United States Regulatory Considerations for the Commercialization of Sprayed or Externally Applied dsRNA-Based Pesticides

iPlanta Webinars: RNAi Based Pesticides

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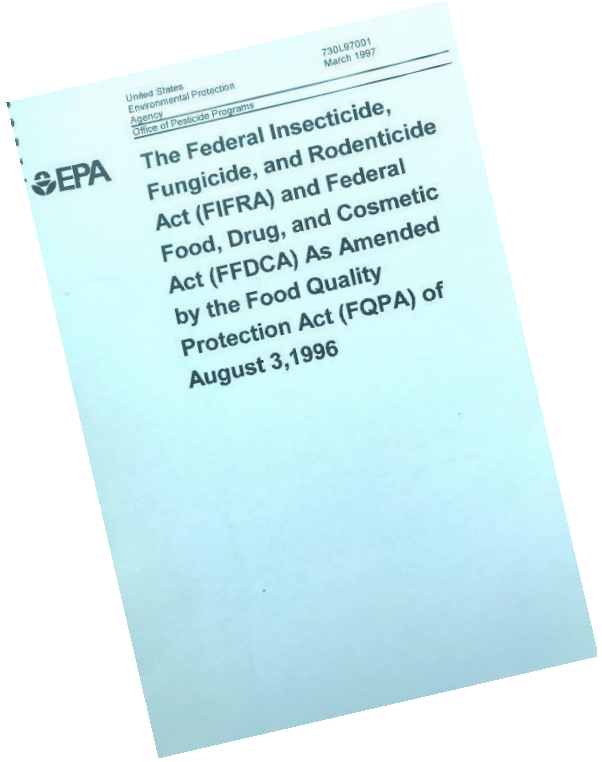
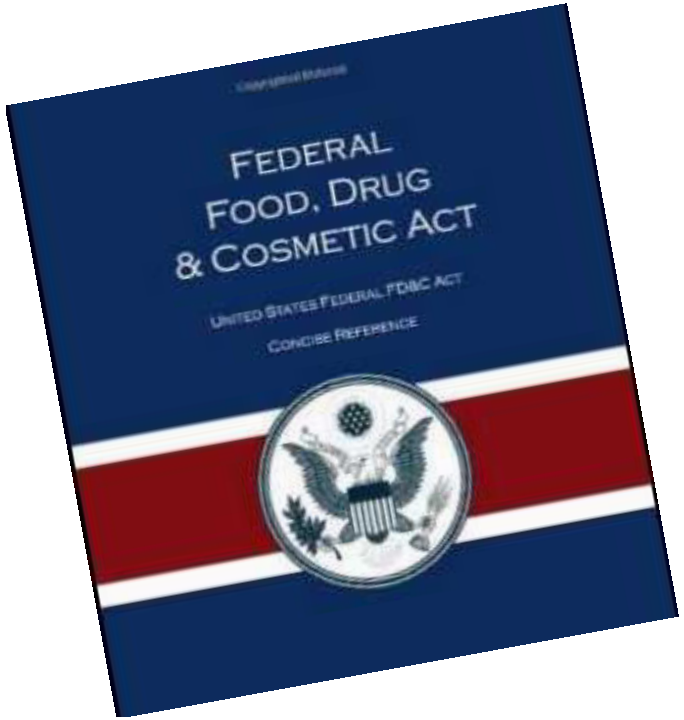
EPA's Regulatory Role

- **Federal Insecticide, Fungicide and Rodenticide Act** (FIFRA) - pesticides
  - No unreasonable adverse effects upon human health and the environment
- **Federal Food Drug and Cosmetic Act** (FFDCA) - food and feed safety
  - Reasonable certainty of no harm from aggregate exposure to a pesticide chemical residue





Background

- January 2014: U.S. EPA Scientific Advisory Panel (SAP) meeting "RNAi Technology as a Pesticide: Problem Formulation for Human Health and Ecological Risk Assessment"
  - Addressed both RNAi plant incorporated protectants (PIPs) and exogenously-applied RNAi pesticides
  - Final Report, https://www.epa.gov/sap/meeting-materials-january-28-2014-scientific-advisory-panel.

- September 2016, U.S. EPA Scientific Advisory Panel (SAP) meeting - Human Health and Ecological Risk Assessments for SmartStax PRO … an RNAi PIP for Corn Rootworm Control
  - SmartStax PRO's RNAi controls corn rootworm by targets the corn rootworm Snf7 gene, DvSnf7, which codes a key membrane transport protein. It is the first RNAi-based pesticide application for a product intended to kill an insect.
  - The meeting was to obtain the panel's scientific opinion and peer review of the EPA's human health and environmental risk assessments for PIPs expressing DvSnf7 for control of corn rootworm.
  - The meeting was also to consider the conclusions and recommendations of the 2014 SAP in evaluating the EPA's risk assessments for DvSnf7.
  - Final Report, https://www.epa.gov/sap/meeting-materials-september-27-28-2016-scientific-advisory-panel.

- September 2020, OECD Working Document - *Considerations for the Environmental Risk Assessment of the Application of Sprayed or Externally Applied ds-RNA-Based Pesticides* Series On Pesticides No. 104 ENV/JM/MONO(2020)26 .

Externally Applied dsRNA Pesticides - Key Considerations

- dsRNA molecules developed for topical application to crops for pest control will be assessed by the U.S. EPA using a similar set of considerations to those applied to biochemical pesticides, https://www.ecfr.gov/cgi-bin/text-idx?SID=738c16c85042ce20aec41a65fa12977e&node=40:24.0.1.1.9&rgn=div5#sp40.26.158.u

- Pesticide use pattern and application method (e.g., greenhouse, outdoor, bait, sprayable) require consideration.

- Additional issues need to be considered such as the potential to silence genes with significant sequence identity with the target gene in the intended pest and the fate of RNA in the environment.

Types of Data for Biochemical Pesticide Products

- Product Characterization
- Human Health
- Environmental effects e.g., non-target organisms, environmental fate
- Product Performance

Externally Applied dsRNA Pesticides - Added Considerations

- Product formulations can be designed to overcome barriers to uptake for the target organism or to be more persistent in the environment.
  - Special attention should be paid to formulations and whether barriers to uptake are proposed to be overcome for the target organism and/or whether the formulation may increase environmental stability and/or mobility since these factors could impact the environmental and human health risk assessments as well as the need to test the formulated product more extensively.

- Information and/or studies on the impact to uptake and environmental persistence/mobility that the formulation presents are important to characterize exposure to the dsRNA.

- Where specific product formulations impact barriers to and uptake of the dsRNA, product-specific formulation toxicology testing on organisms or test surrogates would help better characterize the potential for hazard.

Externally Applied dsRNA Pesticides - Added Considerations

- Sequence information alone should not and cannot be used as a stand-alone predictor of off-target effects.

- Bioinformatics can inform the selection and prioritization of non-target species for toxicity and effects testing.

- Bioinformatics should be augmented by an empirical approach – to introduce dsRNA (that is perfectly complementary to the target gene in a target organism) to a range of other organisms, starting with close relatives and then moving outwards, to see how more phylogenetically-distant organisms respond.

Externally Applied dsRNA Pesticides - Added Considerations

- Available evidence suggests that dsRNAs have a long record of safe consumption by humans and other vertebrates. Nucleic acids are naturally-occurring components of plant- and animal-derived foods and feed and are routinely consumed by humans and animals.
- Significant physiological and biochemical barriers exist in humans and other vertebrates to limit the uptake and distribution of exogenous RNAs.
- The barriers to dsRNA uptake identified in mammals likely applies to other vertebrates.
- Responsiveness across invertebrate taxa to environmental dsRNA cannot currently be predicted. Some are impacted; others are not.

Externally Applied dsRNA Pesticides - Added Considerations

- Non-Target organism toxicity study protocols for addressing risk with dsRNA-based products require some revisions compared to how they are carried out for biochemical pesticides because dsRNA-based pesticides often take longer to display efficacy. Any evaluation needs to account for this time lag by extending the study observation period.

- For organisms that have been demonstrated to be responsive to environmental RNA, consideration of life cycle studies (growth, development and reproduction) and studies on other non-lethal effects should be considered.

- Additionally, risk assessments for a dsRNA-based pesticide should include monitoring for degradation of the dsRNA over time.

Questions?