3. Gustafson et al.'s (2004) model predicted that a greater than ten-fold increase in the time to resistance (resistance allele frequency is greater than 0.5) for CBW when Bollgard® cotton was sprayed with pyrethroids. Research summarized in Greenplate et al. (2004) provides additional data that support the predictions of the Gustafson et al. (2004) model.

4. Pyrethroid sprays/typical insecticide use, as a parameter in the Gustafson et al. (2004) resistance model, will have little impact on model output (years to resistance) CBW on Bollgard® II cotton. Pyrethroid sprays/typical insecticide use is not needed as a parameter in the Gustafson et al. (2004) model for Bollgard® II resistance management since Bollgard® II will not typically be sprayed.

CLASSIFICATION : The Gustafson et al. (2004) modeling study is "supplemental" (partially acceptable). It may be upgraded to "acceptable" pending revision of the Gustafson et al. (2004) with recalculated "effective refuge" size, revised pyrethroid overspray parameters, and revised alternate host parameters. See specific recommendations below.

RECOMMENDATIONS

1. Monsanto should recalculate "effective refuge size." "Effective refuge size" must be the sum total of the

acres of each alternate host weighted by its production ability, fitness per generation. Corn should be included in the effective refuge size calculation for CBW.

2. Monsanto should refine an appropriate CBW resistance management model with the parameters values obtained from these alternative host studies (Head and Voth, 2004) so that both the spatial and temporal dynamics of CBW utilization of alternative hosts by generation can be considered. Each cotton production system (geography) should be modeled, e.g., North Carolina, The Delta, Georgia.

3. Monsanto should refine the Gustafson et al. (2004) model (or another appropriate resistance management model) using the average pyrethroid efficacy value against CBW calculated based on all the field studies conducted in all four states (North Carolina, Louisiana, Mississippi, and South Carolina) as the new parameter value rather than values strictly from Brickle et al. (1999). If there is no statistical difference in the irrigated and non-irrigated plots then these results may be combined.

4. It is recommended that pyrethroid sprays/typical insecticide use not be included as a parameter in the Gustafson et al. (2004) model for Bollgard® II resistance management since Bollgard® II will not typically be sprayed.

BACKGROUND

On September 29, 2001, EPA approved an amendment to Bollgard cotton registration (EPA Reg. No. 524-478) extending the registration until September 30, 2006, except for the 5% external, unsprayed refuge option which expires on September 30, 2004. As a condition of this registration, EPA mandated that Monsanto construct new resistance management models or refine existing ones to include consideration of pyrethroid oversprays and effective refuge based on the required empirical data. EPA mandated these same requirements for Bollgard II cotton, registered December 23, 2002 (EPA Reg. No. 524-522). Typically, Bollgard cotton is sprayed with a pyrethroid insecticide for CBW control late in the season, although Bollgard cotton is sprayed much less than non-Bollgard cotton. The survival of CBW in Bollgard cotton (expresses only a moderate dose of Cry1Ac) has been well-established (Mahaffey et al., 1995; Lambert et al., 1997). Bollgard II cotton expresses two Bt *(Bacillus thuringiensis*) proteins, Cry1Ac and Cry2Ab2, at a high dose or relatively high doses for control of TBW and CBW (see Matten and Reynolds, 2003). In contrast to Bollgard cotton, Bollgard II will not typically be sprayed for lepidopteran control because of its greater efficacy against these pests (Jackson et al., 2003).

CBW has numerous alternate hosts. The HOSTS database lists 108 species from 30 families that are hosts of CBW in the Nearctic region (at http://www.nhm.ac.uk/entomology/hostplants/). While the HOSTS database lists 66 species from 20 families that are hosts of TBW in the Nearctic region. The results from the alternate host and pyrethroid overspray field research can be used to provide parameters for CBW resistance prediction models (e.g., Caprio, 1998a and b; Storer et al. 2003; Gustafson et al., 2004)

In September 2001, Monsanto submitted to EPA a TBW and CBW insect resistance management model based on Caprio (1998a) (Gustafson et al., 2004; original report dated September 10, 2001 submitted as a public comment to EPA Docket OPP-00678B). Models discussed in EPA (2001) did not include the impact of market penetration of Bollgard cotton, the effective refuge size (inclusion of alternate hosts as natural refuge, not just non-Bt cotton, typical insecticide use practices (i.e., use of pyrethroid oversprays), and fitness costs of survivors on Bollgard cotton. Gustafson et al. (2004) incorporates "effective refuge" size and pyrethroid oversprays into the Caprio (1998a) model to demonstrate the sensitivity of the model output (i.e., years to resistance) to these parameters. The pyrethroid overspray data and the alternate host data mandated as conditions of registration (EPA Reg. No. 524-478 and No. 524-522) and the linkage of these data to the Gustafson et al. (2004) model will be discussed separately. This review will focus strictly on the TBW and CBW resistance management model Monsanto developed in 2001 (Gustafson et al., 2004) and its utility.

REVIEW

1. Model summary

The Gustafson et al. model (2004) is based on Caprio (1998a) with a focus on the impact of "effective refuge size" and pyrethroid spray patterns on the predicted number of years to resistance for CBW and TBW to Bollgard cotton. The model input parameters (low, mid, and high values) were assigned using the published scientific literature **(Table 1)**. The low and high values represent the 90% confidence limit of the true value of each input parameter. The mid values represent the most probable parameter value. Triangular distribution for each input parameter were formed using the low, mid, and high values. Marginal sensitivity analyses were performed in which one parameter alone was varied while all other parameters were held at their default ("mid") values.

Effective refuge by county was calculated for total acres of conventional cotton, Bollgard cotton, and soybean using USDA/NASS data from 1999 and a conservative estimate of other alternate hosts including alfalfa, grain sorghum, and wild or weedy plants (10% of the land were not planted to corn or soybeans) (Caprio and Benedict, 1996). Acres of corn were not included in this calculation. To ensure a conservative estimate, values of effective refuge size of greater than 80% were not included in the sensitivity analysis even though this was the case in more than 50% of the counties.

No fitness penalties were included for TBW in the sensitivity analysis. The upper and lower 95% confidence limits on the model predictions as a function of refuge size were obtained empirically by simultaneously varying the critical parameters, ranking the results, and selecting the appropriate percentile levels.

2. Model results

The estimated effective refuge size for all U.S. counties containing cotton ranged from 43% to 100% (i.e., no *Bt* (*Bacillus thuringiensis*) with a mean of 87% **(Figure 1)**. Ninety-nine percent of counties had a calculated effective refuge size greater than 50%.

Figure 2 shows the impact of effective refuge size and pyrethroid oversprays on model results. The model was run using the mid parameter values including pyrethroid efficacy and effective refuge size shown in **Table 2**, except for the effective refuge size which was varied. Table 2 shows the results of the model sensitivity analysis. Model output is calculated as the number of generations until the resistance allele frequency exceeds 0.5. The model predicts that it will take approximately 100 years before field resistance for TBW and CBW occurs as long as there is at least a 40% effective refuge (Figure 2). The time to CBW resistance when Bollgard is sprayed with pyrethroids dramatically increases to 111 years in contrast to when it is unsprayed, the time to CBW resistance is only 8 years with at least a 40% effective refuge. These model predictions are supported by the sensitivity analysis shown in **Table 2**. There is a wide range of predicted values for years to resistance depending on the assumptions used.

Figure 3 shows the mean value and 95% confidence limits for the years to resistance for CBW when Bollgard cotton is treated with a pyrethroid insecticide. If effective refuge size is 40% and all other parameters are allowed to vary, the model predicts that CBW resistance will arise between 15 years and greater than 1250 years.

3. Monsanto's conclusion

Monsanto (Greenplate et al., 2004) concludes that the sensitivity analysis demonstrated that "real-world" parameters for survival on Bollgard cotton following treatment with pyrethroids, effective refuge size, initial allele frequency, and moth movement, result in a wide range of predicted years to resistance. Including effective refuge size and insecticide use practices in the model demonstrates that the 5% external, unsprayed refuge option effectively delays resistance development for both TBW and CBW.

4. EPA review

Monsanto modified Caprio's (1998a) two-patch, deterministic, non-random, population genetics model to create a new model, Gustafson et al. (2001, resubmitted as Gustafson et al. (2004)) that included alternative hosts and synthetic pyrethroid oversprays as parameters. Gustafson et al. (2004) showed how the model output was sensitive to both of these parameters. The model predicted that alternative hosts as "effective" refuge would delay the evolution of CBW resistance to the Cry1Ac toxin expressed in Bollgard cotton. EPA agrees that the model output is very sensitive to effective refuge size and use of insecticide sprays on Bollgard cotton for CBW control. The sensitivity analysis **(Table 2)** shows that using the mid values as parameters, model output is most affected by effective refuge size, resistance allele initial frequency, and survival on Bollgard cotton when it is sprayed with pyrethroids. If effective refuge size is 40%, there is more than a 10-fold difference in the time to CBW resistance when Bollgard is sprayed with pyrethroids (111 years) than when it is unsprayed (8 years) **(Figure 2)**. Modeling output, years to resistance, should not be interpreted on a literal basis. Rather, years to resistance predicted under different scenarios should be used on a comparative basis to evaluate the relative robustness of the refuge options and aid those making resistance management decisions. With this understanding, the Gustafson et al.'s model (2004) predicts that the 5% external, unsprayed structured refuge option, is adequately protective to delay TBW and CBW resistance if effective refuge size and typical use practices (i.e., pyrethroid oversprays of Bollgard fields) are included as parameters in the model. However, empirical data are needed to validate the model. This is why the Agency mandated that Monsanto collect data regarding the utilization of alternate hosts for cotton bollworm resistance management and pyrethroid overspray efficacy against cotton bollworm in Bollgard (and Bollgard II) cotton fields as terms and conditions of the Bollgard registration (EPA Reg. No. 524-478) and Bollgard II registration (EPA Reg. No. 524-522). These studies, Head and Voth (2004) and Greenplate (2004), are reviewed separately.

Monsanto (Lahman, 2004) states that the data in Head and Voth (2004) demonstrate the contribution of alternative hosts and pyrethroid oversprays control is at the levels assumed in the model presented in Gustafson et al. (2004). This means that the alternative host data support the conclusion in Gustafson et al. (2001/2004) that alternative hosts are "effective" refuge and will delay the evolution of CBW resistance to the Cry1Ac toxin expressed in Bollgard cotton. Pyrethroid oversprays on Bollgard cotton fields will amplify delay CBW resistance evolution. CBW resistance will be delayed even further to the two-toxins (Cry1Ac and Cry2Ab2) expressed in Bollgard II cotton. As Lahman (2004) notes, Bollgard II provides significantly higher levels of control of CBW than Bollgard cotton.

Gustafson et al. (2004) have not included acres of corn in the effective refuge size calculation (rationale not provided). This does not make sense for CBW. Gould et al. (2002) used stable carbon isotope analysis to assess alternate host use by CBW. They found that non-*Bt* C_4 plants, probably corn, in Mexico and the U.S. Corn Belt appear to serve as important alternate hosts (non-structured refuge) for CEW. Late-season CEW moths captured in Louisiana and Texas may be migrants whose larvae developed on corn in more northern locations. Gould et al. (2002) provide indirect evidence (they did not establish the origin of these moths, i.e., which C_4 or C_3 plants and the distances they are migrating) for migration of CBW from corn-growing areas in the northern U.S. to cotton-growing areas in the southern U.S. These findings counter the prevailing hypothesis that the majority of late-season moths are produced from larvae feeding on cotton, soybean, and other C_3 plants. The authors conclude that when C_4 plants are suitable (e.g., corn), less than 10% of CBW moths are developing on cotton, and that later in the season, 50% of the moths are produced in cotton and soybean. Corn is most likely serving as the predominant C_4 host for CBW. Southern corn is probably an important C_4 host for early season; while, the Corn-Belt corn serves as an important C_4 host during the mid-season. Currently, approximately 30% of the corn acreage is planted as *Bt* corn.

EPA disagrees with Monsanto's method of calculating "effective" refuge. "Effective" refuge is not the sum of the total acres of conventional cotton, soybean, and other alternate hosts (assumed to be 10%) per county. This assumes that every possible host is equal in its ability to produce moths and that these moths will be equally fit and produced in synchrony to mate with any putative resistant moths from the Bollgard (or Bollgard II) cotton fields. "Effective refuge" size is a weighted average of the proportion of moths coming from each alternative host for each CBW generation (5 to 6 generations) in each cotton production system (geography). The Gustafson et al. (2004) model is limited in its predictive ability because it cannot segregate the relative contribution of each alternative host on the evolution of CBW resistance by generation. The Gustafson et al. (2004) model has two large patches: 1) Bollgard and 2) alternative hosts (i.e., all alternative hosts *en masse*, no generation segregation). It assumes that all alternative hosts are equally effective and that they all produce moths in complete synchrony with cotton (Bollgard or non-Bollgard) and that it is generation independent. This is not a "stepping stone" model, there is no sequential host utilization by generation. While there is synchrony of CBW moth production in alternative hosts and cotton; this synchrony is not perfect as shown by the data in Head and Voth (2004). While CBW is polyphagous and disperses over great distances to feed on attractive hosts (i.e., it feeds on different hosts sequentially so that different generations will feed on different hosts) as they become attractive over the landscape (see literature review, Benedict, 2004). There is also a huge differential in moth production on these alternative hosts as seen in the data summarized by Head and Voth (2004) and in the literature review (Benedict, 2004). There is no spatial or temporal dynamic in this model. Despite the limitations of the Gustafson et al. (2001) model, one can conclude that, on a very qualitative level, the alternative hosts data support the predictions of this model. That is, inclusion of alternative hosts as unstructured refugia will delay CBW resistance longer than without the inclusion of alternative hosts and only if the 5% external,unsprayed structured refuge was considered.

EPA stated in the terms and conditions of registration (see EPA, 2001) that the alternative host data collected in 2002 and 2003 should be used to refine or construct new resistance management models that include alternative hosts appropriate for different cotton production regions. The Gustafson et al. (2001) model or other appropriate resistance management model was not refined with the alternative host data. Because of the limitations of the Gustafson et al. (2004) model, described above, Monsanto should refine an appropriate CBW resistance management model with the parameters values obtained from these alternative host studies (see Head and Voth, 2004) so that both the spatial and temporal dynamics of CBW utilization of alternative hosts by generation can be considered. Each cotton production system (geography) should be modeled, e.g., North Carolina, The Delta, Georgia. Two examples of CBW models that include both spatial and temporal dynamics of CBW by generation are Caprio (1998b) and Storer (2003).

Currently the Gustafson et al. (2004) model is parameterized with pyrethroid efficacy values from Brickle et al. (2001) because there were only limited data available in 2001. Using data from Brickle et al. (2001), the Gustafson et al. (2004) model predicted that a greater than ten-fold increase in the time to resistance (resistance allele frequency is greater than 0.5) for cotton bollworm when Bollgard cotton was sprayed with pyrethroids. Research summarized by Greenplate (2004) should be incorporated into population genetics models, e.g., Gustafson et al. (2004). These data support the utility of pyrethroid oversprays in Bollgard cotton to significantly delay resistance development in CBW populations. However, there are questions regarding the effect of pyrethroid oversprays in irrigated Bollgard cotton versus non-Bollgard cotton in the one irrigated study in South Carolina described in Brickle et al. (2001). It is recommended that Gustafson et al. (2004) model be parameterized with other pyrethroid spray studies that include both irrigated and non-irrigated fields over multiple years, e.g., Jackson et al. (2003).

Results from field studies conducted in North Carolina and Mississippi indicate that pyrethroid sprays on Bollgard II plots do not provide a statistically significant difference in reduction of CBW infestation or damage from untreated Bollgard II fields (Jackson et al., 2003.; Harris et al., 2002). Pyrethroid sprays/typical insecticide use, as a parameter in the Gustafson et al. (2004) resistance model, will have little impact on model output (years to resistance) for CBW on Bollgard II cotton. Pyrethroid sprays/typical insecticide use is not needed as a parameter in the Gustafson et al. (2004) model for Bollgard II resistance management since Bollgard II will not typically be sprayed.

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Table 1. Input parameters for sensitivity analysis. [Reprinted from p. 7 of Gustafson et al. 2004]

Parameter		TBW Low	TBW Mid	TBW High	CBW Low	CBW Mid	CBW High	CBW sprayed Low	CBW sprayed Mid	CBW sprayed High
Survival on Bollgard Cotton	SS	0	1E-06	0.001	0.03	0.15	0.3	0.0015	0.0075	0.015
	Sr	0	0.001	0.01	0.1	0.3	0.5	0.005	0.015	0.025
	Rr	1	1	1	1	1	1	0.05	0.05	0.05
Survival on Conventional Cotton	SS	1	1	1	1	1	1	0.2	0.2	0.2
	Sr	1	1	1	0.95	0.975	1	0.19	0.195	0.2
	Rr	1	1	1	0.9	0.95	1	0.18	0.19	0.2
Refuge	P	0.05	0.2	0.6	0.05	0.3	0.8	0.05	0.3	0.8
Resistance Allele Initial Frequency	q (t=0)	0.0001	0.001	0.01	0.0002	0.002	0.02	0.0002	0.002	0.02
Move outside habitat before mating	R	0.5	0.95	1	0.5	0.95	1	0.5	0.95	1
Move outside habitat before ovipositing	M	0.5	0.95	1	0.5	0.95	1	0.5	0.95	1

† Pyrethroid spray efficacy based on Brickle et al., 2001.

Table 2. Marginal sensitivity analysis results (number of generations until the resistance allele frequency exceeds 0.5) [Reprinted from p. 8 of Gustafson et al., 2004]

Parameter		TBW			CBW			CBW sprayed		
		Low	Mid	High	Low	Mid	High	Low	Mid	High
Survival on Bollgard Cotton	SS	219	162	59	>5000	27	15	>5000	90	47
	Sr	160	61	17	>5000	26	15	>5000	92	42
Survival on Conventional Cotton	Sr	na	na	na	26	25	24	123	86	68
	rr	na	na	na	25	25	25	89	86	84
Refuge	P	48	301	1171	13	36	553	25	147	>5000
Resistance Allele Initial Frequency	q (t=0)	587	153	24	36	26	16	127	85	47
Move outside habitat before mating	R	18	73	170	26	26	25	101	91	86
Move outside habitat before ovipositing	M	202	173	160	27	26	25	101	91	86

[1] Pyrethroid spray efficacy based on Brickle et al., 2001.
na = No sensitivity analysis performed.

Figure 1. Frequency distribution of the effective refuge size across all cotton-growing counties in the U.S. Value on the X axis is calculated as ((1-Bollgard cotton acres planted in 1999/acres of all available refuge). [Reprinted from p. 9 of Gustafson, 2004]

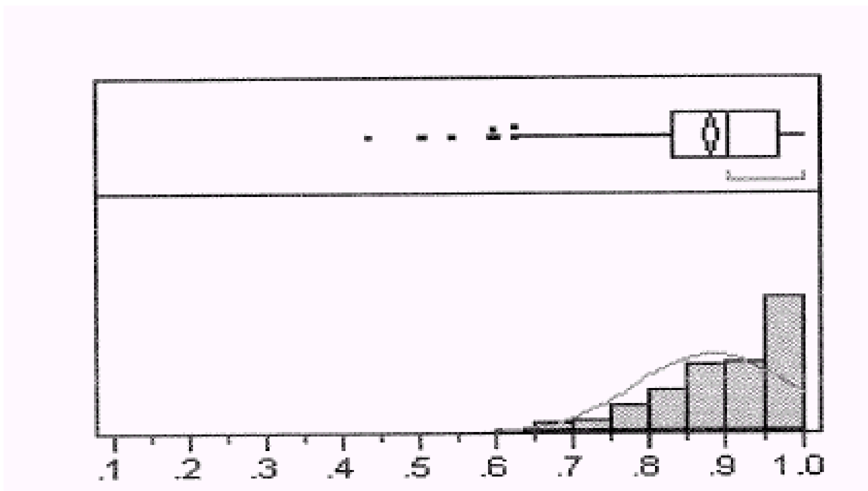

Figure 2. Impact of effective refuge size on model results. TBW Untreated BG = no supplemental insecticide treatment for TBW on the Bollgard cotton; CBW Untreated BG = no supplemental insecticide treatment for CBW on the Bollgard cotton; CBW Treated BG = average of at least one supplemental insecticide treatment of a pyrethroid for CBW on the Bollgard cotton. The "mid" values from Table 2 were used in the model except for effective refuge size which was varied. The shaded area represents the minimum effective refuge size calculated for more than 99% of the cotton-growing counties. [Reprinted from p. 9 of Gustafson, 2004]

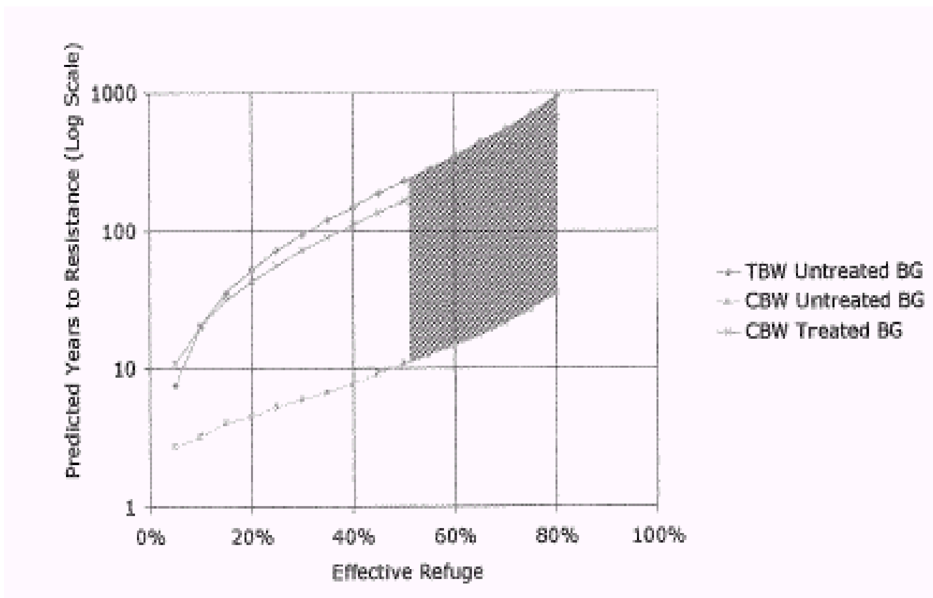

Figure 3. CBW treated BG from Figure 2 with the dashed lines showing the upper and lower 95% confidence limits. The shaded area represents the minimum effective refuge size calculated for more than 99% of the cotton-growing counties in the U.S. [Reprinted from p. 11 of Gustafson et al. 2004]