Exposure Scenarios for Crop Protection Products to Define a Tiered Approach to Develop the Data Necessary for Human Health Risk Assessment

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Start with Exposure

**RISK21-based**

A hypothesis based, systematic, integrative use of exposure and hazard information – EPA

When exposure is minimal or nonexistent, consideration of hazard may be unnecessary (WHO 2009)

Shift the paradigm for safety assessment from one focused on hazard to one that starts with exposure (Pastoor *et al.* 2014)

In practice, exposure is often not considered or considered late in the risk assessment process (Dellarco *et al.* 2017)
Start with Exposure – Already doing this!!!!!

- Exposure tier-based approach to testing crop protection chemicals already in place
  - Food vs. non-food uses
  - Inert assessments (I-DEEM, occupational)
  - Ecotox/Efate requirements
  - Metabolite relevance

- Other cases use exposure and existing hazard data to determine the need for additional studies
  - Comparative Thyroid Assay
  - Immunotoxicity
  - Neurotoxicity
  - Inhalation Toxicity
  - Carcinogenesis
Problem Formulation

• For crop protection human health risk assessments, the problem formulation step is focused on the particular use(s) of the crop protection chemical, the exposure scenarios that arise from these uses, and the existing knowledge of the chemical active ingredient itself, other molecules in the same chemical class, and molecules that have the same or similar pesticidal modes of action or human health modes of action.
Use Existing Information

• What information is available early in pesticide development?
  – GAP/intended use
  – Chemical specific data
    – Physical properties
      – Solubility, Vapor Pressure, $K_{ow}$
      – Model to predict additional physical properties
    – Pesticidal Mode of Action
  – Chemical class/related molecules
  – Initial hazard screening
Use Existing Information – Exposure

• Information contained in GAP Assessment
  – Product uses
  – Indication/Target
  – Application time
    – Seed treatment, pre-harvest, post-harvest
  – Application type and frequency
  – Formulation
  – Use rates

• GAP may be refined but rarely substantially
  – Used for the basis of testing
### GAP and Problem Formulation

#### Crop Disease Formulation Application

<table>
<thead>
<tr>
<th>Crop</th>
<th>Disease</th>
<th>Formulation</th>
<th>Application method</th>
<th>Application Rate (oz/acre)</th>
<th>Number of applications</th>
<th>Application timing</th>
<th>PHI (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pome</td>
<td>Powdery mildew</td>
<td>150 g/L</td>
<td>Foliar</td>
<td>2–4</td>
<td>4</td>
<td>7–10 day intervals</td>
<td>7</td>
</tr>
</tbody>
</table>

- **Dietary exposure**
  - Food crops
  - Animal feed
  - Drinking water

- **Occupational exposure**
  - Inhalation
  - Dermal

- **Other**
  - Aggregate
  - Bystander/Spray drift
  - Env/Eco
Screening Level Risk Assessment

• What UF/LOC – start with 100? 1000? 10000?
  – Refine based on chemical class, testing, toxicokinetics

• POD for risk assessment
  – Default extremely low and refine based on chemical class/SAR?
    – What is low enough?
    – What is the strength of the data that supports refining the POD (up or down)
Screening Level Risk Assessment

• GAP and Occupational Exposure
  – Very good databases on worker exposure exist
  – Sufficient data in GAP to potential “reverse engineer” an “adequate” NOAEL based on GAP for worker exposure
Screening Level Risk Assessment

• GAP and Dietary Exposure
  – DEEM/I-DEEM results
  – Worst case residues based on identified crops
  – DynamiCROP model (for predicting residue levels in various crops) and Dietary Exposure Evaluation Model (DEEM, for predicting human dietary exposure) using very limited residue trials
Screening Level Risk Assessment

• Goal is to predict how exposure impacts the need to toxicity data
• Reverse engineer acceptable PODs
• Testing would be conducted to refine exposure assessment
  – PODs
  – UF

“I want you to find a bold and innovative way to do everything exactly the same way it’s been done for 25 years.”
Screening Level Risk Assessment (based on pome GAP)

• Based on Screening Level Dietary Risk Assessment, if exposure is 0.01 mg/kg/day with a total UF = 1000 applied, then acceptable POD = 10 mg/kg/day

• Based on Screening Level Occupational Risk Assessment, if exposure is 0.25 mg/kg/day with a LOC = 200 applied, then acceptable POD = 50 mg/kg/day
Tiered Testing

• Will additional testing impact the risk assessment?
  – Impact the POD?
  – Impact the uncertainty factors?
  – Impart new knowledge/information (target organs)?

• Tox 21 approaches including receptor binding assays, use Adverse Outcome Pathways (AOPs), and In Vitro to In Vivo Extrapolation (IVIVE) to translate to POD for risk assessment – Not there yet.....
Toxicity Testing – Decision Tree

- Can POD be estimated from other members of chemical class?
  - yes: Explain rationale and address UF, etc.
  - no: Is there a specific endpoint/effect driving the POD?
    - yes: Conduct specific study
    - no: Testing
      - no: no
      - yes: no
Estimating POD from Chemical Class

• What is driving risk assessment for other compounds?
  – Can a worst-case be estimated from existing data?
  – Can the POD be refined based on structure activity relationship within the existing data on chemical class?

• Conduct specific testing based on POD, such as
  – Liver effect/enzyme study
  – Acetylcholinesterase inhibition
Principles of Tiered Toxicity Testing

- Understand TK/ADME (so you are testing the correct ultimate toxicant in the correct species at an appropriate dose)
  - Use of predictive tools
  - Metabolism modeling
  - In vitro comparative metabolism
  - Toxicokinetics/ADME

- Conduct screening study to address target organs/effects
  - 28-day repeated dose toxicity screen with repro/dev screen and neurotoxicity battery? Extended One-Gen (EOGRT)?
Principles of Tiered Toxicity Testing

• Possible outcomes – most sensitive target organ/effect – the range of most frequent target organs can be defined
  – Liver
  – Thyroid
  – Kidney
  – Hematopoietic
  – Body weight

• Human relevance of effect?
  – Enzyme induction
  – Toxicogenomics

• Is there enough information to determine if longer term testing would impact POD?
Putting Everything Together (based on pome GAP)

• Based on Screening Level Dietary Risk Assessment, if exposure is 0.01 mg/kg/day with a total UF = 1000 applied, then acceptable POD = 10 mg/kg/day

• The overall NOAEL is 10 mg/kg/day (estimated from chemical class/tox screen) for both chronic and occupational exposures

• Acceptable overall NOAEL = 10 mg/kg/day
  – Reasonable certainty of no harm?
  – Use existing information to support
  – How refined is the risk assessment?
Putting Everything Together (based on pome GAP)

- Based on Screening Level Occupational Risk Assessment, if exposure is 0.25 mg/kg/day with a LOC = 200 applied, then acceptable POD = 50 mg/kg/day
- The overall NOAEL is 10 mg/kg/day (estimated from chemical class/tox screen) for both chronic and occupational exposures
- Not acceptable overall NOAEL < 50 mg/kg/day
  - Can exposures be further refined?
  - Can an in vitro human dermal absorption study be conducted (if dermal driving)?
  - Can additional engineering control or PPE be applied?
Exposure Scenarios Tier-Based Tox Testing

- There is a way to do this!
- Communication with Agencies
- Eliminate *unnecessary* animal testing that is redundant
- Excellent exposure and hazard models and tools exist
- Use all available information at our disposal
- Iterative process, integrate data, and revise problem formulation
- Transparent process
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References


Thank you for your time!