AGENDA
U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA)
FIFRA SCIENTIFIC ADVISORY PANEL (SAP)
PUBLIC MEETING

September 27-28, 2016

FIFRA SAP WEB SITE http://www.epa.gov/scipoly/sap/
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EPA CONFERENCE CENTER LOBBY LEVEL ONE
POTOMAC YARD (SOUTH BLDG.)
2777 S. CRYSTAL DRIVE, ARLINGTON, VA 22202

Human Health and Ecological Risk Assessments for SmartStax PRO (MON 89034 x TC1507 x MON 87411 x DAS-59122-7), a Plant-incorporated Protectant Intended to Control Corn Rootworm through RNA Interference

Please note that all times are approximate (See Note at End of Agenda)

Day 1
Tuesday, September 27, 2016

9:00 A.M. **Opening of Meeting and Administrative Procedures** – Jim Downing, Designated Federal Official, Office of the Science Advisor/EPA

9:05 A.M. **Introduction and Identification of Panel Members** – James McManaman, Ph.D., FIFRA Scientific Advisory Panel Session Chair

9:10 A.M. **Welcome –** Jack Housenger Director, Office of Pesticide Programs/EPA

9:15 A.M. **Overview** – Robert McNally, Director, Biopesticides and Pollution Prevention Division (BPPD)/Office of Pesticide Programs/EPA

9:25 A.M. **Ecological Risk Assessment for *DvSnf7* dsRNA Expressed in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 –** Shannon Borges, M.S., BPPD/OPP/EPA

10:30 A.M. **Break**

10:45 A.M. **Human Health Risk Assessment for DvSnf7 dsRNA Expressed in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 –** Judy Facey, Ph.D., BPPD/OPP/EPA

11:50 A.M. **Lunch**

1:00 P.M. Public Comments

2:10 P.M. Charge to the Panel

Question 1. The 2014 SAP in general agreed that there were few issues with dietary exposure to dsRNA molecules in mammalian species but recommended several issues be examined to confirm these assumptions. These recommendations include: (1) confirm that special dsRNA forms (e.g., hairpins, super coils) may not degrade as quickly as simple dsRNA; (2) the blood of animals consuming food containing an RNAi-PIP should be examined for the presence of the dsRNA or pieces of dsRNA: (3) although bioinformatics would not give definitive answers, it can be predictive, and as such a useful tool, depending on the search methods and completeness of the database; and (4) consider the possibility that special subpopulations such as the elderly, children or people with gastrointestinal tract illnesses (e.g., Crohn's disease, colitis, or irritable bowel syndrome) may present a different pattern of uptake of dsRNA from the diet.

a. Please comment on the feasibility of creating and successfully deploying in plants, dsRNA structures likely to present greater stability (e.g., supercoil, viroid-like structures). Please comment on EPA's conclusion that the single hairpin structure of the dsRNA for DvSnf7 is one of the simpler structures expected for RNAi inducing molecules, and that this structure is unlikely to present any unique stability to RNA degrading enzymatic attack.

b. Recent evidence suggests that RNAs, including miRNAs, are normally present in blood and are transported to various target tissues and organs as part of normal homeostasis (Freedman et al., 2016). Please comment on this evidence. How might this evidence relate to the subchronic and 28-day studies data supplied in support of this registration that show no effects on whole animals of the DvSnf7 dsRNA. What additional support might confirmatory testing in mammalian blood provide to a risk assessment?

c. Assuming that the SAP continues to believe that bioinformatics can be a useful tool, can the Panel offer advice on what level of similarity might trigger a biologically significant effect? Please comment on what RNA properties, in addition to sequence identity match, (for example, sequence length, context, or biophysical properties) are relevant in assessing the potential for a dsRNA molecule to mediate gene suppression.

d. Please comment on EPA's analysis regarding stability and potential for uptake of DvSnf7 dsRNA by special subpopulations with altered absorption or digestion (e.g., Crohn's disease, colitis, IBS).

3:15 P.M. Break

3:30 P.M. Charge to the Panel (Continued)

Question 2. Please comment on EPA's risk assessment of the combination PIP product including the evaluation of the DvSnf7 gene with regard to product characterization and human health. Does the SAP have any suggestions to improve it?

5:00 P.M. Adjourn

Day 2
Wednesday, September 28, 2016

9:00 A.M. Opening of Meeting and Administrative Procedures – Jim Downing, Designated Federal Official, Office of Science Coordination and Policy, EPA

9:05 A.M. Introduction and Identification of Panel Members – James McManaman, Ph.D., FIFRA Scientific Advisory Panel Session Chair

9:10 A.M. Follow-up from the Previous Day

9:30 A.M. Charge to Panel (Continued)

Question 3

Environmental Fate and Exposure. The 2014 SAP recommended an exposure based model for testing related to dsRNA based pesticides, which places emphasis on the environmental fate and exposure data and analyses. To inform the environmental fate and exposure analysis for the DvSnf7 dsRNA, EPA has reviewed data submitted by Monsanto Company that describes degradation in soil, water, sediment, and DvSnf7 expression levels, and has also examined information from public literature. Based on these data, EPA has concluded that exposure in the terrestrial environment primarily is limited to organisms that consume plant tissue directly and to those that may be exposed secondarily through consumption of herbivorous arthropods. In the aquatic environment, EPA has determined that exposure to DvSnf7 in corn detritus is minimal, and while some exposure may occur in the water column, the exposure will be short lived and not significant.

a. Please comment on the completeness of the data set considered for determining exposure and environmental fate of DvSnf7 in both terrestrial and aquatic environments, taking into consideration the scope of EPA's needs for environmental risk assessment and the recommendations of the 2014 SAP.

b. EPA has based its determination of the aquatic environmental fate of DvSnf7 on assumptions developed for Bacillus thuringiensis derived Cry proteins, which are largely based on information from the literature. Please comment on the applicability of these assumptions to DvSnf7 and describe any additional or alternative information and/or analyses that EPA should consider.

10:45 A.M. Break

11:00 A.M. Charge to Panel (Continued)

Question 3

c. Due to the nature of the data provided, EPA has based estimates of nontarget organism exposure on environmental concentrations. However, as indicated in several publications, a certain threshold of molecules is required to induce RNAi and subsequent gene silencing. An analysis considering these thresholds was included in Monsanto Company's white paper on human safety of

DvSnf7. EPA recognizes that a similar analysis for nontarget organisms might provide more refined exposure estimates for DvSnf7 and for future risk assessments of dsRNA pesticides; however, it is unclear whether sufficient data are available to develop a similar analysis for nontarget organisms. Please comment on the risk assessment for DvSnf7 by such a threshold of exposure based approach, considering the scope of EPA's ecological risk assessments, and any additional information needed to implement such a threshold based analysis.

12:00 P.M. Lunch

1:00 P.M. Charge to Panel (Continued)

Question 4

Nontarget Organism Hazard. EPA has reviewed nontarget hazard data developed for DvSnf7 on two species of birds, two mammal species (from human health testing), a freshwater fish, seven species of nontarget arthropods, an earthworm, and honey bees, and has included these studies in its consideration of nontarget organism risk. This approach for dsRNA is consistent with EPA's testing framework for Bt derived PIPs, with additional data required on nontarget insect reproduction. EPA has also included assumptions about common barriers to dsRNA uptake in vertebrates and bioinformatics analysis as additional lines of evidence in this consideration. Based on the whole of these data, EPA has concluded that adverse effects to nontarget organisms are not anticipated to result from cultivation of MON 89034 x TC1507 x MON 87411 x DAS-59122-7 corn.

a) Please comment on the completeness of the nontarget organism hazard data reviewed forDvSnf7 as it pertains to the needs of the environmental risk assessment and the recommendations for testing made by the 2014 SAP.

b) EPA has concluded that DvSnf7 is unlikely to cause adverse effects to vertebrate nontarget organisms. This conclusion relies in part on an assumption that biological barriers that limit uptake in mammals (see the human health risk assessment for DvSnf7) would also apply to other vertebrates. Please comment on the biological barrier assumption as a line of evidence supporting EPA's conclusion of minimal risk to vertebrate nontarget organisms.

c) EPA concluded that off-target and other unintended effects related to dsRNA exposure are unlikely in nontarget organisms, based on the lack of effects observed in nontarget testing. Please comment on EPA's conclusions regarding these effects.

2:30 P.M. Charge to Panel (Continued)

Question 5

Synergism

EPA requires data to demonstrate that PIPs expressed in combination within the same plant are not synergistic. The purpose of these studies is to allow bridging of data developed on individual PIPs to the combined trait product; otherwise, new data generation would be required on the combination to

determine nontarget risk. EPA reviewed five studies examining synergism among DvSnf7 and the Cry proteins expressed in MON 89034 x TC1507 x MON 87411 x DAS-59122-7 and determined that no synergism is expected. Please comment on EPA's analyses of these data and the scientific value of these data in the risk assessment.

3:30 P.M. Break

3:45 P.M. Charge to Panel (Continued)

Question 6

Insect Resistance

Although the EPA has not requested comment from previous Scientific Advisory Panels on the potential for resistance in corn rootworm to RNAi-based pesticides, the Agency believes this to be an important consideration in its regulation of such pesticides, and uses this opportunity to collect advice and information.

Corn rootworm have demonstrated an ability to adapt to a wide range of chemical and cultural controls, including Bt Plant-Incorporated Protectants. Please discuss the likelihood and potential mechanisms by which corn rootworm could develop resistance to an RNAi-based pesticide such as DvSnf7 dsRNA.

5:00 P.M. Adjourn – Jim Downing, Designated Federal Official, Office of the Science Advisor/EPA

Please be advised that agenda times are approximate; when the discussion for one topic is completed, discussions for the next topic will begin. For further information, please contact the Designated Federal Official for this meeting, Jim Downing, via telephone: (202) 564-2468; or email: downing.jim@epa.gov.