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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: April 20, 2017

SUBJECT: **AMENDMENT**: 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]; submitted by Monsanto Company. Decision Number: 513156, 514589 and 514588; DP Barcode: 431335, 432073 and 432072; Submission Number: 980035, 982159 and 982149.

Response to the Transmission of Meeting Minutes of the September 27-28, 2016 FIFRA SAP Meeting held to consider and review Scientific Issues Associated with "RNAi Technology: Human Health and Ecological Risk Assessments for SmartStax PRO"

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TO: Alan Reynolds, Team Leader
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The Office of Pesticides Programs, Biopesticides and Pollution Prevention Division, Response to the Transmission of Meeting Minutes of the September 27-28, 2016 FIFRA SAP Meeting held to consider and review Scientific Issues Associated with "RNAi Technology: Human Health and Ecological Risk Assessments for SmartStax PRO."

The SAP Panel had **two** recommendations on the Product Characterization and Human Health Risk Assessment for DvSnf7 dsRNA Expressed in MON 89034 x TC1507 x MON 87411 x DAS-59122-7.

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 (pg. 11). The Panel also recommend 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 (pg. 12).

EPA's Comment/Response: The Agency noted that the SAP Panel concurred with the Agency's human health risk assessment and considered it as 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 risk assessment approach for RNAi.

SAP Panel Recommendation #2: The SAP Panel 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's Comment/ Response: The Agency disagrees with the SAP Panel recommendation pertaining to assigning a LOAEL to the 28 -day rodent study. The Agency points out that 2016 SAP Panel 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 was reviewed in detail at a meeting of the Toxicology Science Advisory Committee (ToxSAC) on April 12th, 2017. The ToxSAC agreed with the Biopesticides & Pollution Prevention Division (BPPD) that established a lack of NOAEL and 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 observe effects (decrease ovary and thyroid weight).
- There were no histopathological findings corresponding to the observe 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 dsRNAi will not be taken up as intact molecules in mammals.