Regulation of Plant-Incorporated Protectants by EPA

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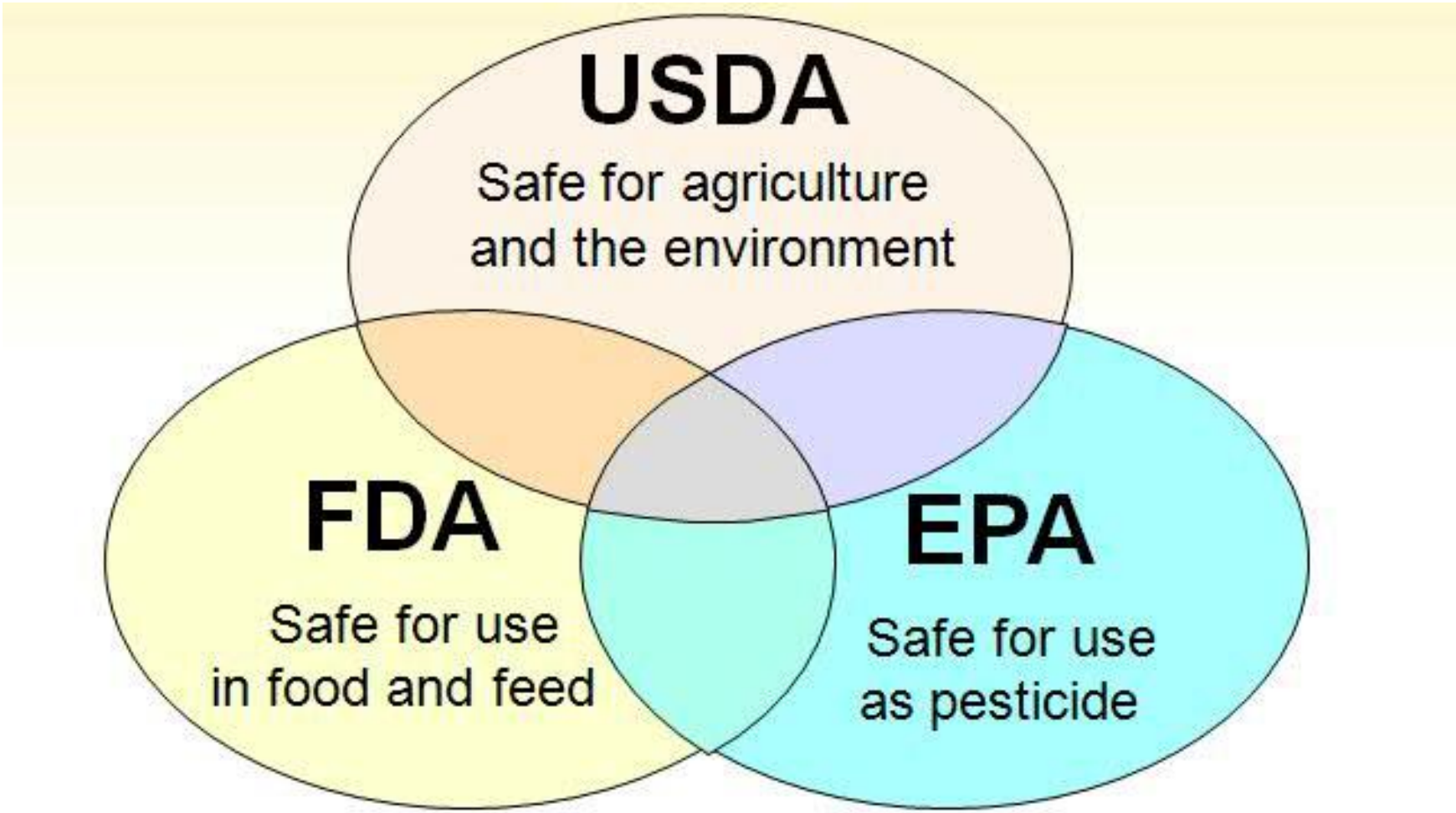
EPA


USDA
Safe for agriculture
and the environment
FDA
Safe for use
in food and feed
EPA
Safe for use
as pesticide

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)

Inert ingredients may include antibiotic resistance genes / proteins and herbicide tolerance markers used in the development of the PIP product

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

EPA's Statutory Authority

- **Federal Insecticide, Fungicide and Rodenticide Act – (FIFRA) - pesticides**
  - **No unreasonable adverse effects upon man and the environment**
- **Federal Food Drug and Cosmetic Act – (FFDCA) - food and feed safety**
  - **Reasonable certainty of no harm from aggregate exposure**

Pesticide Registration Improvement Act (PRIA)

- Fees are associated with regulatory actions performed by EPA-OPP
- Costs vary with type of action and entity / company requesting the action
- Federal Government researchers have fees waived, while land-grant university researchers have reduced fees
- Companies may pay according in part to income and # of employees

Risk Assessment Process

Risk = Hazard x Exposure

RISK

BENEFITS

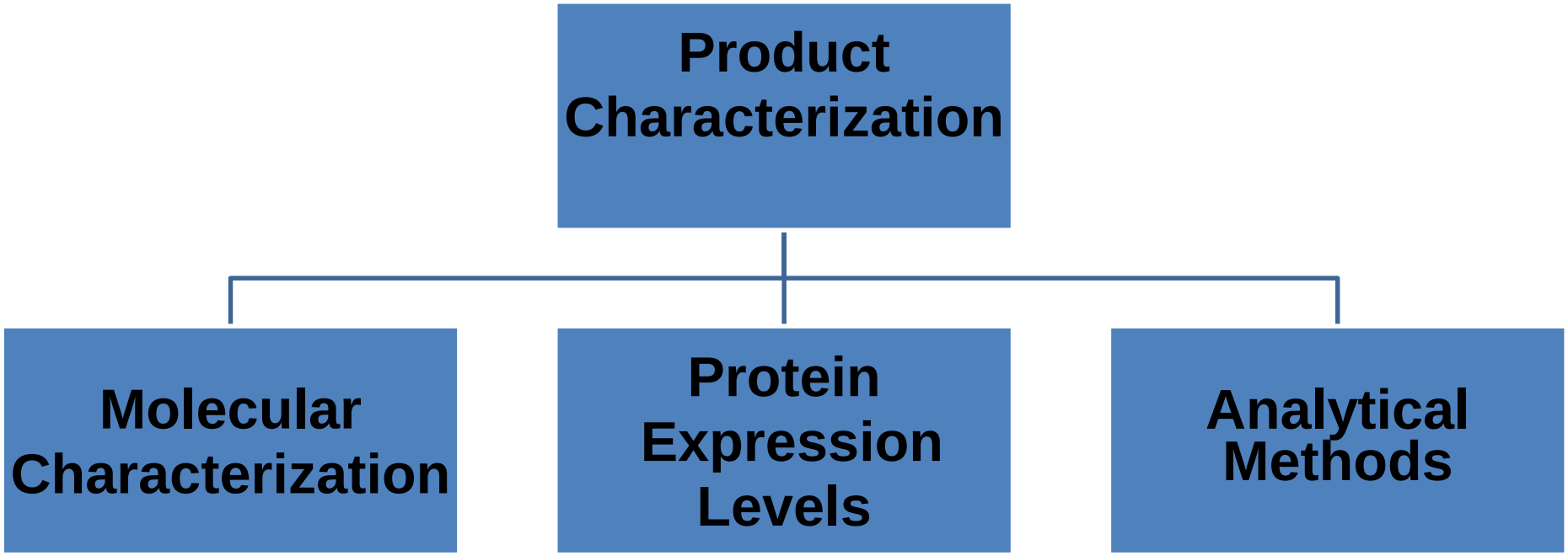
Navigating EPA

- 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**

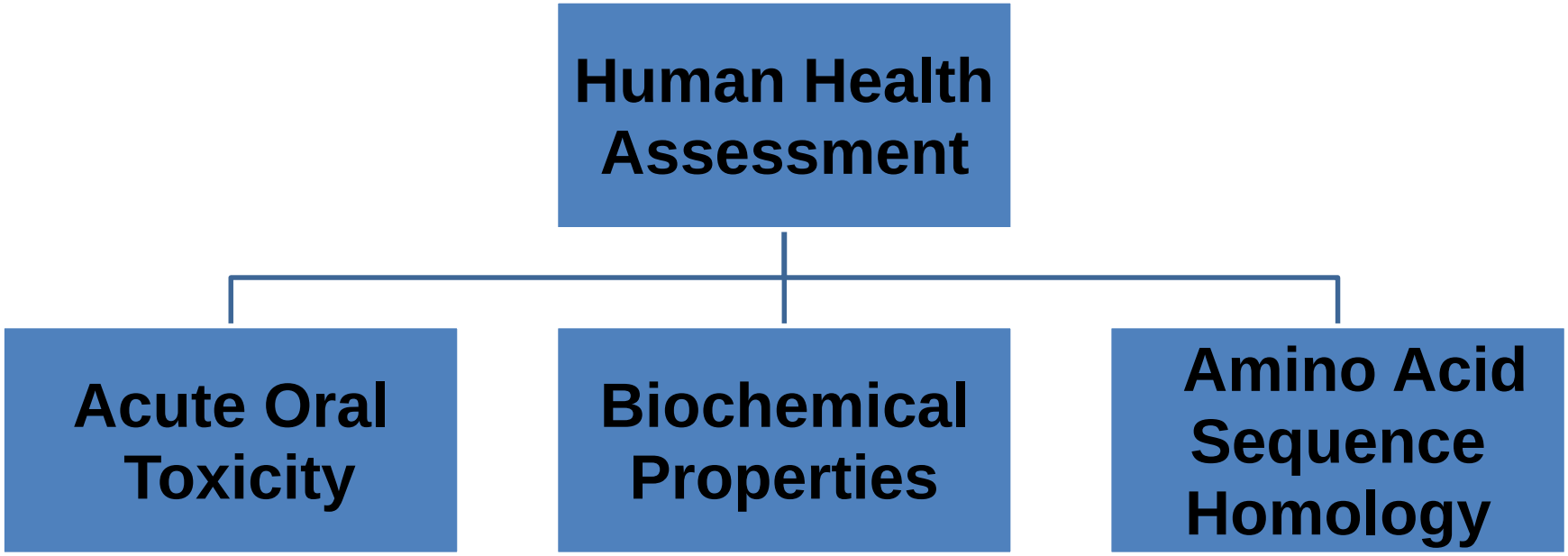
How EPA Characterizes PIPs



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/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



Toxicity Determination

- Amino acid homology to known toxins
- 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
- When multiple PIP traits are combined, evaluation of synergism is required

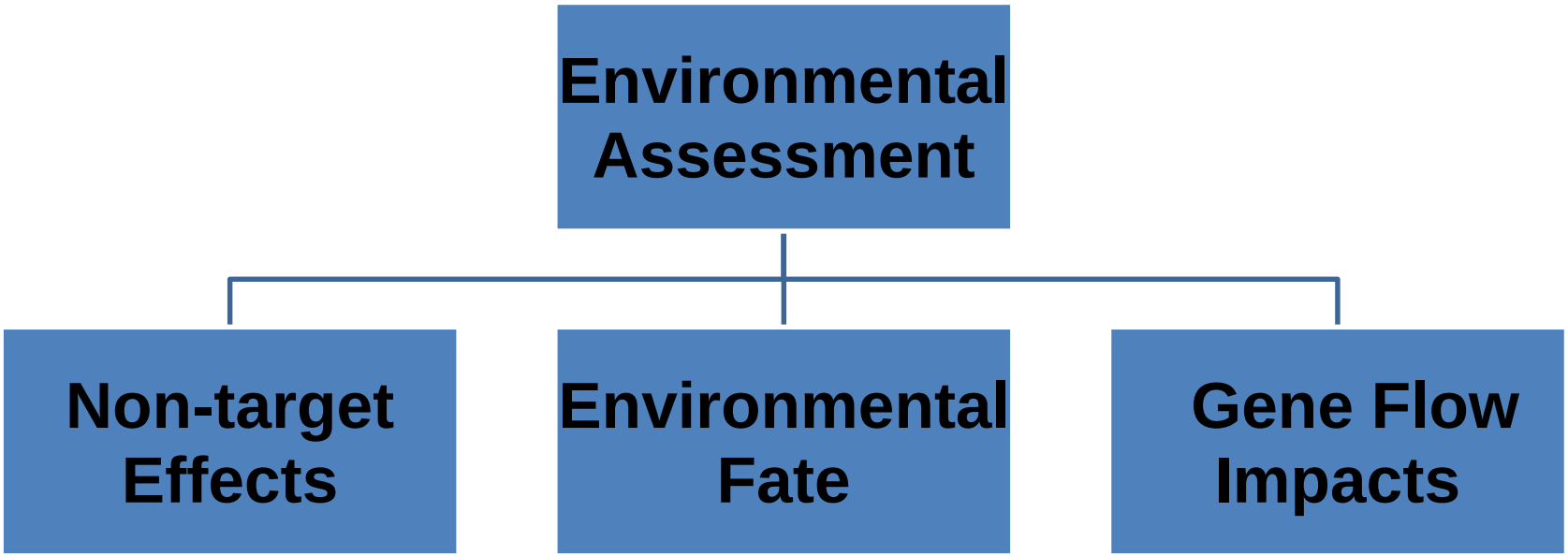
Allergenicity

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

Factors considered:

- **Source of the trait**
- **Prevalence in food**
- **Heat Stability test- protein is inactivated against susceptible pest species when heated**
- **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 (whole hive or larval)
- Non-target arthropod testing (beneficial insects)
- Wild mammal toxicity (acute oral 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**

Food Tolerance - FFDCA

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

Food Tolerance Analysis

- **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**
- **Studies are generally conducted under GLP, however, exceptions exist**

PRN 2011-3 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!**
- https://www.epa.gov/pesticide-registration/prn-2011-3-standard-format-data-submitted-under-fifra-and-certain-provisions

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
- https://www.epa.gov/sap/fifra-scientific-advisory-panel-meetings

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

Summary

- EPA's risk assessment focus is on the gene and pesticidal substance
- A tiered testing approach is used, starting with acute toxicity tests
- Some data requirements may be fulfilled with literature and rationale rather than empirical data generation

Useful websites

- http://www.epa.gov/pesticides/biopesticides/regtools/biotech-reg-prod.htm [Biotech Pesticide Regulation]
- https://www3.epa.gov/pesticides/chem_search/reg_actions/registration/decision_PC-006354_7-May-10.pdf [Plum Pox BRAD]
- http://www.epa.gov/pesticides/biopesticides/reg_of_biotech/eparegofbiotech.htm [Biotech Pest Management]
- https://www.epa.gov/ingredients-used-pesticide-products/current-and-previously-registered-section-3-plant-incorporated [PIPs registered]
  https://www.regulations.gov/document?D=EPA-HQ-OPP-2013-0485-0049 [RNA interference report]

Who can I contact to get started?

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