Problem Formulation in Practice
U.S. Regulatory Perspective

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*The contents of this presentation reflect the thoughts and opinions of the speaker and do not represent an official policy statement from the U.S. Environmental Protection Agency or other federal government agencies. Any mention of a product does not constitute an endorsement by the U.S. federal government.
Biotech products are regulated according to their intended use, with some products being regulated under more than one agency.
EPA’s Office of Pesticide Programs (OPP) regulates the sale, distribution, & use of all pesticides in the United States to protect human health & the environment, including crops containing *Plant-Incorporated protectants (PIPs)*.

Plants containing PIPs are genetically modified through modern biotechnology to express pesticidal properties.
EPA’s Authority

Federal Insecticide, Fungicide & Rodenticide Act (FIFRA)

Pesticides must registered prior to distribution or sale

Sec. 3 – Registration requirements – risks must be weighed against benefits from pesticide use

Sec. 5 – Experimental Use Permits (EUPs) for research, field tests to generate data for registration

→ Required for >10 acres land or 1 acre of water per pest

FIFRA Legal Standard:
“No unreasonable adverse effects to human health and the environment...” taking into account the economic, social, and environmental costs and benefits of the use of any pesticide.
EPA’s Authority

Federal Food, Drug & Cosmetic Act

- Establishes tolerances or MRLs (Maximum Residue Limits) for permissible amount of pesticides residues in food & animal feed or exemptions from the requirement of a tolerance
- Must be established for all pesticide products (including PIPs)

FFDCA Legal Standard:
“...reasonable certainty that no harm will result from aggregate exposure to the pesticide residue in food”
EPA’s Authority

Other Statutes

**Food Quality Protection Act (FQPA)**

- EPA Reviews All Pesticides Every 15 Years to Ensure Data Base Continues to Support Registration

- **Pesticide Registration Improvement Act II (PRIA II)**
  - Established Registration Service Fees & Statutory Deadlines for EPA to Make Registration Decisions
  - Fees, Deadlines Based on Categories of Registration Actions
Environmental Risk Assessment

*Data required for Ecological Effects-NTOs*

- Avian oral toxicity
- Avian oral dietary toxicity
- Freshwater fish oral toxicity
- Freshwater invertebrate testing
- Honey bee oral toxicity testing
- Non-target insect testing
- Wild mammal toxicity *
- Estuarine and marine animal testing *
- Non-target plant toxicity studies *
- Endangered species considerations → exposure determination

* Often waved or satisfied with alternative data citation
Environmental Risk Assessment

Data required for Environmental Fate

✔ Quantification of protein expression levels of the PIP in various plant tissues/ organs (if expressed)
  – *Over plant developmental growth stages*

✔ 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
  – Potential for Weediness
  – Potential for Horizontal Gene Transfer

Established history of use of problem formulation in ERAs
Primary Use of Problem Formulation

*Pre-Submission Meeting*

**Purpose:** Applicant proposes how to satisfy data requirements and provides opportunity for EPA to provide guidance/consultation for best use of relevant data to submit a complete and scientifically sound data package to satisfy the proposed regulatory decision.

- Integration of available data
- Identify assessment endpoints related to management goals
- Agree on applicability of any of existing data to address data requirements:
  - Develop Conceptual model and risk hypotheses
  - Analysis plan- Generation of new data
**Problem Formulation**

**Integration of Available Information**

- **Background & familiarity of PIP**
- **Preliminary data produced during PIP product development**
  - Spectrum of Pesticidal Activity
  - Mode of Action
  - Susceptibility of Non-Target Organisms (NTOs)
- **Data requirements**
  - Requests for Waivers of Data Requirements
  - Citation of Data from publically available, peer-reviewed scientific literature, and published research findings
  - Rely on previously reviewed, acceptable data for similar registered PIPs
Use of Problem Formulation

Identify Assessment Endpoints

Management Goal Assessment:

IN GENERAL: No unreasonable adverse effects to the environment under FIFRA

REFINED TO: No adverse effects to ecologically entities of concern with potential exposure to PIP

Identify Assessment Endpoint:

- NTOs representing a functional group of ecological importance (natural predators and paristoids to target pests, pollinators, decomposers)
- Other non-target herbivores, non-target pests
- Threatened/endangered species
Problem Formulation

Conceptual Model

Delineates hazards to NTOs from potential exposure to PIPs

Source of risk based upon:

- Biology of the transformed plant
- Introduced PIP pesticidal trait and
- Environment where transformed plant is grown

Examination of sources of risk & predicting interactions, pathways & extent of potential harm can be characterized to produce a specific roadmap & narrow the scope of the risk assessment to NTOs most likely to be exposed
Conceptual Model - Pathways of Exposure to PIP

- **Non-target Pests**
- **Target Pests**
- **Natural Enemies**
- **Other Non-target Herbivores**
- **Pollinators**
- **Decomposers**
- **Bt Crop Plant**
- **Plant tissue residues & roots**
- **Pollen drift**
- **Direct effects?**
- **Indirect effects?**

**Pathways of Exposure to PIP**

- **Plant tissue**
- **Plant tissue residues & roots**
- **Pollen drift**
- **Same target pests on other crops**
- **Other Host Plants and Crops**
- **Non-target Herbivores**
- **Target Pests**
- **Natural Enemies**
Decision Tree for Defining the Risk Hypotheses

1. Does the host/prey ingest the toxin?
   - No
   - Yes

2. Is the host/prey susceptible to the toxin?
   - No
   - Yes

3. Does the parasitoid/predator ingest the toxin?
   - No
   - Yes

4. Is the parasitoid/predator susceptible to the toxin?
   - No
   - Yes

- Direct and host/prey-mediated effects expected, but not distinguishable
- Host/prey-mediated effects expected
- Direct effects expected

Use of Problem Formulation

Defining Risk Hypotheses

Based on the conclusions and predictions discussed at the problem formulation stage and pre-submission meeting, plausible risk hypotheses are defined.

Example: “The PIP is not toxic to NTOs at the estimated environmental concentration present in the field.”
Problem Formulation

After Pre-submission Meeting

**FOLLOW-UP ACTIVITIES:**

- Applicant provides summary of key points of discussion from the pre-submission meeting to EPA. EPA concurs or provides additional guidance or clarifications where needed

- Applicant and risk manager maintain on-going communications - very important if additional questions arise while applicant constructs the application

- Applicant may submit proposed protocol(s) to generate required data, EPA reviews protocol, and informs applicant of acceptability of protocol
Use of Problem Formulation

Data Analysis Stage

**Testing the Risk Hypotheses:**

1) Ecological effects (NTOs) are characterized using a **tiered-testing system** via the use of early laboratory studies. The studies must be interpretable in the context of the risk hypothesis.

2) Exposure characterization is based on calculation of **Estimated Environmental Concentration** (ECC) in the field (in context of dose-response of NTOs toxicity testing to quantify hazard).

![Diagram showing the relationship between characterization of exposure and ecological effects, with arrows indicating the flow of information between stages.]
Tiered Testing

**Tier I**
Simple,
Represents worst-case scenarios
High Dose (MHD) – bacterial derived protein
High EEC (10 X)

If triggered:

**Tier II**
Plant material or pure plant protein
(1-5 X EEC)

**Tier III**
Long-term laboratory, greenhouse or semi-field tests

**Tier IV**
Long-term and large scale field tests/multiple locations

Field Monitoring
Data Analysis

Benefits of Tiered Testing

✓ Simple design, hypothesis-driven, with proper statistical analysis due to highly controlled variables
✓ Easily standardized, repeatable, easily interpreted
✓ Worst-Case Scenario- very conservative assumptions compensate degree of uncertainty
✓ High dose increases chance that effects on less-sensitive species may be detected
✓ Negative results extrapolated to predict no adverse effects on NTOs including threatened/endangered species at field levels of exposure; provides high degree of confidence
Other Uses of Problem Formulation

During Registration Process

Phase I: Review of Application

- Screen for completeness
- Identify Data deficiencies

Phase II: Publication in Federal Register

- Receipt of a new active ingredient
- Petition for a tolerance or tolerance exemption

If data deficiencies are noted- additional studies may be required (using problem formulation)
Other Uses of Problem Formulation

**During Registration Process**

**Phase III and IV: Data Review**

- EPA review of submitted data for risk characterization
- Characterization of Risk and Preparation of BRAD
- If unresolved data deficiencies
  - Additional information/data required
  - Letter to registrant (75 days to address)
  - Renegotiation of PRIA due dates (if necessary)
Other Uses of Problem Formulation

Post-Registration Decisions

Phase V: Regulatory Decision

- Decision approved by management
- May have terms and conditions to be fulfilled and expiration dates
- Approval of label with risk mitigations measures as needed
- Issuance of tolerance or exemption (publication in Federal Register as a final rule)
- Documents (BRADs, Fact Sheets, etc.) made publically available
Other Uses of Problem Formulation

Post-Registration Regulatory Actions

- Registrants are required to report cases/incidents of unexpected adverse effects for EPA evaluation [under FIFRA 6(a)2]

- **Registration Review** - Period reevaluation by EPA to ensure existing data continue to support registration

- **New published research studies** - with scientific evidence indicating potential risk

**EPA can issue Data Call-Ins (DCIs):** Authority to ask for additional information/new studies as needed
Problem formulation directs the scope and execution of the ERA and helps eliminate negligible risks from further consideration, to focus on the collection of data that are useful for the ERA.

Collective experiences from the practice of problem formulation in ERAs have demonstrated its effectiveness, especially in the initial stages of data submission.

Use of the tiered-testing approach ensures, to the greatest extent possible, that the Agency utilizes the minimum amount of data needed to make scientifically sound regulatory decision.
The well-defined risk assessment process helps EPA make consistent, well-informed regulatory decisions.

Its use provides guidance for EPA's decision-making process on whether additional data are needed to clarify a potential risk.

Resources are focused on obtaining information that ensures the best possible course of action among the available options.

EPA's mission to protect the environment from unreasonable adverse effects can be more readily fulfilled.
Future Considerations

✓ EPA is *fully committed* to ensure the scientific review for the registration and regulation of PIPs are *based on transparency and best available science*.

✓ As new advances in biotechnology continue to emerge, so will new challenges to assess them. Therefore, the *methods to review, register, and regulate* these technologies *must evolve with them*.

✓ However, the *fundamental principles and proven effectiveness of problem formulation has become the cornerstone in the development of environmental risk assessments for PIPs*.
GM Food for Thought...

Biotechnology to feed the world

“The fact is we cannot turn back the clock on agriculture and only use methods that were developed to feed a much smaller number of people. It took some 10,000 years to expand food production to the current level of about 5 billion tons per year. By 2025 we will have to nearly double that amount, and that cannot be done unless farmers across the world have access to current high-yield crop production methods and to continuing biotechnology breakthroughs.”

– Dr. Norman Borlaug
Nobel Peace Prize laureate
¡Muchas gracias!

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