AGENDA

Meeting of the Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) to Consider and Review Scientific Issues Associated with RNA Interference: Problem Formulation for Human Health and Ecological Risk Assessment

January 28, 2014

Docket Number: EPA-HQ-OPP-2013-0485 **OPP Docket Tel: 703-305-5805**

Please note that all times are approximate (See note at the end of the Agenda)

Tuesday, January 28, 2014

9:00 A.M. **Opening of Meeting and Administrative Procedures** – Sharlene Matten, Ph.D., Designated Federal Official, Office of Science Coordination and Policy, EPA

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

9:10 A.M. **Opening Remarks** – Steven Bradbury, Ph.D., Director, Office of Pesticide Programs (OPP), EPA

9:15 A.M. **Overview** – Robert McNally, Director, Biopesticides and Pollution Prevention Division (BPPD), OPP, EPA

9:25 A.M. **Introduction to the Scientific Issues Associated with RNAi –Based Pesticidal Products** – Chris Wozniak, Ph.D., BPPD, OPP, EPA

9:45 A.M. **Human Health Considerations for RNAi-Based Pesticidal Products**– John Kough, Ph.D., BPPD, OPP, EPA

10:00 A.M. **Environmental Considerations for Plant-Incorporated Protectant (PIP) Expressed dsRNA** – Shannon Borges, BPPD, OPP, EPA

10:15 A.M. **Environmental Considerations for Non-PIP RNAi End-Use Products** – Russell Jones, Ph.D., BPPD, OPP, EPA

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

10:40 A.M. **Public Comments**

12:15 P.M. **Lunch**

1:00 P.M. **Panel Discussion of Charge Questions 1-4**

Introduction

The intent of this meeting is to solicit scientific expertise for the problem formulation phase of risk assessment of pesticidal products based on RNA interference (RNAi). Problem formulation is the first step in the risk assessment process and guides the subsequent questions to pose about hazard and exposure (EPA, 1998b). The framework for the risk assessment of biopesticides is found in the RNAi issue paper in two sections. The current approach for mammalian safety assessment of PIPs and biochemical pesticides can be found at the start of section

III. The framework for ecological safety assessment for PIPS and biochemical pesticides can be found in section IV A and B.

EPA has found that the current approach utilizing reduced data sets and tiered approaches for more involved studies works well for the risk assessment of products based on biological materials. EPA recognizes that biopesticides tend to be more specific in their activity and present a lower risk profile than some alternative pest control measures. Biopesticide products are likely to be developed utilizing RNAi phenomena as both dsRNA PIPs expressed in plants and typical sprays and other products based on isolated dsRNA molecules. EPA is asking the following questions to ascertain the issues unique to RNAi and how they could fit under the existing risk assessment framework.

Human Health Considerations

Question 1. Please discuss the nature and extent of uncertainty in the specificity of long sequences of dsRNA targeted at pest species, if bioinformatic analysis shows no significant similarity to mammalian genes?

Question 2. Based on data indicating degradation of the majority of dsRNA in the digestive system, please discuss the strengths and limitations in concluding there will not be significant absorption of dsRNA with possible mammalian effects on oral exposure?

Question 3. To what extent does the specific structure of dsRNA, if it is super coiled or in a hairpin structure, make it more likely to survive degradation in the gut and lead to possible mammalian effects with oral exposure?

Environmental Considerations: Questions directed toward dsRNA expressed as part of a PIP and applied to the plant as a biochemical

Question 4. EPA needs a clear understanding of the environmental fate of dsRNAs in terrestrial and aquatic environments. In sections IV.A.1. and IV.B.3, respectively, EPA has presented potential scenarios for dsRNA movement within the environment that may result from their pesticidal uses as PIPs or as exogenously applied dsRNAs. Environmental fate of dsRNAs is not well understood; however, EPA has frameworks in place for PIPs and Biochemicals to obtain data related to degradation and movement of pesticides in the environment. These data can be used to refine environmental exposure estimates to dsRNAs.

a. While nontarget exposure to dsRNA PIPs may result primarily from consumption of PIP crop plant tissue, EPA must also assess the exposure of nontarget organisms to dsRNA that may enter the environment through plant exudates and plant tissue breakdown. In section IV.A.2.*a*, EPA presented the current approach for testing to assess environmental fate for PIPs, which focuses on degradation within soil.

   i) To what extent will data on degradation in soil inform EPA on nontarget exposure to dsRNA PIPs?

   ii) What additional information, if any, would EPA need to assess environmental fate of dsRNA PIPs?

b. In section IV.B.4, EPA proposed environmental fate data needs for exogenously applied dsRNAs. To what extent is the proposed testing sufficiently robust to inform nontarget organism exposure for these dsRNAs?

c. For both dsRNA PIPs that may be free in the environment and exogenously applied dsRNAs, knowledge of the initial residue burden, and the dissipation rate of residues, is essential for developing environmental exposure estimates, particularly if models of environmental fate are used to arrive at these estimates.

What analytical methods are available to accurately and precisely measure dsRNAs in diverse plant, soil, and water matrices?

2:50 P.M. Break

3:00 P.M. Panel Discussion of Charge Questions 5-6

Question 5. The primary route of exposure for nontarget organisms to dsRNA PIPs is assumed to be ingestion, either of dsRNAs contained in plant tissue or free in the environment. However, some evidence also indicates the potential for exposure by direct contact in nematodes and some arthropods. For dsRNAs that are applied to plants and/or the environment, the primary routes of exposure are expected to be both ingestion and direct contact.

a. In section III.C. and IV.A.1.c. of the issue paper, EPA discusses potential barriers to uptake of dsRNA in the gut of mammals and arthropods; however, little information exists for other taxa.

   i) In addition to the conditions of the gut environment and enzymes influencing digestion, what other factors may play a role in uptake within the gut and potentially limit exposure to dsRNA?

   ii) Please comment on how these barriers can be generalized across all nontarget taxa that are considered in EPA's risk assessments (e.g., birds, plants, fish, etc.) for both dsRNA PIPs and exogenously applied dsRNA.

b. The degree of exposure by direct contact is likely to differ between nontarget risk assessments for dsRNA PIPs and nontarget risk assessments for exogenously applied dsRNAs.

   i) Please comment on the importance of the contact route of exposure for nontarget risk assessments for each of these types of dsRNAs

   ii) What barriers are likely to exist for this route of exposure for both terrestrial and aquatic organisms, and how can these be generalized across nontarget taxa?

Question 6. In the issue paper, EPA discussed possible effects other than silencing of the target gene in the target organism that may occur as a result of exposure to dsRNA. These unintended effects of dsRNA include off-target effects, silencing the target gene in nontarget organisms, degradation of non-targeted mRNA by transitive RNA, and effects resulting from immune stimulation and saturation of the RNAi machinery. EPA has little information to estimate the range of unintended effects that may occur and their probability of occurrence as a result of exposure to dsRNA in the environment.

a. Please comment on the unintended effects that EPA might reasonably anticipate in nontarget organisms exposed to dsRNAs, the likelihood of such unintended effects, and the biological significance of these effects in nontarget organisms, should they occur.

b. To the extent that additional information would reduce uncertainty in addressing these issues, please describe specifically the nature of additional information that EPA may need and the degree to which this information would reduce uncertainty in the ecological risk assessment.

4:50 P.M. Break

5:00 P.M. Panel Discussion of Charge Question 7

Question 7. In sections IV.A.2.*a*. and IV.B.4. of the issue paper, EPA presents the current framework of testing for determining nontarget effects resulting from exposure to PIPs and biochemicals, respectively. In section IV.A.2.*c*, EPA also raised potential issues related to nontarget testing with dsRNAs that may arise given their unique mode of action, which included 1) the potential influence of latent effects on results of nontarget testing, 2) the appropriate life stage for testing, and 3) the possibility for chronic effects.

a. Please comment on how each of EPA's current PIP and biochemical frameworks for nontarget effects testing will inform risk assessment for dsRNA PIPs and exogenously applied dsRNAs. In providing a response, please address the potential for unintended effects as described in Question 7, as well as the three issues outlined as concerns for nontarget testing listed above.

b. What additional nontarget effects testing, if any, should EPA consider to gain a full understanding of the potential for dsRNAs to cause effects to nontarget organisms?

c. What other approaches, such as bioinformatics analysis, may be used to address concerns for effects on nontarget species and reduce the set of data requirements?

d. In providing answers to the above subquestions, please be specific in discussing the extent to which additional information would reduce the nature and magnitude of these specific areas of uncertainty.

6:00 P.M. Adjournment

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, Dr. Sharlene Matten, telephone: (202)-564-0130, fax: (202) 564-8382, or email: matten.sharlene@epa.gov.