BIOPESTICIDES REGISTRATION ACTION DOCUMENT

MON 89034 x TC1507 x MON 88017 x DAS-59122-7 *(SmartStax®)* *B.t. Corn Seed Blend*

U.S. Environmental Protection Agency (EPA)
Office of Pesticide Programs
Biopesticides and Pollution Prevention Division (BPPD)

November 29, 2011 Update

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This update includes a new expiration date and additional terms and conditions.

I. BACKGROUND

Active Ingredients:

Bacillus thuringiensis Cry 1A.l05 protein and the genetic material necessary (vector PV-ZMIR245) for its production in corn event MON 89034

Bacillus thuringiensis Cry2Ab2 protein and the genetic material necessary (vector PV-ZMIR245) for its production in corn event MON 89034

Bacillus thuringiensis Cry1F protein and the genetic material necessary (vector PHP8999) for its production in corn event TCI507

Bacillus thuringiensis Cry3Bbl protein and the genetic material necessary (vector PV-ZMIR39) for its production in com event MON 88017

Bacillus thuringiensis Cry34Ab1 protein and the genetic material necessary (vector PHP17662) for its production in corn event DAS-59122-7

Bacillus thuringiensis Cry35Ab1 protein and the genetic material necessary (vector PHP I7662) for its production in corn event DAS-59122-7

Trade & Other Names:

MON 89034 x TC1507 x MON 88017 x DAS-59122-7 RIB Complete Insect Protected, Herbicide-Tolerant Corn

MON 89034 x TC1507 x MON 88017 x DAS-59122-7 Insect Protected, Herbicide-Tolerant Corn with Interspersed Refuge

Genuity® SmartStax® RIB Complete

Refuge Advanced™ Powered by SmartStax®

EPA Registration Numbers: 524-595, 68467-16

OPP Chemical Codes: 006490, 006481, 006502, 006515, 006514

Type of Pesticide: Plant-Incorporated Protectants (PIPs)

Basic Manufacturers:

Monsanto Company
800 North Lindbergh Blvd
St. Louis, MO 63167

Mycogen Seeds c/o Dow AgroSciences LLC
9330 Zionsville Road
Indianapolis, Indiana 46268-1054

Target Pest(s):

European corn borer (ECB)
Southwestern corn borer (SWCB)
Southern cornstalk borer (SCSB)
Corn earworm (CEW)
Fall armyworm (FAW)
Stalk borer
Lesser corn stalk borer
Sugarcane borer (SCB)
Western bean cutworm (WBC)
Black cutworm
Western com rootworm (WCRW)
Northern corn rootworm (NCRW)
Mexican corn rootworm (MCRW)

Product Profile:

EPA conditionally registered MON 89034 x TC1507 x MON 88017 x DAS-59122-7 in July 2009. MON 89034 x TC1507 x MON 88017 x DAS-59122-7 is a bioengineered corn PIP product containing two (2) Bt PIPs active against corn rootworm (CRW) and three (3) Bt PIPs active against various corn borer pests. MON 89034 x TC1507 x MON 88017 x DAS-59122-7 currently requires a combined 5% refuge for corn rootworm and lepidopteran pests where the corn earworm is not a significant pest and a 20% combined refuge in cotton growing regions where the corn earworm is a significant pest.

MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend products combine 95% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 corn with 5% refuge non-Bt corn. No external block refuge is required where the corn earworm is not a significant pest. A 20% refuge is required in cotton growing regions where the corn earworm is a significant pest.

II. SCIENCE ASSESSMENT

A. INSECT RESISTANCE MANAGEMENT

Summary

1) Corn Rootworm

BPPD has reviewed Monsanto's and Dow AgroSciences' submissions for a 5% SmartStax seed mixture including biological and efficacy data as well as simulation modeling. In addition, BPPD conducted independent modeling analyses of the applicants' proposal using a model (deterministic and probabilistic) developed by EPA/ORD. After careful review of the applicants' modeling and the analyses conducted by ORD, BPPD concluded that for corn rootworm (CRW), a 5% seed mixture and 5% structured refuge have comparable durabilities. Despite identifying a number of uncertainties with the CRW assessment, the FIFRA SAP (2011) verified BPPD's conclusion that a 5% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend should have comparable durability to a 5% block refuge.

2) Lepidoptera (European Corn Borer and Southwestern Corn Borer)

Based on a review of the Science Advisory Panel (SAP) report (SAP 2011) and revised modeling submitted by Monsanto/Dow, BPPD concludes that a 5% seed blend for MON 89034 x TC1507 x MON 88017 x DAS-59122-7 corn will likely be less durable (perhaps significantly so) than a comparable (5%) block refuge for the product. BPPD notes, however, that a MON 89034 x TC1507 x MON 88017 x DAS-59122-7 5% seed blend should be more durable than a 20% block refuge for a single toxin Bt corn product or a comparable (5%) seed blend for a two toxin pyramid. Larval movement, potential survival (and selection) of heterozygote genotypes, and loss of refuge effectiveness during the growing season are the primary factors that are likely to reduce durability in seed blends.

To improve BPPD's ability to assess the risks of resistance for a MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend, the following topics and uncertainties must be addressed:

- Revised modeling incorporating the structural elements recommended by the SAP (i.e., explicit larval movement, switch from a frequency-based model to one including density-dependent larval mortality, epistatic mechanisms for resistance in target pests) with separate analyses for SWCB and ECB. Non-uniform oviposition should be modeled for both ECB and SWCB, especially (but not only) for the second generation of adults which will more likely lay eggs on Bt rather than on damaged (or crowded out) non-Bt refuge plants in seed blends.

- Biological research on adult movement (related to mating and movement from refuges), larval movement, larval feeding (i.e., selective feeding within corn ears or on pollen), survival of heterozygote genotypes on MON 89034 x TC1507 x MON 88017 x DAS-59122-7 (markers may need to be determined for heterozygotes), and the potential for epistatic mechanisms of resistance (particularly with older instars).

Problem Formulation

BPPD’s risk assessment focused on assessing the risk of resistance developing to a 5% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed mixture in three main target pests: European corn borer, Southwestern corn borer, and corn rootworm. The registrants proposed the continued use of the existing 5% structured refuge requirement for MON 89034 x TC1507 x MON 88017 x DAS-59122-7 in most parts of the Cotton Belt so as to not further contribute to the risk of resistance evolution in corn earworm (CEW). Although it is known that CEW migrate northward during the growing season to corn-growing regions (i.e., the U.S. Corn Belt and Canada), CEW typically are not capable of overwintering in these regions. Rather, CEW are known to overwinter in the South, often in cotton fields. Some reverse migration from the Corn Belt to the Cotton Belt was observed by Gould *et al.* 2002, which sparked interest and the need to quantify the impact of south-north and north-south migration on the adaptation rates in CEW. Computer simulations by the Agricultural Biotechnology Stewardship Technical Committee (ABSTC) showed no significant interaction between the percent of the late summer adult CEW population in the south that is made up of immigrants and the date at which migrants return and no effect of return migration on the resistance gene frequency.

In the case of fall armyworm (FAW), a secondary target pest of MON 89034 x TC1507 x MON 88017 x DAS-59122-7 in the continental US, the species distribution is currently limited to areas of southern Florida and southern Texas; hence FAW are not currently a corn pest in the regions proposed for the adoption of a 5% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed mixture. Should future climate change elicit a range expansion for FAW and expand its overwintering capacity into the Corn Belt, then a revised risk assessment will be needed for this target pest and the proposed 5% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed mixture.

A. Seed Mixture vs. Structured Refuge

Seed mixtures incorporating Bt and non Bt crop seeds have been a topic of discussion for almost two decades. While such an Insect Resistance Management (IRM) strategy has obvious benefits (*i.e.*, no grower compliance component, facilitating the planting of Bt and refuge fields), it has been proposed that under some circumstances this approach could lead to more rapid evolution of resistance in some target pests.

Scientific Advisory Panels (1998 and 2000) discouraged the Agency from the use of Bt seed mixtures to control lepidoptera target pests because substantial larval movement could be expected between Bt and non-Bt plants leading to more rapid selection of resistance. Conversely, the 2009 SAP concluded that a 20% seed blend strategy for Bt corn with low- or medium-dose effects on corn rootworm (Coleoptera: Chrysomelidae) was supported by the insect's limited larval movement. But the SAP specifically noted that this recommendation should not set a precedent for other Bt crops targeting other pests (SAP 2009).

Theoretical work by Mallet and Porter (1992) showed that insect resistance was accelerated in seed mixtures compared to Bt stands where 10% of the population was not exposed to selection, when the probability of larval movement ranged from intermediate to high (≥ 0.2), intensity of selection was great, and dominance of the resistance gene was low. They also reported that when insects selectively chose their food source (avoidance of toxic substances), then effective dominance was increased, and seed mixtures could delay resistance evolution but that predicted outcomes depended also on other circumstances.

Using Mallet and Porter's model, Tabashnik (1994) reported that 10% Bt seed mixtures were more durable than pure Bt stands and that block refuges of 10% were at least as durable (and more) as 10% seed mixtures when inheritance of resistance was recessive, partly recessive, or additive. As the percentage of refuge increased from 0-50%, Tabashnik further reported that a block refuge strategy performed equally well or better than seed mixtures. Seed mixtures in conjunction with refuges were the most durable of all deployment strategies evaluated.

Onstad and Gould (1998) recommended 20% block refuges adjacent to the Bt fields over seed blend strategies because of uncertainties surrounding expression of high-dose against the target pest. Their modeling results predicted that block refuges would be more durable than seed mixtures aimed at controlling lepidopteran pests.

In a 2-yr field study with a seed mixture expressing Cry1Ab and non-Bt corn, Davis and Onstad (2000) obtained larval dispersal data, which were used to parameterize their simulation model and assess the effect on the durability of seed mixtures. Davis and Onstad observed that survival (after recovery) was lower for larvae that successfully dispersed from Bt to non-Bt plants compared to larvae that dispersed from non-Bt to non-Bt plants; this should favor heterozygote genotypes and make inheritance of resistance less recessive (Mallet and Porter 1992). In addition, increased mortality of susceptible larvae moving off refuge plants onto Bt plants would result in a reduced effective refuge. They reported that neonate dispersal away from Bt plants was greater than dispersal observed from non-Bt plants and noted that extensive use of seed mixtures could select for populations with improved dispersal capabilities. The empirical data was used to parameterize the simulation model (Onstad and Gould, 1998), and it was determined that while seed mixtures delay evolution of resistance in ECB they are less effective at doing so than IRM strategies using a 20% block refuge.

Carierre *et al.* (2004) concluded that the differences in Bt trait durability predicted by block refuges and seed mixtures in Mallet and Porter (1992) and Tabashnik (1994) were caused by a reduction in refuge insects in seed mixtures that had moved from non-Bt plants to Bt plants and could be overcome if the percent of non-Bt plants in seed mixtures was increased (compared to blocks).

B. Uncertainties

BPPD's assessment (BPPD 2010) of Monsanto and DowAgroScience's proposal identified a number of uncertainties regarding the biology of the target pests and potential impacts on a seed blend strategy.

1. BPPD recognizes that to determine whether a 5% seed mixture (both lepidoptera and coleopteran controlling agents) is a superior, equivalent, or inferior strategy to the currently approved 5% block refuge for MON 89034 x TC1507 x MON 88017 x DAS-59122-7, a number of uncertainties and questions need to be considered.

2. There is evidence that some fraction of the adult ECB population may take part in long-distance dispersal (references described above) and that this behavior is a normal part of ECB life-history. Evidence suggests that these insects are able to cover more than 12 km in one flight attempt. Results by Dorhout et al (2008) suggest that a fraction of 1-d old females appear to engage in obligate migratory flights. Mark-recapture studies in aggregation sites have failed to collect more than 1% of the released individuals. To determine whether a structured refuge some distance away from the Bt field or an integrated refuge via seed blend is the better IRM option for ECB, information with respect to the proportion of the population engaging in obligate migratory behavior and timing of mating with respect to dispersal is crucial.

3. The proportion of the female ECB population that would have to engage in pre-ovipositional long distance dispersal before durability of a 5% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed mixture became compromised and whether that proportion would be a reasonable assumption is uncertain.

4. When susceptible ECB larvae move from Bt plants to non-Bt plants and their survival is lowered compared to susceptible larvae that have not previously been exposed to Bt (Onstad & Gould 1998), then a seed mixture can be expected to decrease the effective refuge. Likewise, if susceptible larvae leave non-Bt plants, arrive on Bt plants, and are subsequently killed, then seed mixtures can be expected to reduce the refuge population to less than what can be expected to emerge from a block refuge. In either case, literature supports that such conditions would increase the risk of resistance evolution in the target pests. An assessment is needed of whether the reduction in effective refuge is substantial and could reduce the overall durability of the Bt product.

5. Based on the timing of mating for SWCB (within 24-48h) and the pre-copulatory flight behavior over natal fields by males, it has been suggested that random mating occurs in the field for this target pest. Results by Qureshi *et al.* (2006), however, suggest that SWCB are also capable of dispersing greater distances. Based on the limited studies available in the public literature, it appears that mating could primarily take place in natal fields but that greater dispersal may also occur after the mating phase. Whether mating occurs before or after dispersal or whether only a fraction of females disperse during the pre-mating phase is important information and can impact the recommended IRM approach.

6. There may be regions in the continental U.S. where the Cotton Belt and Corn Belt overlap and where corn earworm is known to overwinter. Such potential areas must be identified because they could contribute to increased selection in corn earworm (CEW - aka cotton bollworm, CBW), which is a main target pest of both cotton and corn.

7. A reduction in male CRW in Bt mixtures was discussed by the SAP (2009) with respect to 5% Cry34/35 Bt corn mixtures. The SAP (2009) concluded that a reduction in the number of males could negatively affect refuge effectiveness. This concern also applies for the pyramided Bt corn mixture targeting CRW and should be addressed.

8. Different types of events and behaviors have been documented to affect WCRW adults' dispersal spatially and temporally in the US Corn Belt. Despite this additional evidence for long distance dispersal, some data gaps still exist and should be addressed so that dispersal can be best incorporated into simulation models. For example, Spencer (2009) reported that individuals of the variant WCRW type dispersed more than 200 m/day; however, the proportion of individuals in a population undertaking this sort of long distance movement is unknown. Likewise, uncertainties associated with proportion of populations dispersing during cold front events (wind speeds of > 1.5 m/s) and frequencies of such events make it challenging to include this mode of dispersal.

9. It is unclear what proportion of female CRW populations would have to engage in pre-ovipositional long distance dispersal before durability of a 5% SS seed mixture could potentially be compromised.

10. It is unclear how non-compliance will affect the durability of a 5% block refuge relative to a 5% seed blend and whether such non-compliance assumptions are reasonable for the US.

Corn Rootworm Assessment

BPPD reviewed Monsanto's and Dow AgroSciences' submissions for a 5% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed mixture including biological and efficacy data as well as simulation modeling (BPPD 2010). In addition, BPPD conducted independent modeling analyses of the applicants' proposal using a model (deterministic and probabilistic) developed by EPA/ORD. After careful review of the applicants' modeling and the analyses conducted by ORD, BPPD concludes that or corn rootworm (CRW), a 5% seed mixture and 5% structured refuge have comparable durabilities;

Monsanto Company and Dow AgroSciences separately submitted efficacy, adult emergence, and larval movement data, which served to support some of their assumptions made in their simulation models. The modeling analyses focused on the time to resistance or 'rate of adaptation' for European corn borer, Southwestern corn borer, and corn rootworm from the use of a 5% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed mixture (95% Bt and 5% non-Bt seed). Dow's model predicted similar increases in corn rootworm resistance allele frequencies for both refuge strategies, while

EPA/ORD's simulation analyses were conducted separately for CRW and ECB/SWCB using a two-locus deterministic and probabilistic model, which is an extension of the model used in Caprio and Glaser (2010a). The analysis was conducted by running 1000 simulations, each time re-sampling a group of uncertain parameters using a PERT- Beta distribution (setting a minimum, most likely, and maximum value for each parameter of concern). For each pest, the model output generated a probability distribution for durability (time to resistance) based on the 1000 simulations that were conducted. To analyze these distributions, BPPD established durability estimates for various levels of risk (i.e., the likelihood that a resistance event would occur within a particular timeframe). For example, a 5% level of risk would mean that in 95% of the simulations, resistance evolved in greater time than the durability estimate predicted. Conversely, in the other 5% of the simulations resistance developed within the predicted time frame.

In the CRW model simulations (see Table 1), the mean time to resistance was 82 years for a 5% seed blend and 53 years for a 5% structured refuge. As described above, a probability distribution was also created from the simulations for the estimated time to resistance with a seed blend and structured refuge. With a 5% level of risk, the durability of MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed for CRW was 33 years, while the block refuge was 22 years. This means that in only 5% of the 1000 simulations conducted, resistance evolved within 33 years (seed blend) and 22 years (structured refuge).

Table 1. Durability estimates by EPA/ORD and Dow for 5% SmartStax seed mixture and 5% structured refuge targeting Corn rootworm

Refuge Scenario	Dow CRW Model	ORD CRW model	
	Increase in Resistance Allele Frequency[1]	5% Level of Risk	Average Years
5% Seed Blend	Similar rates of increase[2] for the 20 years modeled	33 years	81.9 years
5% Structured Refuge		22 years	52.9 years

[1] For benchmark and worst-case assumptions
[2] Dow's model predicted similar durability for SmartStax under both refuge scenarios but no actual values were provided.

FIFRA Scientific Advisory Panel

The Agency held a Scientific Advisory Panel meeting on December 8-9, 2010 to address BPPD's risk assessment of 5% MON 89034 x TC1507 x MON 88017 x DAS-59122-7, a multi-toxin double pyramid targeting above ground (Lepidoptera) and below ground (Coleoptera) pests of maize. In the Agency's risk assessment, BPPD evaluated Monsanto's modeling for Lepidoptera pests and Dow's modeling for corn rootworm; additionally, BPPD collaborated with EPA/ORD in an independent modeling effort to evaluate the applicants' proposal (BPPD 2010). The SAP provided its written report to the Agency on March 3, 2011.

Lepidopteran Assessment (ECB, SWCB, CEW)

The SAP expressed concern about the risk of resistance by the European corn borer (ECB) and southwestern corn borer (SWCB) in a 5% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend compared to a 5% structured refuge (approved by the Agency in 2009). Their overall conclusion was that a 5% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 strategy would be substantially less durable than a 5% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 (SSX) structured refuge and that there was "insufficient scientific basis for supporting the SSX RIB as an effective IRM strategy" for ECB and SWCB. The following is a summary of the SAP's main concerns about Monsanto's assumptions and parameter values chosen in their model for European corn borer and southwestern corn borer:

A. Structural equations to model larval movement were not included in the model, and the approximations used by the applicant were structured to minimize the effect of larval movement on the rate of resistance evolution. The durability of 5% SSX RIB was overestimated by modeling larval movement implicitly and by not considering different larval-movement hypotheses (NBI, NBP, BNI, and BNP). Larval movement in Bt/non-Bt seed mixtures may lead to greater heterozygote survival, which in turn would speed up resistance evolution.

B. No cross-resistance was incorporated into the model between Cry1F and Cry1A.105 and Cry2Ab when the applicants' data (Schlenz et al. 2008) indicated some level of epistasis and cross-resistance between Cry1F and the other two toxins.

C. Other forms of epistasis (expression of a gene is suppressed by a gene at another locus) were not considered; rather the applicant assumed that survival of genotypes was multiplicative for all three loci (least conservative assumption because heterozygote survival was, therefore, low). Other forms of epistasis should have been explored for ECB and SWCB such as, for example (but not only), "developmentally restricted expression of low levels of Cry-protease where older larvae survive Bt exposure when moving from non-Bt onto Bt". Additionally, resistance at all loci could be determined by the most rapidly evolving locus, which could drag other resistant loci along and, thereby, increase the rate of resistance evolution.

D. Non-uniform oviposition of 2nd generation ECB and SWCB in seed blends should favor Bt plants because adult females could distinguish between damaged (non-Bt) and protected (Bt) plants. This selective oviposition behavior based on unsuitable non-Bt host plants will reduce the effective refuge in a seed blend compared to a structured refuge. For 1st generation ECB and SWCB, non-uniform oviposition is also a probability, especially when the refuge plants incurred root damage from corn rootworm (CRW) and subsequently experience crowding out by faster growing (CRW protected) Bt plants.

E. Strong density-dependence occurs in SWCB, and this aspect was not incorporated into the applicant's model to estimate resistance evolution. "Soft selection" might be operating in this species in contrast to viability selection; "larvae that win out in cannibalistic encounters in the presence of Bt are likely to be those that have a slight fitness advantage from being more resistant to Bt".

F. The Panel recommended that emphasis in modeling assessments of stacked cultivars should be placed on durability for the pest that shows the greatest potential rate of resistance evolution. The Panel suspected that this may be SWCB for MON 89034 x TC1507 x MON 88017 x DAS-59122-7

G. For corn earworm and SSX RIB, the panel concluded that there were serious risks to both cotton and corn due to pollination concerns of corn ears in a seed blend environment. The panel was unable to quantify the role of selection on the rate of resistance evolution in CEW associated with a SSX RIB in the Corn Belt and migration between the northern corn growing and southern cotton growing regions at the time.

The panel suggested that the current industry and EPA models be revised (or new models created) to address the factors that led to overestimates of durability. In particular, the panel recommended that new modeling focus on improving the parameters for survival of genotypes (especially heterozygotes) in a pyramided toxin environment. Further, the panel indicated that modeling on a regional scale may be suitable to investigate the effects of region-wide pest population suppression from a seed blend deployment.

The panel recommended additional research regarding dispersal/movement of adults, effects of plant-to-plant movement on larvae, survival of different genotypes on Bt toxins (particularly heterozygotes), and effects of kernel pollination effects on corn earworm (CEW) refuge.

The panel suggested that seed blends could be implemented with a phase-in approach in which the seed blend percentage was lowered as data were developed (i.e., resistance monitoring and population density). No specific blend percentage numbers were recommended by the panel for this approach. It was also suggested that the resistance management plan have a well-defined trigger for remedial action (in the event that resistance develops).

Corn Rootworm Assessment

For corn rootworm, the SAP concluded that seed blend and block durability for SSX would be comparable.

BPPD Review of Monsanto/Dow's Submission Responding to the SAP Report

Monsanto and Dow AgroSciences addressed the SAP's concerns and submitted a written response to BPPD. As part of this response, Monsanto and Dow AgroSciences conducted revised modeling to evaluate the proposed seed blend (MRID No. 484234-01).

The applicants agreed with the SAP's conclusion that a 5% SSX RIB would be less durable than a 5% SSX with a structured refuge, they noted however that when realistic levels of non-compliance were incorporated, this difference in durability was reduced. BPPD concurs with this statement and notes that the SAP did not appear to address compliance in their model.

After reviewing the Monsanto/Dow submission, (BPPD 2011) BPPD concludes that a seed blend expressing (such as MON 89034 x TC1507 x MON 88017 x DAS-59122-7) three high-efficacy toxins (against mobile lepidoptera pests) with low potential for cross-resistance and low risk for other epistatic effects should generally be more durable than a seed blend expressing two high-efficacy toxins with low or no epistatic effects. For MON 89034 x TC1507 x MON 88017 x DAS-59122-7, however, the relative difference in durability between a seed blend and a block refuge of equivalent size cannot be quantified until Monsanto and Dow address the SAP's modeling recommendations (i.e., explicit larval movement, epistasis, non-uniform oviposition in seed blends, and density-dependent effects) and other concerns described in this review.

BPPD noted that Dow compared the pyramided seed blend strategy solely to the single PIP with a 20% block refuge and showed that (under their modeling construct) the pyramided product was more durable than the single PIP. As stated by the SAP, a comparison between a pyramid and a 20% single trait structured refuge should always show that the pyramid is more durable. The relative comparison, however, is important between single PIP, pyramided PIP (SSX RIB), and the pyramided PIP with a structured refuge. Monsanto included a comparison between the three IRM strategies and reported that a 5% SSX seed blend would be more durable than a single gene product with a 20% refuge and SSX with a 5% structured refuge with 50% grower non-compliance but somewhat less durable than SSX with a 5% structured refuge and 100% compliance. BPPD concludes that a comparison between the seed blend and a structured refuge with realistic numbers of non-compliance (i.e. 20%-30%, based on surveys conducted by the Agricultural Biotechnology Stewardship Technical Committee) would have improved their analysis. In addition, Monsanto could have used a probability approach to modeling non-compliance with the mean as 20% and worst-case and best-case choice for min and max values. The durability of block refuges should be higher with less non-compliance.

BPPD agrees with the applicants that some of the dose profiles chosen in the SAP's modeling analysis of SSX RIB were lower than what the applicants' empirical data and published literature supported. It is likely that higher dose values would improve overall durability for both blocks and blends.

BPPD's review of the specific concerns raised by the SAP (and Monsanto/Dow's response) is detailed below:

A. LARVAL MOVEMENT:

Explicit larval movement:

BPPD concludes that Monsanto and Dow did not directly address the SAP's recommendation to include explicit larval movement into their model. Instead, Dow and Monsanto provided the Agency with supplemental modeling in their response to the SAP report that (as in the previous modeling) used a spatially implicit model to estimate SSX RIB durability. Hence, both applicants have likely overestimated the durability of a MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend as was done in the initial modeling (see BPPD 2010 and SAP 2011).

Larval movement hypotheses:

The SAP also recommended that the applicants incorporate different larval movement hypotheses into their model. BPPD found that the applicants did not address this recommendation either, presumably because their field data did not support high larval movement and survival or maybe because of limitations with their current model structure.

BPPD notes, however, that in their preliminary efficacy study (one season, two locations; MRID

479437-01 (Appendix 3)) Monsanto and Dow reported that there was some degree of damage in pure stand MON 89034 x TC1507 x MON 88017 x DAS-59122-7 and MON89034 x TC1507 plots and some SWCB larvae were found (unclear how many), although significantly less than what was observed in 90% and 95% seed blend plots with MON89034 x TC1507. Hence, to add additional conservatism to their analysis, BPPD recommends that Monsanto follow the SAPs advice and incorporate different larval movement hypotheses into their model for SSX RIB.

B. EPISTASIS

Cross-resistance: The applicants addressed epistasis by incorporating various degrees of cross-resistance into their new modeling submission using Dow's deterministic, spatially implicit model. The applicants were able to demonstrate that durability of SSX RIB declined greatly initially and then somewhat slower as the degree of cross-resistance increased. With an assumption of 5% cross-resistance the estimated durability decreased from >> 1000 generations (RAF was 0.008 at 1000 gen) to 387. BPPD notes that this is a drastic drop in durability. Although the applicants appear to argue that the potential for cross-resistance is non-existent or minimal, BPPD concludes that based on the SAP's recommendations, a small degree of cross-resistance should be included in the simulations to create a more conservative model.

Other forms of epistasis: The applicants argued that epistasis via a Cry-protease mechanism and altered expression of receptor genes were unlikely to be of relevance because such mechanisms would provide little or no selective advantage to ECB feeding on the three high-dose Bt proteins in MON 89034 x TC1507 x MON 88017 x DAS-59122-7 . BPPD is not convinced of the applicants' argument for not including other forms of epistasis such as, for example, a Cry-protease mechanism. The SAP stated that a Cry-protease could potentially "degrade multiple Cry toxins, reducing or eliminating their toxicity to the insects". The SAP also stated that it is more likely that Cry-protease expression occurs in later instars of ECB and SWCB, which would affect their fitness in a seed mixture when plant-to-plant movement occurred. If such a mechanism confers the ability to tolerate multiple Bt toxins and has genetic heritability, then it should be a "selectable" trait in an environment with significant amounts of Bt corn (SSX). Hence, BPPD recommends that the applicants consider including such a mechanism for older instars of ECB and SWCB in their model.

C. NON-UNIFORM OVIPOSITION

The applicants did not address the SAP's recommendation regarding non-uniform oviposition in seed blends. The Panel stated that: 1) in seed blends of SSX, refuge plants might incur root damage from CRW (and other tissue damage from ECB), which could stunt their growth and allow protected SSX plant to effectively crowd out refuge plants. First generation females would then be more likely to oviposit onto SSX plants in seed blends than non-Bt plants; and 2) in a seed blend environment, second generation females could discriminate between damaged (non-Bt) and non-damaged (Bt protected) plants and could, therefore, be more likely to oviposit onto Bt plants than they would otherwise. Hence, BPPD recommends that the applicants incorporate a degree of non-uniform ovipositing behavior by both first and second generation females favoring Bt plants. This would reduce the seed blend durability due to a reduction in effective refuge compared to a structured refuge of comparable non-Bt proportion.

D. DENSITY-DEPENDENCE FOR SWCB

BPPD disagrees with Monsanto and Dow's justification (lack of movement onto and SWCB larval presence on SSX) for not addressing density-dependence in their model. As stated in section 2.1 above, some SWCB larvae were found in pure stand SSX and MON 89034 x TC1507 plots and seed blend plots. Hence there is evidence for larval establishment on and movement onto SSX plants. BPPD recommends that the applicants incorporate density-dependence into their simulation models as was recommended by the SAP (2011)

E. IRM EMPHASIS ON SPECIES AT GREATEST RISK OF EVOLVING RESISTANCE

The SAP concluded that IRM strategies should be designed around the pest that shows the greatest potential rate of resistance evolution. The Panel suspected that this might be SWCB for MON 89034 x TC1507 x MON 88017 x DAS-59122-7 . Should the applicants conduct new modeling incorporating BPPD's recommendations as outlined in this review, a separate analysis should be provided for ECB and SWCB (as was done in the original submission -- discussed in BPPD 2010).

Overall Lepidopteran Pest Conclusions

- Based on a review of the Science Advisory Panel (SAP) report (SAP 2011) and revised modeling submitted by Monsanto/Dow, BPPD concludes that a 5% seed blend for MON 89034 x TC1507 x MON 88017 x DAS-59122-7 corn will likely be less durable (perhaps significantly so) than a comparable (5%) block refuge for the product. BPPD notes, however, that a MON 89034 x TC1507 x MON 88017 x DAS-59122-7 5% seed blend should be more durable than a 20% block refuge for a single toxin Bt corn product or a comparable (5%) seed blend for a two toxin pyramid. Larval movement, potential survival (and selection) of heterozygote genotypes, and loss of refuge effectiveness during the growing season are the primary factors that are likely to reduce durability in seed blends.
- BPPD has major reservations regarding the modeling approaches taken by Monsanto and Dow (in separate models) to evaluate the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend. Monsanto and Dow addressed larval movement implicitly (as opposed to explicitly as recommended by the SAP) and did not incorporate other important recommendations made by the SAP (i.e., epistatic resistance mechanisms, density-dependent effects). As detailed in the SAP report, this approach is likely to result in overestimates of durability. For this reason, BPPD is unable to quantify the relative differences in durability estimates between refuge options (i.e., 5% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend, 5% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 block refuge, and 20% single toxin block refuge).
- Despite the modeling uncertainties described above, BPPD believes that, in general, a three toxin product such as MON 89034 x TC1507 x MON 88017 x DAS-59122-7 should have greater durability than Bt corn products with two or fewer toxins and comparable refuge deployment. In other words, a three toxin seed blend can be expected to be more durable than a two toxin product with the same blend percentage. Similarly, a block refuge for a three toxin product should be more durable than the same block refuge for a two toxin product. This conclusion assumes that the three toxins have high efficacy and low cross-resistance potential. BPPD cautions, however, that the relative gain and loss in durability with multi-toxin pyramids should be evaluated on a case-by-case basis with product-specific data.
- BPPD agrees with Monsanto/Dow that the SAP's modeling analysis 1) did not include three toxins for lepidoptera (two toxins were modeled for simplicity), 2) incorporated low

dose scenarios for the toxins in MON 89034 x TC1507 x MON 88017 x DAS-59122-7 , and 3) neglected to consider effects of non-compliance on block refuge. The first two factors likely resulted in lower durability estimates for both block and blended refuge; the third probably led to an overestimate of durability for block refuges. Monsanto and Dow's revised modeling addressed these three components.

- Block refuges and seed mixes present different potential risks and benefits for resistance management. A summary of these factors is described below:

Block Refuges

- **Pros:**
  - Greater durability than other refuge approaches (including seed mixes, strip refuges, and natural refuge) in simulation models;
  - Allows for high production of susceptible insects;
  - Refuges can be managed to preserve yield.

- **Cons:**
  - Random mating may be less likely than with seed mixes or strip refuges if adult movement is limited (though not the case for mobile lepidoptera);
  - Compliance must be monitored (i.e., with a compliance assurance plan);
  - Non-compliance can result in no refuge deployment or inadequate refuge distance from Bt field to assure random mating (more important for high-dose PIPs such as in MON 89034 x TC1507 x MON 88017 x DAS-59122-7), which can increase the risk of resistance;
  - Refuge may need to be treated with insecticides (potential economic and environmental costs);
  - There have been reports of a lack of available refuge seed in some areas;
  - Planting refuges can incur inconveniences and expenses for growers.

Seed Blends

- **Pros:**
  - Non-compliance is not an issue -- all seed bags are assumed to have the same amount of refuge seed (± standard error);
  - A compliance monitoring program should not be necessary (cost/resource savings);
  - No separate refuge management and insecticide use are needed;
  - Ease of use for growers.

- **Cons:**
  - Lower durability (perhaps substantially) than block refuges in simulation modeling;
  - Potentially lower "effective" refuge due to damage to non-Bt plants and/or Bt pollination within the growing season, reduced larval movement from Bt onto non-Bt plants, and within-plant density-dependent mortality;
  - Possible yield loss due to lodging of refuge plants within the Bt field, particularly with higher (>10%) blend percentages;
  - Difficulty detecting "unexpected pest damage" (a key component of resistance monitoring);
  - Increased risk of resistance for pests with greater adult dispersal and larval plant-to-plant movement (driven by heterozygous genotypes).

Necessary Additional Information:

To improve BPPD's ability to assess the risks of resistance for a MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend, Monsanto and Dow need to address the following topics and uncertainties:

- Revised modeling incorporating the structural elements recommended by the SAP (i.e., explicit larval movement, switch from a frequency-based model to one including density-dependent larval mortality, epistatic mechanisms for resistance in target pests) with separate analyses for SWCB and ECB. Non-uniform oviposition should be modeled for both ECB and SWCB, especially (but not only) for the second generation of adults which will more likely lay eggs on Bt rather than on damaged (or crowded out) non-Bt refuge plants in seed blends.

- Biological research on adult movement (related to mating and movement from refuges), larval movement, larval feeding (i.e., selective feeding within corn ears or on pollen), survival of heterozygote genotypes on MON 89034 x TC1507 x MON 88017 x DAS-59122-7 (markers may need to be determined for heterozygotes), and the potential for epistatic mechanisms of resistance (particularly with older instars).

<u>Seed Blending –Manufacturing Considerations</u>

1) **<u>Distribution of MON 89034 x TC1507 x MON 88017 x DAS-59122-7 and Refuge Seeds in the Blend</u>**

<u>Monsanto and Dow AgroSciences Position</u>

Monsanto and Dow AgroSciences claim that a uniform in-field distribution of refuge (non-Bt) plants represents the worst case scenario for IRM and that any degree of clumping of refuge plants will tend to reduce the potential negative impacts of seed blends.

With a uniform distribution of refuge plants in a 5% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend, all non-Bt plants will be surrounded by Bt plants. Hence, larvae moving from refuge plants onto neighboring plants will survive on a Bt plant (causing a reduction in effective refuge in seed blends compared to structured refuges of equivalent size). Conversely, larvae moving off Bt plants will have a 5% probability of arriving on a refuge plant (which may introduce the potential for sublethal effects from prior Bt exposure).

A clumped distribution of refuge plants have the effect that some larvae moving off refuge plants will arrive on other refuge plants and, therefore, be more likely to survive than those moving from refuge plants onto surrounding Bt plants in a uniform distribution. In addition, larvae moving off Bt plants in seed blend with a clumped distribution would have less than a 5% probability of arriving on a refuge plant; this smaller proportion may receive sublethal exposure and thus there would be less differential selection of heterozygotes with a clumped versus uniform in-field refuge.

The in-field block refuge scenarios (with 100% compliance) modeled by Monsanto, Dow, and EPA ORO represent the extreme end of the clumped scenario (i.e. minimal larval movement between refuge and Bt plants, highest effective refuge size, lowest relative fitness of heterozygotes). These modeling efforts support that clumped (or block) refuges delay resistance more compared to uniform distributed refuge plants in seed blends.

BPPD Conclusion

BPPD has reviewed Dow's and Monsanto's argument that a seed blend with a uniform distribution represents a worst-case scenario for IRM. BPPD concurs that clumping of refuge plants should be better for IRM than a uniform distribution because of an increase in effective refuge and decreased differential selection on heterozygotes (as stated by the applicants), which makes inheritance of resistance more recessive (Maliet and Porter 1992; Davis and Onstad 2000). In cases, however, where greater asymmetrical dispersal (from Bt to non-Bt) is observed or expected, seed mixtures may prove to be more durable than structured refuges.
European com borer (ECB) and southwestern com borer (SWCB) are the two main target pests of MON 89034 x TC1507 x MON 88017 x DAS-59122-7 in the Com Belt. With respect to asymmetrical movement, Onstad and Gould (199l) modeled dispersal of neonate ECB (55-genotypes) off Bt plants with a 98% probability and off non-Bt plants with a 90% probability. Their data indicate that there is little asymmetrical dispersal between the two plant types. For SWCB, no data on differential dispersal are available in the public literature. Because SWCB is cannibalistic, such behavior should increase the probability of dispersal compared to ECB (FIFRA SAP 2011). BPPD notes that it may, therefore, be assumed that there is no great dispersal differential between neonates leaving Bt or non-Bt plants in response to some asymmetrical dispersal. BPPD concludes that for ECB and SWCB it may be safe to assume that a 5% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend with a uniform distribution represents a worse case than a blend with a clumped distribution.

2) Blended Refuge Percentage Assurance

Both Monsanto and Dow submitted data adequately demonstrating a minimum 5% refuge of non-Bt seed in the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 blends produced at seed processors within their company.

BPPD has reviewed the information provided regarding the manufacturing process in Monsanto and Dow AgroSciences owned facilities and concludes that:

• The seed weighing technology should guarantee high accuracy around the determined target (mean weight or mean percentage) with very low expected variance provided that all of Monsanto's Dow's manufacturing plants maintain and follow the same procedures respectively;

• The seed mixing technology will be set to satisfy growers expectation of uniformity but some degree of clumping of refuge seed may be possible. BPPD does not expect clumping of refuge plants in the field to impact lRM for ECB and SWCB (see BPPD 2011) because of very little expected asymmetrical movement between the two plant types (Bt and non-Bt) for both species as supported by Onstad and Gould (1998);

• Bt and refuge seed will be colored differently when seed blends are mixed in Monsanto or Dow AgroSciences owned manufacturing plants. Monsanto is also encouraging its seed company licensees to color the Bt and refuge seed differently. Coloring the two types of seed differently will provide an additional affirmation that the product is in fact a seed blend. It will also allow the applicant to more easily test for germination of refuge seed (to assure the 5% refuge is still guaranteed).

Monsanto has submitted additional information and a generic standard operating procedure to guarantee the same accuracy and quality assurance from independent seed dealers who are in charge of their own seed mixing process Unfortunately, this information was very general and not specific enough for BPPD to ascertain that the target blend percentage will be assured in non-Monsanto facilities.

It was not clear from reading Dow's document what the actual target weight and percentage will be should a 5% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend be commercialized. This information is needed.

3. **Seed Blend Monitoring under the Federal Seed Act**

The United States Agricultural Marketing Service and State Seed Control Officials are involved with ensuring compliance to the Federal Seed Act by seed producers. Testing of seed blend products for refuge component percentage has and will be taking place. If either USDA or State Seed Control Officials obtain official samples of seed blend products, do color separations on the composite samples collected and find the percentage of the refuge component is lower in those samples than is represented on the label, action may be initiated under the Federal Seed Act.

IRM Refuge Compliance

Critical to an assessment of the likely efficacy of an IRM mitigation program is the level of compliance with that program. Data received by EPA from the Agricultural Biotechnology Stewardship Technical Committee (ABSTC) indicate that compliance with the paradigmatic 20% block refuge requirement for most *B.t.* corn crops has been steadily decreasing. This decreased compliance increases the risk of resistance development (see, e.g., *Complacency on the Farm*, CSPI 2009, and *Impact of Genetically Engineered Crops on Farm Sustainability in the United States,* NAS 2010*)*.

Grower survey results (see Figure 1) show that average compliance with refuge distance requirements for ECB protected corn expressing single PIPs was significantly higher in 2010 than in the previous year (margin of error $\pm$6.0%); compliance with refuge size remained approximately equal compared to 2009. Growers reported to be out of compliance deviated from the 20% requirement in one way or another. Further analysis of non-compliance numbers revealed that most farmers (87%) planted a refuge that was at least 15%, and that 5% of farmers neglected to plant a refuge at all. A regional analysis revealed that growers planting single ECB PIP expressing corn in eastern regions of the Corn Belt were less compliant on average (71% for refuge size, 83% for refuge requirement) than growers in the western regions (81% for refuge size and 90% for distance requirement). Growers in the southern U.S. had significantly lower adherence percentages than the Corn Belt again; the 2010 analysis reveals, however, that compliance in the south has had a small, yet statistically, significant increase in compliance compared to 2009 (from 40% in 2009 to 49% in 2010 for refuge size; from 63% in 2009 to 70% in 2010 for refuge distance). It is unclear whether the observed difference is due to the smaller sample size in the south, which was reduced by 60% compared to the sample size in the eastern and western regions of the US. However, compliance is still below an acceptable level in the south; possible explanations for such lower compliance in the south could include confusion with different requirements between various PIP products or simply blatant disregard of refuge requirements by growers who plant both Bt corn and Bt cotton. ABSTC stated in their 2009 CAP report that these regional results provided them with the opportunity to intensify future educational efforts in the southern corn growing regions. BPPD notes that if higher non-compliance among southern corn growers reflects a willingness to violate refuge requirements rather than a lack of knowledge, then increased efforts to educate them may not be fruitful. Other methods to bring these growers back into compliance may need to be considered.

Grower awareness with IRM requirements was high (94%), yet the number of growers who could recall the correct refuge size (65%) was significantly lower compared to the number of growers who recalled the correct refuge distance requirements (82%). These percentages are reflective of the compliance numbers from the online survey.

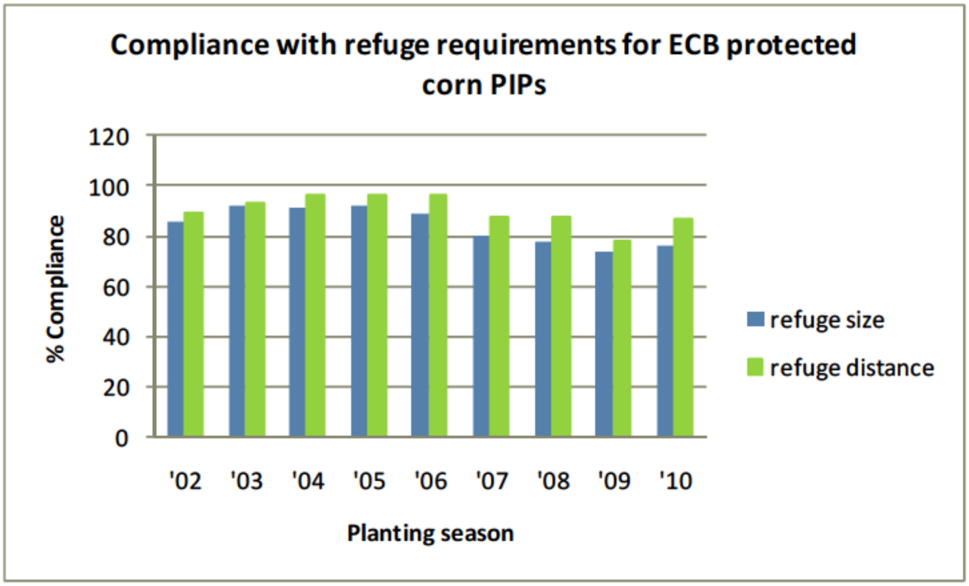

Figure 1 Compliance trend from 2002-2010 for growers planting single ECB PIPs

Overall compliance (per grower) with refuge requirements for single PIPs targeting CRW is displayed in Figure 2. Average compliance in 2010 has again decreased compared to 2009 and is now at the level of compliance (73% for refuge size, 67% for refuge distance) similar to that reported in 2008. The margin of error reported for CRW PIP compliance data is ±13.3%, hence the difference measured between 2010 and 2009 compliance is not statistically significant. The percentage of growers blatantly disregarding refuge requirements in 2010 was again 9%, as in 2009. Eighteen percent (18%) of all corn rootworm protected fields had no refuge associated with them; this is an increase from the 14% reported in 2009.

Grower awareness with IRM requirements in 2010 was higher than in 2009, yet, the percentage of growers who could recall the refuge size and distance requirements was extremely low (33% and 22%, respectively). That is a drastic decline from an already low awareness in 2009 of 58% and 31% for correct refuge size and refuge distance. These percentages are now at an all time low. BPPD believes that this decline in grower knowledge is reason for concern and somewhat reflective of the compliance numbers from the online survey. ABSTC's educational efforts have been unsuccessful at increasing grower education with respect to CRW IRM requirements.

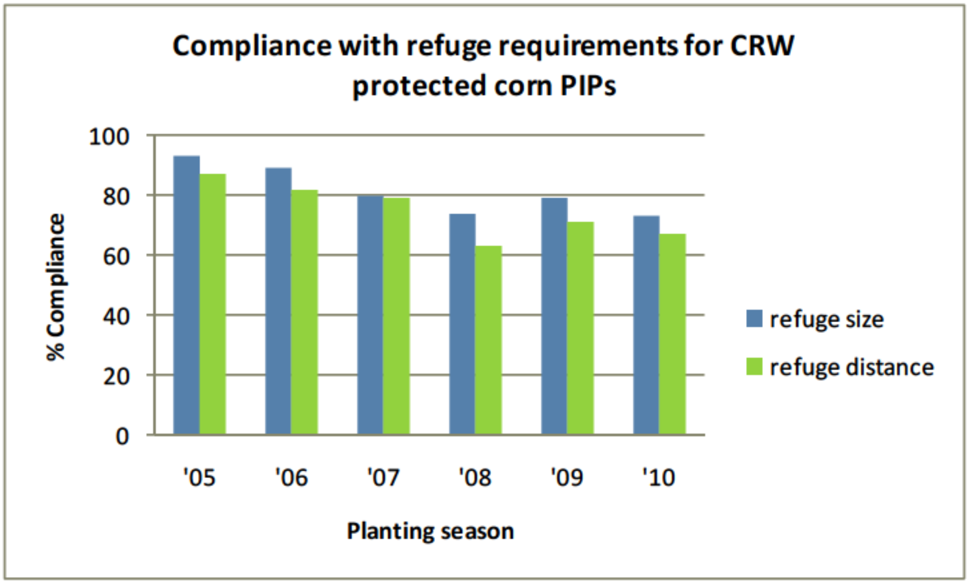

Figure 2 Compliance trend from 2005-2010 for growers planting single CRW PIPs

Overall compliance (per grower) with refuge requirements for stacked corn PIPs is displayed in Figure 3. In 2010, the reported margin of error for adherence with requirements was again ±4.2%; therefore, BPPD concludes that the latest national average compliance results were similar to those reported in prior years. A regional analysis of survey results revealed that growers' compliance in eastern regions of the US significantly declined: adherence to refuge size requirements was 74% in 2009 and declined to 69% in 2010; adherence to refuge distance was 67% in 2009 and declined to 63%. Compliance in the western regions of the Corn Belt remained similar or slightly higher to those reported in 2009. Corn growers in the cotton growing regions had similar compliance in 2010 as in 2009 – 32% and 37% for adherence to refuge size and distance requirements. BPPD notes that the compliance percentages in the south are extremely low.

BPPD notes that the number of growers who were able to correctly recall IRM requirements on an unaided basis reached an all time low since 2007. Only 27% of growers were able to correctly recall the correct distance requirement for the CRW portion of the PIP in 2010. This represents a further decline from the reported 32% in 2009. Only 56% of the growers surveyed recalled that refuge size for the CRW PIP was 20%. The increased educational outreach by ABSTC is not producing the expected results among corn growers planting stacked PIPs.

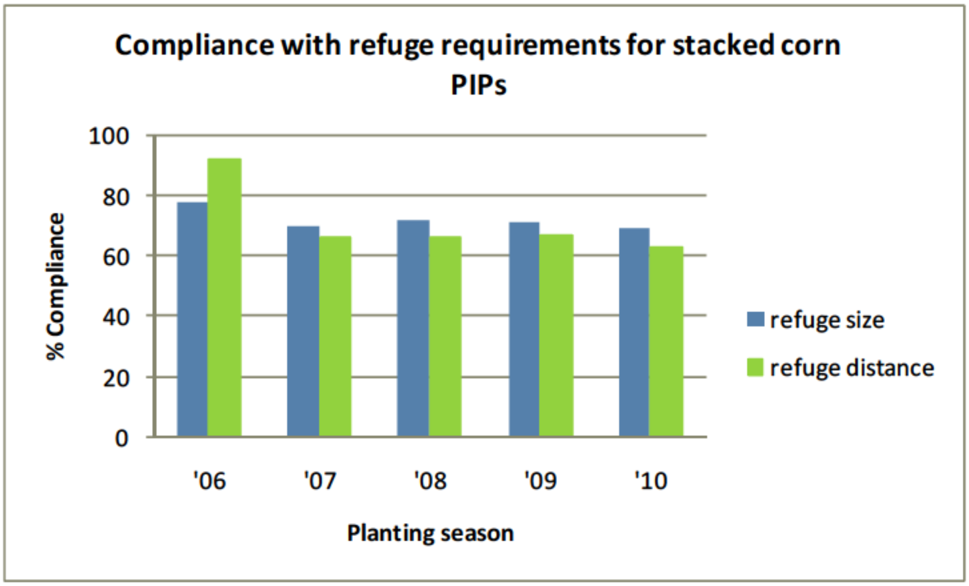

Figure 3 Compliance trend from 2006-2010 for growers planting stacked corn PIPs

Table 2 shows the percent of growers who have blatantly disregarded refuge requirements for the individual PIP products planted in 2009 and 2010. Unfortunately, this information was not provided to the Agency prior to 2009 and no historical comparison can, therefore, be made yet.

Table 2. Percent growers planting a zero % refuge for stacked Corn PIPs (data from 2009-2010)

Product Type	2009[1]	2010[1]
Single ECB PIPs	7%	5%
Single CRW PIPs	9%	9%
Stacked ECB/CRW PIPs	11%	12%

[1]Results are listed on a per grower (not per field) basis

B. Product Characterization and Human Health Assessment

Current tolerance exemptions in 40 CFR Part 174 applicable to MON 89034 × TC1507 × MON 88017 × DAS-59122-7.

§ 174.502 Bacillus thuringiensisCry1A.105 protein; exemption from the requirement of a tolerance.

(a) Residues of *Bacillus thuringiensis* Cry1A.105 protein in or on the food and feed commodities of corn; corn, field, flour; corn, field, forage; corn, field, grain; corn, field, grits; corn, field, meal; corn, field, refined oil; corn, field, stover; corn, sweet, forage; corn, sweet, kernel plus cob with husk removed; corn, sweet, stover; corn, pop, grain and corn, pop, stover are exempt from the requirement of a tolerance when the *Bacillus thuringiensis*

Cry1A.105 protein is used as a plant-incorporated protectant in these food and feed corn commodities.

§ 174.506 Bacillus thuringiensis Cry34Ab1 and Cry35Ab1 proteins in corn; exemption from the requirement of a tolerance.

Residues of *Bacillus thuringiensis* Cry34Ab1 and Cry35Ab1 proteins in corn are exempted from the requirement of a tolerance when used as plant-incorporated protectants in the food and feed commodities of corn; corn, field; corn, sweet; and corn, pop.

§ 174.507 Nucleic acids that are part of a plant-incorporated protectant; exemption from the requirement of a tolerance.

Residues of nucleic acids that are part of a plant-incorporated protectant are exempt from the requirement of a tolerance.

§ 174.518 Bacillus thuringiensis Cry3Bb1 protein in corn; exemption from the requirement of a tolerance.

Residues of *Bacillus thuringiensis* Cry3Bb1 protein in corn are exempt from the requirement of a tolerance when used as plant-incorporated protectants in the food and feed commodities of corn; corn, field; corn, sweet; and corn, pop.

§ 174.519 Bacillus thuringiensis Cry2Ab2 protein in corn and cotton; exemption from the requirement of a tolerance.

Residues of *Bacillus thuringiensis* Cry2Ab2 protein in or on corn or cotton are exempt from the requirement of a tolerance when used as a plant–incorporated protectant in the food and feed commodities of corn; corn, field; corn, sweet; corn, pop; and cotton seed, cotton oil, cotton meal, cotton hay, cotton hulls, cotton forage, and cotton gin byproducts.

§ 174.520 Bacillus thuringiensis Cry1F protein in corn; exemption from the requirement of a tolerance.

Residues of *Bacillus thuringiensis* Cry1F protein in corn are exempt from the requirement of a tolerance when used as plant-incorporated protectants in the food and feed commodities of corn; corn, field; corn, sweet; and corn, pop.

§ 174.523 CP4 Enolpyruvylshikimate-3-phosphate (CP4 EPSPS) synthase in all plants; exemption from the requirement of a tolerance.

Residues of the CP4 Enolpyruvylshikimate-3-phosphate (CP4 EPSPS) synthase enzyme in all plants are exempt from the requirement of a tolerance when used as plant-incorporated protectant inert ingredients in all food commodities.

§ 174.522 Phosphinothricin Acetyltransferase (PAT); exemption from the requirement of a tolerance.

Residues of the Phosphinothricin Acetyltransferase (PAT) enzyme are exempt from the requirement of a tolerance when used as plant-incorporated protectant inert ingredients in all food commodities.

Southern Blot Analysis

Southern blot analysis confirmed in the combined trait corn product MON 89034 × TC1507 × MON 88017 × DAS-59122-7 the presence of sequences identical to sequences derived from MON 89034 and MON 88017.Hybridization patterns for the combined trait product were identical to those of the parental lines with *cry*1F, *cry*34Ab1, *cry*35Ab1, and the *pat* gene probes indicating that the TC1507 and DAS-59122-7 insertions were unaffected by combining with MON 89034 and MON 88017 through conventional breeding.

Expression Levels

MON 89034 x TC1507 x MON 88017 x DAS-59122-7 is a combined trait corn that produces lepidopteran-active and coleopteran-active *Bacillus thuringiensis* (*Bt*) proteins, as well as the 5-enolpyruvylshikimate-3-phosphate synthase protein from *Agrobacterium* sp. strain CP4 (CP4 EPSPS) to confer tolerance to glyphosate herbicides and PAT to confer tolerance to glufosinate herbicides. The levels of the lepidopteran-active Cry1A.105, Cry2Ab2, Cry3Bb1 proteins and the CP4 EPSPS protein were determined in tissues from MON 89034 x TC1507 x MON 88017 x DAS-59122-7 plants grown at five US field sites in 2006. The test also included a conventional corn as a negative control and MON 89034 and MON 88017 corns as positive controls. Leaf, root, and whole plant samples were collected over the growing season, as well as pollen and grain samples at the appropriate times. The samples were extracted and analyzed using enzyme-linked immunosorbent assays. The levels of the Cry1A.105, Cry2Ab2, Cry3Bb1, and CP4 EPSPS proteins in MON 89034 x TC1507 x MON 88017 x DAS-59122-7 corn were comparable to those in the appropriate MON 88017 or MON 89034 positive control.

The levels of the coleopteran-active *Bacillus thuringiensis* (*Bt*) proteins Cry34Ab1, Cry35Ab1, and Cry1F, and the PAT protein were determined in tissues from MON 89034 x TC1507 x MON 88017 x DAS-59122-7 plants grown at five US field sites in 2006. The test also included a conventional corn as a negative control and TC1507 and DAS-59122-7 parental event corn as positive controls. Leaf, root, and whole plant samples were collected over the growing season, as well as pollen and grain samples at the appropriate times. The samples were extracted and analyzed using enzyme-linked immunosorbent assays (ELISA). The results indicate that the levels of Cry34Ab1, Cry35Ab1, and Cry1F in MON 89034 x TC1507 x MON 88017 x DAS-59122-7 were comparable to the levels produced in the appropriate TC1507 or DAS-59122-7 control corn. The level of PAT in MON 89034 x TC1507 x MON 88017 x DAS-59122-7 was higher in the combined trait products compared to TC1507 and DAS-59122-7, likely due to the presence of multiple copies of the *pat* gene in the stacks (one from each of the DAS parent lines).

C. Environmental Assessment

At present, the Agency has not identified any significant adverse effects of the Cry1A.105, Cry2Ab2, Cry1F, Cry3Bb1, or Cry34Ab1/35Ab1 proteins on the abundance of non-target organisms in any field population, whether expressed individually or as MON 89034 x TC1507 x MON 88017 x DAS-59122-7 combined PIP corn product. The potential for synergistic effects has been evaluated and the data that were reviewed for the individual parental events can be bridged to support the Sec. 3 registration of MON 89034 x TC1507 x MON 88017 x DAS-

59122-7 combined PIP corn product.

It is unlikely that direct or indirect harmful effects to non-target organisms, including federally-listed threatened or endangered species, would result from the insecticidal proteins Cry1A.105, Cry2Ab2, Cry1F, Cry3Bb1, or Cry34/35Ab as a result of the proposed Sec. 3 registration. The Agency anticipates that for full commercial cultivation, no hazard will result to the environment.

Event MON 89034 produces the Cry1A.105 and Cry2Ab2 Bt proteins, and Event TC1507 produces Cry1F. These proteins are intended to control or suppress several lepidopteran pests of corn, including European corn borer (ECB, *Ostrinia nubilalis*), corn earworm (CEW, *Helicoverpa zea*), fall army worm (FAW, *Spodoptera frugiperda*), and black cutworm (BCW, *Agrotis ipsilon*). MON 88017 produces the Cry3Bb1 protein, and Event DAS-59122-7 produces the Cry34Ab1 and Cry35Ab1 proteins. These two events provide additional control for coleopteran pests, particularly corn rootworm pests (*Diabrotica* spp.).

It has been determined that each individual event has protein expression levels that are comparable to the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 corn hybrid (Kough, 2009). Therefore, the margins of exposure that were previously determined for the insecticidal proteins in the individual events are applicable for the risk assessment of these proteins in the stacked hybrid. Additionally, no synergistic or antagonistic effects were observed in several combinations of the individual events in MON 89034 x TC1507 x MON 88017 x DAS-59122-7, as well as the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 hybrid itself. As a result, the Agency concludes that there is no indication of synergistic effects or increased levels of protein expressed in the combined PIP product, so the environmental risk assessment for the single PIP lines are applicable to the assessment of MON 89034 x TC1507 x MON 88017 x DAS-59122-7.

As a result, the environmental risk assessment of the individual events, as well as an additional study submitted on the toxicity of MON 89034 x TC1507 x MON 88017 x DAS-59122-7 to a non-target insect, the Agency concluded that there will be no unreasonable adverse effects to the environment, including endangered species, by MON 89034 x TC1507 x MON 88017 x DAS-59122-7 combined trait corn.

D. Benefits

We expect MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend products to have the following benefits: (1) Reduced pesticide use in the refuge. Currently, the block refuge may be sprayed with pesticide to mitigate pest damage. The blended in-field refuge will not be sprayable. (2) Significantly less complicated refuge deployment for the corn rootworm and lepidopteran active ingredients. Currently, to be fully compliant with the refuge requirements, growers must accurately calculate percentage of the field, accurately determine the proper distance for the refuge field, and properly plant the required acreage in the correct location. Moreover, there are temporal concerns, as the refuge field must be planted at, essentially, the same time as the yield field so that emergence of refuge rootworms is contemporaneous with emergence of field rootworms. Anecdotal reports from growers make clear that meeting each of these requirements can be challenging in the actual on-farm environment. A product with the refuge blended with the field seed will ease deployment of the refuges. (3) Grower compliance with IRM requirements for the corn rootworm and lepidopteran active ingredients. A seed blend product incorporating an effective refuge in the seed bag would lead to 100% grower compliance for planting a refuge. This is a significant benefit, although perhaps not as great as the raw data on refuge compliance might suggest.

In addition, *indirect benefits* of introducing MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends may include reduced energy consumption for manufacture, transport, and application of chemical insecticides; reduced waste streams arising from pesticide manufacture; reduced disposal of pesticide waste containers; and reduced residues from pesticide applications.

III. REGULATORY RATIONALE

Section 3(c)(7)(A) of FIFRA provides for the registration or amendment of a pesticide when the pesticide and proposed use "…are identical or substantially similar to any currently registered pesticide and use thereof, or differ only in ways that would not significantly increase the risk of unreasonable adverse effects on the environment, and (ii) approving the registration or amendment in the manner proposed by the applicant would not significantly increase the risk of any unreasonable adverse effect on the environment." Unreasonable adverse effects on the environment are defined under Section 2(bb) of FIFRA as "… any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide…" Thus, pursuant to Section 3(c)(7)(A), EPA may conditionally register a pesticide if (1) the pesticide and its proposed use are identical or substantially similar to a currently registered pesticide; or (2) the pesticide and its proposed use differ only in ways that would not significantly increase the risk of unreasonable adverse effects; and (3) approving the registration would not significantly increase the risk of any unreasonable adverse effect.

We find that the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends meet criteria (2) and (3) of Section 3(c)(7)(A) for a time-limited registration to expire October 31, 2011. MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends consist of a currently registered products, 95% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 (MON 89034 x TC1507 x MON 88017 x DAS-59122-7) and 5% non-B.t. corn. Thus, both products are substantially similar to already registered PIPs in composition and use site (field corn). These products do not meet criteria (1), however, because the proposed use of the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends achieves the lepidopteran insect resistance management refuge via a seed mix rather than a block refuge is not substantially similar to any currently registered pesticide.

We determine, however, that the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends meet criteria (2) as, when used in accordance with the terms and conditions of a time-limited registration set to expire October 31, 2011, and would not significantly increase the risk of unreasonable adverse effects on the environment. Since the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends are substantially similar to already registered PIPs in composition and use site, EPA's consideration of whether these new products would significantly increase the risk of any unreasonable adverse effect on the environment is limited to the change in lepiidopteran insect resistance management refuge deployment, i.e., a seed blend in the bag versus a block refuge. The unreasonable adverse effect of concern is the development of resistance to Cry1F, Cry2Ab2, and Cry1A.105 in corn. Thus, we consider: (1) how does the registration of the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends contribute to the development of corn rootworm resistance to Cry1F, Cry2Ab2, and Cry1A.105 in corn; (2) should this resistance develop, what risk does it pose to man or the environment; and (3) taking into account the economic, social, and environmental costs and benefits, does this risk constitute an unreasonable adverse effect?

The Risk of the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 Seed Blend Registrations Causing Lepidopteran Resistance to Cry1F, Cry2Ab2, and Cry1A.105

Based on a review of the Science Advisory Panel (SAP) report (SAP 2011) and revised modeling submitted by Monsanto/Dow, BPPD concludes that a 5% seed blend for MON 89034 x TC1507 x MON 88017 x DAS-59122-7 corn will likely be less durable (perhaps significantly so) than a comparable (5%) block refuge for the product, as is currently required for the non –seed blend MON 89034 x TC1507 x MON 88017 x DAS-59122-7 products under EPA registration numbers 524-581 and 69467-7. BPPD notes, however, that a MON 89034 x TC1507 x MON 88017 x DAS-59122-7 5% seed blend should be more durable than a 20% block refuge for a single toxin Bt corn product (of which many are currently registered) or a comparable (5%) seed blend for a two toxin pyramid.

Should Resistance Develop, What Risk Does it Pose to Man or the Environment, and What Economic and Social Costs?

Should Cry1F, Cry2Ab2, or Cry1A.105 resistance develop, there may be an increase in conventional chemical insecticide use for U.S. corn production. Although there are other lepidopteran controlling PIPs in the marketplace and under development, Cry1F, Cry2Ab2, or Cry1A.105 resistance would not only impact MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends and non- seed blend products, but also HERCULEX®, and MON89034 . Increased use of conventional insecticides would increase impacts on the environment and man. There would also be indirect impacts in increased consumption for manufacture, transport, and application of chemical insecticides; increased waste streams arising from pesticide manufacture; and increased disposal of pesticide waste containers and residues from pesticide applications.

What are the Economic, Social, and Environmental Benefits of MON 89034 x TC1507 x MON 88017 x DAS-59122-7 Seed Blend Registrations?

MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends have been determined by EPA to be efficacious in their control of
European corn borer, southwester corn borer, corn earworm (and corn rootworm).

MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends should increase grower compliance with lepidopteran refuge requirements by providing an effective way of simplifying the refuge deployment process for growers as the lepidopteran refuge is deployed as a seed blend rather than a separate block in the field.

MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends should also reduce the insecticide use in the lepidopteran refuge. Indirect benefits of decreased insecticide use include reduced energy consumption for manufacture, transport, and application of chemical insecticides; reduced waste streams arising from pesticide manufacture; reduced disposal of pesticide waste containers and residues from pesticide applications.

MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends should benefit growers by simplifying the planting process.

Registration Decision

We conclude that the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends meet the criteria for registration under FIFRA Section 3(c)(7)(A). Our assessment supports the determination that these products are not likely to contribute towards the development of resistance to Cry1F, Cry2Ab2, or Cry1A.105 during period of the time-limited registration in effect for the 2011 growing season. Our assessment of the likely impacts concerning ease of use, increased grower compliance, efficacy, and reduced insecticide use coupled with our determination that the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends are not likely to increase the risk of resistance to Cry1F, Cry2Ab2, or Cry1A.105 developing during the 2011growing season support the conclusion that the criteria under FIFRA Section 3(c)(7)(A) are met such that registration of the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends will not pose a risk of unreasonable adverse effects on the environment during this period.

On October 1, 2009, EPA announced a new policy to provide a more meaningful opportunity for the public to participate on major registration decisions before they occur. According to this new policy, EPA intends to provide a public comment period prior to making a registration decision for, at minimum, the following types of applications: new active ingredients; first food use; first outdoor use; first residential use; and other actions for which the Agency anticipates that there will be significant public interest.

Notwithstanding that the current actions on the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends qualify as "actions for which the Agency anticipates that there will be significant public interest," EPA believes that it is in the best interests of the public and the environment to issue the registrations for the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends without delay. The PRIA (Pesticide Registration Improvement Act) deadline date of April 12, 2011, is sufficiently late in the growing season that a 30-day delay would lessen the likelihood that significant acreage of these products could be planted in 2011. Given the potential benefits attendant to the blended refuge concept for both lepidopteran and corn rootworm pests, EPA concludes that it is in the best interests of the public and the environment to issue the registrations for the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blends without delay for 2011 growing season. The registration is only effective for the current growing season. Therefore, consistent with the Agency's policy for making certain registration actions more transparent, EPA is issuing these time-limited registrations with an initial period to expire October 31, 2011, and, concurrent with their issuance, providing a 30-day public comment period on the time-limited registrations. EPA is registering this product as a time-limited registration, with the understanding that public comments could bring to light new information or concerns that could inform EPA's initial decision. Any subsequent action taken on these registrations will be informed by any information received during the public comment period. At present, the Agency anticipates renewing the expiration date to October 31, 2013.

IV. TERMS AND CONDITIONS OF THE REGISTRATION(S)

1) The subject registration will automatically expire at midnight November 30, 2013.

2) The subject registration will be limited to MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend in field corn.

3) Submit or cite all data required to support MON 89034 x TC1507 x MON 88017 x DAS-

59122-7 plant-incorporated protectant products within the timeframes required by the terms and conditions of EPA Registration Numbers 68467-7 (Dow AgroSciences) and 524-581 (Monsanto).

4) Provided the registration expiration date is extended, submit an interim report on the following data within one year and a final report within two years.

- Revised modeling incorporating the structural elements recommended by the SAP (i.e., explicit larval movement, switch from a frequency-based model to one including density-dependent larval mortality, epistatic mechanisms for resistance in target pests) with separate analyses for SWCB and ECB. Non-uniform oviposition should be modeled for both ECB and SWCB, especially (but not only) for the second generation of adults which will more likely lay eggs on Bt rather than on damaged (or crowded out) non-Bt refuge plants in seed blends.

- Biological research on adult movement (related to mating and movement from refuges), larval movement, larval feeding (i.e., selective feeding within corn ears or on pollen), survival of heterozygote genotypes on MON 89034 x TC1507 x MON 88017 x DAS-59122-7 (markers may need to be determined for heterozygotes), and the potential for epistatic mechanisms of resistance (particularly with older instars).

5) Do the following Insect Resistance Management Program for MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn.

a) Refuge Requirements for MON 89034 x TC1507 x MON 88017 x DAS-59122-7

The following information must be included on the product bag or bag-tag as sold per respective region:

<u>Bag or Bag-Tag for the Corn-Growing Region</u>
There are no requirements for a separate structured refuge for MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn when planted in the U.S. corn-growing region. The refuge seed of MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn is contained in the bag resulting in a refuge configuration that is interspersed within the field. SEE THE IRM/GROWER GUIDE FOR DETAILED IRM REQUIREMENTS, including the areas making up the corn-growing region.

<u>Bag or Bag-Tag for the Cotton-Growing Region</u>
Growers in the cotton-growing region of the U.S. who plant MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn are required to plant an additional 20% structured refuge (i.e. 20 acres of non-*B.t.* corn for every 80 acres of MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn planted). The 20% refuge must be planted with corn hybrids that do not contain *B.t.* technologies for the control of corn rootworms or corn borers. The refuge and the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn should be sown on the same day, or with the shortest window possible between planting dates to ensure that corn root development is similar among varieties. The structured refuge may be planted as an in-field or adjacent (e.g., across the road) refuge, or as a separate block that is within ½ mile of the MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn field. SEE THE IRM/GROWER GUIDE FOR DETAILED

IRM REQUIREMENTS, including the areas making up the cotton-growing region.

The cotton-growing region requiring the additional 20% refuge consists of the following states: Alabama, Arkansas, Georgia, Florida, Louisiana, North Carolina, Mississippi, South Carolina, Oklahoma (only the counties of Beckham, Caddo, Comanche, Custer, Greer, Harmon, Jackson, Kay, Kiowa, Tillman, and Washita), Tennessee (only the counties of Carroll, Chester, Crockett, Dyer, Fayette, Franklin, Gibson, Hardeman, Hardin, Haywood, Lake, Lauderdale, Lincoln, Madison, Obion, Rutherford, Shelby, and Tipton), Texas (except the counties of Carson, Dallam, Hansford, Hartley, Hutchinson, Lipscomb, Moore, Ochiltree, Roberts, and Sherman), Virginia (only the counties of Dinwiddie, Franklin City, Greensville, Isle of Wight, Northampton, Southampton, Suffolk City, Surrey, and Sussex) and Missouri (only the counties of Dunklin, New Madrid, Pemiscot, Scott, and Stoddard).

The following information regarding refuge placement for commercial production must be included in the IRM/Grower Guide:

This product includes refuge that is interspersed within the field by planting a licensed seed-mixture containing MON 89034 × TC1507 × MON 88017 × DAS-59122-7 and a minimum of 5% non-PIP seed. The seed mix refuge option for MON 89034 × TC1507 × MON 88017 × DAS-59122-7 seed blend corn satisfies the refuge requirements in all regions other than in cotton growing regions where corn earworm is a significant pest as defined below.

The seed producer must ensure a minimum of 5% non-PIP refuge seed is included with the MON 89034 × TC1507 × MON 88017 × DAS-59122-7 in each lot of seed corn.

The interspersed refuge can only be used by planting seed corn specifically generated by qualified seed producers/conditioners licensed by the registrant. The refuge seed in the seed mixture may not be treated with seed-applied insecticides for corn rootworm (CRW) control unless the MON 89034 × TC1507 × MON 88017 × DAS-59122-7 seed in the seed mixture receives the same treatment. Insecticidal treatments labeled for adult CRW control are discouraged during the time of adult CRW emergence.

Additional refuge requirements in cotton-growing regions where corn earworm is a significant pest

In cotton-growing regions where corn earworm is a significant pest, as defined below, MON 89034 × TC1507 × MON 88017 × DAS-59122-7 seed blend corn requires the planting of an additional 20% structured refuge (i.e. 20 acres of non-Bt corn for every 80 acres of MON 89034 × TC1507 × MON 88017 × DAS-59122-7 seed blend corn planted).

The 20% refuge must be planted with corn hybrids that do not contain Bt technologies for the control of corn rootworms or corn borers. The refuge and the MON 89034 × TC1507 × MON 88017 × DAS-59122-7 seed blend corn should be sown on the same day, or with the shortest window possible between planting dates to ensure that corn root development is similar among varieties. The structured refuge may be planted as an in-field or adjacent (e.g., across the road) refuge, or as a separate block that is within ½ mile of the MON 89034 × TC1507 × MON 88017 × DAS-59122-7 seed blend corn field. In-field refuge options include blocks, perimeter strips (i.e., strips around the field), or in-field strips. If perimeter or in-field strips are implemented, the strips must be at least 4 consecutive rows wide. The refuge can be protected from lepidopteran damage by use of non-Bt insecticides if the population of one or more target lepidopteran pests of MON 89034 × TC1507 × MON 88017 × DAS-59122-7 seed blend corn in the refuge exceeds economic thresholds. In addition, the refuge can be protected from CRW damage by an appropriate seed treatment or soil insecticide; however, insecticides labeled for adult CRW control must be avoided in the refuge during the period of CRW adult emergence. Economic thresholds will be determined using methods recommended by local or regional professionals (e.g., Extension Service agents, crop consultants).

The cotton-growing region requiring the additional 20% refuge consists of the following states: Alabama, Arkansas, Georgia, Florida, Louisiana, North Carolina, Mississippi, South Carolina, Oklahoma (only the counties of Beckham, Caddo, Comanche, Custer, Greer, Harmon, Jackson, Kay, Kiowa, Tillman, and Washita), Tennessee (only the counties of Carroll, Chester, Crockett, Dyer, Fayette, Franklin, Gibson, Hardeman, Hardin, Haywood, Lake, Lauderdale, Lincoln, Madison, Obion, Rutherford, Shelby, and Tipton), Texas (except the counties of Carson, Dallam, Hansford, Hartley, Hutchinson, Lipscomb, Moore, Ochiltree, Roberts, and Sherman), Virginia (only the counties of Dinwiddie, Franklin City, Greensville, Isle of Wight, Northampton, Southampton, Suffolk City, Surrey, and Sussex) and Missouri (only the counties of Dunklin, New Madrid, Pemiscot, Scott, and Stoddard).

b) Grower Agreement for MON 89034 x TC1507 x MON 88017 x DAS-59122-7 Seed Blend Corn

1) Persons purchasing MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn must sign a grower agreement. The term "grower agreement" refers to any grower purchase contract, license agreement, or similar legal document.

2) The grower agreement and/or specific stewardship documents referenced in the grower agreement must clearly set forth the terms of the current IRM program. By signing the grower agreement, a grower must be contractually bound to comply with the requirements of the IRM program.

3) Monsanto and Dow must implement a system (equivalent to what is already approved for previously registered Monsanto and Dow *Bt* corn products), which is reasonably likely to assure that persons purchasing *MON* 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn will affirm annually that they are contractually bound to comply with the requirements of the IRM program. A description of the system must be submitted to EPA within 90 days from the date of registration.

4) Monsanto and Dow must use a grower agreement and must submit to EPA, within 90 days from the date of registration, a copy of that agreement and any specific stewardship documents referenced in the grower agreement. If Monsanto and Dow wish to change any part of the grower agreement or any specific stewardship documents referenced in the grower agreement that would affect either the content of the IRM program or the legal enforceability of the provisions of the agreement relating to the IRM program, 30 days prior to implementing a proposed change, Monsanto and Dow must submit to EPA the text of such changes to ensure that it is consistent with the terms and conditions of this registration.

5) Monsanto and Dow must implement a system (equivalent to what is already approved for previously registered Monsanto and Dow *Bt* corn products), which is reasonably likely to assure that persons purchasing MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn

sign grower agreement(s). A description of the system must be submitted to EPA within 90 days from the date of registration.

6) Monsanto and Dow shall maintain records of all MON 89034 x TC1507x MON 88017 x DAS-59122-7 seed blend corn grower agreements for a period of three years from December 31st of the year in which the agreement was signed.

7) Beginning on January 31, 2012 and annually thereafter, Monsanto and Dow shall provide EPA with a report on the number of units of MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn seed shipped and not returned, and the number of such units that were sold to persons who have signed grower agreements. The report shall cover the time frame of a twelve-month period. Note: The first report shall contain the specified information from the time frame starting with the date of registration and extending through the 2010 growing season.

8) Monsanto and Dow must allow a review of the grower agreements and grower agreement records by EPA or by a State pesticide regulatory agency if the State agency can demonstrate that confidential business information, including names, personal information, and grower license number, will be protected.

c) IRM Education and IRM Compliance Monitoring Program for MON 89034 x TC1507 x MON 88017 x DAS-59122-7 Seed Blend Corn

1) Monsanto and Dow must design and implement a comprehensive, ongoing IRM education program designed to convey to MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn users the importance of complying with the IRM program. The education program shall involve the use of multiple media, e.g. face-to-face meetings, mailing written materials, EPA-reviewed language on IRM requirements on the bag or bag tag, and electronic communications such as by internet, radio, or television commercials. Copies of the materials will be provided to EPA for their records. The program shall involve at least one written communication annually to each MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn user separate from the grower technical guide. The communication shall inform the user of the current IRM requirements. Monsanto and Dow shall coordinate its education program with the educational efforts of other registrants and other organizations, such as the National Corn Growers Association and state extension programs.

2) Annually, Monsanto/Dow shall revise, and expand as necessary, its education program to take into account the information collected through the compliance survey and from other sources. The changes shall address aspects of grower compliance that are not sufficiently high.

3) Beginning January 31, 2012, Monsanto and Dow must provide a report to EPA summarizing the activities it carried out under its education program for the prior year. Annually thereafter, Monsanto and Dow must provide EPA any substantive changes to its grower education activities as part of the overall IRM compliance assurance program report. Monsanto/Dow must either submit a separate report or contribute to the report from the industry working group, Agricultural Biotechnology Stewardship Technical Committee (ABSTC).

4) Given that MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend will likely have different refuge strategies for lepidoptera and CRW than other registered Bt corn products, Monsanto/Dow must submit a revised compliance assurance program (CAP) within 90 days of

the date of registration. This revised CAP must be found acceptable by BPPD by April 1, 2012. This strategy should be specific for MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn and the new refuge requirements. Availability of non-Bt corn refuge seeds in desirable varieties must be addressed. Compliance is an area of ongoing concern -- recent data have shown that refuge compliance for Bt corn has fallen in recent years.

d) Insect Resistance Monitoring and Remedial Action Plans for MON 89034 x TC1507 x MON 88017 x DAS-59122-7 Corn

Existing programs for resistance monitoring and remedial action for MON 89034 x TC1507 x MON 88017 x DAS-59122-7 are applicable and required for MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn. Monsanto/Dow must submit a revised definition of unexpected damage in MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn for resistance monitoring must also submit a remedial action plan within 90 days of the date of registration that must be found acceptable to BPPD by April 1, 2012.

A report on results of resistance monitoring and investigations of damage reports must be submitted to the Agency annually by August 31st each year, beginning in 2012, for the duration of the conditional registration.

e) Annual Reporting Requirements for MON 89034 x TC1507 x MON 88017 x DAS-59122-7 Seed Blend Corn

1) Annual Sales: reported and summed by state (county level data available by request) January 31st each year, beginning in 2012;

2) Grower Agreements: number of units of MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn seed shipped or sold and not returned, and the number of such units that were soldto persons who have signed grower agreements, January 31st each year, beginning in 2011;

3) Grower Education: substantive changes to education program completed previous year, January 31st each year, beginning in 2012;

4) Compliance Assurance Program: compliance assurance program activities and results for the prior year and plans for the compliance assurance program for the current year, January 31st each year, beginning in 2012;

5) Compliance Survey Results: results of annual surveys for the prior year and survey plans for the current year; full report January 31st each year, beginning in 2012;

6) Insect Resistance Monitoring Results: results of monitoring and investigations of damage reports, August 31st each year, beginning in 2012.

f**) Refuge Assurance Program for MON 89034 x TC1507 x MON 88017 x DAS-59122-7 Seed Blend Corn**

Monsanto, Monsanto's seed company licensees, and Dow must continue to implement a blended seed refuge assurance program designed to ensure MON 89034 x TC1507 x MON 88017 x

DAS-59122-7 seed blend corn products are formulated with the appropriate rate of refuge seeds.

The program must include the following four elements:

1. Trait purity check on seed lots prior to blending (Monsanto and Monsanto Licensees) Trait purity check on component seed lots prior to release of the blend for sale (Dow)
2. Standard Operating Procedures for the blending process;
3. Calibration of blending equipment; and
4. Records and data retention records for seed blend products.

    - Calibration records – Monsanto, Monsanto's Licensees, and Dow will retain documentation for three (3) years on the equipment calibration including the procedure, when it was conducted and the results.
    - Blend proportion records (weight and kernel based) – Monsanto, Monsanto Licensees, and Dow will retain documentation for three (3) years on the kernel per pound data of the components, the calculations to determine the proportions based on weight and the actual weights that are blended together to make up an MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn product by seed lot.

All records must be maintained at the Monsanto, Monsanto Licensees, and Dow blending facility and must be available for the EPA review upon request.

Within one year of the date of registration Monsanto will collect documentation from qualification test runs that validate blend percentages from their licensees/conditioners that produce MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend corn and submit this data to the Agency. Any licensee/conditioner that is unable to verify their blend accuracy will provide evidence demonstrating application and participation in the USDA USA Accredited Seed Conditioning Program (ASCP) as outlined in ARC 1005D Appendix, http://www.ams.usda.gov/AMSv1.0/ams.fetchTemplateData.do?template=TemplateN&navID=AccreditedSeedPrograms&rightNav1=AccreditedSeedPrograms&topNav=&leftNav=&page=ASLProgram&resultType=&acct=audrevcom.

Should Monsanto, Monsanto's Licencees, or Dow be notified by the USDA/AMS or State Seed Control Officials that your seed blend products have been found to have a lower percentage of the refuge component than is represented on the label, they must notify EPA within 30 days. This would constitute information reportable under FIFRA section 6(a)(2).

Dow must document what the actual target weight and percentage will be for a 5% MON 89034 x TC1507 x MON 88017 x DAS-59122-7 seed blend within 1 year.

6) Monsanto must submit revised product labeling that indicates one seed tag for use in both cotton and non-cotton growing areas within six months.

7) Monsanto must report on how many of their licensees (by number and percentage) color seed January 31st each year, beginning in 2012.

Additional Terms and Conditions as of November 22, 2011

1) The Agency recognizes that large corn rootworm populations, environmental conditions, and protein expression levels can influence corn root damage and may affect the definition of suspected CRW resistance. The Agency plans to work with the registrants to refine the definition of suspected resistance based on these factors. Until such time that the Agency accepts a modified definition of suspected resistance to corn rootworm, resistance will be suspected in cases where the average root damage in the SmartStax field is > 0.5 on the nodal injury scale (NIS) and the frequency of SmartStax with > 0.5 nodes destroyed exceeds 50% of the sampled plants.

2) Within 90 days of this amendment, you must submit an enhanced rootworm resistance monitoring plan for SmartStax that accounts for reports of suspected and/or confirmed resistance. The rootworm resistance monitoring plan and the revised definitions for suspected and confirmed resistance for SmartStax must be found acceptable to BPPD by May 1, 2012 and utilized by The registrant beginning in the 2012 season. This enhanced monitoring program should:

    - Be practical and adaptable, and provide information on relevant changes in corn rootworm population sensitivity to SmartStax;

    - Be focused on areas where the potential for resistance is greatest for SmartStax and for the corn rootworm active single event components of SmartStax (Cry3Bb1and Cry34Ab1/Cry35Ab1), based on available information on historical pest pressure, unexpected performance issues, historical suspected and/or confirmed resistance incidents as currently defined or as modified in EPA accepted enhanced monitoring programs, prevailing agronomic practices (e.g. crop rotation versus continuous corn), and academic and extension publications on Bt corn field performance;

    - Involve coordination to the extent possible with other stakeholders, such as academic and extension experts in the states where corn rootworm is a major pest, other registrants of SmartStax, and other registrants of similar products, as appropriate;

    - Be responsive to incidents of suspected or confirmed resistance to the registrant's other products containing the same active ingredient(s), as well as to publicly available reports of suspected or confirmed resistance to other *Bt* protein toxins in SmartStax.

3) Within 90 days of this amendment, you must submit an enhanced remedial action plan for SmartStax that includes actions to be taken in response to both suspected and confirmed resistance. This remedial action plan must include a description of steps to be taken in response to customer product performance inquiries and annual reporting to the agency on the outcomes of investigations into any such inquiries that might indicate potential resistance. The program must include revised definitions of unexpected damage to SmartStax corn that could indicate potential suspected resistance. The enhanced remedial action plan must be found acceptable to BPPD by May 1, 2012.

4) The Grower Guide or its supplements must include language directing the user to contact a company representative if they observe unexpected insect feeding damage to their SmartStax corn. As part of its follow up on reports of unexpected damage to SmartStax corn, the registrant must determine the nodal injury scale (NIS) of affected corn. If the NIS results fall within the definition of suspected resistance for SmartStax, then until such time as the Agency accepts a modified remedial action plan, the registrant must provide specific guidance to affected growers in managing corn rootworms in the affected fields. This will include 1) providing specific grower guidance to control the adult stage of corn rootworms, where adult beetles are still present and laying eggs during the season that unexpected damage meets the suspected resistance definition; and 2) where the grower continues to be an existing customer of the registrant or seed company licensee into the following season, providing specific grower guidance and assistance to use an additional or alternative pest control method during the season following the initial finding that unexpected damage meets the suspected resistance definition.

5) The registrant will submit additional modeling, scientific literature, and other scientific information addressing the impact of pyramid PIP use in areas of confirmed resistance to one of the rootworm-active components of the pyramid by August 30, 2012.

6) Should resistance to any of the constituent toxins of SmartStax be confirmed (from target pest populations collected in 2012 or prior growing seasons) in accordance with the existing definition of "confirmed resistance" for the appropriate toxin, EPA will reassess and, if EPA concludes it is necessary, The registrant will revise the refuge/seed blend requirements for SmartStax. The registrants may independently submit updated definitions of confirmed resistance for their respective SmartStax active proteins for EPA's consideration in order to harmonize and/or keep definitions current with scientific standards; any such submission must be found acceptable to BPPD by May 1, 2012. EPA will incorporate all relevant scientific information (including the data required above) in its reassessment of the refuge/seed blend requirements. The revised refuge/seed blend requirements will be effective for the following growing season (after resistance confirmation) in the geographic areas in which resistance was confirmed. The geographic area of confirmed resistance could be less than a single county, a single county, or multiple counties, depending on EPA's analysis of the collected data.

7) For the SmartStax block refuge products, submit a revised Compliance Assurance plan by February 28, 2012.

REFERENCES

D. Andow. 2010. Personal comment at the Scientific Advisory Panel meeting for a 5% SmartStax seed blend in Arlington. Virginia, December 8-9.

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