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General overview of registering biopesticides in the US

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Agenda

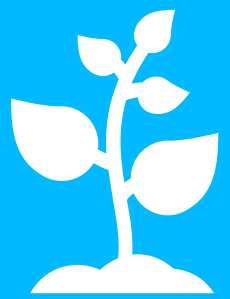
- Biopesticides and Pollution Prevention Division (BPPD)
- Biopesticides data requirements
- Options for satisfying biopesticide data requirements
- Application package

Biopesticides and Pollution Prevention Division (BPPD)

Overview of EPA's Office of Pesticide Programs (OPP)

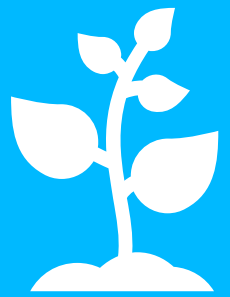
- OPP website: www.epa.gov/pesticides

- OPP divisions include
  - Registration Division (RD)
  - Antimicrobial Division (AD)
  - **Biopesticides and Pollution Prevention Division (BPPD)**
  - Pesticide Re-evaluation Division (PRD)
  - Health Effects Division (HED)
  - Environmental Fate and Effects Division (EFED)
  - Biological and Economic Analysis Division (BEAD)



BPPD division in the EPA's Office of Pesticide Programs

- Approximately 50 FTEs (Managers and staff)
    - Risk managers and risk assessors in one division
- Charles "Billy" Smith, Director
- Two registering branches: Biochemicals - Linda Hollis, Chief (PM 91), and Microbials - Seiichi Murasaki, Chief (PM 92)
- Risk Assessment Branch – Shannon Borges, Chief
    - Science reviews and risk assessments for biochemical and microbial pesticides; occasionally consult with HED and EFED
- Emerging Technologies Branch – Mike Mendelsohn, Chief
    - Registration & risk assessment review for PIPs, policy/rulemaking for products of biotechnology, Wolbachia, genetically engineered mosquitoes, (PIPs), and insect resistance management/ new technologies
- Environmental Stewardship Branch – LaShonia Richardson, Acting Chief
    - Pollution prevention outreach and stewardship activities



Biopesticide regulation in the United States

- Biopesticides are regulated at the federal level by the US Environmental Protection Agency (EPA) and then by the States
- EPA regulates pesticides under two laws:
  - Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) - the primary pesticide statute.
  - the Federal Food, Drug, and Cosmetic Act (FFDCA) - allows EPA to set tolerances, or exemption from tolerances, for the allowable residues of pesticides (food additives) that are applied to food and animal feed.
- The federal regulations pertaining to biopesticide registration are listed in Title 40 of the Code of Federal Regulations, parts 150 -189

Biopesticides

Biochemicals

1. Naturally occurring chemicals or synthetically derived equivalents;
2. Have a history of exposure to humans and the environment demonstrating minimal toxicity, or in the case of synthetically derived biochemical pesticides, are equivalent to a naturally occurring chemical that has such a history; and
3. Have a nontoxic mode of action to the target pest(s) (Ex: pheromones, plant extracts, oils, animal urines)

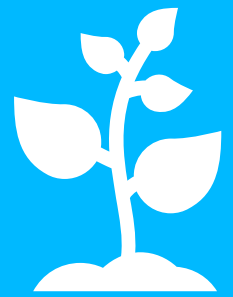
Microbials (microorganisms that produce a pesticidal effect)

1. Eukaryotic microorganisms (ex. protozoa, algae, and fungi)
2. Prokaryotic microorganisms (ex. bacteria); or
3. Autonomous replicating microscopic elements (ex. viruses)

Plant Incorporated Protectants (PIPs)

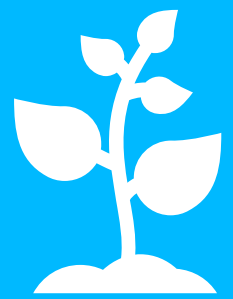
Pesticidal substances produced by plants & the genetic material necessary added to the plant to produce them

- DNA “incorporated” into plants by genetic engineering (“GMOs”)
- Both the protein and its genetic material are regulated by EPA; the plant itself is not regulated
- Interesting and challenging from scientific and regulatory points of view
- EPA requires extensive studies to assess various factors: risks to human health, potential for gene flow and the need for insect resistance plans



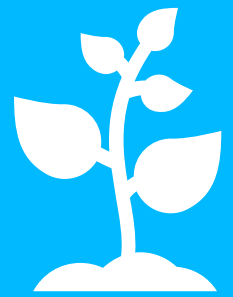
Characteristics of biopesticides

- Low impacts on human health and the environment
- Low toxicity to non-target organisms
- No or low environmental persistence
- Low use rates
- Target specificity
- No or low potential for the development of pest resistance



Biopesticide advantages

- Shorter PRIA review timelines and fees than RD & AD pesticides
- Usually, no significant safety issues regarding toxicity
- Broad use patterns – agriculture, greenhouse, residential, forestry, aquatic
- Concurrent reviews for new active ingredients with California's DPR
- Most are exempted from the requirement of a tolerance for residues in food and animal feed commodities (no maximum residue levels)
- No or low pre-harvest intervals for food crops
- Low (4 or 12 hour) re-entry intervals for agricultural uses
- Recognition from upper levels of EPA as low-risk:
    - Potential for DfE and Safer Choice designations
    - Potential for OMRI-listing of products allowed for organic uses



Biopesticide data requirements

Biopesticides data requirements

Disciplines

- Product Chemistry
- Residue
- Toxicology (Human Health Assessment)
- Non-target and Environmental Fate
- Efficacy (Product Performance)

Note: biochemical pesticides have a much-reduced data set

Biopesticides data requirements

Biochemical classification*

- Biochemical classification of active ingredient(s) required before submission of registration application
    - Key criteria: 1. natural occurrence
      2. **clear non-toxic mode of action against the target pest**
      3. evidence of safe exposure to humans & environment
- Being FDA GRAS or a food additive has no bearing

** biochemical pesticides, so far*

Product chemistry (40 CFR §158.2030)

- Identity, composition
- Analysis of samples
- Manufacturing process description
- Analytical method of analysis
- Physical/chemical properties

Biopesticides data requirements

Residue data (TGAI*) (40 CFR §158.2040)

- Nature and magnitude of the residue
- Plant and/or animal tissues
- Residue/multiresidue analytical methods

*TGAI – Technical Grade Active Ingredient

Toxicology (TGAI unless specified differently) (40 CFR §158.2050)

- Acute six-pack (limit dose or dose-response) (oral, dermal,** inhalation LD_{50}/LC_{50}, eye/skin irritation, dermal sensitization; limit dose or dose-response) (**both TGAI & EP*****)
  - bridging rationale - if EP is a simple dilution of TGAI

  ***Acute dermal tox can be waived if acute oral tox is low*

  ****EP – End-use-product*
- Subchronic (repeated-dose studies)
  - 90-day oral – *critical to support food uses/dietary safety*
  - 90-day dermal – *key for skin-applied repellents*
  - 90-day inhalation – *important for aerosols*
- Prenatal Developmental (1 species) – *critical to support food uses/dietary safety*
- Genotoxicity (2 studies required, bacterial reverse-mutation, and in vitro mammalian cell assay)
- Exposure (Product-Specific Data Requirements)

Biopesticides data requirements

Non-target and Environmental Fate (40 CFR §158.2060)

Tier I (TGAI & EP)

- Avian studies: acute oral & dietary toxicity
- Aquatic studies: freshwater fish & invertebrate toxicity
- Non-target plants: terrestrial plants toxicity – seedling emergence & vegetative vigor
- Non-target insects (only TGAI)

Tier II Environmental Fate Testing (TGAI)

- Degradation (hydrolysis, photodegradation in soil and water, soil metabolism (aero & anaerobic))
- Mobility in soil (leaching, adsorption/desorption, dissipation, volatility)
- Non-target plant: seedling emergence & vegetative vigor

Tier III Environmental Fate Testing (TGAI, unless specified differently)

- Aquatic Fauna chronic, Life Cycle and Field Studies: freshwater/marine fish & invertebrate; aquatic field fish (EP)
- Terrestrial Wildlife: avian reproduction, wild mammal tox, terrestrial field (EP)
- Beneficial insects: honeybees (EP)
- Non-target plants

Efficacy (Product Performance) (40 CFR §158.2070)

- All biopesticides.

Options for satisfying biopesticide data requirements

How to satisfy biopesticide data requirements

- Guideline studies conducted on the proposed biopesticide
  - Preferred by the EPA, highest potential to satisfy data requirements
- Citation of existing data previously submitted and reviewed by the EPA
  - Exclusive use and data compensation privileges apply
- Data waivers
  - "Test Notes" (under the data tables) for each data requirement, which may describe when a data requirement may be waived
  - Test substances with extremely low or high pH, cause severe corrosion to skin or eyes, therefore no need to cause excessive pain and suffering in the test animals
  - When the test material cannot be tested due to its physical, chemical or biological properties
    - Ethylene – a gas at room temperature; cannot be applied to the skin or administered via the oral route of exposure, so acute oral and dermal toxicity, dermal irritation, dermal sensitization, and 90-day oral and dermal toxicity, developmental toxicity studies, non-targets, could not be conducted
  - Formulator's exemption
- Rationales – formal arguments presented by registrants that demonstrate sufficient data already exist for a given data requirement in lieu of conducting a guideline study

Application package

The application package

- Application form (8570-1)
- Cover letter
- Proposed label
- Confidential Statement of Formula (8750-4)
- Formulator’s exemption, if applicable (8570-27)
- Data Citation Form (8570-34)
- Data Matrix (8570-35; confidential and non-confidential)
- Transmittal document
- Data volumes
- Copy of PRIA fee pre-payment receipt (pay.gov receipt or copy of check)

(https://www.epa.gov/pesticide-registration/pesticide-registration-manual-blank-forms)

Pesticide Registration Improvement Act (PRIA)

- Pesticide Registration Improvement Extension Act
  - Codes create a more predictable evaluation process for affected pesticide decisions
- 5 phases:
  - Phase I: 21-day content screen
  - Phase II: 45/90-day preliminary technical screen (10-day letters)
  - Phase III: primary science review
  - Phase IV: secondary science review (risk assessment) (75-day letters)
  - Phase V: final Federal Register notice of decision
- Small Business PRIA Fee Reduction

PRIA 5 (effective February 27, 2023)

- The fee tables are based by type of pesticide, not type of action
  - Tables 1-6 – conventional pesticides (RD)
  - Tables 7-10 – antimicrobial pesticides (AD)
  - Tables 11-17 – biopesticides (BPPD)
    - 79 BPPD categories
    - Table 11 - New Active Ingredients (9-22 months + 21 days)
    - Table 12 - New Uses (7-19 months + 21 days)
    - Table 13 - New Products (4-15 months + 21 days)
    - Table 14 – Amendments (5-13 months + 21 days)
    - Table 15 – Straight-Chain Lepidopteran Pheromones (SCLP) (4-7 months + 21 days)
    - **Table 16 - Other Actions** (3-5 months + 21 days)
    - **Table 17 – PIP** (3-22 months + 21 days)
  - Table 18 – Inert Ingredients
  - Table 19 – Miscellaneous actions

Table 11 – New Active Ingredients

EPA No.	Action	Decision Review Time (Months) (4)	FY'23-FY'24 Fees ($)
B580	New active ingredient; petition to establish a tolerance. (2) (3) (4)	22	73,173
B590	New active ingredient; petition to establish a tolerance exemption. (2) (3) (4)	20	45,737
B600	New active ingredient; no change to a permanent tolerance or tolerance exemption (includes non-food uses). (2) (3) (4)	15	27,443
B610	New active ingredient; Experimental Use Permit application; petition to establish a permanent or temporary tolerance or temporary tolerance exemption. (3) (4)	12	18,296
B620	New active ingredient; Experimental Use Permit application; non-food use (includes crop destruct). (3) (4)	9	9,151

2 All requests for new uses (food and/or nonfood) contained in any application for a new active ingredient or a first food use are covered by the base fee for that new active ingredient or first food use application and retain the same decision time review period as the new active ingredient or first food use application. The application must be received by the Agency in one package. The base fee for the category covers a maximum of five new products. Each application for an additional new product registration and new inert approval that is submitted in the new active ingredient application package or first food use application package is subject to the registration service fee for a new product or a new inert approval. All such associated applications that are submitted together will be subject to the new active ingredient or first food use decision review time. In the case of a new active ingredient application, until that new active ingredient is approved, any subsequent application for another new product containing the same active ingredient or an amendment to the proposed labeling will be deemed a new active ingredient application, subject to the registration service fee and decision review time for a new active ingredient. In the case of a first food use application, until that first food use is approved, any subsequent application for an additional new food use or uses will be subject to the registration service fee and decision review time for a first food use.
Any information that (a) was neither requested nor required by the Agency, and (b) is submitted by the applicant at the applicant's initiative to support the application after completion of the preliminary technical screening, and (c) is not itself a covered registration application, must be assessed 25% of the full registration service fee for the new active ingredient or first food use application.
3 Where the action involves approval of a new or amended label, on or before the end date of the decision review time, the Agency shall provide to the applicant a draft accepted label, including any changes made by the Agency that differ from the applicant-submitted label and relevant supporting data reviewed by the Agency. The applicant will notify the Agency that the applicant either (a) agrees to all of the terms associated with the draft accepted label as amended by the Agency and requests that it be issued as the accepted final Agency-stamped label; or (b) does not agree to one or more of the terms of the draft accepted label as amended by the Agency and requests additional time to resolve the difference(s); or (c) withdraws the application without prejudice for subsequent resubmission, but forfeits the associated registration service fee. For cases described in (b), the applicant shall have up to 30 calendar days to reach agreement with the Agency on the final terms of the Agency-accepted label. If the applicant agrees to all of the terms of the accepted label as in (a), including upon resolution of differences in (b), the Agency shall provide an accepted final Agency-stamped label to the registrant within 2 business days following the registrant's written or electronic confirmation of agreement to the Agency.
4 If the Administrator determines that endangered species analysis is required for this action, using guidance finalized according to section 33(c)(3)(B) for this specific type of action, the decision review time can be extended for endangered species assessment one time only for up to 50%, upon written notification to the applicant, prior to completion of the technical screening. To the extent practicable, any reason for renegotiation should be resolved during the same extension.

Thank you!

Thank you!

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