Regulation of Plant-Incorporated Protectants (PIPs)

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SCRA
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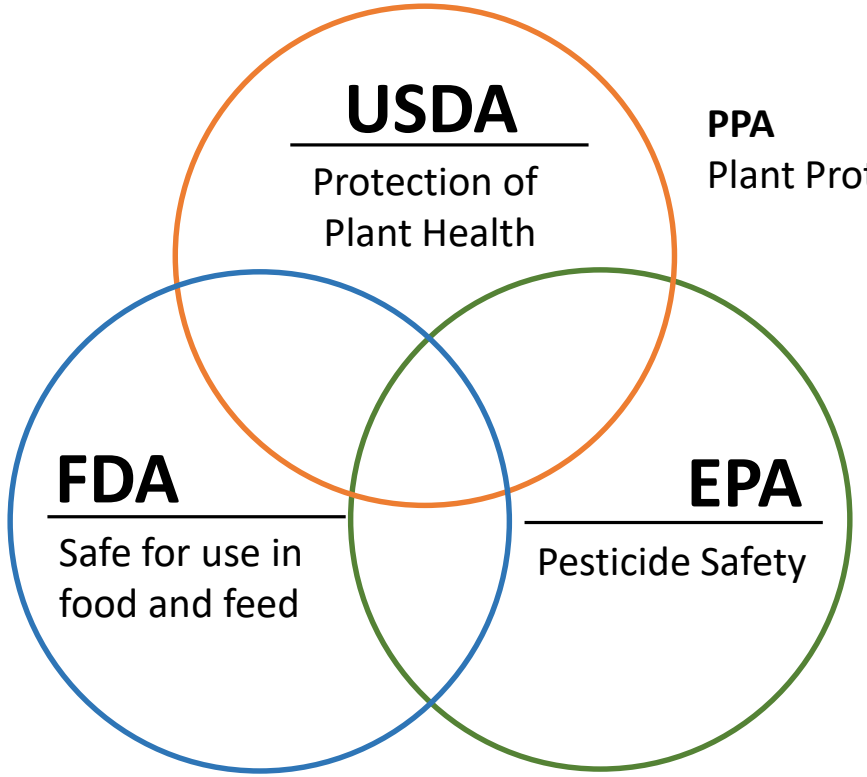
Nuts and Bolts of Biotech Regulations 2018 Workshop

The Coordinated Framework for Regulation of Biotechnology (CF)

Regulatory oversight over genetically engineered plants

- Each Federal Agency has specific statutes for regulatory oversight
  - Associated with own protection goals



PPA
Plant Protection Act

FFDCA
Federal Food Drug and Cosmetic Act

FIFRA
Federal Insecticide Fungicide and Rodenticide Act

FFDCA
Federal Food Drug and Cosmetic Act

Biotechnology in Pesticides

Types of biotech pesticides regulated by EPA

- Plant-incorporated protectants
  - Defined as 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.
  - e.g. DNA, RNA, protein (e.g. Bt Cry1Ab protein and *cry1Ab* gene)
  - e.g. selectable markers and genes (e.g. CP4 Enolpyruvylshikimate-3-phosphate (CP4 EPSPS) synthase and *cp4 epsps* gene)
- Genetically engineered microbials
- RNAi – in PIPs or as exogenous "sprayable" products
- Genetically engineered mosquitoes (population suppression)

About PIPs

- PIPs have resulted in reduced chemical usage
- Registered 100+ PIP products to date
  - Majority are *Bacillus thuringiensis* Cry protein-based for insect control
    - Mainly corn, cotton, and soy
  - RNAi (DvSnf7) for corn rootworm recently approved
    - First RNAi approved for control of a macro organism
  - Plant disease resistant PIPs
    - Viral coat proteins (papaya, plum)
    - Defensin proteins (citrus greening)
    - Resistance proteins (VNT1 in potato)
- Change of PIP landscape anticipated in near future
  - Increased product diversity
  - Greater involvement of smaller developers

Photos: USDA-ARS; Keith Weller, Peggy Gren, Scott Bauer

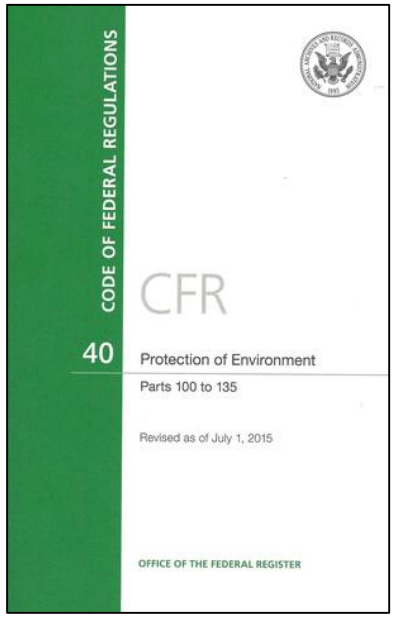
EPA - Pesticides

Pesticide-related statutes - laws written by Congress

1. Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)
2. Federal Food, Drug, and Cosmetic Act (FFDCA)
3. Food Quality Protection Act (FQPA)
4. Pesticide Registration Improvement Act (PRIA)

Regulations – how EPA implements the pesticide statutes

- Code of Federal Regulations – Title 40 (Protection of the Environment)
  - Pesticides addressed in Parts 150 – 189
  - PIPs: Part 174



EPA - Regulatory Oversight of Biotechnology

FIFRA

- Distribution, use and sale of pesticides:
  - Registration (§3)
  - Emergency exemption (§18)
  - State registration for special local need (§24(c))
- Re-evaluation of older pesticides (§4)
- Field testing and distribution of experimental pesticides (§5)
  - Experimental Use Permits
  - Biotech notifications – small scale testing of GE microbes

FFDCA

- Establishes tolerances (maximum residue levels) for pesticide chemical residues in/on food and feed (§408)
- Tolerances apply to both domestic and imported foods
- All PIPs registered to date have tolerance exemptions – i.e., no maximum residue limit established
  - PIP tolerance exemptions are published in 40 CFR 174

EPA - Regulatory Oversight of Biotechnology

Protection goals

FIFRA Standard

- EPA may register a pesticide if, when used in accordance with widespread and commonly recognized practice, it generally:

  Will not cause unreasonable adverse effects on human health or the environment

FFDCA Standard

- EPA may establish a tolerance or tolerance exemption if it is determined to be safe:

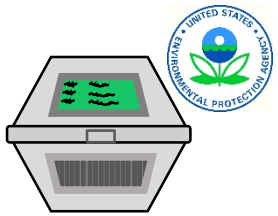
  Safe means that there is a **reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information**

PIP Registration

Requirements

- If a PIP is tested in the field at greater than 10 acres, an experimental use permit is required.
- If a PIP is distributed or sold for commercial use, including seed increase, a pesticide registration is required.
- If a PIP is used in a food or feed crop, a tolerance or an exemption from the FFDCA section 408 requirement of a tolerance for residues is required.

PIP Commercial Development and EPA



Step 1 → **Step 2** → **Step 3** → **Step 4**

Consult with EPA during R&D

Experimental Use Permit & Temporary Tolerance Exemption

Seed Increase Registration & Tolerance Exemption

Full Registration & Tolerance Exemption

Experimental Use Permits (EUP)

Purpose and requirements

- Enables developer to generate the data for full registration
- Testing on a cumulative total (per pest) of over 10 acres of land or 1 acre of water requires an experimental use permit.
- A tolerance or tolerance exemption is needed if PIP residues result in the food supply.
- EUP data requirements are usually a subset of registration data
  - Including information reviewed for the FFDCA 408 tolerance exemption (temporary or full)
- EPA evaluates all **active** and **inert** ingredients
  - Inerts for PIPs are frequently herbicide tolerance selectable markers.

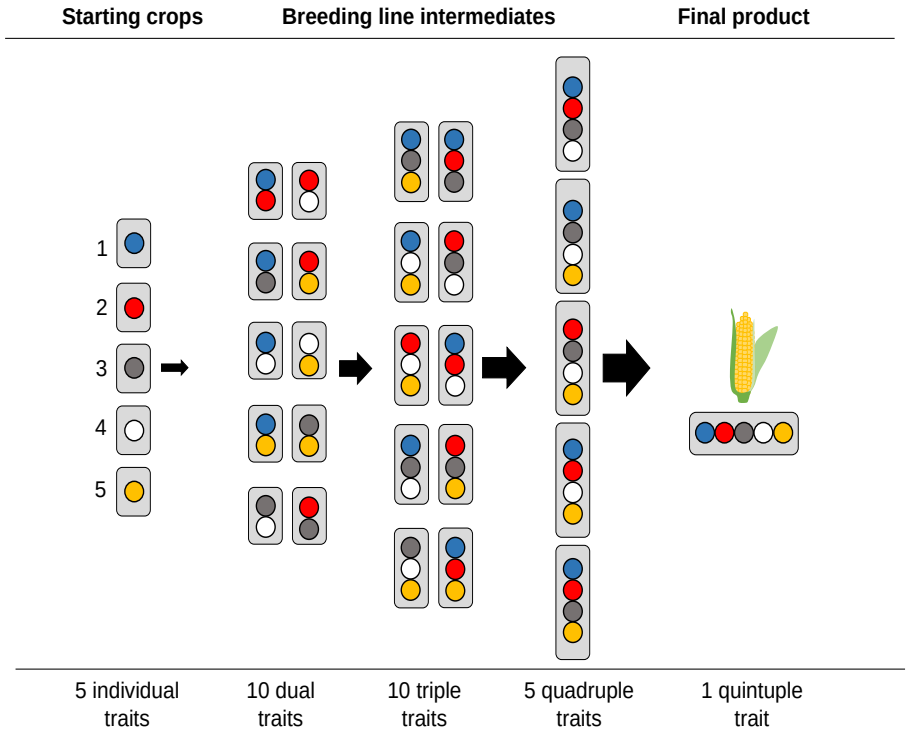
Containment

- Out-crossing of PIP pollen must be prevented regardless of test plot size if no tolerance or tolerance exemption. Dependent on biology of crop.
  - Example for corn: Spatial isolation (e.g. distances to prevent out-crossing), Reproductive isolation (e.g. bagging or detasseling corn), Temporal isolation (e.g. planting times to prevent synchronous pollination)
- Without a tolerance (or exemption), harvested crop must not enter commerce or food supply (e.g., crop destruction must be employed)
- Guidance on Small-Scale Field Testing and Low-level Presence in Food of PIPs:
  - www.epa.gov/pesticide-registration/prn-2007-2-guidance-small-scale-field-testing-and-low-level-presence-food

PIP Registrations

Seed Increase Registration

- Enables seed companies to produce enough seed for distribution to farmers
- Breeding line intermediates
  - Contain a subset of the traits in the commercial product
  - Conventional breeding used to create the final product
- Annual acreage caps for resistance management purposes
- Tolerance or tolerance exemption needed for food crops



Commercial Use Registration

- For general sale and use in commercial agricultural production
- Generally no acreage caps
- Resistance management strategy may be required
- Tolerance or tolerance exemption needed for food crops

Biotech Registration – Pesticide Registration Improvement Act

PRIA amended FIFRA to establish a fee-for-service registration paradigm

- Establishes regulatory decision time frames
- Covers all pesticide registration activities: product registrations (§3), EUPs (§5), tolerance exemptions, amendments, and more
- Fees and decision times depend on the regulatory action
  - Complex actions (e.g., new active ingredients) = larger fees, longer time frames
  - Basic actions (e.g., amendments, old a.i.s) = smaller fees, shorter time frames
  - Fee waivers (up to 75%) for qualifying small businesses; fee exemptions for federal and state agencies

PRIA biotech categories

- PIPs – Table 17
- Biopesticides (Tables 11 – 16) – covers GE microbes, could also include exogenous RNAi, GE mosquitoes
- For more information: www.epa.gov/pria-fees

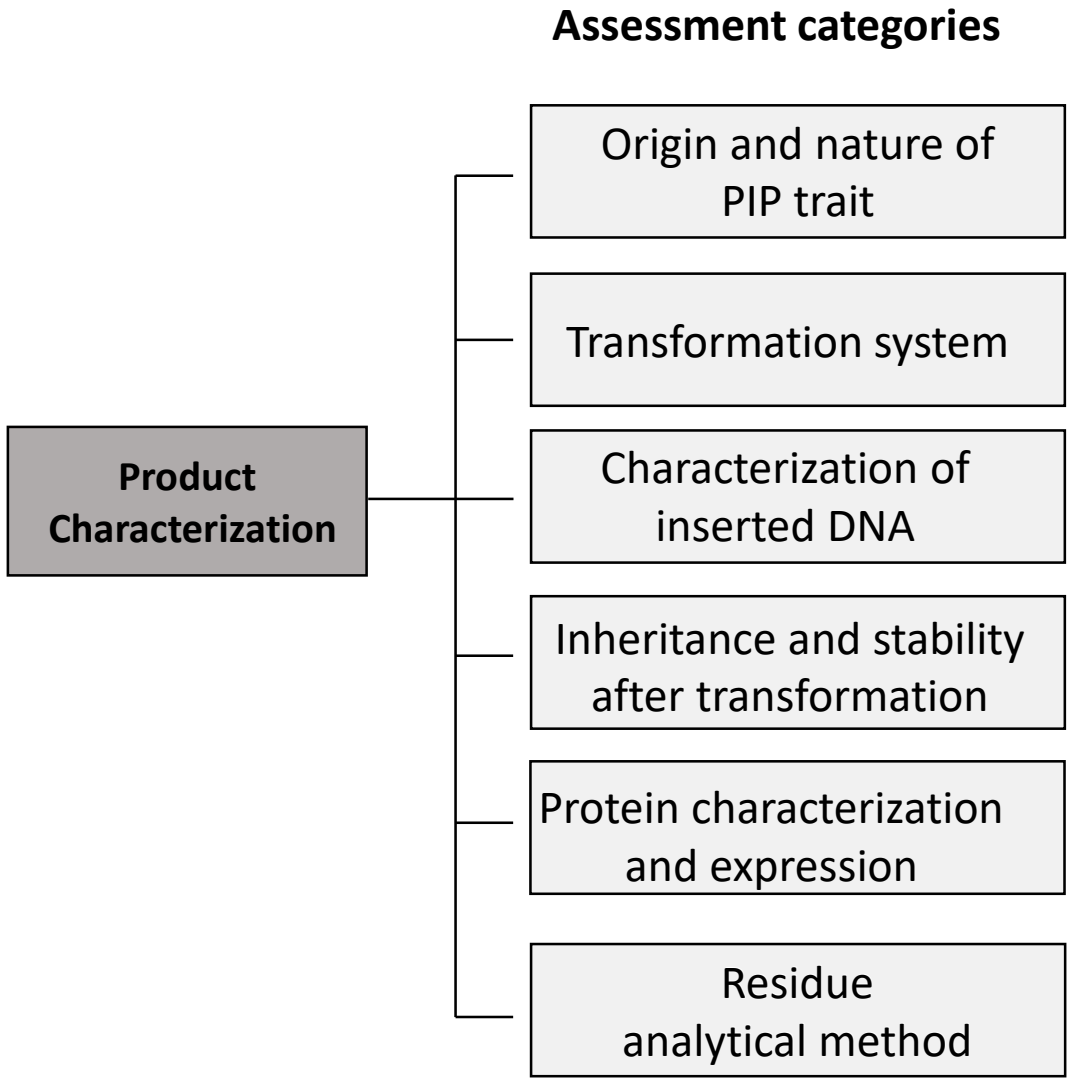
PIP Registration – Data Evaluation (cont.)

To evaluate the safety of PIPs for human health and the environment, EPA considers data and other information to address the following topics:

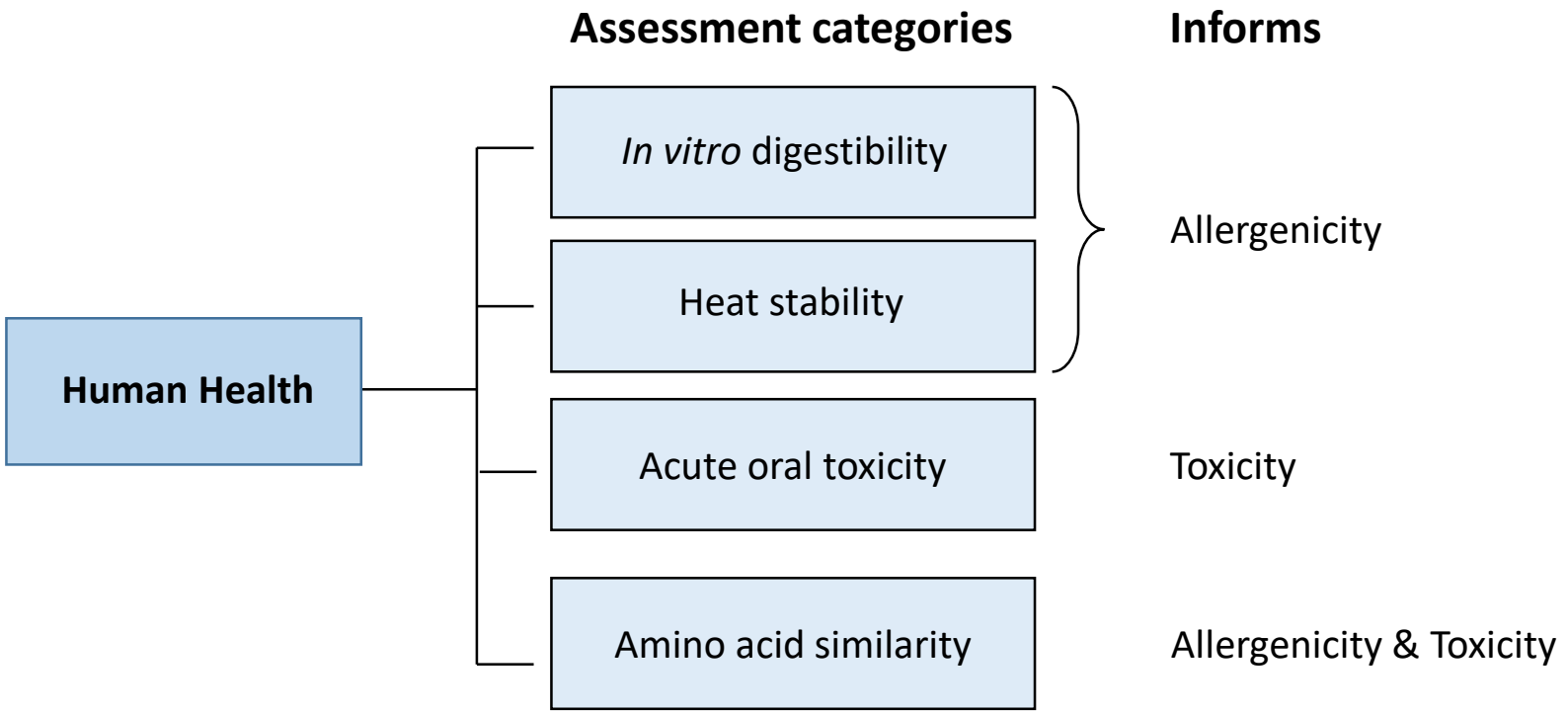
- Product Characterization
- Human Health
- Non-target organisms
- Environmental Fate
- Gene Flow
- Threatened and endangered species
- Resistance Management

For more detailed information on data evaluation for PIPs, please refer to EPA's "Plant-Incorporated Protectants Data Symposium" at: https://www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/plant-incorporated-protectants-data-symposium

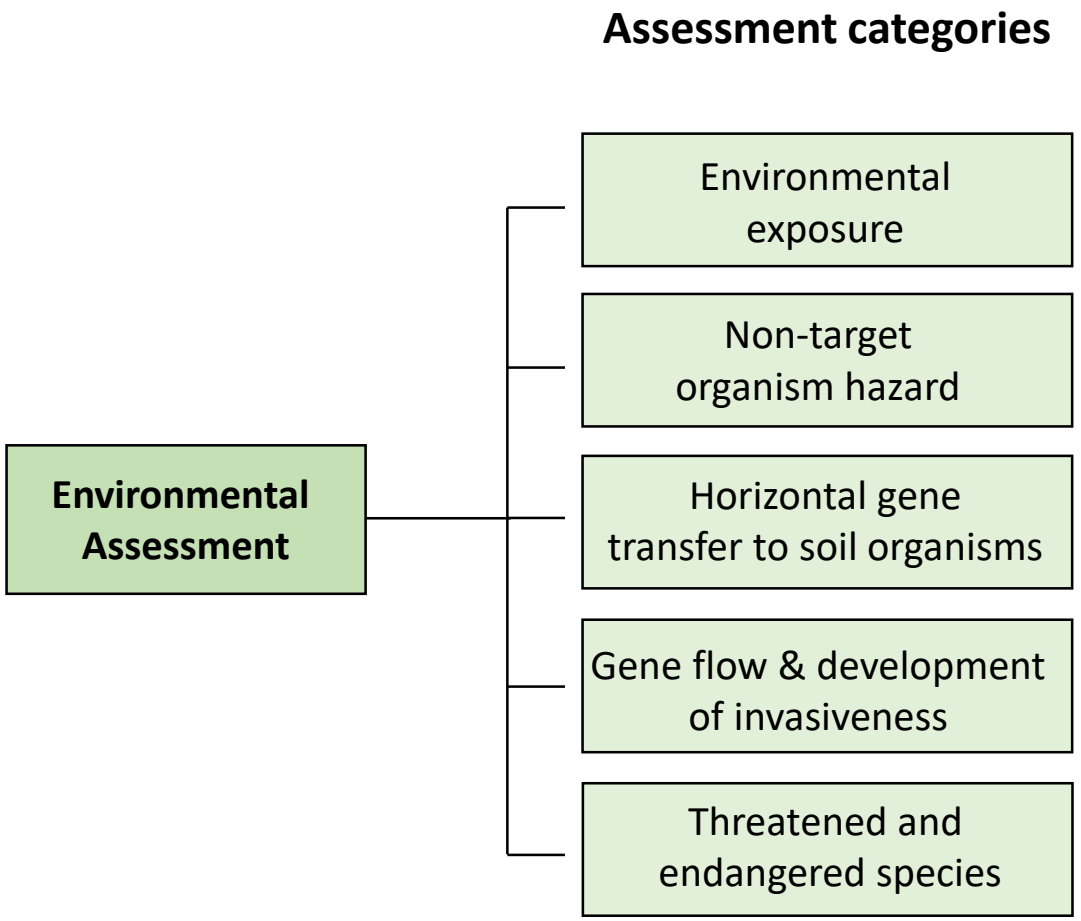
PIP Registration – Data Evaluation (cont.)



PIP Registration – Data Evaluation (cont.)



PIP Registration – Data Evaluation (cont.)



PIPs – Resistance Management

What is resistance management?

- Pest management and pesticide (PIP) use strategies to delay the evolution of resistance and prolong the effective lifespan of registered PIPs

Why resistance management?

- Risk of resistance: expression of PIP at high levels in plant tissues throughout lifespan; target pests may have multiple generations per year and specialize on the PIP crop
- Preservation of benefits: PIPs can provide substantial human health, environmental, and economic benefits
- Resistance to Bt PIPs is considered a reportable unreasonable adverse effect under FIFRA section 6(a)(2)

When is RM needed?

- PIPs targeting insects (e.g., Bt PIPs)
- PIPs targeting pests with a history of pesticide resistance (e.g., certain plant diseases)
- Other target pests: case-by-case, considering feasibility, risk-benefit
- RM strategies required for commercial use (section 3) registrations
    - Not required for Experimental Use Permits, seed increase registrations due to low acreage
    - Required by the terms of registration

PIPs – Resistance Management (cont.)

Risk Assessment
(information used to develop the RM strategy)

- Pest biology
- Dose of the PIP
- Mechanism of resistance and potential for cross resistance
- Simulation modeling
- Mitigation strategy

Stewardship
(post-registration activities to enact the RM strategy)

- Resistance monitoring
- Remedial action strategy
- Compliance program (structured refuges)
- Grower education program
- Reports to EPA

PIPs – Information Resources

- **Biopesticides** - www.epa.gov/pesticides/biopesticides
- **Pesticide Registration Manual** - www.epa.gov/pesticide-registration/pesticide-registration-manual
- **Registration Fees under PRIA** - www.epa.gov/pria-fees
- **Pesticide Registration** - www.epa.gov/pesticide-registration
- **Plant-Incorporated Protectants** - www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/overview-plant-incorporated-protectants
- **Current and Previously Registered PIPs and their Risk Assessments** - www.epa.gov/ingredients-used-pesticide-products/current-and-previously-registered-section-3-plant-incorporated
- **Tips for PIP Experimental Use Permit Submission -** www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/tips-plant-incorporated-protectant-pip-experimental
- **Guidance on Small-Scale Field Testing and Low-level Presence in Food of PIPs** - www.epa.gov/pesticide-registration/prn-2007-2-guidance-small-scale-field-testing-and-low-level-presence-food
- **PIP Data Symposium -** www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/plant-incorporated-protectants-data-symposium