ES/RP 532
Applied Environmental Toxicology

Lecture 11
Pesticides: Human Health Risk Assessment
(How EPA Assesses Aggregate & Cumulative Exposure & Characterizes Risk)

Mandates of the FQPA

- All tolerances are safe
  - Reasonable certainty of no harm from single or lifetime exposure to residues from all sources of exposure (aggregate risk)
  - Consider multiple residues if same mode of toxic action
  - Consider special sensitivity of children
  - Consider effects on endocrine system
  - Consider carcinogenic potential

Mandate of FIFRA

- No registration without tolerance
  - Tolerance may be waived, but same degree of risk assessment scrutiny
- How is tolerance developed?
  - Pre-FQPA
    - Tolerances only consider food sources of exposure
  - Post-FQPA
    - Tolerances consider aggregate exposure
    - Must consider children’s health
    - Must consider cumulative exposure

Tolerance

- Legal limit of residues on food
  - Mechanism of satisfying the mandates of the Federal Food Drug and Cosmetic Act (FFDCA), which is risk oriented, and Federal Insecticide, Fungicide, and Rodenticide Act, which is benefits oriented
- NOT a safety standard
- Expression of pesticide residues on food
  - ppm
  - mg/kg
  - µg/g

FQPA Mandate

- FQPA amendments made pesticide law risk oriented;
  - i.e., tolerances must be safe;
  - No consideration of benefits of pesticide use with several exceptions;
    - Applies to consumers only;
    - Benefits can be considered for ecological risk and worker risk
    - If compound is non-threshold, i.e., EPA deems it is carcinogenic, benefits may be considered if pesticide found necessary to ensure safe food supply and alternatives not available

How Tolerance Is Developed

- Manufacturer proposes tolerance
  - Based on field studies of residues on commodity in major growing regions parts of the country
    - Tolerance always a little higher than the highest residues to hedge bets against exceeding it
- EPA validates tolerance
  - Risk assessment
  - TMRC (Total Maximum Residue Contribution) analysis
Risk Assessment

- Hazard Identification
- Dose-Response Characterization
- Exposure Assessment
- Risk Characterization

TMRC (Theoretical Maximum Residue Contribution)

- Tolerances are residues
- Toxicological endpoints are doses relative to an effect and body weight
- The sum of all exposures to residues at the tolerance level cannot exceed the Reference Dose, the “safe” level by policy design
  - Pre-FQPA: considered food residues only
  - Post-FQPA: tolerance would have to account for aggregate exposures

The Risk Cup Metaphor

- Top of Cup = RID (mg/kg/day)
- FQPA Risk Cup w/ Child Endocrine, Cancer Hazard
- “Old” Risk Cup
- FQPA Risk Cup
- Risk Cup May Shrink by a Factor of 10X

Field Residue Studies

- Recommended application rates and one or two levels higher
- Harvest at the recommended or desired Pre-Harvest Interval (PHI)
- Normally samples are composited
  - But for many fresh fruits, a single unit (single serving) contributes to acute exposure

TMRC--Basic Procedure

- Applicable to new registrations
  - Screening tool when tolerances are used as the exposure residue
  - Can use field residues (higher tier or refined analysis)
  - Modify residues by % Crop Treated
- Need food consumption information
  - USDA Continuing Survey of Food Intake by Individuals
- Multiply residue tolerance by food consumption of that food to give exposure
- Sum all exposure possibilities
- Total exposure cannot exceed RID

Example

- Tolerance (old) for chlorpyrifos on apples at 1.5 ppm
- Tolerance for chlorpyrifos on wheat at 0.5 ppm
- Average male eats 100 g/day wheat and 75 g/day apples

\[
\text{Sum} = (1.5 \, \mu g/g \times 75 \, g/day) + (0.5 \, \mu g/g \times 100 \, g/day)
\]
\[
= 162.5 \, \mu g/day \times 0.1625 \, \mu g/day
\]
\[
\text{Daily Exposure} = 162.5 \, \mu g/day \times 0.00232 \, \mu g/kg = 2.23 \, \mu g/kg \text{ bw/day} = 0.00232 \, mg/kg
\]
Example (cont’d.)

- The RfD for chlorpyrifos is 0.0003 mg/kg/day for chronic exposure
- Thus, just from the two commodities alone, the RfD is exceeded for an adult
- Note that average consumption based on the FDA Total Diet Study is only 0.000015 mg/kg/day (for an infant of 10 kg)

Modern Day Dietary Exposure Assessment

- Chronic Exposure
  - 70 year lifetime of daily exposure
  - Must meet standards of the chronic RfD
  - Use average residues
  - Use average food consumption data
- Acute Exposure
  - 24-hour time frame of exposure
  - Must meet acute RfD
  - Considers exposures at 99.9th percentile

Dietary Exposure Assessment

- DEEM (Dietary Exposure Evaluation Model)
  - Contains USDA CFSII database
    - Three-day record of consumption for about 15,000 people
    - Divided by population subgroup
    - Foods are deconvoluted
      - Pizza is tomatoes, wheat, cheese, and other vegetables as appropriate
      - French fries are potatoes, spices, and vegetable soils

Dietary Exposure Assessment

- Residues
  - Tolerances (TMRC)
  - Maximum residues in field trials
  - Field residues at 95th percentile
  - Average residues from field
  - Government surveillance and dietary monitoring programs
    - FDA
    - USDA PDP
  - Industry generated market basket surveys

Real Residue Data Advantages

- Probabilistic assessment employing Monte Carlo analysis
  - The entire distribution of food consumption and food residue data are used
  - Essentially, the two distributions are multiplied together to yield a distribution of exposures
- Chronic exposure assessment is deterministic
  - Point estimates of food consumption and residues are used
In probabilistic dietary exposure assessment, the distribution of weights of specific foods consumed are multiplied by the distribution of pesticide residues in those food. The Monte Carlo technique samples from each distribution, multiplies them, and then repeats the process for as many iterations as the risk assessor wants.

### Monte Carlo Technique

- The Monte Carlo program randomly selects a food consumption value for each type of food and matches it to a randomly selected residue value for that food
  - The food consumption and residue value are multiplied together to yield the exposure
- For every food consumption and residue selection, the process is repeated hundreds or thousands of time to obtain a stable distribution of exposures

### Residue Data Matrix (mg/kg)

<table>
<thead>
<tr>
<th>Food matrix</th>
<th>Sample 1</th>
<th>Sample 2</th>
<th>Sample 3</th>
<th>Sample 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple</td>
<td>0.00</td>
<td>0.05</td>
<td>0.02</td>
<td>0.00</td>
</tr>
<tr>
<td>Peach</td>
<td>0.01</td>
<td>0.02</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Raisins</td>
<td>0.03</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Corn flakes</td>
<td>0.00</td>
<td>0.02</td>
<td>0.04</td>
<td>0.00</td>
</tr>
<tr>
<td>Pizza</td>
<td>0.06</td>
<td>0.00</td>
<td>0.05</td>
<td>0.20</td>
</tr>
<tr>
<td>Cookies</td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Granola Bar</td>
<td>0.02</td>
<td>0.00</td>
<td>0.00</td>
<td>0.02</td>
</tr>
<tr>
<td>Hot Dog</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>French Fries</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Milk</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

### Probabilistic Exposure Assessment

- All exposures are summed together to obtain an overall dietary exposure
- All the exposures are ranked by percentile to find the 99.9th percentile of exposure
  - The exposure level greater than 99.9% of all other exposures
  - Or, the exposure level only exceeded by 0.1% of the population

### Food Consumption Matrix (kg/day)

<table>
<thead>
<tr>
<th>Food matrix</th>
<th>Person 1</th>
<th>Person 1</th>
<th>Person 1</th>
<th>Person 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 3</td>
<td>Day 1</td>
</tr>
<tr>
<td>Apple</td>
<td>0.10</td>
<td>0.15</td>
<td>0.00</td>
<td>0.05</td>
</tr>
<tr>
<td>Peach</td>
<td>0.02</td>
<td>0.10</td>
<td>0.00</td>
<td>0.10</td>
</tr>
<tr>
<td>Raisins</td>
<td>0.03</td>
<td>0.05</td>
<td>0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>Corn flakes</td>
<td>0.00</td>
<td>0.75</td>
<td>0.04</td>
<td>0.10</td>
</tr>
<tr>
<td>Pizza</td>
<td>0.06</td>
<td>0.00</td>
<td>0.05</td>
<td>0.20</td>
</tr>
<tr>
<td>Cookies</td>
<td>0.04</td>
<td>0.06</td>
<td>0.04</td>
<td>0.03</td>
</tr>
<tr>
<td>Granola Bar</td>
<td>0.02</td>
<td>0.03</td>
<td>0.06</td>
<td>0.02</td>
</tr>
<tr>
<td>Hot Dog</td>
<td>0.08</td>
<td>0.08</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>French Fries</td>
<td>0.08</td>
<td>0.06</td>
<td>0.04</td>
<td>0.00</td>
</tr>
<tr>
<td>Milk</td>
<td>0.06</td>
<td>0.20</td>
<td>0.10</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Estimated Exposure to Chlorpyrifos in Strawberries Using a Monte Carlo Analysis (1-6 year old)

A Tale of Two Risk Assessments

<table>
<thead>
<tr>
<th>Toxicity Parameter</th>
<th>Azinphos-methyl</th>
<th>Methyl Parathion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Oral LD50</td>
<td>4.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Acute Dermal LD50</td>
<td>2000 Rabbit</td>
<td>6</td>
</tr>
<tr>
<td>Acute NOEL</td>
<td>0.3</td>
<td>0.11</td>
</tr>
<tr>
<td>Chronic NOEL</td>
<td>0.149</td>
<td>0.02</td>
</tr>
</tbody>
</table>
**Acute Reference Dose**

<table>
<thead>
<tr>
<th>Exposure Endpoints</th>
<th>Azinphos-methyl</th>
<th>Methyl Parathion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Reference Dose</td>
<td>0.003</td>
<td>0.0011</td>
</tr>
<tr>
<td>Acute Population Adjusted Dose</td>
<td>0.003</td>
<td>0.0011</td>
</tr>
<tr>
<td>Chronic Reference Dose</td>
<td>0.00149</td>
<td>0.0002</td>
</tr>
<tr>
<td>Chronic Population Adjusted Dose</td>
<td>0.00149</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

**Chronic Reference Dose**

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Exposure mg/kg/day</th>
<th>% aPAD</th>
<th>Exposure mg/kg/day</th>
<th>% aPAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. Population</td>
<td>0.000416</td>
<td>378</td>
<td>0.000068</td>
<td>60</td>
</tr>
<tr>
<td>All infants &lt; 1 yr</td>
<td>0.000415</td>
<td>377</td>
<td>0.000067</td>
<td>61</td>
</tr>
<tr>
<td>Children 1-6 yrs</td>
<td>0.000969</td>
<td>881</td>
<td>0.000086</td>
<td>78</td>
</tr>
<tr>
<td>Children 7-12 yrs</td>
<td>0.000428</td>
<td>388</td>
<td>0.000087</td>
<td>78</td>
</tr>
</tbody>
</table>

**Hypothetical Dose-Response Curve for Methyl Parathion**

- **Average Daily Exposure**
- **LD_{50}**
- **cPAD**
- **cNOEL**

**Aggregate Exposure & Risk Assessment**

- FQPA mandated that all exposures to consumers be aggregated for determination of safety (the unreasonable certainty of no harm)

**Home & Lawn Water Food**

Exposure > 100% of RfD or PAD
General Principles For Performing Aggregate Exposure And Risk Assessments

Some Pathways & Routes to be Considered in an Aggregate Exposure and Risk Assessment

- Residential
- Drinking Water
- Food

- Dermal Route
- Inhalation Route
- Oral Route

Exposure (mg/kg)

- Residential
- Drinking Water
- Food

Toxicity Endpoints:
- Acute Short-Term
- Acute Short-Term
- Acute Short-Term

Food Exposure

Drinking Water Exposure

Residential Exposure

Total Aggregate Exposure

Time (Days)
Drinking Water Levels of Comparison (DWLOC)

- EPA calculates a DWLOC on the basis of how much room is left over in the risk cup after considering dietary exposure.

\[
\text{DWLOC (µg/L)} = \frac{\text{Chronic water exp. (mg/kg/d)} \times \text{Body wt. (kg)}}{\text{Consumption (L/d)} \times 10^{-3} \text{mg/µg}}
\]

Methyl Parathion Drinking Water Assessment

- PDR = UE x AR x A
  - PDR = potential dose rate (mg/day)
  - Empirical
  - PHED (Pesticide Handler Exposure Database)
  - UE = unit exposure (mg/lb AI)
  - AR = application rate (lb AI/acre; lb AI/gallon)
  - A = area treated (acres/day or gallons/day)
- Exposure = PDR/kg body weight
  - (mg/kg/day)

Residential Exposure Assessment--Applying

- Dislodgeable residue (from surface or foliage)
  - µg or mg per unit area (cm²)
- Dermal Transfer Coefficient (Tc)
  - Designates how much surface area is exposed in a unit time
  - cm²/hr
- Length of contact (hr)
- Fraction of residue dissipating daily (rate)

Residential Exposure Assessment--Post Application

- Biomonitoring
  - Volunteers carry out “residential activity”
    - Extract clothes
    - Extract gloves; wash hands
    - Air monitoring in breathing zone using portable sampler
  - Assess biomarkers
    - For ex., metabolite in urine
      - Back calculate whole body exposure
Cumulative Exposure & Risk Assessment

- FQPA mandates cumulation of exposure from pesticide residues having a common mechanism of toxicity
  - Pertains to two or more pesticides or other substances that cause a common toxic effect(s)O to human health by the same, or essentially the same, sequence of major biochemical events
  - Do not confuse with a common toxic effect
    - Same toxic effect in or at the same anatomical or physiological site or locus, but not necessarily by the same biochemical mechanism

Rationale

- "A person exposed to a single pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause the same toxic effect by a mechanism as that of the subject pesticide, even if the exposure levels to the other substances are also considered safe."
- Assumes dose additivity is the only interaction
  - No synergism, antagonism, nor neutrality

Cumulative Toxicity

- Cumulative toxicity represents the net change in toxicity that results from the combined exposure to multiple chemical substances relative to the toxicity cause by each substance alone.
- Factors influencing
  - Exposure pattern—temporal co-occurrence of same MOA residues
  - Toxicokinetics
  - Duration of common toxic effect
  - Interactions between the substances causing the effect

EPA revised the CRA and released a new report during June 2002
The Process

- Analyze exposure scenarios
  - Food
    - USDA Pesticide Data Program database
    - Assume nationally uniform consumption (CFSII database)
    - Contains subpopulations to be assessed
      - 1.0 years; 3.5 years; 20-48 years; >50 years
  - Drinking water
    - 7 EPA regions (based on geographic specificity of commodities grown; climatic similarities)
    - Modeling output data using PRZM and EXAMS
  - Residential (non-occupational)
    - Proprietary data, PHED, or published studies
    - National use statistics

Drinking Water & Non-Occupational Exposure

- Less well studied than food residues
- Temporal variation
- Geographic variation
  - For water exposure, choose a “representative” vulnerable watershed basin in each of the seven EPA regions based on previous detections, use of OPs, runoff potential
  - Must be modeled on a one-day time step, similarly to food residue exposure
  - Use of Calendex, a proprietary model that integrates all exposure scenarios across time

Combining Residues

- Choose Point of Departure (PoD)
  - The point on the dose-response curve that signifies an effect definitively tied to a dose
    - Below the PoD, the responses are usually modeled mathematically, not directly observed
- ED10 (Effective Dose to 10% response) or the BMD10 (Benchmark Dose for 10% response)
  - Dose giving 10% inhibition of brain acetylcholinesterase (female, 21 day or greater)
  - Determined by fitting response data to exponential function
Dealing with the FQPA 10X Factor

- For most of the OPs, EPA decided to incorporate an extra 3X FQPA safety factor by increasing the size of the RPF by 3
  - Result is to make potential exposure three times bigger

Combining Residues

- Normalize individual OPs to same potency using index chemical
  - Methamidophos (Monitor) chosen as index chemical
- Calculate RPF (relative potency factor)
  - \( RPF = \frac{BMD10_{\text{index}}}{BMD10_{\text{chemical}}} \)
  - Relevant for oral dose-response exposures only
  - For dermal and inhalation, use the Comparable Effect Level (CEL)
    - Corresponds to 15% inhibition response relative to control animals in dermal and inhalational exposure studies
    - Analogous calculation for the RPF
Exposure Determination

- Multiply RPF by residue concentrations resulting from each exposure scenario to create index equivalent residue
  - Sum all the index equivalent residues for each exposure scenario
- Add all index equivalent residues across exposure scenarios employing a one-day time step for each individual modeled by Calendex
  - Repeat modeling for each person represented in the CFSII database

Cumulative Risk Characterization

- The MOE approach is used wherein exposure is compared to the NOAEL for the index chemical, methamidophos
  - As opposed to a single chemical RA, EPA does not conclude that exposure exceeded their levels of concern (i.e., the risk management benchmark)
- EPA plots the daily MOE relative to the percentile of exposure

EPA’s Conclusions

- Drinking water contributed very little to cumulative exposure
- Residential exposure was the major contributor to cumulative exposure
  - DDVP pest strips (inhalation exposure)
  - Hand-to-mouth behavior in children
- Certain foods contributed more to dietary exposure than others (for example, grapes, apples, pears)
- Even with the extra FQPA safety factor of 3 incorporated into the RPFs, MOE for 1-2 year old was about 50 or greater