Background on Risk Assessment at DPR

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DPR Brown Bag Lunch Series
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Human Health Assessment Branch

Data Review Section
- Review data submitted in support of pesticide registration
- Identify potential acute, sub-chronic, and chronic health effects

Risk Assessment Section
- Determine doses below which health impacts are not expected
- Compare these doses with estimated exposures to determine risk

Exposure Assessment Section
- Identify situations when exposure to pesticides can occur
- Estimate exposures associated with legal uses of pesticides
DPR Mission

Our mission is to protect human health and the environment by regulating pesticide sales and use, and by fostering reduced-risk pest management.
Protect Human Health

- Need to determine, when pesticides are used...
  - What health impacts may occur
  - Circumstances when adverse effects could happen

- Can take measures if needed to decrease exposures
  - May require changes in how pesticide products are used
  - May cancel certain uses
What Is Risk Assessment?

- Risk assessment is a process regulators use to evaluate the safety of pesticide uses.
- Risk includes both toxicity and exposure:
  - If there is no exposure, then no risk.
  - Low (or practically no) toxicity, low risk.
- Risk assessment compares the exposure to the dose where no effects were seen or to a negligible risk level:
  - Include safety and uncertainty factors.
When Is Risk Assessment Done?

- Before pesticides are registered
  - DPR required by law to have complete toxicity database and to review for adverse health effects
  - In some cases, DPR conducts a formal risk assessment to determine potential risks of proposed new uses
- Pesticides already in use
  - Determine if new regulations or use restrictions are needed
- Risks are assessed when needed
  - Can be triggered by new data, changes in uses, etc.

California is the only state that conducts risk assessments
Risk Assessment Goal

- Realistic, health protective estimates of risk
  - Protect individuals from injury when pesticide is properly used
  - Improper uses are handled in the enforcement process
  - Balance protective assumptions with best available scientific information

(USDA Photo)
How Are People Exposed?

- Can be exposed directly when pesticides are applied
  - Individuals involved in pesticide applications
  - Airborne exposures to others
- Can be exposed to residues on crops or in the environment
  - Entering area where pesticide was applied
  - Dietary from eating treated crops
  - Drinking water

(Photo from UFL)
Sources for Data

- Data used in assessments come from many sources
  - Pesticide registrants must submit certain data
  - Scientific papers by university and other researchers
  - DPR sometimes conducts studies

- Required studies for registration include several types
  - For example, chemistry and environmental fate studies
  - Toxicity studies to indicate potential health hazards

- Exposure studies are not necessarily required
  - Measure pesticides on skin and clothing, in blood and other body fluids, or in the environment (air, water, food, soil, etc.)
New Kinds of Data

- Traditional toxicity and exposure studies use methods developed in 1970s through 1990s (and earlier)
- 21st Century Toxicology
  - Understand toxicity without use of animals
- Models to better characterize exposure
Incorporating New Methods into the Risk Assessment Process

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Human Health Risk Assessment

- Estimates the risk to humans from exposure to pesticides
  - Based on scientific data
- Predicts:
  - Type of health effects
  - Magnitude of the effects
- Uses of conventions, extrapolations and uncertainties
- Toxicologically-based risk assessments are valid within their assumptions
Risk Assessment Process

- California 1807 and SB950 Acts:
  - adverse effects to pesticides are determined through the risk assessment process
- 1983 National Academy of Sciences (NAS) Framework:
  - 4-step process

(Figure from U.S. EPA)
Risk Assessment Section

• Typically, the DPR’s Risk Assessments are about 100-200 pages

• The best available scientific information is used to estimate the risk to humans
  I. Hazard Identification
  II. Dose Response Evaluation
  III. Exposure Assessment
  IV. Risk Characterization
Hazard Identification

- Hazard Identification is about half of the risk assessment
- This part summarizes available studies
  - Studies submitted by registrants: follow Federal Fungicide, Insecticide and Rodenticide Act (FIFRA) guidelines
  - Published studies: not following specific guidelines
HHAB Reviewing Studies
Dose-Response Evaluation

- Non-cancer effects: determines critical No-Observed Effect Level (NOEL) for toxic effects (e.g., body weight reductions, liver or brain pathology)
- Cancer: estimates potency based on tumor incidence in animal studies
- Approaches: mathematical models (e.g. Benchmark Dose Analysis) are used to estimate NOELs and cancer potency
## Hazard Identification

### Table 1. Acute/Short term Effects of Chemical X and Respective NOELs

<table>
<thead>
<tr>
<th>Species</th>
<th>Exposure</th>
<th>NOEL mg/kg</th>
<th>Critical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat\textsuperscript{a}</td>
<td>Single, gavage</td>
<td>1.0</td>
<td>↓ ChE in cortex of males</td>
</tr>
<tr>
<td>Mouse</td>
<td>7 days, diet</td>
<td>5.0</td>
<td>Decreased body weight</td>
</tr>
<tr>
<td>Rabbit\textsuperscript{b}</td>
<td>9 days, gavage</td>
<td>1.0</td>
<td>Maternal: Cholinergic signs, Fetal: decreased birth weight</td>
</tr>
<tr>
<td>Rat\textsuperscript{b}</td>
<td>9 days, gavage</td>
<td>2.5</td>
<td>Maternal: Cholinergic signs</td>
</tr>
<tr>
<td>Rat\textsuperscript{a}</td>
<td>14 days, diet</td>
<td>0.18</td>
<td>↓ ChE in cortex of males</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Neurotoxicity study  
\textsuperscript{b} Developmental toxicity study
Benchmark Dose Analysis

Probit Model, with BMR of 5% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMD

Fraction Affected

Probit
BMD Lower Bound

BMDL BMD

dose

15:25 04/04 2014
Exposure Assessment Section

- Typically, the DPR’s Risk Assessments are about 100-200 pages
- The best available scientific information is used to estimate the risk to humans
  I. Hazard Identification
  II. Dose Response Evaluation
  III. Exposure Assessment
  IV. Risk Characterization
How to Evaluate Pesticide Risk
Computer Modeling Plus
Laboratory and Fieldwork to Build Understanding

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Senior Toxicologist
Exposure Assessment Section
Human Health Assessment Branch
Equation for Exposure Calculation

\[ \text{Exposure} = \int \left( \frac{\text{Concentration} \times \text{Exposure Factors}}{\text{dt}} \right) \]

Two Questions for Determining Exposure:

1. What are the concentrations?
2. What are the exposure factors?
Sources and Releases
Example: Escape of Pesticide from Field to Air
Monitoring at Application Site
Example: Ground-Rig Blower to 60-Acre Orange Orchard

CDPR Sampler

Example of low-volume samplers with personal sample pumps

Sample tube

Pump

Battery
Pesticide Transport Through the Environment
Example: Air dispersion

Source: Barry and Johnson, 2011
Air Dispersion Model
Example: Industrial Sources Complex Short Term Version 3 (ISCST3 Model)

Source: Barry and Johnson, 2011
Soil Fumigant Exposure Assessment System (SOFEA)

Agronomic Practices
- Field size
- Application Rate
- Tarp Presence
- Drip or Shank
- Depth of Incorporation
- Buffer Zone setback
- Reentry interval

GIS Information (Optional)
- Land cover
- Elevation
- Population

Simulates Multiple Fields in Time and Space for Multiple Years

Output Summaries
- Concentration Profiles for:
  - Acute (24-hr max)
  - Subchronic (user specified)
  - Chronic (Annual)

Spatial Analysis
- (x,y,z) receptor location with:
  - Air concentration (acute, subchronic, chronic)
  - Population density
  - Elevation
  - Land type (urban, water, ag-land)

Source: Cryer and van Wesenbeeck, 2015
SOFEA is an intelligent input file generator and output repository for agronomic use of the Gaussian plume model ISCST3

Source: Cryer and van Wesenbeeck, 2015
Contour plot of ISCST modeled average 1,3-D air concentrations (µg/m³). Black crosses are the locations of the monitored air concentrations. Purple text are the measured 14.5 month 1,3-D air concentrations (µg/m³).

Source: Barry, 2015
Empirical quantile-quantile plots of the simulated versus observed 72-hour values of 1,3-D concentrations in air at 9 contiguous townships of Merced County, CA.
Exposed Population

Infants, Children, and Adults

Pesticide in Air
Core Elements of Exposure Science

Population-Based Exposure Models

Examples:
1. High End Exposure Version 5 Crystal Ball (HEE5CB) Model
2. Monte Carlo Annual Based estimate of Lifetime Exposure (MCABLE) Model
Population-Based Exposure Model

\[
LADD = \left( \sum_{i=1}^{10} RT_i \left[ \frac{\text{Conc}_i \times \text{BR}_i}{\text{BW}_i} \right] \right) \times \frac{1}{70}
\]

where the summation is over 10 age intervals,

- \( RT_i \) = number of years in age interval \( i \) that the person resides in the high 1,3-D use area,
- \( \text{Conc}_i \) = annual average of air concentrations (\( \mu g/m^3 \)) in 5 locations weighted by the proportion of time spent in each location in interval \( i \),
- \( \text{BR}_i \) = average breathing rate (\( m^3/day \)) at each of 4 activity levels weighted by proportion of time spent at each level in interval \( i \),
- \( \text{BW}_i \) = body weight (kg) in interval \( i \), and 70 years is the assumed lifetime.
Risk Characterization

- Final step: used by the risk manager to develop control or mitigation strategies
- Combines the exposure and the dose response assessment
- For effects other than cancer:
  - Risk is calculated as Margin of Exposures: \( MOE = \frac{NOEL}{\text{exposure}} \)
  - Estimated MOEs are compared to a target MOE
- For cancer effects:
  - Risk is expressed as the probability of an individual to develop cancer over a life time exposure (e.g., one individual in a million)
Human Studies

• Human Studies
  • Human studies are most useful in risk assessment
  • Rarely available
  • DPR prefers studies that have been approved by USEPA’s Human Studies Review Board

• Epidemiology studies, human case reports human illness reports
  • Informative
  • Exposure level is uncertain
Laboratory Animal Studies

- Required studies for pesticides include dosing by oral, dermal and inhalation routes
  - Routes by which people can be exposed
  - Multiple laboratory animal species
  - Both short and long-term studies

- Look for most sensitive animals and the lowest dose at which health effects appear

- Uncertainties in moving from animals to people
  - High doses in lab vs. low exposures in field or from food

(Photo from National Cancer Institute)
Extrapolating the Dose from Animals to Humans

- Scaling of the dose among and within species:
  - Body weight-based scaling: extrapolating the animal dose to the equivalent human dose based on differences in body weight
  - Target tissue-based scaling: new science allows extrapolation of the animal dose to the equivalent human dose based on the dose at the target organ (e.g., lung)
  - DPR recently employed a target-tissue scaling called Regional Gas Dose Ratio (RGDR) in a fumigant risk assessment
Extrapolating the Dose
Pressures Against Animal Testing

- Animal welfare concerns
- Relevance of animal tests to humans
- Number of chemicals needing risk decisions
  - too many chemicals and not enough data
  - Over 65,000
  - No tox data = 46,000
- Cost of animal studies
  - $2-4 million and 3-5 years for a life time rodent study
New Types of Toxicity Data

- In 2007, NAS published a report on the future of toxicity testing.
- Toxicology in the 21st Century (Tox21):
  - Federal program that includes government, universities and industry.
  - Develops better toxicity assessment methods; to reduce animal tests.
  - Focus is on mechanisms of toxicity.
  - Uses cell cultures and biochemical reactions in test tubes (*in vitro*).
  - Automated methods.
  - Fast, can test many chemicals.
  - Can run many tests on each plate.
Use of New Toxicity Data

- DPR now receives some *in vitro* toxicity data for pesticides
  - Submitted by the registrants to supplement current toxicity screening procedures
- DPR utilized Tox21 approaches in its three most recent risk assessments

(Image from 2015 Chlorpyrifos Risk Assessment)
Tox21

CPFoxon

Overall ToxPi score: 12.126

Scores calculated relative to number of substances

- Transporter
  - Value: 1.6 CI=[0.911.0], Scaling: -log100=6, Missing data: 0.0%
- cell adhesion
  - Value: 9.985 CI=[0.5351.0], Scaling: -log100=6, Missing data: 0.0%
- gPCR
  - Value: 1.6 CI=[0.911.0], Scaling: -log100=6, Missing data: 0.0%
- steroid hormone
  - Value: 9.237 CI=[0.2320.243], Scaling: -log100=6, Missing data: 0.0%
- esterase
  - Value: 1.6 CI=[0.911.0], Scaling: -log100=6, Missing data: 0.0%
- cytochrome
  - Value: 9.987 CI=[0.7231.0], Scaling: -log100=6, Missing data: 4.348%
- background measurement
  - Value: 1.6 CI=[0.911.0], Scaling: -log100=6, Missing data: 0.0%
- cholinergic
  - Value: 9.38 CI=[0.4121.0], Scaling: -log100=6, Missing data: 0.0%
- peroxidase
  - Value: 9.412 CI=[0.1641.0], Scaling: -log100=6, Missing data: 0.0%
- cell morphology
  - Value: 1.6 CI=[0.3641.0], Scaling: -log100=6, Missing data: 0.0%
- oxidoreductase
  - Value: 9.615 CI=[0.9100.910], Scaling: -log100=6, Missing data: 0.0%
- nuclear receptor
  - Value: 1.6 CI=[0.7691.0], Scaling: -log100=6, Missing data: 0.0%
- cell cycle
  - Value: 1.6 CI=[0.9051.0], Scaling: -log100=6, Missing data: 0.0%
- Nrf
  - Value: 1.6 CI=[0.911.0], Scaling: -log100=6, Missing data: 0.0%

Missing data in percent:
Conclusions

- New techniques are promising and give us useful information
- A lot of work is still needed before we can rely completely on non-animal methods in risk assessment
- Linkages between old and new are being developed

“Risk assessment is easy. You can learn it in two steps....Each step takes 10 years.”

Attributed to Arnold Lehman, US FDA, in the early 1950s
DPR Scientists win 2016 James G. Wilson Award

A team led by DPR scientists won this year’s prestigious James G. Wilson Publication Award for research on use of in vitro cell-based assays, systems toxicity models and computational approaches in predicting pesticide-induced toxic effects, including birth defects.