U.S. EPA Regulation of Plant-Incorporated Protectants (PIPs)

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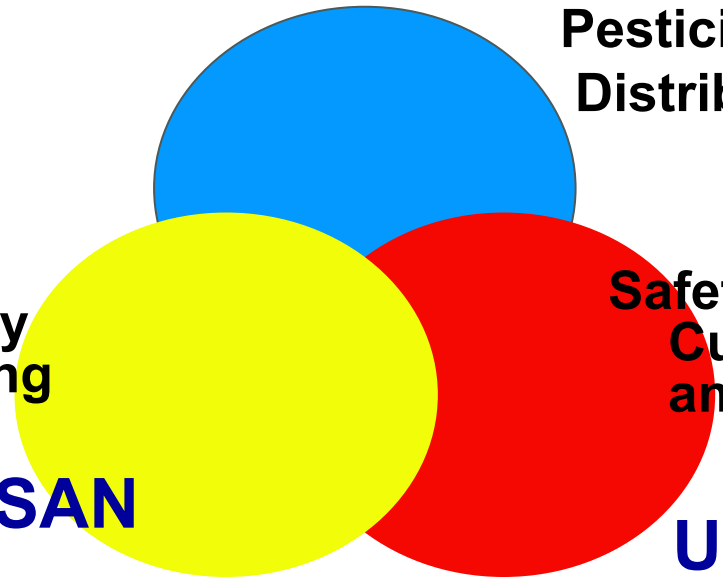
Federal Oversight of Biotechnology Coordinated Framework

EPA/OPP

Safety Assessment for Pesticides (Including Distribution and Labels)



Food Safety and Labeling

FDA/CFSAN

Safety Assessment for Cultivation, Movement and/or Importation

USDA/APHIS

Animal and Plant Health Protection

Plant Incorporated Protectants

- Plants that are genetically modified, through modern biotechnology, to express pesticidal substances
- The substance expressed by the plant and the introduced genetic material necessary for its production in the plant comprise the legal definition of a plant incorporated protectant (PIP)
- Also includes any inert ingredient contained in the plant, or produce thereof
- Case-by-case approach

Human Health and Environmental Safety Standard

Reasonable Certainty of No Harm will Result from Aggregate Exposure

→ **A Finding Necessary for Tolerance Exemption under FFDCA**

No Unreasonable Adverse Effects Upon Man and the Environment

→ **A Finding Necessary to Support Registration under FIFRA**

Risk Assessment Process

Risk = Hazard x Exposure

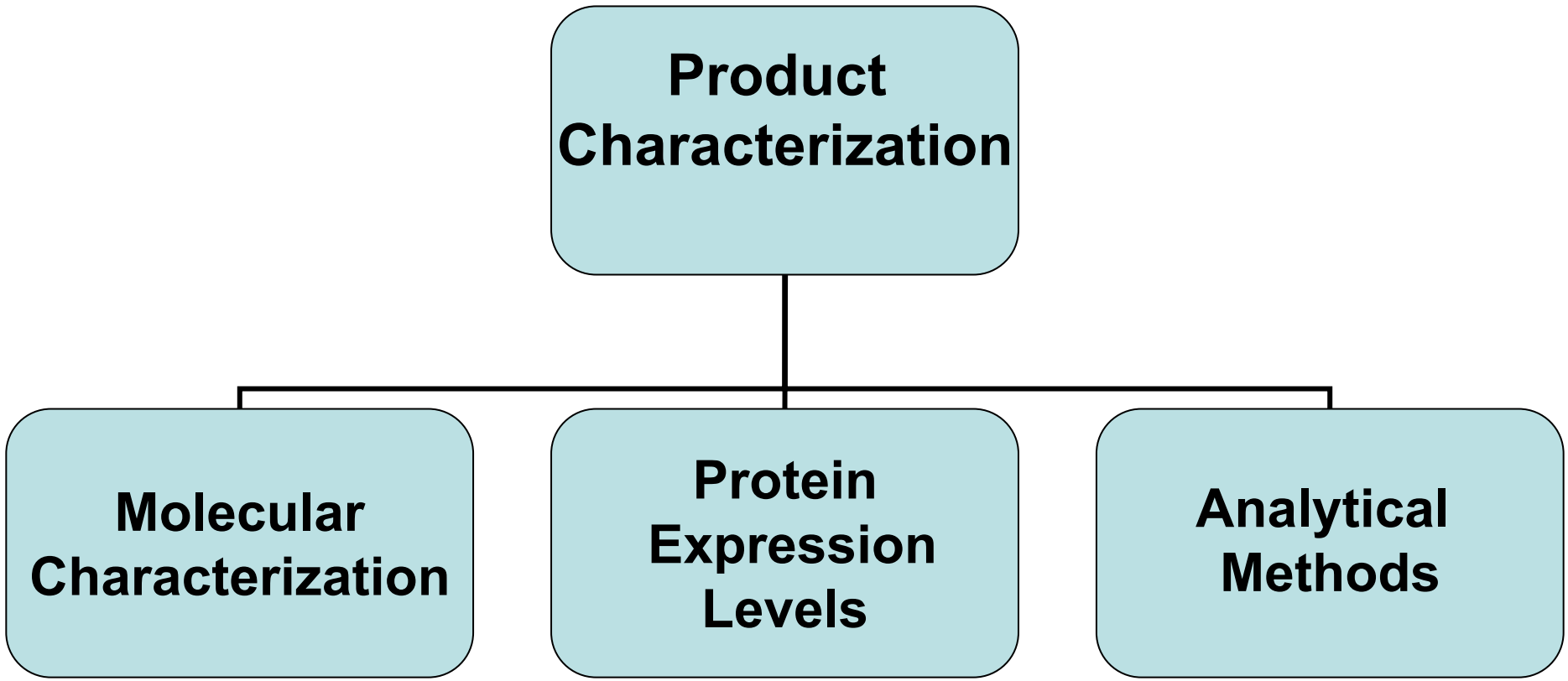
RISK

BENEFITS

PIP Data Requirements

- Product Characterization
- Human health Effects
  - Toxicity
  - Allergenicity
- Ecological Effects
  - Non-target effects
  - Environmental fate & persistence
- Gene Flow Assessment

How EPA Characterizes PIPs



Molecular Characterization

- Description of the genetic material delivered to the recipient plant.
- Inheritance and stability of the introduced traits.
- Protein characterization and expression in plant.
- Transformation method and copy #

Protein Expression Levels

- Quantitative changes with plant development / phenology
- Protein levels - various plant organs during growing season + by location
- Data are presented in terms of dry weight from statistically significant sample sizes
- All control samples should be negative (no cross reactivity)

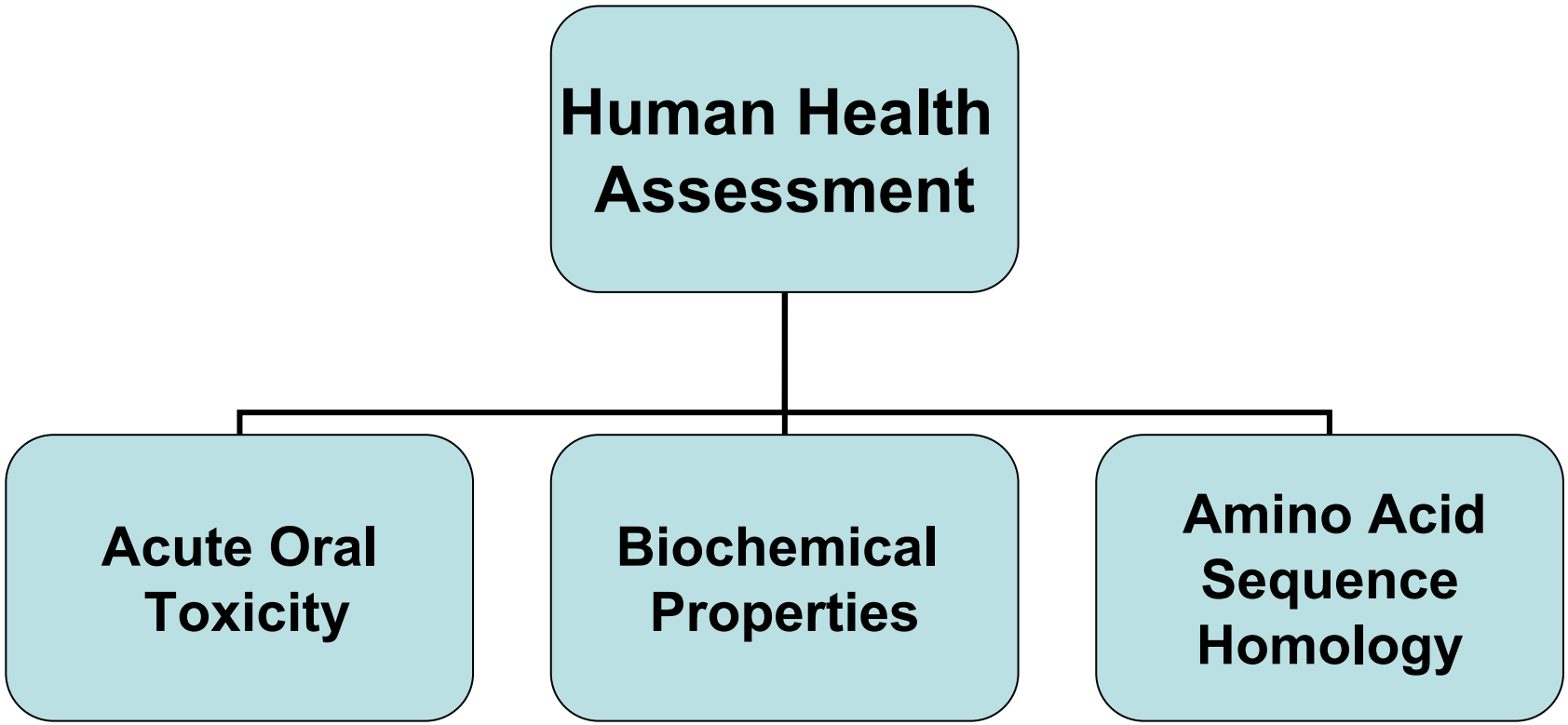
Analytical Methods

Registrant must provide analytical detection method and data within a commodity.

Validation of method by independent 3rd party laboratory for sensitivity and cross-reactivity

→ No cross reactivity with other commercially available conventional and transgenic tissue should be detected; and assay should exhibit high sensitivity

How EPA Assesses Human Health Effects for PIPs



HUMAN HEALTH EFFECTS

- **Acute Oral Toxicity at limit dose with pure PIP Protein at 2 – 5 g / kg BW.**
- **No chronic toxicity testing triggered to date.**
- **Allergenicity assessment- “weight of evidence” approach.**
- **Source of protein, AA sequence similarity of PIP protein to databases of toxins, allergens & anti-nutrients.**
- **Data sufficient to support a tolerance exemption.**

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* tests- protein degradation in simulated gastric environment**

Environmental Effects

- **Non-target organisms (NTOs)**
  - Avian oral (poultry / quail)
  - Wild mammal (rat / mouse)
  - Freshwater fish (rainbow trout)
  - Freshwater invertebrate testing (Daphnia)
  - Estuarine & marine animal testing (shrimp & estuarine or marine fish spp.)
  - Non-target insects / earthworms
- **Endangered species assessment**

Environmental Fate

- **Protein expression**
  - **Various stages and organs**
- **Protein persistence and degradation**
  - **Soil binding and DT_{50}**
- **Effects on soil microorganisms**
  - **Toxicity to bacteria, fungi, protozoa**
- **Horizontal Gene transfer**
  - **Probability of integration and expression**

Where do the genes go?

Gene Flow Assessment

- Potential for Weediness / Invasiveness
- Sexual compatibility w/ indigenous and feral plants / NTO effects
- Population dynamics
- Will the recipient plant be at any significant dis / advantage for selection?
- How does one assess such potential?

Cotton – *Gossypium hirsutum*

Gossypium tomentosum

Hawaiian cotton – Ma’O

When Is an EUP Required?

- **Testing an area of cumulative total ≥ 10 A requires an Experimental Use Permit for pests that occur in different geographical situations, (≥ 10 acres per pest)**
- **A tolerance may be needed and is advised with an EUP**

Food Tolerance Issues

- **Containment of PIP by isolation or mitigation (bagging / detasseling corn, GURTs, etc.) can negate need for a tolerance / tolerance exemption**

- **Without a tolerance and containment , the harvested crop must not enter commerce and out-crossing of PIP pollen must be prevented regardless of test plot size**

Current Agency Concerns

- Post-gene flow risk assessment
- RNAi-based mechanisms – what is the a.i.? Non-target effects? Fate?
- Viral coat protein mediated resistance
- Allergenicity assessment
- Defining plant-growth regulators

Summary

→Speak with your favorite regulator **prior to any field tests**

→**Be aware of food tolerance issues for pesticidal substances (PIPs) !!**

→Consider the Big Picture when selecting genes for expression *in planta*

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Useful Links

- www.epa.gov/pesticides/biopesticides
- http://usbiotechreg.nbii.gov
- http://www.aphis.usda.gov/biotechnology/index.shtml
- http://vm.cfsan.fda.gov/~lrd/biotechm.html
- http://www.ostp.gov/cs/issues/CEQ_OSTP_Environmental_Regulation.html

Questions ?