Registration Decision for Commercial Use Corn Products Containing the *DvSnf7* dsRNA Plant-Incorporated Protectant (Event MON 87411)

Approved by:

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1. Summary

This document announces that the U.S. Environmental Protection Agency (EPA) has completed its evaluation of new corn plant-incorporated protectant (PIP) products containing event MON 87411 and has concluded that they meet the regulatory and safety standards for conditional registration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). These products are the first commercial use of MON 87411; previously approved registrations were limited to breeding purposes (see "Background" below).

Monsanto Company (Monsanto) and Dow AgroSciences (Dow) submitted applications for separate FIFRA Sec. 3(c)(5) registrations for products containing MON 87411 in combination with other (previously-registered) PIPs derived from the bacterium *Bacillus thuringiensis* (trade name SmartStax PRO). The products include the following event combination: MON 89034 (Cry1A.105, Cry2Ab2) x TC1507 (Cry1F) x MON 87411 (DvSnf7 dsRNA, Cry3Bb1) x DAS-59122-7 (Cry34/35Ab1). Two types of commercial use products are being registered: one product contains 100% PIP seed (a separate non-PIP refuge must be planted for resistance management), while the second is a "refuge-in-the-bag" product in which 5% non-PIP seed is blended with 95% PIP seed in the bag units sold to growers.

MON 87411 expresses a double-stranded ribonucleic acid (dsRNA) transcript that targets the *DvSnf7* gene in western corn rootworm (*Diabrotica virgifera virgifera*). Once ingested by the insect and recognized by the insect's RNAi machinery, it down-regulates the targeted *DvSnf7* gene leading to the insect's death. In addition to *DvSnf7*, the event also encodes the Cry3Bb1 protein derived from the bacterium *Bacillus thuringiensis*, which also targets corn rootworm. The other Bt PIPs in the products target either corn rootworm (Cry34/35Ab1) or lepidopteran (Cry1A.105, Cry2Ab2, Cry1F) corn pests.

After reviewing submitted and publicly available data and information, EPA concludes that the *DvSnf7* dsRNA and Bt Cry3Bb1 protein expressed in MON 87411and the genetic material necessary for its production will not cause any unreasonable adverse effects to human health or the environment. A resistance management strategy for the trait has been submitted and will be implemented as terms of registration. The products are also expected to provide benefits to growers through improved control of corn rootworm. In addition, *DvSnf7* dsRNA will provide benefits for resistance management by providing another PIP mode-of-action for control of corn rootworm. Resistance has developed to several Bt PIP traits; the combination of *DvSnf7* dsRNA with existing Bt PIP traits will likely extend the durability of these products.

The EPA is registering four commercial use products containing event MON 87411 with a time limitation of 5 years. Additional protein expression and degradation data, as well as a resistance monitoring bioassay for DvSn7 dsRNA, will be required as conditions of registration. Therefore, the Agency is conditionally registering the commercial use products containing MON 87411 (SmartStax PRO) under FIFRA section 3(c)(7)(A).

2. Background

Regulatory Background

In March 2016, the U.S. Environmental Protection Agency (EPA) received registration applications from Monsanto Company (Monsanto) and Dow AgroSciences (Dow) for new plant-incorporated protectant (PIP) products containing event MON 87411. These products also contain PIP active ingredients derived from *Bacillus thuringiensis* (*Bt*) that have been previously registered by the EPA. The products being registered are described in Table 1 below.

The products listed in Table 1 are the first commercial use applications of MON 87411. Previously, the event was registered in "breeding only" products that are limited to seed development (see list in Table 2 below). As breeding registrations, these products were approved with acreage limitations and cannot be used for commercial seed. For the initial MON 87411 breeding product (EPA Reg. No. 524-618), a proposed decision was issued for public comment (U.S. EPA 2015a) prior to approval of the registration.

In addition to the MON 87411 event, the commercial use products have been combined with other Bt PIPs that confer resistance to coleopteran (corn rootworm) or lepidopteran corn pests. These traits include the following events: TC1507 (expresses *Bt* Cry1F protein), DAS 59122-7 (Cry34/35Ab1), and MON 89034 (Cry1A.105 and Cry2Ab2). Table 3 below provides additional details for these Bt traits, including the dates registered and links to documents for more information on EPA's risk assessments and regulatory decisions.

Table 1: Summary of Monsanto and Dow's applications for products containing MON 87411

Product Name	Applicant	Application Received	EPA File Symbol	Refuge Configuration
SmartStax PRO	Monsanto	3/1/2016	524-AGE	Block Refuge
SmartStax PRO RIB Complete	Monsanto	3/1/2016	524-AGR	Seed Blend
SmartStax PRO Enlist	Dow	3/15/2016	62719-TNA	Block Refuge
SmartStax PRO Enlist Refuge Advanced	Dow	3/15/2016	62719-TNT	Seed Blend

Table 2: Currently registered breeding products containing MON 87411

Product	Registrant	Date Registered	EPA File Symbol	Acreage (per year)	Expires
MON 87411	Monsanto	10/29/2015	524-618	15,000	10/31/2017
MON 87411 x DAS 59122-7	Monsanto	3/1/2017	524-633	5,000	3/1/2018
MON 89034 x MIR162 x MON 87411	Monsanto	3/1/2017	524-635	5,000	3/1/2018
MON 89034 × MON 87411 × DAS-59122-7	Dow	3/1/2017	62719-708	200	3/1/2018
MON 87411 × DAS-59122-7	Dow	3/1/2017	62719-709	750	3/1/2018
TC1507 × MON 87411 × DAS-59122-7	Dow	3/1/2017	62719-710	200	3/1/2018
MON 89034 x TC1507 x MON 87411	Dow	3/1/2017	62719-711	750	3/1/2018
MON 89034 × MON 87411	Dow	3/6/2017	62719-712	900	3/1/2018
MON 89034 × TC1507 × MON 87411 × DAS-59122-7	Dow	3/1/2017	62719-713	200	3/1/2018
TC1507 × MON 87411	Dow	3/1/2017	62719-714	750	3/1/2018

Table 3: Summary of the PIP Active Ingredients found in the MON 87411 Commercial Use Products

PIP (toxin)	Event	PC Code	Target Pests	Year Registered	Regulatory Document
Cry1F	TC1507	006481	Lepidoptera	2001	U.S. EPA 2010c
Cry34/35	59122-7	006490	Coleoptera	2005	U.S. EPA 2010d
Cry1A.105	MON 89034	006514	Lepidoptera	2008	U.S. EPA 2010e
Cry2Ab2	MON 89034	006515	Lepidoptera	2008	U.S EPA 2010e
Cry3Bb1	MON 87411	006580	Coleoptera	2015[1]	U.S. EPA 2015
DvSnf7 dsRNA	MON 87411	006566	Coleoptera	2015	U.S. EPA 2015

[1]Cry3Bb1 was previously registered as MON 863 corn in 2003 and MON 88017 in 2005.

Mode of Action

Event MON 87411 was produced by *Agrobacterium tumefaciens*-mediated transformation of corn tissue using the plant transformation vector PV-ZMIR10871. MON 87411 expresses the 5-enolpyruvylshikimate-3-phosphate synthase (CP4 EPSPS) protein, which confers tolerance to glyphosate, and the following pesticidal active ingredients:

(1) Double-stranded ribonucleic acid (dsRNA) transcript comprising a *DvSnf7* inverted repeat sequence from western corn rootworm (*Diabrotica virgifera virgifera*) and the genetic material necessary for its production (vector PV-ZMIR10871) in MON 87411 corn (*DvSnf7* dsRNA).

(2) *Bacillus thuringiensis* (*Bt*) Cry3Bb1 protein and the genetic material necessary for its production (vector PV-ZMIR10871) in MON 87411 corn (*Bt* Cry3Bb1 protein).[1]

These active ingredients control several coleopteran corn pests (i.e., corn rootworm complex) by two different modes of action, one well known (*Bt* Cry3Bb1 protein) and the other novel amongst pesticides (*DvSnf7* dsRNA). Additional Bt PIPs (Table 3) have been combined with Event MON 87411 to create the products intended for commercial use.

The mode of action for Bt PIPs has been well established. In general terms, when a susceptible insect larva ingests a *Bt* delta-endotoxin protein (e.g., Cry3Bb1), the protein acts on that pest by the Cry toxicity pathway (Knowles and Ellar, 1987; OECD, 2007):

(1) The insect's midgut solubilizes the protein, thereby releasing protoxins.
(2) The insect's proteases cleave these protoxins and release the active toxin.
(3) The active toxin binds to specific receptors on the insect's midgut epithelium.
(4) Toxin subunits form pore structures that inject into the insect's midgut membrane.
(5) Ions and water pass through the pores, resulting in swelling, cell rupture, and eventually the insect's death.

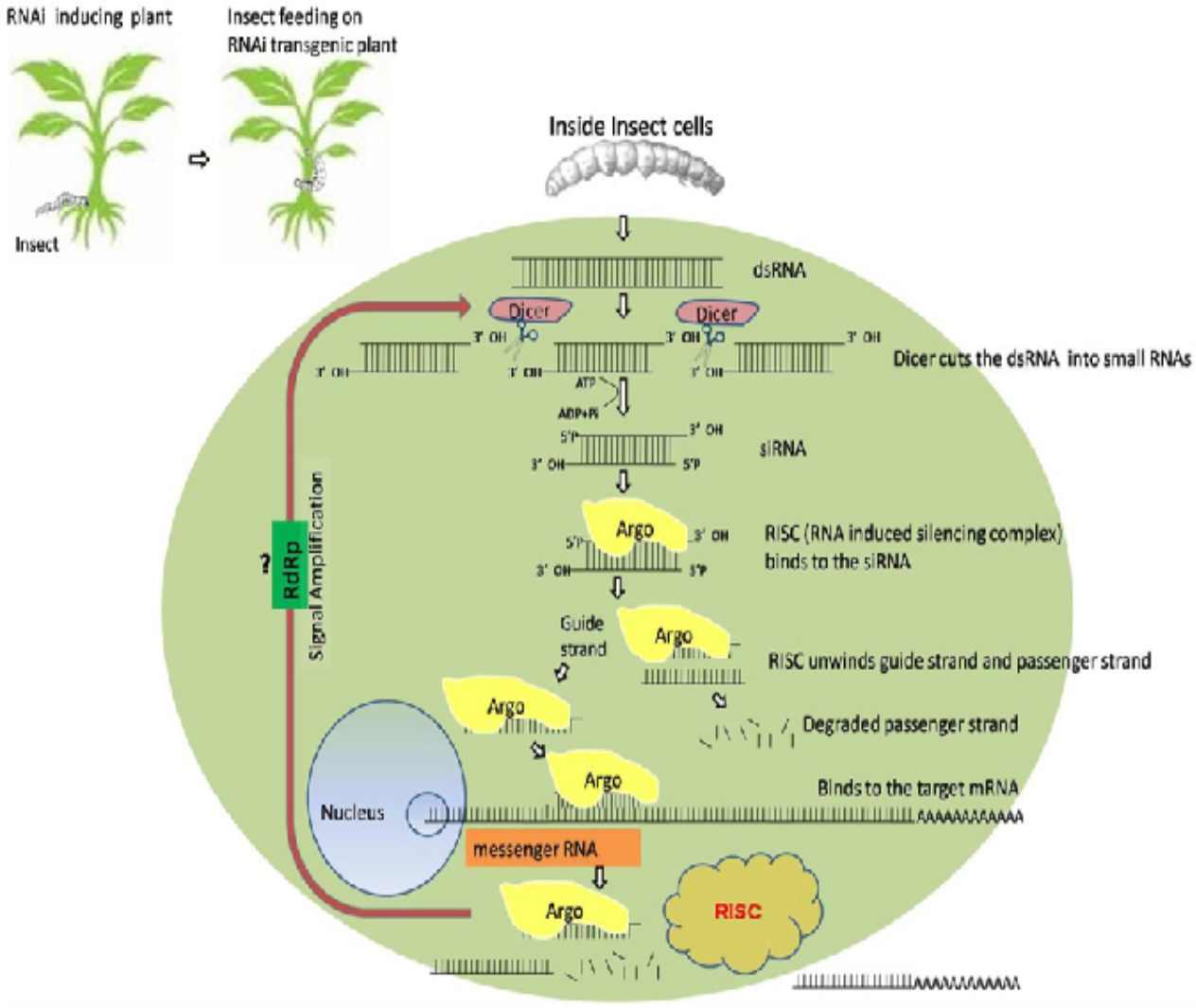
Bt corn PIPs, including those listed in Table 3, have been widely adopted to control insect pests. The EPA has an extensive amount of product characterization, toxicology, and ecological data and information on *Bt* proteins expressed by PIPs and completed a reassessment in 2010 for most of the currently registered corn PIPs (e.g., MON 88017 expressing the *Bt* Cry3Bb1 protein), concluding that these corn PIPs would not cause unreasonable adverse effects on the environment.[2]

DvSnf7 dsRNA presents a novel mode of action relative to the Bt PIPs. *DvSnf7* dsRNA is ingested by the insect and subsequently recognized by the insect's RNAi machinery, resulting in down-regulation of the targeted *DvSnf7* gene and leading to the insect's death. More specifically,

[1] Although the EPA registered PIPs expressing the *Bt* Cry3Bb1 protein in 2003 (MON 863 corn) and in 2005 (MON 88017 corn), the EPA considers this *Bt* Cry3Bb1 protein, consistent with past practice, to be a discrete active ingredient due to its origination from a different genetic event (MON 87411 corn).

[2] Search for "EPA-HQ-OPP-2010-0607" at http://www.regulations.gov to access the documents associated with the public process for the 2010 reassessment.

the RNAi pathway is initiated by cleavage of *DvSnf7* dsRNA into short interfering RNAs (siRNA) by the nuclease Dicer (Fire et al., 1998). The siRNAs then bind to a complex of proteins known as the RNA-induced silencing complex (RISC), and this leads to specific suppression of the target messenger RNA (mRNA). Since the mRNA encodes a protein with an essential function within the insect, in this case a vacuolar sorting protein belonging to the Endosomal Sorting Complex Required for Transport (ESCRT)-III complex, this suppression causes lethality. A diagram of this process generally, which is from Kola et al. (2015), follows immediately below.



Cleaves the target site and no more protein is synthesized. Larval growth and metabolism consequently arrest

(Kola VSR, Renuka P, Madhav MS, and Mangrauthia SK (2015) Front. Physiol. 6:119)

Although ribonucleic acid interference (RNAi) is the mechanism of action in other registered PIPs (i.e., New Leaf® Plus Potatoes and C5 Honeysweet Plum; see U.S. EPA (2000), U.S. EPA (2010b), and U.S. EPA (2013a)), the active ingredients in these PIPs involve a targeted dsRNA with specificity for a viral ribonucleic acid (RNA) encoding of either a replicase enzyme or a

coat protein. *DvSnf7* dsRNA is the first registered RNAi PIP that controls a macro-organism such as corn rootworm.

FIFRA Scientific Advisory Panel (SAP) Meetings

The EPA has held two FIFRA Scientific Advisory Panel (SAP) meetings that were germane to the Agency's review of MON 87411. The first meeting was not specific to MON 87411, but was convened to provide general guidance on risk assessments for RNAi-based pesticides. The second meeting was held to provide a peer review of the Agency's risk assessments for MON 87411's commercial use.

Due to uncertainties of dsRNA pesticide active ingredients identified in the literature and potentially associated with human and nontarget organism risks, the EPA first consulted with the SAP in 2014 for guidance in understanding and addressing these issues. Specifically, the Agency asked the panel to provide recommendations on problem formulation for human health and ecological risk assessment for RNAi-based pesticides. The meeting of the SAP was held January 28, 2014, with minutes published in May of that year (SAP 2014). This SAP consultation was held independently of any registration involving a dsRNA-based pesticide, including MON 87411.

The 2014 SAP generally agreed that the EPA's current risk assessment framework for pesticides would provide a good base of information, but recommended several additional considerations. For human health risk assessment, the panel recommended considering two questions:

- Is the dsRNA capable of overcoming natural defenses that could prevent entry into the human body?

- If so, would the dsRNA be able to find and trigger a reaction that interferes with cellular function?

For ecological risk assessment, the panel suggested addressing three pertinent questions:

- Where will the dsRNA be found in the environment and how long will it persist?

- Assuming environmental persistence, which non-target organisms will be exposed to it?

- Assuming exposure, will the dsRNA enter the organism, find a target gene, and cause interference with a key cellular process?

The panel proposed an exposure-based conceptual model for environmental risk assessment. This model includes six "steps" to characterize the dsRNA, identify potentially exposed non-target organisms, conduct model feeding studies to obtain toxicity endpoints, conduct cellular and molecular studies to characterize any effects, determine population level effects, and develop mitigation strategies if necessary.

Subsequent to the 2014 SAP meeting, Monsanto and Dow submitted applications for commercial use registrations of products containing MON 87411 (*DvSnf7* dsRNA). These applications were accompanied by data to address human health and environmental risks. In reviewing these data, the EPA applied the risk assessment framework recommended by the 2014 SAP. The Agency then convened a second SAP meeting in 2016 to provide peer review of the MON 87411 risk assessments. This meeting was held September 27-28, 2016 and the final report was issued on December 27, 2016 (SAP 2016).

A summary of the EPA's MON 87411 risk assessments as well as the Agency's responses to the 2016 SAP recommendations are described in the "Evaluation" portion of this document.

3. Evaluation

In evaluating a pesticide registration application, the EPA assesses a wide variety of studies to determine the likelihood of adverse effects (i.e., risk) from exposures associated with the proposed use of the product. Risk assessments are developed to evaluate how the compound might affect a wide range of nontarget organisms, including humans and terrestrial and aquatic wildlife (plants and animals).

Based on these assessments, the EPA evaluates and approves language for each pesticide label to ensure the directions for use and safety measures are appropriate to mitigate any potential risk. In this way, the pesticide's label helps to communicate essential limitations and mitigations that are necessary for public safety. In fact, the pesticide law has a provision that indicates it is a violation to use a pesticide in a way that conflicts with the label.

3.1 Assessment of Risk to Human Health

In order to assess a PIP's risk to human health, the EPA requires allergenicity and toxicity data/information, generally consisting of amino acid sequence homology comparisons to known allergens and toxins, heat stability testing, an acute oral toxicity test at maximum hazard dose, and an *in vitro* digestion assay in a simulated gastric environment. As purified test substance is used in the acute oral toxicity test and the purified test substance often needs to be produced in an alternate production system (e.g., within a yeast or bacterium) to obtain enough for testing, the EPA also requires that the microbially produced and plant-produced substances be shown to have similar biochemical characteristics and bioactivity. On a case-by-case basis, the EPA may require data other than what is described in this document in order to be able to fully evaluate a PIP in accordance with our safety standards.

As described in the Background section of this document, the EPA has held two FIFRA SAP meetings that were germane to the Agency's review of MON 87411. Guidance from the SAP meetings was used to develop data requirements to inform the risk assessments for *DvSnf7* dsRNA (see U.S. EPA 2016b and 2017a). For *DvSnf7* dsRNA and Bt Cry3Bb1 protein expressed in the commercial use registrations of MON 87411, the database of studies required to support the assessment of risk to human health is complete.

The EPA conducted three (3) human health risk assessment reviews for *DvSnf7* dsRNA (MON 87411). These assessments, which are summarized below, are available in the regulatory docket for MON 87411 (EPA-HQ-OPP-2014-0293 at *http://www.regulations.gov*):

1. U.S. EPA. 2015c. Review of Product Characterization and toxicity data in support for a seed increase Sec. 3 Registration of Plant-Incorporated Protectant (PIP) MON 87411 corn. Memorandum from J. Facey through J. Kough and C. Wozniak to J. Kausch, dated August 10, 2015.

2. U.S. EPA. 2016b. Human Health Risk Assessment: Review of Product Characterization and Protein Expression Analysis Data in support for a Sec. 3 Registration of Combination Plant-Incorporated Protectant (PIP): MON 89034 x TC1507 x MON 87411 x DAS-59122-7 20% structured refuge product [EPA Reg. No. 524-AGE] and MON 89034 x TC1507 x MON 87411 x DAS-59122-7 95/5% Seed Blend [EPA Reg. No. 524-AGR]. Memorandum from J. Facey through J. Kough and C. Wozniak to J. Kausch and A. Reynolds, dated August 16, 2016.

3. U.S. EPA. 2017a. Amendment to the Human Health Risk Assessment: Review of Product Characterization and Protein Expression Analysis Data in support for a Sec. 3 Registration of Combination Plant- Incorporated Protectant (PIP): MON 89034 x TC1507 x MON 87411 x DAS-59122-7 20% structured refuge product [EPA Reg. No. 524-AGE] and MON 89034 x TC1507 x MON 87411 x DAS-59122-7 95/5% Seed Blend [EPA Reg. No. 524-AGR]. Memorandum from J. Facey through J. Kough and C. Wozniak to A. Reynolds, dated April 20, 2017.

A. Risk to Humans from the *Bt* Cry3Bb1Protein Expressed in SmartStax PRO

The data submitted and reviewed for the *Bt* Cry3Bb1 protein as expressed in MON 87411 justify bridging the existing findings and conclusions from the human health assessments conducted for MON 88017 (EPA Reg. No. 524-551; see U.S. EPA (2010a)) and support its inclusion in the existing tolerance exemption (40 CFR § 174.518).

The EPA concludes that there are no unreasonable adverse effects and there is a reasonable certainty that no harm will result from aggregate exposure to the U.S. population, including infants and children, to the *Bt* Cry3Bb1 protein and the genetic material necessary for its production in MON 87411. This includes all anticipated dietary exposures as a result of the registration and all other exposures for which there is reliable information. The EPA has arrived at this conclusion because no toxicity to mammals has been observed, and there is no indication of allergenicity potential for the PIP from available information.

B. Risk to Humans from *DvSnf7* dsRNA Expressed in MON 87411

A tolerance exemption currently exists for plant-incorporated protectant nucleic acids (40 CFR 174.507). Given this tolerance exemption and the lack of mammalian toxicity reported for *DvSnf7* dsRNA, a dietary risk assessment would not normally be considered necessary to affirm safety. However, in order to provide additional assurances that no harm will result from exposure

to *DvSnf7* dsRNA, EPA has conducted a dietary risk assessment for DvSnf7 RNA (U.S. EPA 2016b).

1. Structure of *DvSnf7* dsRNA (e.g., hairpins, super coil)

In MON 87411, the predominant RNA transcript produced from the suppression cassette is identified as being 968 nucleotides (nt) in length. The *DvSnf7* suppression cassette contains two *DvSnf7* sequences (240 nt each) in an inverted orientation separated by 150 nt of intervening sequence. When the suppression cassette is transcribed, the expressed RNA forms a hairpin loop consisting of the 240 base pair *DvSnf7* dsRNA with a 150 nt loop region (Urquhart *et al*., 2013). The single hairpin structure of the dsRNA for *DvSnf7* is one of the simpler structures expected for RNAi inducing molecules. EPA does not expect this structure to present any unique stability to RNA degrading enzymatic attack.

The *DvSnf7* dsRNA expressed in MON 87411 is a native RNA sequence, having no synthetic modifications altering its stability. As indicated in the 2014 SAP panel report (SAP 2014), "The combination of RNases and acids found in the human digestive system are likely to ensure that all forms of RNA structure are degraded throughout the digestive process." Furthermore, the panel report discusses susceptibility of plant and animal RNA samples to RNases and concludes that such evidence "supports the likelihood that PIP and non-PIP RNAs expressed in plant material consumed by humans are likely to be degraded no matter the type of RNA or its structural status when entering the human digestive system." Therefore, there are no potential hazards indicated by the structure of the *DvSnf7* dsRNA expressed in MON 87411.

2. Stability of *DvSnf7* dsRNA in Animal Blood

The 2014 SAP report described concerns relating to the stability of *DvSnf7* dsRNA in animal blood. Extensive physical and biochemical barriers present a significant challenge to oral delivery of nucleic acids (Lawrence 2014) and these barriers would preclude *DvSnf7* dsRNA absorption and also stability in animal blood. These biological barriers include nucleases in the saliva and gastrointestinal tract, acidic conditions in the stomach, and multiple membrane barriers, which collectively limit the delivery of ingested RNA into the blood. In addition, lack of toxicity after repeat oral dosing of *DvSnf7* dsRNA (see below) indicate that *DvSnf7* dsRNA will not be stable in blood, and that there is a minimal potential for hazard to mammals even at high levels of exposure.

3. Mammalian Toxicity Assessment

To evaluate the potential hazard from pesticidal use, the Agency assessed the toxicological database for *DvSnf7* dsRNA. The toxicological database for *DvSnf7* dsRNA is considered adequate for risk assessment under the Food Quality Protection Act (FQPA). The route of administration for the toxicity studies is consistent with the potential exposure (oral/dietary) scenario. The available toxicity studies are described below.

a. Subchronic Toxicity Studies

In a 28-day oral toxicity study, DvSnf7_968 RNA was administered to 10 CD-1 mice/sex/dose by gavage at dose levels of 0 (vehicle control- nuclease free water), 1.06, 11.0, or 105 mg/kg bw/day. A group of 10 CD-1 mice/sex served as negative controls and received 104 mg/kg bw/day of Torula yeast RNA. The animals were examined for clinical signs, mortality, body weight, food consumption, clinical pathology, organ weights, and gross and histopathology examination. There were no treatment-related effects on clinical signs, mortality, body weight parameters, food consumption or gross and histologic pathology. The NOAEL is 105 mg/kg/day, max dose tested. The LOAEL was not established.

In a 90-day oral toxicity study, MON 87411 (Cry3Bb1 protein), a biotechnology-derived corn conferring resistance to corn rootworm and containing a modified *Bacillus thuringiensis* Cry3Bb1 protein, was administered to 16 Sprague Dawley rats/sex in the diet at 33% (w/w) (equivalent to 1899 and 2303 mg/kg cage body weight/day for males, and female, respectively). The mean *DvSnf7* expression value in grain was 0.091×10^{-3} µg/g fresh weight (SD= 0.028×10^{-3} µg/g). Control animals (16/sex) received conventional ground corn grain in the diet at 33% (w/w) (equivalent to 1924 and 2168 levels of mg/kg cage body weight/day for males, and female, respectively). Evaluated parameters included clinical signs, mortality, functional observation battery (FOB), body weight, food consumption, clinical pathology, organ weights, and gross and histopathology examination. There were no treatment-related effects on mortality, clinical signs, FOB, body weight, body weight gain, food consumption, food efficiency, clinical pathology, organ weights, gross pathology, or microscopic pathology. The LOAEL for MON 87411 is not established. The NOAEL is 1899 and 2303 mg/kg (grain) total cage body weight/day for males and females, respectively.

Collectively, the results from these two studies show the absence of any dietary hazard associated with *DvSnf7* dsRNA at very high doses. No acute effects were shown to be caused by MON 87411 even at relatively high dose levels, indicating that the *DvSnf7* dsRNA is not toxic.

In addition, direct intravenous (i.v.) injection of therapeutic siRNAs with 100% identity to the mouse ApoE gene did not produce gene silencing in the mouse liver (expected target site) at doses of 50 mg/kg, without a cholesterol tag to facilitate distribution, thus showing that presence in blood does not necessarily indicate a potential for gene silencing or toxicity (Soutschek et al., 2004). Thompson and colleagues reported that at i.v. doses of up to 200 mg/kg in rats, injection of stabilized siRNA matching rat p53, a key transcript, was readily degraded and was not toxic (Thompson et al., 2012). These doses are millions of times higher than anticipated human oral exposures to *DvSnf7* dsRNA. A similar lack of toxicity or efficacy in mice was noted for orally administered siRNAs and a long dsRNA with 100% sequence identity to mouse vacuolar ATPase at doses of up to 48 mg/kg and 64 mg/kg, respectively, doses millions of times higher than anticipated dietary exposures to *DvSnf7* dsRNA (Petrick et al., 2015).

b. Uptake of *DvSnf7* dsRNA in Humans with Altered Absorption or Digestion

The 2014 SAP recommended that the EPA address the uptake of *DvSnf7* dsRNA in individuals with altered absorption or digestion. The extensive physical and biochemical barriers described

previously (Lawrence 2014) and reviewed by Petrick et al. (2013) are multifaceted, consisting of pH, nucleases, and many membrane barriers (e.g. into GI cells, across GI cell to endothelium, across endothelium to blood, across endothelium to tissue, across tissue membrane, etc.). Thus, no single barrier is responsible for limiting functional uptake of exogenous dsRNA from the diet. Functional uptake implies ability not to reach the blood, but to reach a target tissue at a sufficient concentration to mediate the RNAi process. Although there are individuals that may have higher intestinal pH or more permeable GI epithelium, there are still a multitude of other barriers that would preclude functional uptake of ingested RNAs.

In addition, pharmaceutical studies demonstrate a very short half-life for injected RNAs that have been chemically stabilized (Christensen et al., 2013), implying that absorption from the GI tract and digestive barriers are not the only critical barriers to potential activity of ingested RNAs. Injection of a stabilized but unformulated RNA targeting a mouse gene did not demonstrate biodistribution to or gene suppression in the liver or jejunum, despite an i.v. dose of 50 mg/kg (Soutschek et al., 2004), indicating that barriers outside the GI tract are sufficient to preclude activity of exogenous naked nucleic acids.

Furthermore, the most robust studies examining the potential for cross kingdom gene regulation in mammals via ingested RNAs have concluded that it is neither a potent nor specific pathway for initiating RNAi. Snow and colleagues from Harvard University have demonstrated that the level of plant miRNA uptake in humans is negligible (Snow *et al*., 2013). This negligible level of plant miRNA uptake from the diet was also demonstrated in primates by Witwer et al. (2013) and in mice by several independent groups using different dietary sources (Baier et al., 2014; Dickinson et al., 2013; Snow et al., 2013).

Lastly, susceptible individuals are accounted for by utilizing standard safety factors that are incorporated into risk assessments conducted by the Agency. Given the above information and the safety profile identified for *DvSnf7* dsRNA in the 28-day and 90- day oral repeat dose rat toxicology studies at limit doses of 105 mg/kg/day *DvSnf7* dsRNA and 1899 [M]/ 2303 [F] mg/kg/day MON 87411 corn grain, respectively, along with the chronic dietary exposure (food only) estimate that is well below the EPA's level of concern for the general U.S. population and all population subgroups (DEEM model results – see below), the weight of the evidence supports the conclusion that any humans with digestive deficiencies are not at risk from exposure to *DvSnf7* dsRNA in MON 87411.

c. Potential Exposure and Safety of *DvSnf7* dsRNA from the Consumption of Food Derived from MON 87411

A chronic (food only) dietary assessment was conducted assuming average residue for corn and that 100% crop (corn) treated (CT). An acute assessment was not conducted based on the absence of an appropriate endpoint attributable to a single dose. The analysis was performed using the Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 4.02. This software uses 2005-2010 food consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA). The DEEM-FCID is a dietary exposure model that is used to estimate exposure to pesticides in foods in the diets of the U.S. population. The chronic analysis

of DEEM-FCID can be used to estimate total exposure for the both the U.S. population as a whole and subgroups of the population.

The input estimates were robust, as an uncertainty factor of 1000X, a NOAEL of 105 mg/kg day *DvSnf7* dsRNA (28-day oral toxicity study) and 1899 mg/kg/day MON 87411 corn grain (90-day oral toxicity study) and an average DvSnf7 RNA residue (protein expression) of 0.0009 µg/g fresh weight were used. The uncertainty factor of 1000X is composed of 10X for extrapolation from animal to human (interspecies); 10X for the potential variation in sensitivity among members of the human population (intraspecies); and 10X FQPA safety factor (the FQPA factor was retained though the repeat dose oral studies indicate no adverse effects from exposure to MON 87411). This assessment assumed no loss of RNA content or degradation during the high temperature treatments, hydrolyses, soaking in slightly acidic water, or drying employed during maize processing (Hammond and Jez, 2011), nor any potential impact of cooking on the DvSnf7 RNA. The results of the chronic dietary (food only) risk estimates were below EPA's level of concern (i.e. <100% cPAD) for the general U.S. population and all population subgroups (cPAD 0.0%).

4. Bioinformatics

In order to demonstrate the safe consumption of small RNAs (encoded by longer dsRNAs and processed into small RNAs) with 100% identity to human transcripts, the presence of such small RNAs in corn grain was analyzed by Monsanto using a bioinformatics analysis comparing endogenous corn grain small RNAs to the human transcriptome. A total of 386,557 small RNA sequence reads (includes sequences 21-26 nucleotides in length) were obtained from the corn grain small RNA libraries and were used for subsequent analysis. This corn endogenous small RNA library was compared to a library of 98,650 human transcript sequences (transcriptome). The results of the analysis revealed that there are 150 endogenous corn grain small RNAs that have 100% sequence identity (21 out of 21 nucleotides or greater) to a total of 500 likely protein coding human transcripts. This bioinformatics dataset provides further support for the history of safe consumption of endogenous plant small RNAs (and their dsRNA precursors), including those with 100% sequence identity to human transcripts. These data illustrate the key functional role that barriers to exogenous RNA molecules (described above) play in higher organisms that regularly consume these dietary components in significant amounts; and the data demonstrate that matches between small RNAs in the diet and human transcripts do not constitute a safety concern.

A second bioinformatics analysis was conducted for all of the 21 base pair small RNAs encoded by the 240 bp dsRNA DvSnf7 sequence to evaluate whether there were any matches to human transcripts. This search, using the same algorithms and search criteria for endogenous corn small RNAs, did not produce any matches between *DvSnf7* dsRNA and human transcripts. The bioinformatics data set demonstrates that MON 87411 does not contribute any additional small RNAs to the diet that have identity to human transcripts. In addition, the new siRNAs from MON 87411 do not present the possibility of triggering RNAi in humans based on the sequence search.

5. Aggregate Exposure

In examining aggregate exposure, EPA considers available information concerning exposures from the pesticide residue in food and all other non- occupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

No occupational inhalation or dermal risks are anticipated from exposure from the proposed commercial use SmartStax PRO products that express *DvSnf7* dsRNA. Agricultural workers can be exposed to plant material due to inhalation of pollen and agricultural dusts. Corn pollen is not respirable, as it consists of spherical particles ranging in size from 90 to 100 µm (Goldstein et al., 2004), in contrast with respirable particles that are less than 10 µm. In the case of agricultural dusts derived from activities such as planting, cultivation, and harvest, these particles also tend to be non-respirable sizes (Goldstein et al., 2004). Exposure to RNA through agricultural dusts would also be limited as noncoding RNAs (*e.g.* dsRNAs, siRNAs) are located intracellularly. Large particles typically deposit in the upper airways, resulting in clearing and swallowing, leading to secondary oral exposure rather than deposition in the deep lung tissue. This information, taken together with extremely low expression of construct-derived RNA in plant tissues from MON 87411, indicates that there will be negligible inhalation exposures to these plant-derived RNAs. Based on significant barriers to oral uptake of RNA and lack of oral toxicity of *DvSnf7* dsRNA described previously, secondary oral exposure after breathing agricultural dusts and pollen containing construct-derived RNA from MON 87411 would not present a health hazard to agricultural workers.

As for agricultural exposure via the dermal route, clinical trials have been initiated with siRNA drugs delivered via the dermal route (Vaishnaw et al., 2010). However, the skin is generally impermeable to high molecular weight charged molecules such as RNA (Lewin et al., 2005) and these drug trials involve the use of specialized delivery agents to promote absorption (Geusens et al., 2009).

6. Overall Safety Conclusions

The EPA concludes that there are no unreasonable adverse effects and there is a reasonable certainty that no harm will result from aggregate exposure to the U.S. population, including infants and children, to *DvSnf7* dsRNA and the genetic material necessary for its production in the proposed commercial use product expressing MON 87411 (SmartStax PRO). This includes all anticipated dietary exposures as a result of the registration and all other exposures for which there is reliable information. The EPA has arrived at this conclusion because no toxicity to mammals has been observed and because of the lack of significant sequence homology between human transcripts and *DvSnf7* dsRNA.

The information presented demonstrates that there is a robust history of safe consumption of dsRNAs, including siRNAs and miRNAs from various dietary sources. Many of these sequences have exact matches to human transcripts. This safe consumption is due to multiple and redundant biological barriers that limit the uptake and distribution of ingested RNAs. The weight of the evidence from the peer reviewed scientific literature, including pharmaceutical research (*e.g.*

bioavailability, fate in blood, safety), empirical toxicology data on administered siRNAs and long dsRNAs in the literature (Petrick et al., 2015; Thompson et al., 2012), and from provided toxicology studies on DvSnf7 RNA and MON 87411 collectively show that ingested RNAs from MON 87411 do not present a food safety hazard to consumers. In addition, the results of the chronic dietary (food only) risk estimates are below EPA's level of concern (i.e. <100% cPAD) for the general U.S. population and all population subgroups (cPAD 0.0%).

C. Response to Issues Raised by the 2016 SAP

As described in the Background section, the EPA convened an SAP meeting in September, 2016 to provide guidance on the Agency's risk assessments for the proposed MON 87411 commercial use products. The panel report (SAP 2016) outlined two recommendations with respect to the human health risk assessment (U.S. EPA 2016b). The Agency's response to those recommendations is described below.

SAP Panel Recommendation #1: The Panel suggested "omics" studies (e.g., metabolomics, proteomics, genomics) be conducted in order to address unknown sequence signatures or secondary dsRNA as a result of introducing the intended RNA producing construct. In the laboratory, the synthesis of *in silico* dsRNA frequently produces unintended structures that can be observed in agarose gel electrophoretograms (SAP 2016, pg. 11). The Panel also recommended the use of *in vivo* studies and experimental evidence to be analyzed at all times in the overall assessment in order to validate the "omics" derived *in silico* results since *in silico* studies are not singularly conclusive (SAP 2016, pg. 12).

EPA Response: The Agency noted that the SAP concurred with the Agency's human health risk assessment and considered it robust and complete. The Agency also noted, that one Panel member disagreed with the suggestion in considering "omics" studies for risk assessment purposes in this effort. Ultimately, the Panel did not consider the use of "omics" techniques appropriate as a human health risk assessment approach for RNAi.

SAP Panel Recommendation #2: The SAP recommended assigning a no-observed-adverse-effect-level (NOAEL) of 1 and the lowest-observed-adverse-effect-level (LOAEL) as 10 for the 28-day rodent study or classifying the study as deficient. Citing errors within the study procedure cannot be the basis for allowing a study to be acceptable and to be utilized to establish the NOAEL.

EPA Response: The Agency disagrees with the SAP recommendation pertaining to assigning a LOAEL to the 28-day rodent study. The Agency points out that 2016 SAP report concluded that there is "no reliable evidence that exogenous dsRNAs are taken up from the gut". This supports the lack of impact to mammals in the repeat dose studies. In addition, the 28-day study was reviewed in detail at a meeting of the Office of Pesticide Program's Toxicology Science Advisory Committee (ToxSAC) on April 12th, 2017. The ToxSAC agreed with the Agency's conclusions that established a lack of LOAEL for the 28-day oral (gavage) toxicity study. The decisions were based on the following observations :

- There were no dose-response correlations for the observed effects (decrease ovary and

thyroid weight).
- There were no histopathological findings corresponding to the observed effects (decrease ovary and thyroid weight).
- Change within the variables ((vs) % change); the ovary weights in the test substance treated groups were comparable to the negative control group, thereby indicating that the observed differences between the test substance and control groups did not represent a change from the normal range expected for this parameter.
- The body of evidence in the literature indicate that exogenous dsRNA will not be taken up as intact molecules in mammals.

3.2 Assessment of Ecological Risk

To assess risk to the environment for PIPs, the EPA requires nontarget organism toxicity data/information, generally consisting of testing with birds; mammals; freshwater and marine/estuarine fish and invertebrates; nontarget insects, including honey bees; nontarget plants; and soil invertebrates. Other data are also considered regarding the environmental persistence of PIPs, as well as the potential for gene flow and development of weediness. On a case-by-case basis, the EPA may require data other than what is described in this document in order to be able to fully evaluate a PIP in accordance with our safety standards. Since DvSnf7 dsRNA is a new type of PIP, some additional information was required for the ecological risk assessment, as advised, in part, by the 2014 SAP.

As described in the Background section of this document, the EPA has held two FIFRA SAP meetings that were germane to the Agency's review of MON 87411. Guidance from the SAP meetings was used to develop data requirements to inform the risk assessments for *DvSnf7* dsRNA (see U.S. EPA 2016a and 2017b). For the SmartStax PRO commercial use products containing MON 87411 (*DvSnf7* dsRNA), the database of studies required to support the assessment of risk to the environment is complete.

The EPA has conducted three (3) ecological risk assessment reviews for *DvSnf7* dsRNA (MON 87411). These assessments, which are summarized below, are available in the regulatory docket for MON 87411 (EPA-HQ-OPP-2014-0293 at http://www.regulations.gov):

1. U.S. EPA. 2015b. Environmental Risk Assessment for a FIFRA Section 3 Limited Seed Increase Registration of DvSnf7 Double Stranded RNA (dsRNA) and Cry3Bb1 *Bacillus thuringiensis* Derived Insecticidal Protein as Expressed in MON 87411 Maize. Memorandum from S. Borges through C. Wozniak to J. Kausch., dated August 24, 2015.

2. U.S. EPA, 2016a. Environmental Risk Assessment for a FIFRA Section 3 Registration of MON 89034 x TC1507 x MON 87411 x DAS-59122-7 Combined Trait Maize Expressing Cry1A.105, Cry2Ab2, Cry1F, Cry3Bb1, Cry34/35Ab1 *Bacillus thuringiensis* Derived Insecticidal Protein, and DvSnf7 Double Stranded RNA (dsRNA). Memorandum from S. Borges to J. Kausch, dated August 16, 2016.

3. U.S. EPA. 2017b. Addendum to Environmental Risk Assessment for a FIFRA Section 3 Registration of MON 89034 x TC1507 x MON 87411 x DAS-59122-7 Combined Trait

Maize Expressing Cry1A.105, Cry2Ab2, Cry1F, Cry3Bb1, Cry34/35Ab1 *Bacillus thuringiensis* Derived Insecticidal Protein, and DvSnf7 Double Stranded RNA (dsRNA). Memorandum from S. Borges to A. Reynolds, dated May 3, 2017.

A. Environmental Fate of *DvSnf7* dsRNA Expressed in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 Corn

Expression

The expression of the *DvSnf7* dsRNA was measured in various plant organs and tissues collected from trials with MON 87411 and SmartStax PRO within the U.S. and Argentina. The EPA uses these data to determine environmental exposure and ensure that nontarget organism testing has been performed at levels high enough to account for all potential exposures. Based on the submitted expression data for SmartStax PRO corn exposure levels in nontarget organism testing were determined to be at least 10.4 times the highest mean expression level. Therefore, the EPA determined that the testing was sufficient to identify and characterize nontarget hazard. The SAP raised some concern that not all expression data had been made available to EPA. The EPA subsequently determined that this was not the case, as clarified by Monsanto in a meeting held May 4, 2017 (recorded in meeting minutes communicated May 8, 2017).

Terrestrial Fate

The primary source of exposure of terrestrial nontarget organisms to the *DvSnf7* dsRNA expressed in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn is expected to be the corn tissue, which is ultimately expected to be deposited on or in the soil in terrestrial environments. Therefore, degradation of the *DvSnf7* dsRNA in soil is important to determine the potential for its persistence. Results from a soil degradation study submitted by Monsanto indicated that most of the *DvSnf7* dsRNA degraded within approximately 2 days after application to soil, regardless of texture, pH, clay content and other soil differences. Based on the results of this study, *DvSnf7* dsRNA is unlikely to persist or accumulate in the environment.

Aquatic Fate

DvSnf7 is primarily expected to reach aquatic habitats through deposition of post-harvest plant debris by the action of wind and water. The EPA determined that dsRNA would have fate in aquatic environments similar to that of Cry proteins in that they would leach out of plant debris and break down rapidly in the water. Therefore, exposure through consumption of plant debris in the water was determined to be insignificant. Additionally, the rapid degradation of *DvSnf7* dsRNA in soil is expected to limit its presence in runoff. Monsanto submitted a study on persistence of *DvSnf7* dsRNA in water and sediment, which showed rapid degradation in all compartments (half-lives < 1 to < 3 days), with the exception of certain sediment samples in which *DvSnf7* dsRNA remained detectable for 14 (by bioassay) to >28 days (through molecular analyses). The latter samples consisted of sediment without overlaying water, and as Albright III et al. (2016) showed in a similar study, dsRNA does not readily partition to sediment in the presence of overlaying water. It is important to note in this case that bioassays are more reliable indicators of bioactivity, since molecular analyses may detect non-bioactive fragments. Thus,

while the *DvSnf7* dsRNA was detectable for some time by molecular analyses, it did not remain bioactive. Therefore, based on the available data, the EPA determined that, under realistic environmental conditions, *DvSnf7* dsRNA would degrade rapidly in aquatic systems. The 2016 SAP raised concerns with the persistence shown in the sediment samples described above, and suggested that *DvSnf7* dsRNA may persist longer. However, the additional data available in Albright III et al. (2016), submitted since the SAP, also supports the EPA's conclusions. Therefore, the SAP's comments on this issue do not change the EPA's conclusions that *DvSnf7* dsRNA will degrade rapidly in aquatic environments. However, in light of the SAP concerns about applying assumptions of Cry protein environmental fate to *DvSnf7* dsRNA, additional confirmatory data on degradation of *DvSnf7* dsRNA within plant tissues in aquatic environments will be required as a condition of the registration.

B. Risk to Nontarget Organisms from *DvSnf7* dsRNA Expressed in MON 87411

i. ***Birds and Mammals***

EPA reviewed two studies related to the toxicity of *DvSnf7* dsRNA to birds. These studies include a 6-week study of broiler chickens fed a diet containing 57% MON 87411 grain, and a 14-day dietary toxicity study with Northern bobwhite exposed at 1000 µg DvSnf7/kg diet. No adverse effects were observed in the birds in either study.

Bioinformatic analyses with red junglefowl/chicken, rock pigeon, and mallard indicated no exact 21 nt matches with the *DvSnf7* dsRNA sequence, providing an additional line of evidence toward expectation of no effects.

Data available for mammals includes the studies described above that support the human health risk assessment, which both indicated no adverse effects to mammals. As with birds, bioinformatic analyses provides an additional line of evidence that the target gene does not exist in several mammalian species. This analysis involved several mammalian species, including cattle, domestic dog, horse, house mouse, Norway rat, and pig, and no exact 21 nt matches were found with the *DvSnf7* dsRNA sequence.

In the human heath review for *DvSnf7* dsRNA for the seed increase registration and for the commercial use (U.S. EPA 2015c, 2016b), the EPA discussed physiological barriers that exist that minimize exposure of humans. Such barriers include nucleases in saliva and the digestive tract (Park et al. 2006, Stevens and Hume 1995), acidic gut environments (Akhtar 2009, Loretz et al. 2006, O'Neill et al. 2011), membrane barriers, and rapid elimination from the blood (see U.S. EPA 2016b and references therein). In fact, in the case of dsRNAs for therapeutic use, problems with delivery related to these barriers have been considered major obstacles in their development (Gavrilov and Saltzman 2012, Krieg 2011, Meade and Dowdy 2009). Birds, wild mammals, and other vertebrates would be expected to have similar barriers, and although there is likely some variation such that not all of them may be present, several of them would be. Therefore, even if high levels of *DvSnf7* dsRNA are consumed by birds and mammals, these barriers are expected to significantly limit uptake and the potential for effects.

Based on all of these lines of evidence, including the lack of effects observed in the available toxicity studies, bioinformatic analyses, and expected biological barriers to uptake, the EPA does not anticipate that the *DvSnf7* dsRNA as expressed in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn will result in adverse effects to birds and mammals.

ii. ***Freshwater Fish and Invertebrates***

Once in the water, preliminary data have shown that *DvSnf7* dsRNA will not persist. Based on a standard pond scenario, "worst-case" estimates of *DvSnf7* dsRNA concentration in water range from 0.0014 – 0.0087 ng DvSnf7/mL. These concentrations are far below the dietary LC_{50}s for target insects, which are presumed to be most sensitive, since they have the gene targeted by *DvSnf7* dsRNA. LC_{50}s for DvSnf7 in WCR and SCR were 1.2 ng/g diet and 4.4 ng/g diet, respectively (Bachman et al. 2013). NOEC values for less sensitive insects, some of which were closely related, ranged from 500 ng/g diet to 5000 ng/g diet. While toxicity values for insects are not normally compared to aquatic exposure estimates, these data show that *DvSnf7* dsRNA is highly specific for its targeted gene. Therefore, sensitivity in other organisms is expected to be lower. Since exposure values in water are two to three orders of magnitude below the LC_{50} for highly sensitive organisms, it can be concluded that adverse effects in less sensitive organisms are unlikely. A study in which channel catfish were fed a diet of 30% MON 87411 grain also showed no adverse effects at this exposure level. Additionally, the bioinformatic analysis indicated no 21 nt sequence matches with *DvSnf7* dsRNA for two fish (zebra fish and medaka) and two aquatic invertebrates (water flea and scud). Physiological barriers as described above are also likely present in freshwater fish, which would limit uptake and potential effects if exposure were to occur.

Based on the available information, adverse effects to freshwater fish and invertebrates are not expected to occur as a result of exposure to *DvSnf7* dsRNA as expressed in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn. As with birds and mammals, conclusions are drawn from expected low environmental exposure, specificity of the *DvSnf7* dsRNA for its target gene in the target pests, and the role of physiological barriers to uptake.

iii. ***Marine and Estuarine Fish and Invertebrates***

As described above, significant exposure to *DvSnf7* dsRNA is not expected in aquatic environments, this "worst case" estimate extends to marine and estuarine systems. Therefore, adverse effects are not anticipated for fish or invertebrates in these environments.

iv. ***Nontarget Plants***

Uptake and transport of dsRNA by plants has been documented (Hunter et al. 2012, Li et al. 2015); however, *DvSnf7* dsRNA is not expected to be present at high levels or to persist in soil such that significant uptake would occur. Therefore, adverse effects to plants are not anticipated.

v. ***Bees, Nontarget Insects and Other Invertebrates***

DvSnf7 dsRNA is only active within the Chrysomelidae Family of coleopterans Bachman et al. (2013); therefore, specificity of the intended effect of *DvSnf7* dsRNA is expected to be limited to its target species. The EPA also reviewed several nontarget invertebrate studies that were conducted on a wide range of species, including other coleopterans. Specifically, the species tested included lady beetle (*Coleomegilla maculata*) parasitic wasp (*Pediobus foveolatus*), insidious flower bug (*Orius insidiosus*), carabid beetle (*Poecilus chalcites*), green lacewing (*Chrysoperla carnea*), honey bee (*Apis mellifera*), earthworm (*Eisenia andrei*), and springtail (*Folsomia candida*). Each of these studies reported no adverse effects on survival, development, growth, and/or reproduction at test levels of ≥1000 ng DvSnf7/g diet, which represents an exposure level at least 10.3 times the expected maximum in the field. Combined, these studies provide strong evidence that adverse effects are unlikely in nontarget arthropods exposed at least 10 times the highest anticipated environmental exposure level.

While not specifically submitted to address nontarget organism risk, EPA also notes that synergism data (described below in Section III) included tests with Colorado potato beetle (*Leptinotarsa decemlineata*, CPB) and European corn borer (*Ostrinia nubilalis*, ECB). Neither of these indicated adverse effects that differed from expected values. In ECB, no additional effects resulted from exposure to the coleopteran active PIP pesticidal substances tested, including *DvSnf7* dsRNA.

Based on the specificity of the intended effect and the lack of adverse effects observed through testing with several nontarget arthropod species, the EPA concludes that adverse effects to nontarget insects and other terrestrial invertebrates are not expected to occur as a result of exposure to *DvSnf7* dsRNA as expressed in MON 89034 x TC1507 X MON 87411 x DAS-59122-7 corn. Honey bees and other pollinators are included in this conclusion, and the results of testing with both larvae and adult honey bees provide strong evidence in support of a conclusion that adverse effects are not anticipated. Additionally, Monsanto Company has provided results of bioinformatic analyses with both honey bee and bumble bee, neither of which identified exact 21 nt matches with *DvSnf7* dsRNA, which provides supplemental information to support this conclusion.

Regarding bioinformatic analyses as they relate to nontarget organisms, the EPA does not necessarily discount their applicability, particularly to nontarget invertebrates. As described above in section 3.1C, the EPA agrees with the SAP that such analyses are not relevant to human health risk assessment, since multiple physiological barriers will prevent uptake of the dsRNA. However, similar barriers may not exist in other nontarget organisms, such as invertebrates. Therefore, while these analyses are not necessarily predictive of effects, the EPA views them as supplemental information that provides an additional line of evidence to support nontarget risk conclusions.

vi. ***Off-Target and Other Unintended Effects of DvSnf7 dsRNA***

As discussed in the EPA's white paper presented to the SAP in 2014 (U.S. EPA 2013a), exposure to dsRNA may bring about unintended effects, such as immune stimulation, over-

saturation of RNAi machinery, and off-target effects. Of these, off-target effects are more likely to be of greater concern, particularly for nontarget invertebrates with potential for greater exposure. While nontarget organisms do not have the gene specifically targeted by the *DvSnf7* dsRNA, off-target effects have been an additional consideration in ecological risk assessment, since they may potentially result is unpredicted downregulation of genes within the nontarget organisms' genomes.

Without further in vitro testing to observe more directly the potential for off-target silencing, the EPA cannot discount the possibility that these effects occur with exposure to *DvSnf7* dsRNA. However, off-target and other unintended effects from dsRNA may result in a range of biological consequences, and may be more likely to be observed in nontarget organisms that are more closely related to the target pest. Therefore, the EPA required additional testing on reproductive effects of *DvSnf7* dsRNA in nontarget insects to provide data on additional endpoints for more closely related organisms. With the studies submitted, the nontarget data available for *DvSnf7* dsRNA includes testing across a wide range of taxa, with additional and more intensive focus on species most likely to be impacted (insects and other arthropods). Testing has also been performed at high concentrations, with continuous dietary exposure over many days and with study durations that are considered reasonably sufficient to allow observation of adverse effects. No adverse effects have been observed. Therefore, the EPA concludes that unintended effects, if they occur, are unlikely to be of biological significance for *DvSnf7* dsRNA as expressed in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn.

vii. ***Risk Assessment Conclusions for DvSnf7 dsRNA***

Based on the data presented and anticipated minimal exposure in certain environments, adverse effects to nontarget organisms are not expected as a result of *DvSnf7* dsRNA as expressed in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn. Data provided to the EPA show that the intended effect of downregulation of the *Snf7* gene is likely only to be observed in the target insect and very close relatives, and unintended effects of dsRNA, like those discussed at the 2014 SAP, if they occur, do not cause significant biological consequences, at exposure levels expected in the environment.

The 2014 SAP report outlined potential scenarios that could minimize concern for nontarget exposure and effects related to dsRNA PIPs, which included scenarios in which:

1. The dsRNA PIP is very specific without homology to any of the genomics entries in sequence databases
2. The dsRNA PIP is not modified and therefore likely to degrade rapidly in the environment
3. The dsRNA PIP is expressed at extremely low levels and is tissue specific in its site of production.

DvSnf7 dsRNA has been shown to be very specific in its intended effect in the target insect and very close relatives, and a search of a limited number of databases for nontarget organisms across a wide taxonomic range did not find exact matches of 21 nt or greater with any of the sequences searched. *DvSnf7* dsRNA is also not modified in such a way to be more stable in the

environment, and its hairpin structure is such that would not provide added environmental stability (e.g., as may be seen with dsRNA with multiple stem-and-loop structures). Degradation data presented also show that it degrades rapidly in soil, and data indicate that it will not persist in water. While it is not tissue specific, *DvSnf7* dsRNA also is expressed at extremely low levels. It does function as a pesticide at these levels; however, its expression is much reduced over the season and likely degrades further *in planta* at senescence (see Blank and McKeon 1991, Miller et al. 1999). Additionally, when it is released into the surrounding environment from plant tissues, its concentrations are expected to be very low. Therefore, based on these characteristics, and the data available that show minimal nontarget hazard, the EPA concludes that *DvSnf7* dsRNA meets these criteria (the only exception is that it is not tissue specific in its expression), and should be considered to have minimal risk to nontarget organisms and the environment.

C. Ecological Risk Assessment for Cry1A.105, Cry2Ab2, Cry1F, Cry3Bb1, and Cry34/35Ab1 as Expressed in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 Corn

The *Bacillus thuringiensis* derived Cry proteins in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 are expressed in other single- and combined-trait corn products, including SmartStax (MON 89034 x TC1507 x MON 88017 x DAS-59122-7; EPA Reg. No. 524-581), in which they are expressed together. The EPA has previously determined that these proteins do not present risks to nontarget organisms and the environment (see ecological assessments in U.S. EPA 2010a, c, d, e). Data developed on the individual proteins expressed in these events is being bridged to support the registration of MON 89034 x TC1507 x MON 87411 x DAS-59122-7.

In addition to assessing risks to nontarget organisms, interactions between the PIP pesticidal substances in the combined trait hybrid also must be assessed to support bridging to data developed on the individual PIPs. Data to evaluate the potential for synergism between the Cry1A.105, Cry2Ab2, Cry1F, Cry3Bb1, and Cry34/35Ab1 proteins and the *DvSnf7* dsRNA expressed in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn were submitted. The results of these studies confirmed that no interaction is expected between the PIP proteins in SmartStax PRO (MON 89034 x TC1507 x MON 87411 x DAS-59122-7).

D. Outcrossing and Development of Invasiveness

The EPA has previously determined that there is no significant risk of gene flow and introgression of any *Bt* endotoxin trait by wild or weedy relatives of corn in the U.S., its possessions or territories (see extensive discussion in U.S. EPA 2010a, c). Since these conclusions are based on the nature of pollination, survival of hybrid offspring, and development of invasiveness in corn and its relatives, these conclusions would apply to all of the Cry proteins and also *DvSnf7* dsRNA expressed in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn.

E. Endangered Species Conclusions

The EPA has determined that *DvSnf7* dsRNA as expressed in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn is unlikely to have adverse effects on nontarget organisms. Therefore, a "No Effect" determination was made for direct and indirect effects to all federally listed threatened and endangered ("listed") species and their designated critical habitats (U.S. EPA 2016a).

Because the Cry1A.105, Cry2Ab2, Cry1F, Cry3Bb1, and Cry34/35Ab1 proteins expressed in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn are selective for either coleopteran or lepidopteran species, any adverse effects to listed species other than insects within those taxonomic orders are unlikely. Therefore, a "No Effect" determination is made for direct and indirect effects to all other listed species and their designated habitats, and the endangered species assessment for MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn is thus focused on potential direct effects to listed coleopteran and lepidopteran species.

Exposure to coleopteran and lepidopteran species is expected to be limited to direct consumption of MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn, including incidental exposure to pollen that may be deposited within the margins around corn fields planted with MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn. Therefore, since most listed coleopteran and lepidopteran species are habitat specialists and do not utilize corn or corn fields as habitat, many can be eliminated from consideration because exposure is not anticipated to occur.

The EPA's most recent assessment of the potential risks to listed threatened or endangered coleopteran and lepidopteran species was addressed in relation to the most recent new PIP (other than *DvSnf7* dsRNA) registered in corn (U.S. EPA 2012). Updates have been completed for registrations of new PIP combinations in corn, but have largely remained unchanged. The EPA most recently updated the assessment for coleopteran species for the MON 87411 seed increase registration (U.S. EPA 2015b). Thus far, the EPA has made "No Effect" determinations for direct and indirect effects to listed coleopterans and lepidopterans and their designated critical habitats for Cry proteins expressed in corn. Conclusions drawn in those assessments would also apply to the assessment for MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn. Since these assessments, additional lepidopteran and coleopteran species have been added for consideration, and further analysis determined that these additional species are not present on the corn field and would not be exposed. Therefore, based on the approach used in previous risk assessments, the EPA also makes "no effect" determinations for direct and indirect effects to listed species and their designated critical habitats.

F. Risk Assessment Addendum – Response to 2016 SAP

The 2016 SAP generally concluded that the data reviewed to support the ecological risk assessment for *DvSnf7* dsRNA expressed by event MON 87411 in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 combined trait corn were adequate. The SAP indicated some specific concerns; however, none of the issues raised by the SAP changes the EPA's initial risk assessment conclusions for DvSnf7 expressed in alone or in combination with Cry1A.105, Cry2Ab2, Cry1F, Cry3Bb1, and Cry34/35Ab1 proteins in MON 89034 x TC1507 x MON 87411

x DAS-59122-7 corn. Therefore, the EPA's previous conclusions that *DvSnf7* dsRNA is not expected to cause adverse effects to nontarget organisms are still applicable, including conclusions for listed species. The EPA also updated the listed species assessment for Cry proteins expressed in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 combined trait corn, and made "no effect" determinations for all listed species and concluded no modification to any designated critical habitats.

To address uncertainties raised by the SAP, additional data will be required to confirm environmental fate assumptions used in the risk assessment. These data include:

1) *DvSnf7* dsRNA concentrations in soils collected during the growing season and after harvest from fields planted with MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn; these data would provide in situ concentrations of *DvSnf7* dsRNA, the lack of which the SAP indicated was an uncertainty;
2) Data showing degradation of *DvSnf7* dsRNA in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn plant tissue in aquatic environments; these data would address uncertainties regarding environmental fate of *DvSnf7* dsRNA in corn plant debris deposited in aquatic environments.

3.3 Resistance Management

In support of their applications for commercial registrations of PIP products containing MON 87411 (*DvSnf7* dsRNA), Monsanto submitted an Insect Resistance Management (IRM) strategy (Dow also cited this submission in their applications). Though the commercial products contain PIP traits active against both corn rootworm and lepidopteran corn pests, the submitted IRM strategy focused primarily on corn rootworm. An existing IRM paradigm is in place for Bt PIPs targeting lepidoptera; this strategy will also be applied to the commercial use MON 87411 products (SmartStax PRO).

Submitted IRM data for MON 87411 included efficacy and dose studies, an analysis of cross resistance between *DvSnf7* dsRNA and Bt PIPs, a discussion of potential resistance mechanisms to *DvSnf7* dsRNA, and simulation modeling to assess the risk of resistance.

Data provided by Monsanto demonstrated that *DvSnf7* dsRNA is a novel mode of action with high efficacy against corn rootworm (CRW) larvae. The trait is expected to function as an independent mode of action in a pyramid with two Bt traits, Cry3Bb1 and Cry34/35, that also provide activity against CRW. Simulation modeling shows that the durability of SmartStax PRO with *DvSnf7* dsRNA is greater than previously-registered SmartStax products containing only Cry3Bb1 and Cry34/35, even under improbable "worst case" scenarios.

DvSnf7 dsRNA is unlikely to have a high risk of cross resistance with Bt PIPs, including Cry3Bb1 and Cry34/35. It is doubtful that a single physiological mutation would confer resistance to both *DvSnf7* dsRNA and Bt toxins, since the two types of PIPs target much different processes within the insect. However, some of the results from Monsanto's efficacy testing showed that Cry3Bb1-resistant CRW were able to survive exposure to DvSnf7 at slightly higher levels than Cry3Bb-susceptible CRW. Since the magnitude of survival was slight and

statistically relevant only in a few cases, the results were not emphasized in Monsanto's submission. While BPPD expects that there may be explanations other than cross resistance for the results, the development of a *DvSnf7*-resistant colony could help confirm that lack of cross resistance potential.

Although *DvSnf7* dsRNA will increase the overall durability of SmartStax PRO, there is still scientific uncertainty with respect to the risk of resistance for the trait. Several potential mechanisms of resistance to RNAi-based pesticides have been proposed, but it is unclear specifically how (or if) CRW larvae may adapt to *DvSnf7*. The EPA notes that a small portion of CRW larvae developed to adulthood in efficacy testing; however, it is unknown if these insects were resistant to *DvSnf7*, avoided exposure to the PIP, or had other means to develop. To better understand potential resistance to *DvSnf7*, the EPA recommends that Monsanto attempt to develop a resistant CRW colony. Such a colony would also be useful for resistance monitoring and investigating cross resistance with other PIPs.

Monsanto and Dow have proposed to apply the existing IRM programs for lepidopteran and CRW pests to the SmartStax PRO products. The EPA concludes that, as a three trait pyramid with expected high durability, SmartStax PRO is compatible with current refuge, resistance monitoring, and remedial action strategies. The current structured refuge strategies for pyramided Bt corn are a 5% refuge in the Corn Belt and a 20% refuge in cotton-growing regions. Seed blends must include 5% non-Bt corn and when planted in cotton growing regions, must be accompanied by a 20% structured refuge. In addition, the new IRM framework for CRW will be applied to the SmartStax PRO products (see https://www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/framework-delay-corn-rootworm-resistance).

As a condition of registration, Dow and Monsanto must develop and submit a resistance detection assay for *DvSnf7* dsRNA that meets EPA's criteria (see EPA 2016d). Other aspects of resistance monitoring for *DvSnf7*, including unexpected damage investigations and resistance mitigation, are addressed by the new CRW resistance monitoring framework that will be applied to the terms of registration.

The EPA's IRM assessment for MON 87411 and SmartStax PRO (U.S. EPA 2016c) can be found in the regulatory docket for MON 87411 (EPA-HQ-OPP-2014-0293 at *http://www.regulations.gov*).

4. Alternatives

Corn rootworm is managed in the U.S. with PIPs, conventional pesticides, and cultural controls.

As described in the Background section, PIPs derived from the bacterium *Bacillus thuringiensis* (Bt) have been registered for control of corn rootworm. To date, four Bt PIPs have been approved: Cry3Bb1, Cry34/35Ab1, mCry3A, and eCry3.1Ab. These PIPs have been combined together in "pyramids" to provide better control and lower the risk of resistance. Growers have widely adopted Bt PIPs in the U.S. for control of corn rootworm. From 2011 to 2013 an annual average of 94.6 million acres of corn were grown in the U.S. Of these, approximately 50 million

acres were planted with rootworm-protected Bt PIPs (acreage figures are annual averages based on 2011-13 proprietary survey data).

Conventional pesticide use has targeted both the larval and adult life stages. Larvicides for corn rootworm primarily include seed treatments and soil insecticides applied at the time of planting. Commonly-used seed treatments, which may also target other corn pests such as wireworms, include clothianidin (trade names Acceleron and Poncho) and thiamethoxam (Cruiser). Soil-applied insecticides are largely synthetic pyrethroids or organophosphates, and include the following examples (not all registered active ingredients/products are listed):

- Bifenthrin (Bifenture, Brigade, Capture, Discipline, Fanfare, Sniper)
- Tefluthrin (Force)
- Lambda-cyhalothrin (Grizzly, Kaiso, Lambda-T)
- Tebupirimphos & cyfluthrin (Aztec, Defcon)
- Terbufos (Counter)
- Chlorpyrifos (Govern, Hatchet, Lorsban, Pilot, Saurus, Warhawk, Whirlwind)
- Chlorethoxyfos (Fortress)
- Ethoprop (Mocap)
- Phorate
- Fipronil (Regent)

Adulticides are typically used as rescue treatments when large number of beetles are present. Many registered products are synthetic pyrethroids, though other classes of chemicals such as organophosphates and carbamates have also been used for adult control. The following list provides examples of approved adulticides for rootworm:

- Bifenthrin (Bifenture, Brigade, Capture, Discipline, Fanfare, Sniper)
- Cyfluthrin (Baythroid, Tombstone)
- Deltamethrin (Battalion, Delta Gold)
- Esfenvalerate (Adjourn, Asana)
- Lambda-cyhalothrin (Grizzly, Kaiso, Lambda-T, LambdaStar, Mystic, Silencer, Taiga, Warrior)
- Gamma-cyhalothrin (Cobalt, Proaxis, Prolex)
- Permethrin (Ambush, Artic, PermaStar, Perm-UP, Pounce)
- Zeta-cypermethrin (Hero, Mustang, Respect)
- Chlorpyrifos (Govern, Hatchet, Lorsban, Nufos, Pilot, Warhawk, Whirlwind, Yuma)
- Dimethoate
- Malathion
- Carbaryl (Sevin)
- Methomyl (Lannate)
- Spinosad & gamma-cyhalothrin (Consero)

Cultural control for corn rootworm has involved the use of crop rotation to non-rootworm host, primarily soybean in the Corn Belt. Integrated Pest Management (IPM) practices are also employed, including scouting and economic thresholds. Under the EPA's new resistance

management framework for rootworm (see U.S. EPA 2016d), Bt PIP registrants are required to work with growers to encourage IPM practices to preserve trait durability.

5. Benefits and Public Comments

Benefits

Biopesticides are pesticides derived from such natural materials as animals, plants, bacteria, and certain minerals. PIPs, a class of biopesticides, are pesticidal substances that plants produce from genetic material that has been added to the plant and may have the following benefits:

- Usually are inherently less harmful than conventional pesticides.
- Generally affect only the target pest and closely related organisms, in contrast to broad-spectrum conventional pesticides that may affect many different organisms (e.g., birds, insects, and mammals).
- Often effective in very small quantities and often decompose quickly, thereby resulting in lower exposures and largely avoiding the pollution problems caused by conventional pesticides.
- Can greatly decrease the use of conventional pesticides while crop yields remain high, when used as a component of integrated pest management programs.
- Can offer another tool for pest management in areas where environmental concerns limit the use of conventional pesticides.

The EPA previously assessed the benefits of corn rootworm PIPs like MON 87411 and more thoroughly described many of the benefits summarized in the bullets directly above and others, including durability extension[3] of PIP control measures for corn rootworm (U.S. EPA, 2010a, 2010d, and 2010e). Benefits for PIPs in general are also discussed in the public literature. For example, Klümper and Qaim (2014) carried out a meta-analysis of 147 studies that reported on the impact of genetically modified crops on yield, pesticide use, and/or farmer profits and found that, "[o]n average, [genetically modified] GM technology adoption has reduced chemical pesticide use by 37%, increased crop yields by 22%, and increased farmer profits by 68%." Additionally, Coupe and Capel (2015) describe a substantial reduction in the use of insecticides on corn from the introduction of GM plants in 1996 (8.5 million kilograms of pesticidal active ingredient used) until 2009 (1.8 million kilograms pesticidal active ingredient used), cautioning that some of this decrease could be attributed to other factors like regulatory restrictions on conventional pesticides and adjustments to farming practices.

The commercial use products containing MON 87411 are expected to provide benefits to growers by providing effective control of corn rootworm. Efficacy studies submitted by Monsanto demonstrated that MON 87411 combined with Bt PIPs in the commercial use products (MON 89034 x TC1507 x MON 87411 x DAS-59122-7) provides comparable or superior control to current products containing only Bt PIPs (data reviewed in U.S. EPA 2016c).

[3] See *http://www2.epa.gov/sap/meeting-materials-december-4-6-2013-scientific-advisory-panel* for more details on recent issues related to corn rootworm resistance and *Bt* corn PIPs.

In addition to the benefits described above, MON 87411 will likely provide benefits for insect resistance management (IRM). *DvSnf7* dsRNA provides a novel mode of action for corn rootworm and will be combined with existing Bt traits. Simulation modeling showed that the durability of *DvSnf7* dsRNA combined with existing Bt PIPs is greater than a combination of Bt PIPs alone (data reviewed in U.S. EPA 2016c). Further, resistance has developed to some of the currently-registered Bt PIPs (U.S. EPA 2013b, Gassmann et al. 2014). The use of MON 87411 may help manage such populations -- data submitted by Monsanto showed that MON 87411 effectively controlled corn rootworm with resistance to Cry3Bb1 (U.S. EPA 2016c).

Public Comment

Overall, the EPA has provided the public with three opportunities to comment on MON 87411 registration actions.

In the Federal Register of August 13, 2014 (79 FR 47453), the EPA announced receipt of an application to register a pesticide product containing the new active ingredients *DvSnf7* dsRNA and *Bt* Cry3Bb1 protein and opened a 30-day public comment period. The EPA received approximately 500 comments on this publication. Most of the comments were from private citizens through what appears to be a letter-writing campaign, while one was received from the Pollinator Stewardship Council. A summary of these comments, and the EPA's response to these comments is below.

Human Health-Related Comments

The comments were uniformly negative and against approving the action and ranged from people concerned about children with allergies to GM foods and an increase in children with "special needs" to an autistic child with Crohn's disease to a person with pancreatic cancer. These commenters also objected to the lack of food labeling for GM-containing food. Most of the commenters stated that "the incomplete understanding of this field has hampered their translation into successful therapeutic strategies, with many mammalian studies highlighting the potential lethality and/or toxicity of RNA-based treatments" but did not provide any scientific rationale or citations to justify the statement about adverse mammalian effects. The one article cited by the commenters was published by Monsanto scientists to describe the mode of action of *DvSnf7* dsRNA against the corn rootworm. This article contained no information about effects on mammalian species.

While the EPA is concerned about the safety of any pesticidal product presented for registration and performs a rigorous assessment of the data presented to justify its safety findings, including special consideration for children, it was unable to discern any new substantive information in these comments to add to its safety considerations.

Ecological-Related Comments

The comments were negative, with some comments simply opposed to the registration or genetically modified organisms in general. Most comments generally expressed concern for uncertainties related to this new technology and the need to gather additional information on nontarget effects and environmental fate. Several comments were focused more specifically on concern for honey bees and other pollinators. Most comments did not provide background to

support claims of potential effects. One comment was received from the Pollinator Stewardship Council (PSC), expressing concern for bees and other nontarget organisms and citing to both published and unpublished data.

Specifically, the PSC stated the following:

(1) Need more definitive assessment of the spectrum of activity.
(2) Need more comprehensive assessment of environmental fate of small RNAs.
(3) Risk needs to be explored under real scenarios.
(4) Data developed by pesticide companies is conflict of interest.

Regarding the concern for review of data developed by pesticide companies, the EPA directs commenters, including the PSC, to its website where this issue has been raised and addressed previously.[4]

Regarding the other concerns raised by the PSC, the EPA believes that it has evaluated data that addresses these concerns and that no additional substantive information was presented that requires consideration at this time. *DvSnf7* dsRNA's insecticidal effect appears to be highly specific as testing shows effects only to nontarget insects of the Galerucinae Subfamily of Family Chrysomelidae within Order Coleoptera (beetles). Further, multiple lines of evidence suggest a lack of adverse effects from *DvSnf7* dsRNA to pollinators like bees (i.e., larval and adult honey bee testing and bioinformatics with honey and bumble bees). Please see the "Nontarget Insects and Other Invertebrates" section in this document (on pages 9–10) and the environmental risk assessment in the regulatory docket for more details.

Other Comments

Most comments focused on human health- and/or ecological-related issues, but some focused on other topics, such as a dislike for corporations, claims that the EPA's decision-making process for pesticide registrations is unduly influenced by pesticide applicants/registrants, and reference to the regulatory processes in other countries where biotechnology is not accepted. Although the EPA appreciates the input and diverse perspectives of all of the commenters, these other comments did not provide any additional data or information that the EPA could analyze as part of its scientifically based and deliberate risk assessment and decision-making processes under FIFRA and FFDCA.

A second comment period was established for the registration of the MON 87411 breeding only registration (EPA Reg. No. 524-618). Since this registration involved two new active ingredients, *DvSnf7* dsRNA and the *Bt* Cry3Bb1 protein expressed by MON 87411, the EPA opened a 15-day public comment period in October 2015. This comment period was conducted in accordance with a policy, first implemented in October 2009, designed to provide a more meaningful opportunity for the public to participate in major registration actions. During the comment period, the EPA received 6 comments, one from an anonymous individual and the rest from private citizens representing the National Corn Growers Association, the University of

[4] See the following questions on the EPA's website: Why does EPA rely on studies submitted from pesticide companies when the Agency is considering whether or not to register a pesticide? Shouldn't the government be performing independent studies?

Texas at Tyler, the University of Massachusetts, the University of Manitoba, or Preclinsight. All of the comments were positive and indicated support for registration of *DvSnf7* dsRNA and the *Bt* Cry3Bb1 protein expressed by MON 87411.

Because the products being registered (Table 1) are the first commercial uses of MON 87411 for control of corn rootworm, the EPA established a third (15-day) public comment period in May 2017. This comment period was also conducted in accordance with the policy designed to provide a more meaningful opportunity for the public to participate in major registration actions. During the comment period, the EPA received 5 comments from private citizens representing the Information Technology and Innovation Foundation (ITIF), the Biotechnology Innovation Organization (BIO), the National Corn Growers Association (NCGA), the Iowa Corn Growers Association (ICGA), and the University of Georgia.

Two of the comments (NCGA, ICGA) supported registration of the MON 87411 commercial use products and indicated that MON 87411 will be an important tool for management of corn rootworm. The other three commenters encouraged approval of MON 87411, but objected to the conditions for additional data imposed on the registrations and/or the five-year registration period. Two commenters (ITIF, University of Georgia) argued that the additional data requirements are not supported by science or credible risk hypotheses. Three commenters (ITIF, University of Georgia, and BIO) urged the EPA to issue "normal product registrations" without the five-year conditional time frame. Although sufficient data were submitted to make a no unreasonable adverse effects determination for a conditional registration, the EPA determined that the additional studies are needed to complete the risk assessment databases for the products. The first two conditions (described in section 6 below) address scientific uncertainties regarding environmental fate of DvSnf7 dsRNA, which was a key issue highlighted by the 2016 FIFRA Scientific Advisory Panel (SAP). The scientific rationale addressing the need for these fate studies is discussed in section 3.2 of this document. The third condition requires a resistance detection assay for DvSnf7 dsRNA. As described in section 3.3, a resistance management strategy is necessary to mitigate potential resistance, one of the key risk concerns for PIPs. A resistance detection assay is a critical component of this strategy, and will serve as the primary means to monitor potential resistance among corn rootworm populations exposed to *DvSnf7* dsRNA. The five-year registration period will allow sufficient time for the registrants to generate the data and for the EPA to complete a review of the studies. In addition, a five-year registration is consistent with the time frames recently approved for other novel PIP registrations. Provided the conditions are sufficiently addressed, the EPA will consider extensions to the registrations beyond the initial five-year time frame.

6. Regulatory Decision

Section 3(c)(7)(A) of Federal Insecticide, Fungicide, and Rodenticide Act (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.

The Agency concludes that the MON 87411 commercial use products (Table 1) that are described in-depth throughout this document, meet both criteria (1) and (2).

These MON 87411 corn products are substantially similar in both composition and use (corn) to plant-incorporated protectants that are currently registered. Thus, criterion (1) has been fulfilled. With regard to criterion (2), the Agency maintains that cultivation of MON 87411-containing corn will not cause unreasonable adverse effects on the environment. Lastly, the use of these products will likely provide benefits as described in section 5 of this document.

Although data provided were satisfactory to make the determinations required by section 3(c)(7)(A) of FIFRA, they were not sufficient to support an unconditional registration under FIFRA section 3(c)(5). Additional data, specifically in relation to environmental fate and insect resistance management, are necessary for registration under FIFRA section 3(c)(5). As conditions of registration, the following additional confirmatory data will be required:

1) *DvSnf7* dsRNA concentrations in soils collected during the growing season and after harvest from fields planted with MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn; these data would provide in situ concentrations of *DvSnf7* dsRNA, the lack of which the SAP indicated was an uncertainty;
2) Data showing degradation of *DvSnf7* dsRNA in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn plant tissue in aquatic environments; these data would address uncertainties regarding environmental fate of *DvSnf7* dsRNA in corn plant debris deposited in aquatic environments;
3) A resistance monitoring bioassay for *DvSnf7* dsRNA that meets EPA's criteria (see EPA 2016d). As part of this effort, it is highly recommended that the registrants work to develop a *DvSnf7*-resistant colony to serve as a positive control in the bioassay.

In conclusion, since the proposed MON 87411 commercial use products have met the required criteria, the Agency is granting conditional registrations under FIFRA section 3(c)(7)(A). The registrations will be time-limited to 5 years.

The risk assessments supporting this decision can be found in the associated regulatory docket (search for "EPA-HQ-OPP-2014-0293" at *http://www.regulations.gov*).

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