UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of the Public Interest Document in Support of the Section 3(c)(7)(C) Registrations of Monsanto Company's Insect-protected *Bacillus thuringiensis* Corn Products, MON 89034 [Reg. No. 524-LTL; Decision Number 371189; S819890; DP Barcode 346850; MRID# 472797-01] and MON 89034 x MON 88017 [Reg. No. 524-LTA; Decision Number 371190; MRID# 472797-01]

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ACTION REQUESTED: The Biopesticides and Pollution Prevention Division (hereafter referred to as BPPD) has been asked to review the public interest document submitted by Monsanto Company (hereafter referred to as Monsanto) to support a public interest finding for Section 3(c)(7)(C) registrations of insect-protected *Bacillus thuringiensis* corn products, MON 89034 (producing Cry1A.105 and Cry2Ab2 proteins) and MON 89034 x MON 88017 (producing Cry1A.105, Cry2Ab2, and Cry3Bb1 proteins).

CONCLUSIONS

To grant a conditional registration under Section 3(c)(7)(C) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the Environmental Protection Agency (hereafter referred to as EPA or "the Agency") must determine that such conditional registration will, *inter alia*, be in the public interest. EPA determines whether conditional registration of a pesticide is in the public interest in accordance with the criteria set forth in 51 Fed. Reg. 7628 (*Conditional Registration of New Pesticides* dated March 5, 1986; OPP-32500; FRL-2977-2). There is a presumption that registration of a pesticide is in the public interest if one of the following criteria are met: (i) the use is for a minor crop; (ii) the use is a replacement for another pesticide that is of continuing concern to EPA; (iii) the use is one for which an emergency exemption under FIFRA Section 18 has been granted (i.e. the basis for the exemption was lack of a registered alternative product); or (iv) the use is against a pest of public health significance. Notwithstanding whether a registration of a pesticide may be presumed to be in the public interest, EPA may determine that such a registration is in the public interest on the basis of one of the following criteria: (i) there is a need for the new chemical that is not being met by currently registered pesticides; (ii) the new pesticide is comparatively less risky to health or the environment than currently registered pesticides; or (iii) the benefits (including economic benefits) from the use of the new active ingredient exceed those of alternative registered pesticides and other available non-chemical techniques.

MON 89034 and MON 89034 x MON 88017 do not meet any of the criteria for a presumption of public interest; however, BPPD has determined that MON 89034 and MON 89034 x MON 88017 are in the public interest based on criteria (ii) and (iii) mentioned above. Specifically, under criteria (ii), both MON 89034 and MON 89034 x MON 88017 should allow growers the opportunity to reduce the use of higher risk, and often less effective and more expensive, conventional pesticides. A reduction in use of conventional pesticides equates to less potential for adverse effects to human health and the environment. Additionally, MON 89034 and MON 89034 x MON 88017 provide a wider spectrum of protection against primary and secondary corn pests, which should facilitate greater grain quality, a reduction of mycotoxin contamination, increased yield and ultimately have positive implications for human health.

I. Agricultural Benefits

MON 89034

BPPD recognizes that MON 89034's unique combination of Cry1A.105 and Cry2Ab2 proteins expands the spectrum of protection for corn against lepidopteran pests - past that offered by already-registered MON 810 (BPPD, 2007a). In addition to providing protection against primary pests such as European corn borer (*Ostrinia nubilalis*, ECB), MON 89034 also protects against secondary corn pests such as corn earworm (*Helicoverpa zea*, CEW), fall armyworm (*Spodoptera frugiperda*, FAW), and black cutworm (*Agrotis ipsilon*, BCW) (BPPD, 2007a; BPPD, 2007c; BPPD, 2007d). Use of

MON 89034 could reduce or eliminate the need for conventional pesticide applications on acreage infested with secondary pests, although most growers do not use conventional pesticides to treat pests that are not part of the soil pest complex (BPPD, 2001). Finally, yield appears to be comparable to other Bt insect-protected corn. In situations of increased lepidopteran pressure, yield could be higher than other Bt insect-protected corn because of the presence of two insecticidal toxins and the effective protection against particular primary and secondary corn pests.

MON 89034 x MON 88017

In addition to the agricultural benefits mentioned above for MON 89034, MON 89034 x MON 88017 provides control of corn rootworm complex (*Diabrotica spp.*, CRW) that is functionally equivalent to already-registered MON 863 and MON 88017. Use of MON 89034 x MON 88017 should encourage replacement and reduction of higher-risk conventional pesticides currently utilized for CRW control (BPPD, 2003). Additionally, MON 89034 x MON 88017, which has tolerance for glyphosate, should allow corn growers to utilize a conventional chemical, Roundup, that is recognized by the Agency as a Category E chemical (i.e. there is evidence of non-carcinogenicity for humans). Finally, yield appears to be comparable to other Bt insect-protected corn. In situations of increased lepidopteran and/or coleopteran pressure, yield could be higher than other Bt insect-protected corn because of the presence of three insecticidal toxins and the effective protection against particular primary and secondary corn pests.

II. Economic (Grower) Benefits

MON 89034

MON 89034 will offer protection against a wider spectrum of primary and secondary corn pests (to include FAW and CEW), should create conditions that allow for a reduction in the amount of mycotoxin contamination, and should facilitate replacement and reduction of the amount of a small amount of conventional pesticides that may be used against particular non-soil complex corn pests. It is reasonable to believe that all of these characteristics should result in increased yield, increased grain quantity, and increased grain quality.

MON 89034 x MON 88017

Because of the presence of MON 88017, which offers protection against CRW, MON 89034 x MON 88017 should offer the same benefits as MON 89034 with perhaps more reduction in conventional pesticide use and a slight advantage over the single event for growers that require protection against lepidopteran pests and CRW.

III. Human Health and Environmental Benefits

MON 89034

Human Health

The Cry1A.105 and Cry2Ab2 proteins produced by MON 89034 should not present toxicity or allergenicity problems in humans based on the reviews of the studies submitted in support of MON 89034's conditional registration. As with other Bt corn products, it is reasonable to assume that the utilization of MON 89034 should reduce the use of some conventional pesticides (BPPD, 2001). Finally, because the Cry1A.105 and Cry2Ab2 proteins target secondary corn pests - such as FAW and CEW - and protect the ear from damage caused by these pests, decreased amounts of mycotoxin contamination should be recognized as a substantial benefit.

Environmental

Generally, there should be no risk from the proposed uses for MON 89034 to non-target organisms (to include the following: mammalian wildlife species, aquatic species, avian species, non-target insects, and endangered species) (BPPD, 2007i; BPPD, 2007j). However, based on a recently published laboratory study showing reduced growth in shedding caddis flies exposed to anti-lepidopteran Cry1A protein corn litter (Rosi-Marshall, et al. 2007), BPPD will require additional aquatic invertebrate data. A 21-day *Daphnia* study, per the 885 Series Office of Prevention, Pesticides, and Toxic Substances (OPPTS) Guidelines, will be submitted as a condition of registration. Finally, use of MON 89034 should encourage a small reduction in the use of conventional pesticides. Fewer chemical insecticide applications generally result in increased populations of beneficial organisms that control secondary pests, such as aphids and leafhoppers.

MON 89034 x MON 88017

Human Health

In addition to Cry1A.105 and Cry2Ab2 proteins produced in MON 89034, the introduction of MON 88017 in the pyramided product results in production of Cry3Bb1 protein. Human risk assessment data has previously been reviewed for MON 88017 and BPPD concluded that there is reasonable certainty that no harm will result from aggregate exposure to the United States (U.S.) population, including infants and children (BPPD, 2007g). Additionally, an exemption from tolerance was established for Cry3Bb1 protein under 40 CFR 174.518. As with other Bt corn products, it is reasonable to assume that the utilization of MON 89034 x MON 88017 should reduce the use of conventional pesticides. In particular, the use of MON 89034 x MON 88017 should result in the reduction of many conventional pesticides that are currently used, which have significant adverse effects on human health (BPPD, 2003).

Environment

Cry3Bb1 protein, produced in MON 88017, posed no significant risk to test organisms (BPPD, 2003). The only potential concern, brought to BPPD's attention by a recently published study, relates to MON 89034 and will be dealt with by submission of 21-day

Daphnia study. Additionally, use of MON 89034 x MON 88017 should reduce the amount of conventional pesticides used in the environment. All of the conventional pesticides used for CRW control or suppression currently cause significant adverse environmental effects under conditions of normal use (BPPD, 2003). Fewer chemical insecticide applications generally result in increased populations of beneficial organisms that control secondary pests, such as aphids and leafhoppers.

IV. Insect Resistance Management (IRM) Benefits

MON 89034 (mention of MON 89034 assumes the same conclusions for MON 89034 x MON 88017 also)

MON 89034's two modes of action are better than one for reducing insect resistance. However, due to uncertainties in the data submitted to support the MON 89034 IRM plan, a 5% refuge cannot be established until additional data can be submitted to support such a reduction. Instead, BPPD recommends that the separate refuge option include a 20% lepidopteran refuge (as has been required for other Bt products). A 20% refuge is likely to be supported for MON 89034 in cotton-growing regions of the southeastern U.S. where a 50% refuge has been previously required. This will likely provide an economic benefit to certain growers, since they will be required to plant less structured refuge. In addition, the Cry1A.105 and Cry2Ab2 toxins are new proteins targeting lepidopteran pests in corn. These additional modes of action will likely provide a benefit to IRM programs (i.e. a toxin "mosaic" in corn-growing regions may reduce the likelihood of resistance developing in individual toxins). Also, the use of pyramided Bt corn products (containing 2 or more toxins targeting the same pest) should further reduce the potential for resistance (BPPD, 2007b; BPPD, 2007h).

BACKGROUND

I. General Information

Corn (*Zea mays* L.) is the largest cultivated crop grown in the United States (U.S.) in terms of acreage planted and net value. Monsanto states that 93.6 million of acres of corn were planted in the U.S. during 2007 and that the net value of the 2006 corn crop was 33.7 billion dollars. However, the corn industry also suffers substantial economic losses from the damage caused by specific lepidopteran and coleopteran pests.

Two primary corn pests of particular concern to growers are corn rootworm complex (*Diabrotica spp.*, CRW) and European corn borer (*Ostrinia nubilalis*, ECB). According to Monsanto, CRW causes damage to all portions of the plant (i.e. those above and below ground) depending on the insect's life stage. In 2003, EPA estimated that approximately 28 million acres of corn were infested with CRW and that untreated corn could result in severe yield loss, which was typically in the range of 8 -16% reduction but could be as high as 28% (BPPD, 2003). ECB has been identified as the second most important insect pest of corn after CRW. ECB causes damage to the plant based upon the generation: i)

the first generation causes leaf and stalk damage; ii) the second generation causes stalk, leaf sheath, collar, and ear damage; and iii) the third generation causes leaf sheath, collar, and ear damage. Monsanto estimates that the average annual U.S. yield loss from ECB infestation is within the range of 3-7%. Exceptions to this range are attributed to level of infestation and region.

Two secondary corn pests of particular concern to growers are corn earworm (*Helicoverpa zea*, CEW) and fall armyworm (*Spodoptera frugiperda*, FAW). FAW typically has a limited range as it is primarily found in the Gulf States and over winters only in extreme southern Texas and Florida. Monsanto provides an estimate that FAW damage to untreated acreage in Georgia between 1991 and 1997 resulted in average yield loss of approximately 10%. No average yield loss for all of the U.S. due to FAW damage was provided. On the other hand, CEW is found throughout the U.S. corn-growing region, but Monsanto cites its economic damage as being low and dependent on timing of infestation, region, and number of moth flights per year.

II. MON 89034

Monsanto has developed MON 89034, a corn product that produces *Bacillus thuringiensis* (Bt)-derived insecticidal proteins Cry1A.105 and Cry2Ab2. The Cry1A.105 toxin is a "chimeric" protein containing domains I and II and the C-terminal from Cry1Ac and domain III from Cry1F. The Cry2Ab2 protein is functionally equivalent to that currently expressed in Monsanto's Bollgard II cotton. MON 89034 is protected from damage caused by larval feeding of ECB, southwestern corn borer (*Diatraea grandiosella*, SCWB), Sugarcane borer (*Diatraea saccharalis*, SCB), FAW, and CEW (BPPD, 2007a).

III. MON 89034 x MON 88017

Monsanto has also developed a second generation corn product, MON 89034 x MON 88017. MON 88017 (EPA Reg. No. 524-551) (plasmid vector ZMIR39) expresses the Cry3Bb1 Bt toxin and is targeted against CRW larvae. The toxin is the same as expressed by MON 863 corn (EPA Reg. No. 525-528), which was registered by Monsanto for the 2003 growing season. The Cry3Bb1 protein produced in MON 88017 and MON 863 is a variant of the wild-type Cry3Bb1 protein from Bt subsp. *kumamotoensis*. When compared by amino acid sequencing, the Cry3Bb1 protein expressed in MON 88017 has been reported to be 99.8% similar to the Cry3Bb1 protein expressed in MON 863. The primary difference between the two hybrids is that MON 88017 also expresses a gene for resistance to glyphosate (Roundup)-based herbicides (BPPD, 2005). By crossing MON 89034 and MON 88017 through conventional breeding, Monsanto has obtained an insect-protected corn product that expresses the Cry1A.105, Cry2Ab2, and Cry3Bb1 Bt toxins, is targeted against lepidopteran corn pests including ECB, SWCB, CEW, and FAW as well as coleopteran CRW, and is tolerant of glyphosate (BPPD, 2007b).

IV. Monsanto's Public Interest Assertions for MON 89034 and MON 89034 x MON 88017

In the introduction of their public interest document (PID), Monsanto outlines the following reasons why MON 89034 and MON 89034 x MON 88017 are in the public interest according to some of the criteria set forth in 51 Fed. Reg. 7628:

- *Enhanced spectrum of control.* MON 89034 provides protection against an expanded spectrum of lepidopteran pests when compared to current Bt corn products. MON 89034 x MON 88017 protects against both particular lepidopteran and coleopteran pests. The increased protection found in both products improves overall grain quality and limits yield losses due to root, leaf, stalk, and ear damage.

- *Reduced mycotoxin levels.* Because MON 89034 and MON 89034 x MON 88017 control the secondary pests, FAW and CEW, the opportunity for fungal infections to thrive due to plant damage is reduced. This leads to less mycotoxin contamination.

- *Improved breeding efficiency.* Vector-stacking, which increases the efficiency of breeding multiple traits into new corn hybrids, was utilized in the creation of MON 89034 and MON 89034 x MON 88017.

- *Compatibility with integrated pest management (IPM) systems.* Both MON 89034 and MON 89034 x MON 88017 provide two different modes of action in a single plant and reduce the probability of lepidopteran pests developing resistance to the Bt proteins. This allows for a smaller refuge, helps the product maintain efficacy, and guards against potential insect resistance to Bt crops.

- *Reduced use of chemical pesticides.* MON 89034 and MON 89034 x MON 88017 reduce the use of conventional chemicals, which saves costs and protects human health and the environment.

- *Easy implementation.* No additional labor or machinery is needed to plant, grow, or harvest MON 89034 and MON 89034 x MON 88017 relative to conventional corn.

- *Presence of glyphosate tolerance.* MON 89034 x MON 88017 produces 5-enolpyruvylshikimate-3-phosphate synthase protein from *Agrobacterium* sp. Strain CP4, which confers tolerance to glyphosate. Therefore, the agricultural herbicide, Roundup, can be utilized on MON 89034 x MON 88017 corn to control weeds and enhance the ability of the corn plants to access soil nutrients. EPA has classified glyphosate as a Category E Chemical, meaning there is evidence of non-carcinogenicity for humans.

This review will evaluate most of the assertions presented above in order to determine if MON 89034 and MON 89034 x MON 88017 are in the public interest.

EPA'S REVIEW OF MONSANTO'S PUBLIC INTEREST DOCUMENT

Monsanto submitted a public interest document in support of the Section 3(c)(7)(C) registrations of MON 89034 and MON 89034 x MON 88017 (Crawford and Bogdanova 2007, MRID 472797-01). The main portion of this document is divided into the following five sections: i) agricultural benefits; ii) economic (grower) benefits; iii) human health benefits; iv) environmental benefits; and v) insect resistance management benefits. This document also includes three appendices: Appendix I provides a summary of reports submitted by Monsanto to the EPA that support registration of MON 89034 and MON 89034 x MON 88017, Appendix II contains a study that analyzes the mycotoxin levels in grain of MON 89034 corn exposed to lepidopteran insect infestation and inoculation with *Aspergillus flavus* or *Fusarium verticillioides*, and Appendix III contains an assessment of efficacy of MON 89034 x MON 88017 corn against corn rootworm complex (*Diabrotica spp.*, CRW) in the US during 2005 and 2006. Information provided by Monsanto will be discussed below, as applicable.

I. Agricultural Benefits

A. Pest Spectrum and Efficacy - Monsanto's Summary (MRID 472797-01)

MON 89034

MON 89034 exhibits the Cry proteins, Cry1A.105 and Cry2Ab2, which specifically target lepidopteran pests (See Tables 1 and 2). The primary benefit of MON 89034 is that it provides equal (as compared to MON 810) or improved protection (as compared to MON 810, other Bt corn products, and non-Bt corn products) from feeding damage caused by particular lepidopteran pest larvae. The spectrum of protection against lepidopteran insects includes the following: European corn borer (*Ostrinia nubilalis*, ECB), southwestern corn borer (*Diatraea grandiosella*, SCWB), Sugarcane borer (*Diatraea saccharalis*, SCB), fall armyworm (*Spodoptera frugiperda*, FAW), black cutworm (*Agrotis ipsilon*, BCW), and corn earworm (*Helicoverpa zea*, CEW).

During the 2003 and 2004 growing seasons, Monsanto conducted efficacy field trials in the U.S., Puerto Rico, and Argentina. MON 89034's control of ECB, SWCB, and SCB was found to be comparable to MON 810 (See Table 3). However, because of the production of Cry1A.105 protein by MON 89034 and the subsequent control of FAW throughout the season and not just the plant's vegetative growth phase, Monsanto claims a higher level of protection and increased activity against FAW are shown by MON 89034 as opposed to MON 810 (See Table 3). Of particular note, under heavy FAW pressure, MON 810 did not provide the significant amount of protection from leaf damage that MON 89034 exhibited. Finally, the Cry2Ab2 protein produced by MON 89034 provided improved control from CEW, when compared to the activity of MON 810's Cry1Ab protein (See Table 3).

Table 1. Summary of arthropod LC_{50} values for the Cry1A.105 protein exposure in diet bioassays

In the event that no adverse effect was observed, the LC_{50} value is considered to be greater than the maximum concentration tested.

Test Insect (Order/Family/Species)	Insect Stage Tested	Assay Duration (days)	Diet Assay Type	Maximum Concentration tested (µg/mL or g diet)	LC_{50} (µg/mL or g diet)[1]
Lepidoptera					
Noctuidae					
Helicoverpa zea	larvae	7	Incorporation	N/A	6
Agrotis ipsilon	larvae	7	Incorporation	N/A	33
Spodoptera frugiperda	larvae	7	Incorporation	N/A	6.9
Crambidae					
Diatraea grandiosella	larvae	12	Incorporation	N/A	37
Ostrinia nubilalis	larvae	12	Incorporation	N/A	0.43
Collembola					
Folsomia candida	nymphs	28	Overlay	80[2]	>80
Coleoptera					
Curculinoidae					
Anthonomus grandis grandis	larvae	7	Overlay	100	>100
Chrysomelidae					
Diabrotica undecimpunctata howardi **Coccinellidae**	larvae	5	Overlay	100	>100
Coleomegilla maculata	larvae	20	Incorporation	240	>240

*Table from page 15 of MRID 472797-01

[1] LC_{50} values with a greater than sign represent the highest dose tested.
[2] Assay was performed with lyophilized leaf tissue from MON 89034.

Table 1 (cont). Summary of arthropod LC_{50} values for the Cry1A.105 protein exposure in diet bioassays

In the event that no adverse effect was observed, the LC_{50} value is considered to be greater than the maximum concentration tested.

Test Insect (Order/Family/Species)	Insect Stage Tested	Assay Duration (days)	Diet Assay Type	Maximum Concentration tested (µg/mL or g diet)	LC_{50} (µg/mL or g diet)[1]
Hymenoptera					
Ichneumonidae					
Ichneumon promissorius	adults	21	Incorporation	240	>240
Apidae					
Apis mellifera	adults	18	Incorporation	550	>550
Apis mellifera	larvae	18	Overlay	1100 µg/mL as a single dose	>1100 µg/mL as a single dose
Hemiptera					
Aphididae					
Myzus persiscae	adults/ nymphs	5	Incorporation	80	>80
Miridae					
Lygus hesperus	nymphs	5	Incorporation	80	>80
Anthocoridae					
Orius insidiosus	nymphs	14	Incorporation	N/A	240[2]

*Table from page 16 of MRID 472797-01

[1] LC_{50} values with a greater than sign represent the highest dose tested.
[2] The no observed effect concentration was determined to be 120 µg/g diet.

Table 2. Summary of arthropod LC50 values for the Cry2Ab2 protein exposure in diet bioassays

In the event that no adverse effect was observed, the LC_{50} value is considered to be greater than the maximum concentration tested.

Test Insect (Order/Family/Species)	Insect Stage Tested	Assay Duration (days)	Diet Assay Type	Maximum Concentration tested (µg/mL or g diet)	LC_{50} (µg/mL or g diet)[1]
Lepidoptera					
Noctuidae					
Helicoverpa zea	larvae	7	Incorporation	N/A	9.9
Agrotis ipsilon	larvae	5	Overlay	N/A	>100[2]
Spodoptera frugiperda	larvae	7	Overlay	N/A	<50[3]
Crambidae					
Ostrinia nubilalis	larvae	12	Incorporation	N/A	1.5
Diatraea grandiosella	larvae	7	Incorporation	N/A	>100[4]
Collembola					
Folsomia candida	nymphs	28	Incorporation	70[5]	>70
Coleoptera					
Curculinoidae					
Anthonomus grandis grandis	larvae	7	Overlay	100	>100
Chrysomelidae					
Dibrotica undecimpunctata howardi	larvae	5	Overlay	100	>100

*Table from page 17 of MRID 472797-01

[1] LC_{50} values with a greater than sign represent the highest dose tested.
[2] 42% mortality was observed at the lowest tested dose of 100 µg/mL diet.
[3] 61% mortality was observed at the lowest tested dose of 50 µg/mL diet.
[4] Significant mortality was not observed at the highest tested dose of 100 ug/mL diet, however, at the highest tested dose of 100 ug/mL diet >95% growth inhibition was observed relative to the control treatment in three independent assays
[5] Assay was performed with lyophilized leaf tissue derived from MON 89034.

Table 2 (cont). Summary of Arthropod LC_{50} Values for the Cry2Ab2 Protein Exposure in Diet Bioassays

In the event that no adverse effect was observed, the LC_{50} value is considered to be greater than the maximum concentration tested.

Test Insect (Order/Family/Species)	Insect Stage Tested	Assay Duration (days)	Diet Assay Type	Maximum Concentration tested (µg/mL or g diet)	LC_{50} (µg/mL or g diet)[1]
Coccinellidae					
Coleomegilla maculata	larvae	20	Incorporation	120	>120
Hymenoptera					
Ichneumonidae					
Ichneumon promissorius	adults	21	Incorporation	100	>100
Nasonia vetripennis	adults	10	Incorporation	4500	>4500
Apidae					
Apis mellifera	adults	19	Incorporation	68	>68
Apis mellifera	larvae	12	Overlay	100 µg/mL (as a single dose)	>100 µg/mL (as a single dose)
Hemiptera					
Aphididae					
Myzus persiscae	adults/ nymphs	5	Overlay	80	>80
Miridae					
Lygus hesperus	nymphs	5	Overlay	80	>80
Anthocoridae					
Orius insidiosus	nymphs	14	Incorporation	100	>100

*Table from page 18 of MRID 472797-01

[1] LC_{50} values with a greater than sign represent the highest dose tested.

Table 3. Summary of field efficacy of MON 89034, MON 810 and control corn against major lepidopteran pests during the 2003-2004 growing season

Field Location	Infestation method	Damage measured	Infestation level	Trait performance[1]
Fall Armyworm				
Puerto Rico (I)	Natural	Leaf	High	MON 89034>MON 810>Control
Puerto Rico (II)	Natural	Leaf	Severe	MON 89034>MON 810=Control
U.S.	Artificial	Leaf	50 larvae /plant	MON 89034>MON 810>Control
Argentina	Natural	Leaf	Low	MON 89034>MON 810>Control
Corn Earworm				
Puerto Rico (I)	Natural	Ear	Moderate	MON 89034>MON 810>Control
U.S.	Artificial	Ear	15 larvae /plant	MON 89034>MON 810>Control
Argentina	Natural	Ear	Low-moderate	MON 89034>MON 810>Control
Southwest Corn Borer				
U.S.	Artificial	Stalk tunneling	7 larvae /plant	MON 89034=MON 810>Control
European Corn Borer				
U.S.	Artificial	Stalk tunneling	50 larvae /plant	MON 89034=MON 810>Control
Sugarcane Borer				
Argentina	Natural	Stalk tunneling	Moderate-high	MON 89034=MON 810>Control

*Table from page 20 of MRID 472797-01

[1] Level of protection against lepidopteran pest damage.

> represents statistically significantly improved performance compared to other treatment

= represents no statistically significant difference in performance

MON 89034 x MON 88017

In addition to producing the Cry1A.105 and Cry2Ab2 proteins, MON 89034 x MON 88017 also produces the insecticidal protein, Cry3Bb1, that controls damage caused by CRW.

The efficacy of MON 89034 x MON 88017 against CRW was compared in field trials in the U.S. in 2005 and 2006 and against lepidopteran pests in 2006. The pyramided product showed protection from feeding damage by lepidopteran pests that was comparable to MON 89034, as well as protection from damage by CRW that was comparable to MON 88017. The average root damage rating (RDR) for MON 88017 and MON 89034 x MON 88017 was significantly less than the RDR for non-CRW protected controls (See Table 4).

Table 4. Field efficacy of MON 88017 and MON 89034 x MON 88017 and non-CRW-protected control corn against corn rootworm tested in 2005 and 2006

Entry	RDR[1,2]
2005	
Control	1.399 A
MON 88017	0.165 B
MON 89034 x MON 88017	0.164 B
2006	
Control	0.774 A
MON 89034 x MON 88017	0.092 B

*Table from page 21 of MRID 472797-01

[1] RDR - Root damage rating calculated as a least-square mean of n=5 plants per plot in 2005 and n = 6 plants per plot in 2006.
[2] Values indicated by the same letter in the same column are not statistically different (Fisher's protected LSD p=0.05 level).

The efficacy of MON 89034 x MON 88017 against ECB was also assessed in 2005 U.S. trials. Significantly less feeding was observed on MON 89034 and MON 89034 x MON 88017 and these two insect-protected corn crops also provided a high level of control against leaf damage and stalk tunneling by ECB.

B. Pest Spectrum and Efficacy – BPPD's Response

MON 89034

BPPD agrees with Monsanto that MON 89034 targets lepidopteran pests specifically. In two studies conducted by Monsanto, both the Cry1A.105 protein and Cry2Ab2 protein exhibited insecticidal activity in the order Lepidoptera but not in the orders Coleoptera and Hemiptera (BPPD, 2007c; BPPD, 2007d). The Cry1A.105 protein, administered at 50 µg/mL and 100 µg/mL concentrations to insects in the orders Lepidoptera, Coleoptera, and Hemiptera, caused a range of mortality of 32% to 96% in CEW, ECB, and FAW (BPPD, 2007c). Additionally, all four lepidopteran insects (CEW, ECB, FAW, and BCW) had a range of 32% to 100% growth stunting (BPPD, 2007c). On the other hand, the Cry2Ab2 protein, administered at 50 µg/mL and 100 µg/mL concentrations to insects in the orders Lepidoptera, Coleoptera, and Hemiptera, caused at least 61% mortality (corrected) against CEW, ECB, and FAW (BPPD, 2007d). All four lepidopteran insects (CEW, ECB, FAW, and BCW) had a range of 97 to 100% growth stunting (BPPD, 2007d).

BPPD agrees with Monsanto's conclusions from the field trials conducted in the U.S., Puerto Rico, and Argentina. Across all geographies, the efficacy of MON 89034 against ECB, SWCB, CEW, FAW, and SCB was equal to or greater than that of YieldGard Corn Borer (MON 810), a lepidopteran control corn product that expresses the Cry1Ab protein.

However, MON 89034 did offer a broader spectrum of insect protection activity than MON 810 and demonstrated better control of CEW, FAW, and SCB than MON 810 in these trials (BPPD, 2007a).

MON 89034 x MON 88017

In the past, BPPD has concluded that MON 88017 is functionally equivalent to MON 863 for CRW control (BPPD, 2005). Therefore, BPPD finds the efficacy benefits of MON 89034 x MON 88017 are similar to the efficacy benefits of MON 863 (BPPD, 2003) and MON 88017 (BPPD, 2005). A summary of these benefits can also be found in BPPD's Biopesticides Registration Action Document – *Bacillus thuringiensis* Plant-Incorporated Protectants (BPPD, 2001). BPPD agrees that the efficacy of MON 89034 x MON 88017 should be comparable to efficacy of the MON 89034 and MON 88017 isolines for FAW and western corn rootworm (WCRW, *Diabrotica virgifera)* and to the MON 89034 isoline for ECB, SWCB, CEW, and FAW. Furthermore, similar to MON 89034, MON 89034 x MON 88017 provides a broader spectrum of efficacy than MON 810 against lepidopteran pests. Although no SCB, WBCW, or BCW field trials were conducted with MON 89034 x MON 88017, based on the efficacy against the other pests, it is reasonable to assume comparable efficacy to MON 89034 for these pests as well (BPPD, 2007b).

C. Yield – Monsanto's Summary (MRID 472797-01)

MON 89034 and MON 89034 x MON 88017

In 2006, Monsanto conducted field trials with the objective of comparing yield between MON 89034, MON 89034 x MON 88017, MON 810, MON 810 x MON 88017, and other hybrids not producing Bt proteins. Results showed comparable yield across several hybrids tested for insect-protected hybrids and higher yields compared to hybrids that did not produce Bt proteins (See Table 5). Additionally, the assumption is made that under intense lepidopteran pressure, the yield benefit from MON 89034 would be significantly higher. Although no economic benefits can be assessed for MON 89034 until it is actually used by growers, Monsanto predicts that the economic benefits would be equal or even more advantageous depending on the level and type of pest infestation that occurs.

Table 5. Yield comparison between MON 89034, MON 89034 x MON 88017, MON 810, MON 810 x MON 88017, and non-Bt hybrids grown in the U.S. during 2006

Product	Yield (Bu/Acre)	Number of hybrids tested
MON 89034	180.4	60
MON 810	180.6	29
MON 89034 x MON 88017	189.3	80
MON 810 x MON 88017	185.7	36
Non-Bt	171.5	2

*Table from page 13 of MRID 472797-01

D. Yield – BPPD's Response

BPPD believes that it is reasonable for Monsanto to assume that significant pressure from lepidopteran pests would cause the yield benefit for MON 89034 to be higher because of the presence of 2 insecticidal toxins, Cry1A.105 and Cry2Ab2. Furthermore, if the pressure is from secondary corn pests such as FAW and CEW, then increase of yield is even more logical. Although Monsanto assumes that economic benefits will be equal or more advantageous for MON 89034 and is probably correct, BPPD will not assume complete validity of this assumption until MON 89034 is used over the course of several years and reliable yield data is available. Although use of MON 89034 x MON 88017 could also result in an overall increase in yield, BPPD does not expect an increase in yield that exceeds that of the previously-registered single gene MON 88017 as any increase in yield will result mostly from the characteristics of MON 89034: expanded pest spectrum and the presence of two toxins instead of one.

II. Economic (Grower) Benefits

A. Monsanto's Summary (MRID 472797-01)

MON 89034

For economic benefits, Monsanto cites to National Center for Food and Agricultural Policy statistics that are based on planted acreage of MON 810 corn in 2005. The numbers estimated that MON 810 increased corn production by 103.9 million bushels because of the corn borer resistant trait. Net returns, decreased costs (fuel, labor, and conventional pesticides purchased), and premium price of protected seeds were estimated to be 197 million dollars. The decreased use of conventional pesticides was estimated at 4.85 million pounds. In percentage terms, MON 810 planted in 2005 resulted in a 24% increase in yield, a 27% decrease in pesticide use, and increased monetary gain of 26% when compared to 2004.

The major economic benefits of MON 89034 are the following: i) a wider spectrum of pest protection (to include FAW and CEW), which results in increased grain quality and increased yield; ii) reduction in mycotoxin contamination levels which contributes to economic recovery; iii) protection that is more effective in controlling corn borers and therefore results in increased yield, grain quality, and grain quantity; and iv) reduction in conventional pesticide use that results in less costs (See Table 6).

Table 6. Summary of economic benefits to growers using corn-borer protected corn

Benefit	Per acre benefit ($)	Total benefit ($ Millions)
Yield increase	13.59 (-3.67 – 48.76)	217 (-59 – 780)
Pesticide reduction	1.99 (1.00 – 2.98)	32 (16 – 48)
Mycotoxin reduction	1.98 (0.52 – 7.12)	32 (8.3 – 114)

*Table from page 29 of MRID 472797-01

MON 89034 x MON 88017

Monsanto states that the pyramided product will offer the combined benefits of the individual parents, MON 89034 and MON 88017. The addition of MON 88017 creates enhanced protection against CRW, a primary corn pest that can cause total yield losses that exceed $1 billion dollars annually, and adds the glyphosate tolerance trait that limits yield loss from weed pressure. Overall, MON 89034 x MON 88017 will limit yield losses from corn borer insects, CRW, and weed pressure, reduce conventional pesticide use, and reduce mycotoxin contamination while increasing yield, grain quantity, and grain quality.

B. BPPD's Response

MON 89034

Overall, BPPD agrees that MON 89034 should produce economic benefits for many growers. Monsanto's numbers are estimates and actual economic benefits may be affected by factors including pest pressure, climatic fluctuations, and commodity pricing. MON 89034 is effective against a wider spectrum of corn pests and it is reasonable to assume that this should result in increased yield. Additionally, BPPD has concluded that a slight decrease in pesticide use should be realized with the use of Bt corn products similar to MON 89034 (BPPD, 2001); therefore, BPPD agrees with Monsanto's assertion of possible conventional pesticide use reduction and associated reduced costs.

BPPD agrees with Monsanto's conclusion that MON 89034 should reduce mycotoxin contamination. Overall, if primary and secondary corn pest pressure is reduced, then less mycotoxin contamination will be present, which will in turn lead to increased yield, grain quantity, and grain quality (BPPD, 2001). Furthermore, field evidence has demonstrated the ability of Bt corn to reduce the infestation rates of certain mycotoxins (Wu, 2008). This article specifically associates CEW with aflatoxin accumulation in corn and claims that Bt corn varieties, perhaps those such as MON 89034, are being developed to combat this insect pest in order to reduce particular mycotoxin contamination.

MON 89034 x MON 88017

BPPD believes that use of MON 89034 x MON 88017, much like MON 89034, should produce the same economic benefits mentioned above. Additionally, the combination with MON 88017, which protects corn against CRW and exhibits glyphosate tolerance, can be expected to create slightly greater economic benefits than MON 89034 for growers needing to treat both lepidopteran pests and CRW. The economic benefits of MON 88017 (minus an evaluation of glyphosate tolerance) have previously been assessed in MON 863's public interest finding document (BPPD, 2003).

III. Human Health and Environmental Benefits

A. Monsanto's Summary (MRID 472797-01)

MON 89034

Human Health

Monsanto states that the Cry1A.105 and Cry2Ab2 proteins produced by MON 89034 are structurally and functionally related to Cry proteins that have a history of use both as active ingredients in Bt microbial pesticides and bio-tech derived food and feed. Furthermore, they state that Bt has been commercially used in the U.S. since 1958 to produce microbial-derived pesticides and no adverse effects on humans or animals has been reported during their use on food or feed crops. Additionally, Monsanto asserts that Cry1A.105 and Cry2Ab2 proteins are highly unlikely to create any concerns of toxicity or allergenicity to humans. These assertions are based on acute oral toxicity data, which produced results that agreed with literature showing that Bt proteins only impact insect species and that no mammalian toxicity or issues have been reported in nearly 60 years of Bt protein insecticide use, and a comparison to known allergens, which indicated no allergenicity in the Cry1A.105 and Cry2Ab2 proteins.

Two of the specific human health benefits that Monsanto attributes to use of MON 89034 are pesticide reduction and mycotoxin reduction. Using numbers from an article from the National Center for Food and Agricultural Policy, Monsanto demonstrates current usage levels of MON 810, a functional equivalent of MON 89034, results in an estimated decrease in use of approximately 4.85 million pounds of conventional pesticides per year (equivalent to a 27% decrease in conventional pesticide use to control corn-boring pests). According to Monsanto, mycotoxin reduction is also evident with the use of MON 89034 because of its ability to suppress or control secondary corn pests, such as CEW and FAW, that play a role in damaging corn ears and facilitating the inoculation and growth of mycotoxin-producing fungi. Monsanto cites to two types of fungi, *Fusarium* and *Aspergillus*, that produce fumonisin and aflatoxin, respectively. A study conducted by Monsanto indicates that MON 89034 is subject to less damage from corn pests and subsequently, it suffers less mycotoxin contamination, particularly from *Aspergillus*.

Environmental

Monsanto states that Cry1A.105 and Cry2Ab2 have no toxic effects on non-target organisms (to include the following: mammalian wildlife species, aquatic species, avian species, non-target insects, and endangered species) based on studies they submitted to the Agency in conjunction with the registration application for MON 89034. Additionally, the proteins rapidly degrade in soil which also minimizes exposure to non-target species.

MON 89034 x MON 88017

Human Health

Since MON 89034 is present in the pyramided product, Monsanto's contentions for the safety of MON 89034 with regard to human health also apply to MON 89034 x MON 88017. However, in addition to the presence of the Cry1A.105 and Cry2Ab2 proteins found in MON 89034, the pyramided product also produces Cry3Bb1 protein. Since MON 88017 is already a product registered by the EPA, Monsanto states that the Cry3Bb1 protein produced by MON 89034 x MON 88017 already has an exemption from tolerance. Furthermore, human risk assessment data reviewed by the EPA for registration of MON 88017 has resulted in a conclusion that there is reasonable certainty that no harm will result from aggregate exposure to the U.S. population, including infants and children. As with MON 89034, MON 89034 x MON 88017 is expected to result in both reduced pesticide use (and perhaps more because of MON 88017's protection from primary corn pest, CRW) and mycotoxin contamination.

Environmental

Since MON 89034 is present in the pyramided product, Monsanto's contentions for the safety of MON 89034 with regard to environmental effects also apply to MON 89034 x MON 88017. MON 89034 x MON 88017 also produces the Cry3Bb1 protein, which is in the previously registered MON 88017. Upon review of the environmental effects data for MON 88017's registration, EPA concluded that no unreasonable adverse effects are expected to the environment from the cultivation of MON 88017 and MON 88017 x MON 810 corn.

B. BPPD's Response

MON 89034

Human Health

BPPD agrees with Monsanto's conclusions that the Cry1A.105 and Cry2Ab2 proteins produced by MON 89034 should not cause toxicity or allergenicity problems in humans. The data submitted and cited regarding potential health effects for the Cry1A.105 and Cry2Ab2 proteins include the characterization of the expressed proteins in corn, as well as acute oral toxicity studies, amino acid sequence comparisons to known allergens and toxins, and in vitro digestibility of the proteins. The results of these studies were used to evaluate human risk (BPPD, 2007e).

The acute oral toxicity data submitted support the prediction that the Cry1A.105 and Cry2Ab2 proteins would be non-toxic to humans. When proteins are toxic, they are known to act via acute mechanisms and at very low dose levels. Since no treatment-related adverse effects were shown to be caused by the Cry1A.105 and Cry2Ab2 proteins, even at relatively high dose levels, the Cry1A.105 and Cry2Ab2 proteins are not considered toxic. Basing this conclusion on acute oral toxicity data without requiring further toxicity testing or residue data is similar to the Agency position regarding toxicity and the requirement of residue data for the microbial Bt products from which this plant-incorporated protectant was derived (See 40 CFR 158.740(b)(2)(i)) (BPPD, 2007e).

Since Cry1A.105 and Cry2Ab2 are proteins, potential allergenicity was also considered as part of the toxicity assessment. Considering all of the available information (1) Cry1A.105 and Cry2Ab2 originate from a non-allergenic sources; (2) Cry1A.105 and Cry2Ab2 have no sequence similarities with known allergens; (3) Cry1A.105 and Cry2Ab2 are not glycosylated; and (4) Cry1A.105 and Cry2Ab2 are rapidly digested in simulated gastric fluid; EPA has concluded that the potential for Cry1A.105 and Cry2Ab2 to be a food allergens is minimal (BPPD, 2007e).

The lack of mammalian toxicity at high levels of exposure to the Cry1A.105 and Cry2Ab2 proteins, as well as the minimal potential to be a food allergens, demonstrate the safety of the product at levels well above possible maximum exposure levels anticipated (BPPD, 2007e).

BPPD agrees with Monsanto's conclusion that MON 89034 should reduce mycotoxin contamination. Overall, if primary and secondary corn pest pressure is reduced, then less mycotoxin contamination will be present, which will in turn lead to increased yield, grain quantity, and grain quality (BPPD, 2001). Furthermore, field evidence has demonstrated the ability of Bt corn to reduce the infestation rates of certain mycotoxins (Wu, 2008). This article specifically associates CEW with aflatoxin accumulation in corn and claims that Bt corn varieties, perhaps such as MON 89034, are being developed to combat this insect pest in order to reduce particular mycotoxin contamination.

Environmental

BPPD agrees with Monsanto's assessment that there should be no risk from the proposed uses for MON 89034 to non-target organisms (to include the following: mammalian wildlife species, aquatic species, avian species, non-target insects, and endangered species) (BPPD, 2007i; BPPD, 2007j). However, based on a recently-published laboratory study showing reduced growth in shedding caddis flies exposed to anti-lepidopteran Cry1A protein corn litter (Rosi-Marshall, et al. 2007), BPPD will require additional aquatic invertebrate data. A 21-day *Daphnia* study, per the 885 Series Office of Prevention, Pesticides, and Toxic Substances (OPPTS) Guidelines, will be submitted as a condition of registration.

In addition to Monsanto's submitted rationale for environmental benefits, Monsanto could have included a reference to MON 89034 use potentially reducing the amount of conventional pesticides applied in the environment and the subsequent environmental benefits. BPPD believes that cultivation of MON 89034 corn may have fewer adverse impacts on non-target organisms than use of chemical pesticides for corn production, because under normal circumstances, MON 89034 corn should require substantially fewer applications of chemical pesticides, compared to production of non-Bt corn. Fewer chemical insecticide applications generally result in increased populations of beneficial organisms that control secondary pests, such as aphids and leafhoppers.

MON 89034 x MON 88017

Human Health

BPPD agrees with Monsanto that the use of MON 89034 x MON 88017 should not result in any unreasonable adverse effects to human health. In addition to Cry1A.105 and Cry2Ab2 proteins produced in MON 89034, the introduction of MON 88017 results in production of Cry3Bb1 protein. BPPD has already reviewed human risk assessment data for MON 88017 and reached a conclusion that there is reasonable certainty that no harm will result from aggregate exposure to the U.S. population, including infants and children (BPPD, 2007g). Additionally, Cry3Bb1 currently has an exemption from tolerance established under 40 CFR 174.518.

BPPD also agrees with the claim that there should be a reduction of some pesticide use (BPPD, 2001). Additionally, Cry3Bb1 protein primarily protects corn plants against CRW. Virtually all of the registered conventional insecticides used to control CRW are of special concern to the EPA because of risks to humans. Each year, there are confirmed reports of human illness associated with these registered conventional chemicals (See BPPD, 2003).

Finally, BPPD agrees with the claim that use of MON 89034 x MON 88017 should combat mycotoxin contamination because of the production of the Cry1A.105 and Cry2Ab2 proteins (as mentioned previously).

Environmental

BPPD agrees with Monsanto's assessment that there should be no risk from the proposed uses for MON 89034 x MON 88017 to non-target organisms (to include the following: mammalian wildlife species, aquatic species, avian species, non-target insects, and endangered species). The only potential concern will be addressed through a 21-day *Daphnia* study. For the registration of MON 88017, a series of studies were completed by Monsanto that exposed non-target organisms to high doses of leaf tissue, grain, or pollen containing a plant-produced Cry3Bb1 variant or to an artificial diet containing a Bt-produced Cry3Bb1 variant. Results indicated that the Cry3Bb1 protein posed no significant risk to test organisms (BPPD, 2003). Additionally, a study was conducted on MON 89034 x MON 88017 to ensure that the interaction between Cry1A.105, Cry2Ab2, and Cry3Bb1 proteins in the pyramided product would not change the overall properties of each individual component. BPPD concluded that the activity of Cry1A.105 and Cry2Ab2 proteins was not significantly altered by the presence of Cry3Bb1, and the activity of Cry3Bb1 was not significantly altered by the presence of Cry1A.105 and/or Cry2Ab2. The study, along with the previously reviewed interaction study between Cry1A.105 and Cry2Ab2, indicated that MON 89034 x MON 88017 corn should not result in any unexpected interaction with regards to target and non-target insects (BPPD, 2007f).

In addition to the submitted rationale for environmental benefits, Monsanto could have included reference to MON 89034 x MON 88017 use reducing the amount of

conventional pesticides applied in the environment and the subsequent environmental benefits. BPPD believes that cultivation of MON 89034 x MON 88017 corn may have fewer adverse impacts on non-target organisms than use of chemical pesticides for corn production, because under normal circumstances, MON 89034 x MON 88017 corn should require substantially fewer applications of chemical pesticides, compared to production of non-Bt corn. The reduction in conventional pesticide use should essentially be the same seen from MON 88017 and MON 863 use (BPPD, 2003). Fewer chemical insecticide applications generally result in increased populations of beneficial organisms that control secondary pests, such as aphids and leafhoppers. Furthermore, all of the conventional pesticides used for CRW control or suppression cause significant adverse environmental effects under conditions of normal use (BPPD, 2003).

IV. Insect Resistance Management (IRM)

A. Monsanto's Summary (MRID 472797-01)

MON 89034 (mention of MON 89034 assumes the same conclusions for MON 89034 x MON 88017 also)

Monsanto establishes that MON 89034, which produces Cry1A.105 and Cry2Ab2 proteins, has two different modes of action against lepidopterans, particularly in the way the proteins bind to the midgut. Therefore, based on the distinct modes of action of the two proteins and reduced likelihood of insect resistance, Monsanto proposes that a reduced structured refuge is possible: 5% for the corn belt, down from 20% and 20% for cotton-growing regions, down from 50%.

B. BPPD's Response

MON 89034 (mention of MON 89034 assumes the same conclusions for MON 89034 x MON 88017 also)

BPPD agrees with Monsanto in that two modes of action are better than one for reducing the risk of insect resistance to MON 89034. However, due to uncertainties in the data submitted to support the MON 89034 IRM plan, a 5% refuge cannot be established until additional data can be submitted to support such a reduction. Instead, BPPD recommends that the separate refuge option include a 20% lepidopteran refuge (as has been required for other Bt products). A 20% refuge is likely to be supported for MON 89034 in cotton-growing regions of the southeastern U.S. where a 50% refuge has been previously required (BPPD, 2007b; BPPD, 2007h).

Overall, MON 89034 should present two immediate IRM benefits: i) dual (novel) modes of action for Bt corn and ii) reduced refuge in cotton regions (and the resulting economic benefits to growers). These benefits can likely be achieved without an unreasonable risk of resistance to Cry1A.105 and Cry2Ab2. Additional grower benefits may be realized in the long term, if a 5% refuge can be supported.

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Chemical: **Bacillus thuringiensis Cry2Ab2 protein and the genetic material necessary (vector PV-ZMIR245) for its production in corn**
Bacillus thuringiensis Cry1A.105 protein and genetic material necessary (vector PV-ZMIR245) for its production in corn
Bacillus thuringiensis Cry3Bb1 protein and the genetic material necessary (vector ZMIR39) for its production in corn

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