Regulation of Plant-Incorporated Protectants by EPA

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What is a Plant-Incorporated Protectant (PIP)?

“... a pesticidal substance that is intended to be produced and used in a living plant, or in the produce thereof, and the genetic material necessary for production of such a pesticidal substance. It also includes any inert ingredient contained in the plant, or produce thereof.” (40 CFR Sec. 174.3)
EPA’s Regulatory Role

– Federal Insecticide, Fungicide and Rodenticide Act – (FIFRA) pesticides
– Federal Food Drug and Cosmetic Act – (FFDCA) food and feed safety
– Food Quality Protection Act - (FQPA) amends FIFRA and FFDCA; sensitive groups included in assessment
– Endangered Species Act - (ESA) any impact on threatened or endangered species
Risk Assessment Process

FIFRA

Risk = Hazard x Exposure

RISK

BENEFITS
Experimental Use Permits

- Cumulative acreage $\geq 10$ A (4 HA) terrestrial or $\geq 1$A aquatic per year per pest requires EPA approval
- Food / feed tolerance required (at any size)
- EUPs are all time limited and require reporting of results as well as any adverse events
  - [6(a)2 of FIFRA]
- Products of EUPs are not eligible for advertising or promotion, but can be marketed with a tolerance
- EUPs are for research purposes
How EPA Characterizes PIPs

- Product Characterization
  - Molecular Characterization
  - Protein Expression Levels
  - Analytical Methods
Test Substances

• Proteinaceous test substances are often produced in microbial systems

• It is the responsibility of the registrant to ensure the test substance from the native source (*in planta*) and microbe are equivalent

• Mr, MALDI-TOF / MS, and glycosylation status are all parameters to examine

• Bioassays can also be informational in establishing equivalency
How EPA Assesses Human Health Effects for PIPs

Human Health Assessment

- Acute Oral Toxicity
- Biochemical Properties
- Amino Acid Sequence Homology
How EPA Assesses Environmental Effects for PIPs

Environmental Assessment

- Non-target Effects
- Environmental Fate
- Gene Flow Impacts
Data Required for Ecological Effects
Non-target Organisms

- Avian oral/dietary toxicity studies
  - Quail, acute/42-day poultry feeding
- Freshwater fish oral/dietary toxicity studies
  - Rainbow trout or sunfish acute/catfish feeding
- Freshwater invertebrate testing (*Daphnia*)
- Honey bee oral toxicity testing
- Non-target arthropod testing
- Wild mammal toxicity (acute oral for rat/mouse)
- Estuarine and marine animal testing *
- Non-target plant toxicity studies *
- Endangered species considerations → exposure determination

* Often waived or satisfied with alternative data citation
Navigating EPA

• For a biotech plant producing a plant-incorporated protectant (PIP)
  - EPA sets tolerances (i.e., Maximum Residue Levels) for all pesticides in or on food and feed products
  - A pesticide residue present on food or feed products which is not covered by a tolerance or an exemption from the requirement of a tolerance results in that product being considered as ‘adulterated’ under the Federal Food Drug and Cosmetic Act (FFDCA)
Navigating EPA

• Tolerance actions consider data from an acute oral toxicity test, sequence comparison to known toxins and allergens, *in vitro* digestibility and the source of the gene used for PIP or inert ingredient production

• A food tolerance action is usually required prior to field testing of a PIP expressing plant
  – If adequate containment measures are in place, a tolerance may not be needed for an EUP.
Food for Thought

• Most data requirements are designed with proteins as the test substance
• RNA-based mechanisms may save some time and money when possible to achieve action
• Nucleic acid exemption exists for food and feed tolerances under FFDCA
• Choosing previously approved inert ingredients saves time and money
PRN 11-3 Formatting

• Format for data submitted to EPA under FIFRA section 3 and FFDCA sections 408 and 409
• Data packages submitted to the Agency outside of this format will most likely be rejected (BPPD may never see them)
• This is where a consultant comes in handy!
Where to begin

- The Pesticide Registration Manual ("Blue Book")
  [http://www.epa.gov/pesticides/bluebook/](http://www.epa.gov/pesticides/bluebook/)
  - Chapter 20: Forms & How to Obtain Them
  - Chapter 21: Submitting Applications, Contacting EPA
  - Chapter 11: Tolerance Petitions
  - Appendix A: Guidance Documents
  - Appendix B: Examples of Registrant Documents
  - Appendix C: Forms Overview Table
  - Appendix D: Examples of Completed Forms
Pesticide Registration Improvement Act (PRIA 3)

Statute that directs EPA to collect fees to regulate and register pesticides

Establishes a decision* Time Frame
  - Fee Category Determines Fee & Time Frame

Assumes the Application is Complete:
  - Administrative Documents
  - Data Requirements are Addressed
  - Fees are Paid, or
  - 25% (or 50%) of Fees Paid if Requesting a Fee Waiver

  * Not necessarily a registration!
SUMMARY - Navigating EPA

• Early consultation before submission of application is encouraged
• “Pre-submission” meeting(s) - confidential
• Determination of applicable data requirements needed early on in process
• Formatting requirements are mandatory and a consultant is recommended for formal submissions to the Agency
Useful websites

• http://www.epa.gov/pesticides/biopesticides/regtools/biotech-reg-prod.htm
• http://www.epa.gov/scipoly/sap/meetings/2000/october/brad3_enviroassessment.pdf
• http://www.epa.gov/pesticides/biopesticides/reg_of_biotech/eparegofbiotech.htm
• http://www.epa.gov/scipoly/sap/meetings/2009/022509meeting.htm
• http://www.epa.gov/oppbppd1/biopesticides/pips/pip_list.htm
Who can I contact to get started?

- EPA – Kimberly Nesci, Branch Chief, Microbial Pesticides  
  [Nesci.Kimberly@epa.gov](mailto:Nesci.Kimberly@epa.gov)  
  – Chris Wozniak, Biotechnology Special Assistant  
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