# Regulation of Plant-Incorporated Protectants by EPA

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# Navigating EPA

- **EPA, Office of Pesticide Programs, oversees the sale, distribution and use of all pesticides in the US, including PIPs**

- **EPA recommends early, confidential consultations regarding PIP products prior to environmental release or entry into the food or feed supply**

# 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
- Endangered Species Act - (ESA) any impact on threatened or endangered species

# Risk Assessment Process

**Risk = Hazard x Exposure**

RISK

BENEFITS

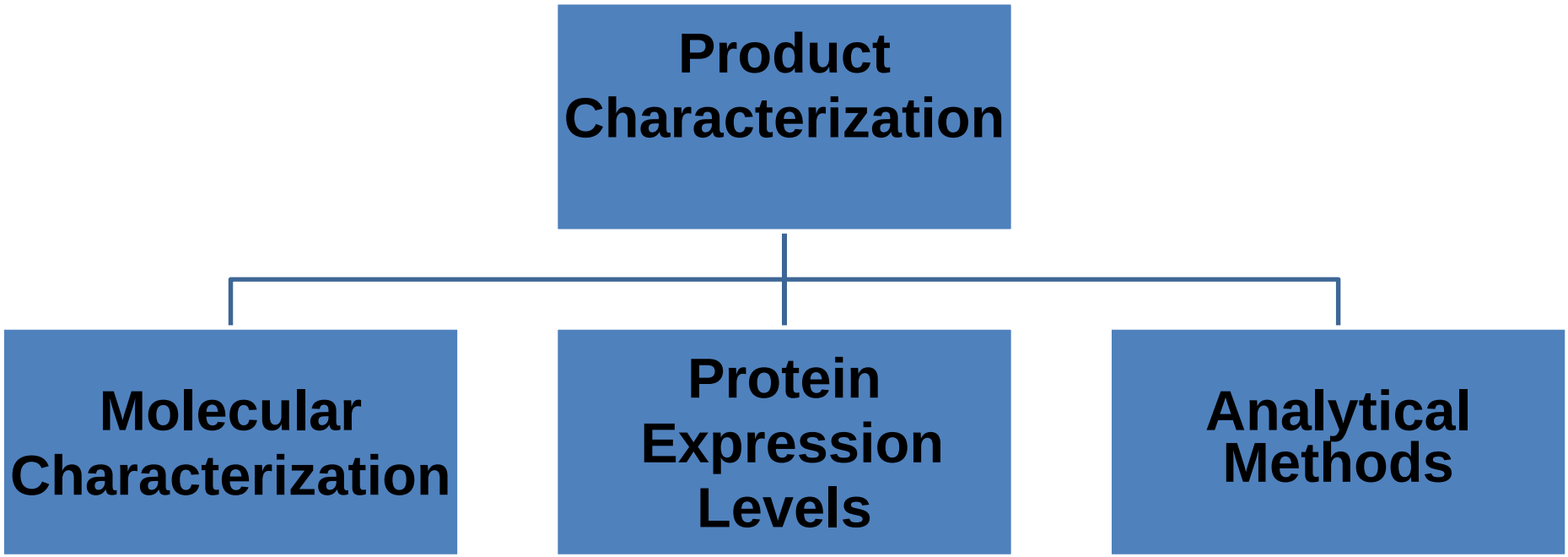
# Navigating EPA

- For pesticidal products intended for cultivation in the US, FIFRA is applicable
- Food and Feed products entering into commerce require appropriate tolerance actions under FFDCA for legal entry; if viable seed or propagules, then possibly FIFRA too.
- Tolerance actions require examination of DNA and Protein sequence information with toxicological assessment as well

# Experimental Use Permits

- Cumulative acreage ≥ 10 A (4 HA) terrestrial or ≥ 1A 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

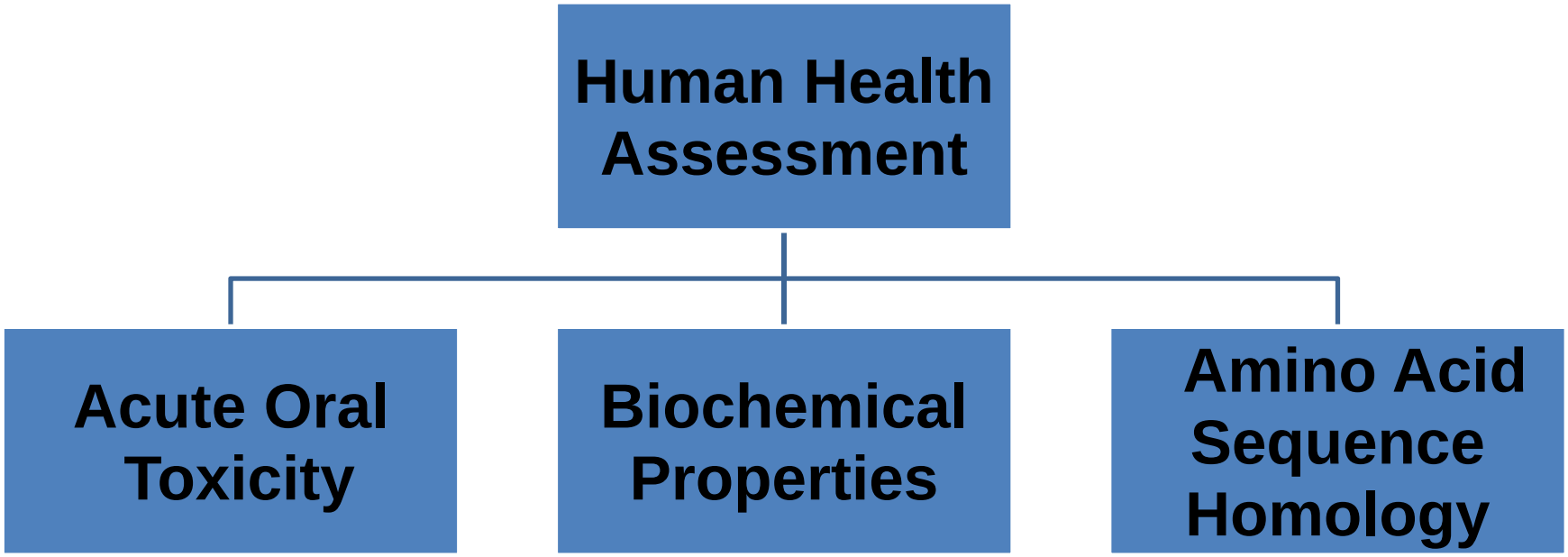
# How EPA Characterizes PIPs



# 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, and glycosylation status are all parameters to examine**
- **Bioassays can also be informational in establishing equivalency**

# How EPA Assesses Human Health Effects for PIPs



# Toxicity Determination

- **Amino acid homology to known toxins**
- **Heat Stability test- protein is inactivated against susceptible pest species when heated**
- **Lack of mammalian toxicity at high levels of exposure to the pure PIP protein (oral tox test)**
- **Safety of the products at levels well above maximum possible exposure levels that are reasonably anticipated in the crops**

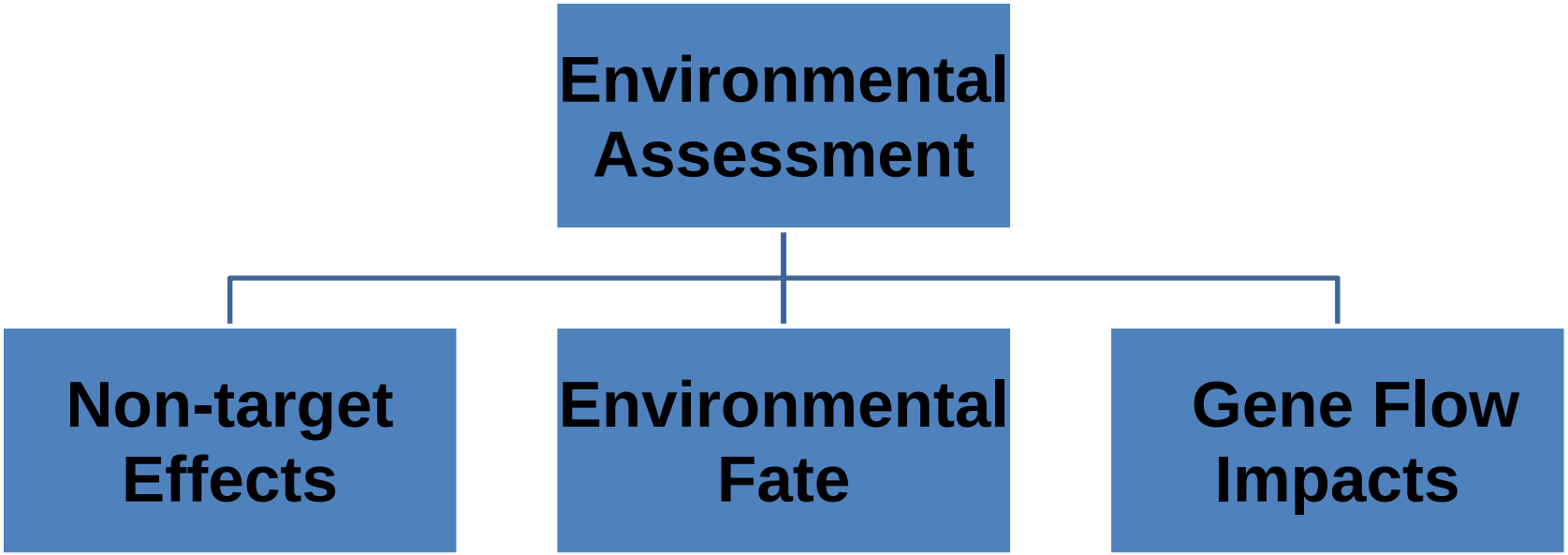
# Allergenicity

***Codex* Standard: "Weight of evidence approach"**

**Factors considered:**

- **Source of the trait**
- **Prevalence in food**
- **Amino acid sequence similarity with known allergens**
- **Biochemical properties of the protein**
- ***In vitro* digestibility (gastric / intestinal)**
- **No single predictive criterion**

# How EPA Assesses Environmental Effects for PIPs



# 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***

# Data Required for Environmental Fate

- **Quantification of protein expression levels of the PIP in various plant tissues / organs**
  - **Over plant developmental growth stages**
  - **At multiple locations**
- **Determination of fate of PIP residues in environment-**
  - **Protein persistence and degradation in soil**
- **Based on biology of the plant:**
  - **Environmental Impact Assessment of Gene Flow**

# 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

- **Food or Feed which is considered adulterated may be quarantined, seized or rejected at the port of entry**

- **FDA carries out the enforcement aspects associated with EPA's tolerance actions**

# Navigating EPA

- **Tolerance actions consider data from an acute oral toxicity test, sequence comparison to known toxins and allergens, *in vitro* digestability 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.**

# Navigating EPA

- **Submission of data to EPA in support of a tolerance or registration action is made with the understanding that the performing laboratory may be inspected to ensure compliance with good laboratory practices.**

# PRN 86-5 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!**
- http://www.epa.gov/PR_Notices/pr86-5.html

# PRN 86-5 Formatting

- ATTACHMENT 4

  SUPPLEMENTAL STATEMENT OF DATA CONFIDENTIALITY CLAIMS

  For any portion of a submitted study that is not described by FIFRA section 10(d)(1)(A), (B), or (C), but for which you claim confidential treatment on another basis, the following information must be included within a Supplemental Statement of Data Confidentiality Claims:

  o Identify specifically by page and line number(s) each portion of the study for which you claim confidentiality.

  o Cite the reasons why the cited passage qualifies for confidential treatment.

  o Indicate the length of time--until a specific date or event, or permanently--for which the information should be treated as confidential

# Other Considerations

- **FIFRA authorizes the use of Scientific Advisory Panels (SAPs) for novel pesticides or new uses or for larger issues for which the Agency feels it needs a public forum and expertise from outside of EPA**
- **Questions posed, deliberations and final reports are posted on the EPA website by year or A-Z**
- http://www.epa.gov/scipoly/sap/meetings/index.htm
- http://www.epa.gov/scipoly/sap/tools/atozindex/atozindex.htm

# Navigating EPA

- **Early consultation before submission of application is encouraged**
- **“Pre-submission” meeting(s) - confidential**
- **Determination of applicable data requirements needed early on**
- **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 – Mike Mendelsohn, Regulatory Action Leader (Mendelsohn.Mike@epa.gov)
  - Chris Wozniak, Biotechnology Special Assistant
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