Office of Pesticide Programs

Cumulative Risk Assessment and Incorporation of Probabilistic Approaches in Exposure Assessment

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Science Advisory Board
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Overview of Presentation

- Cumulative Risk Assessment & Food Quality Protection Act
- Hazard & Dose-Response
- Food, Drinking Water & Residential Probabilistic Exposure
- Cumulative Risk Results
- What's Next?

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Food Quality Protection Act (1996)

- Aggregate Risk: Multi-pathway & Single chemical
  - All toxicities and durations considered
- Cumulative Risk: Multi-pathway & Multi-chemical
  - FQPA requires EPA to take into account when setting pesticide tolerances:
    "available evidence concerning the cumulative effects on infants and children of such residues and other substances that have a common mechanism of toxicity."
  - Common mechanism endpoint and most relevant duration for common mechanism

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Public Participation Process

- Numerous Public Technical Briefings on methods and approaches for cumulative risk assessment and results of preliminary OP CRA
  - At least one full day briefing for each major section
- Tolerance Reassessment Advisory Committee (TRAC)
- Committee to Advise Reassessment and Transition (CARAT)
- FIFRA Science Advisory Panel meetings on methods and approaches
  - More than 20
- Preliminary assessment –public comment and Science Advisory Panel meetings
- Revised assessment –public comment
- Website dedicated to cumulative risk assessment http://www.epa.gov/pesticides/cumulative/

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OPP & Cumulative Risk Assessment

- OPP developed guidance document for cumulative risks assessments under FQPA (2002)
  - Established core principles for performing cumulative risk assessments
  - Developed tools for calculating multichemical and multipathway risk estimates

http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf

http://www.epa.gov/pesticides/trac/science/cumulative_resp.pdf

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OPP & Cumulative Risk Assessment

- Basic steps:
  - Identify common mechanism effect and common mechanism group (CMG)
  - Identify cumulative assessment group (CAG)
  - Determine relevant exposure scenarios/pathways
  - Consider appropriate method(s)
  - Conduct cumulative risk assessment

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Relative Potency Factor Method

- PBPK models would be preferred
  - *In vivo* and *in vitro* pharmacokinetic data not available at this time
  - Multi-chemical, multi-pathway models not available
- Relative toxic potency of each chemical is calculated in comparison to "index chemical"

$$RPF = \frac{\text{Index Chemical}_{BMD}}{\text{Chemical } n_{BMD}}$$

- Exposure equivalents of index chemical are combined in the cumulative risk assessment

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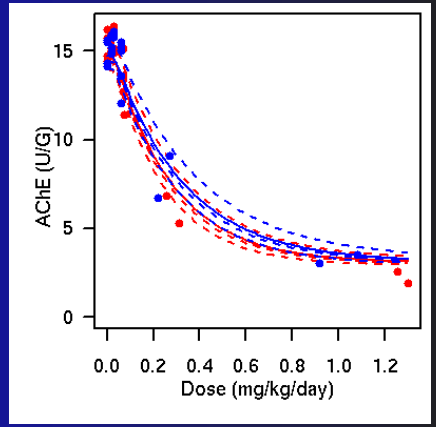
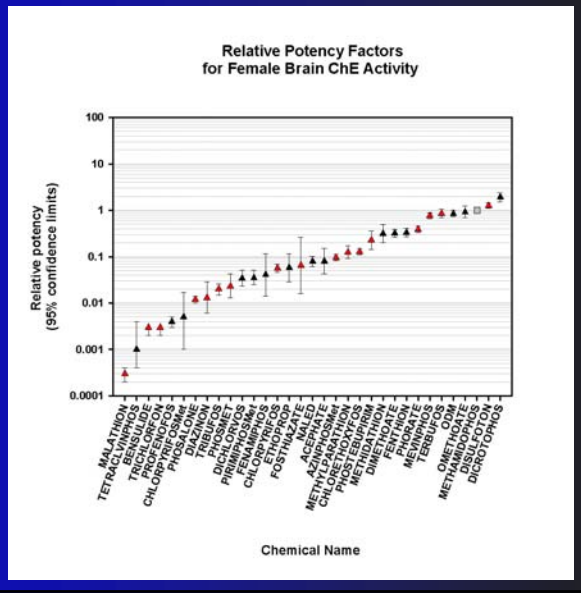
OP CRA Hazard & Dose Response

- Collaborative effort with EPA-ORD
- Rat data collected from studies at 21 days or longer where inhibition is no longer changing (ie, steady state)
- Decreasing exponential dose response model
- Use of multiple studies provides robust estimate of pesticide potency & incorporates variability across studies



Relative Potency Factors from **OP** Cumulative Risk Assessment



NMC CRA Hazard & Dose Response

- Collaborative effort with ORD
  - Benchmark modeling and dose-response and time course laboratory studies
- Relative potencies are estimated along with recovery half lives from acute (single dose) rat dose-time response data at or near peak
- Dose & Time Course Model Used
  - Dose-response portion of model is similar to that used for AChE inhibition by organophosphates
  - Time course model reflects an exponential decay of inhibition
- Estimation process accounts for variability among studies
  - When appropriate data are available

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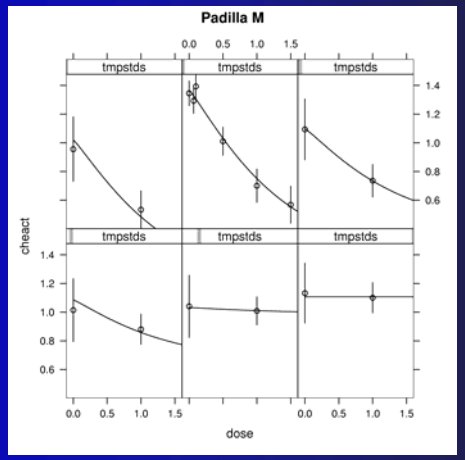
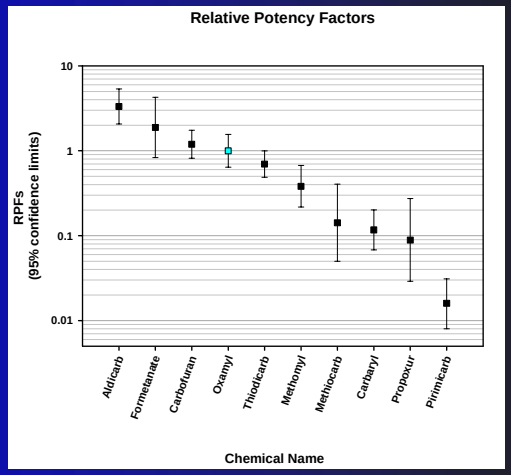
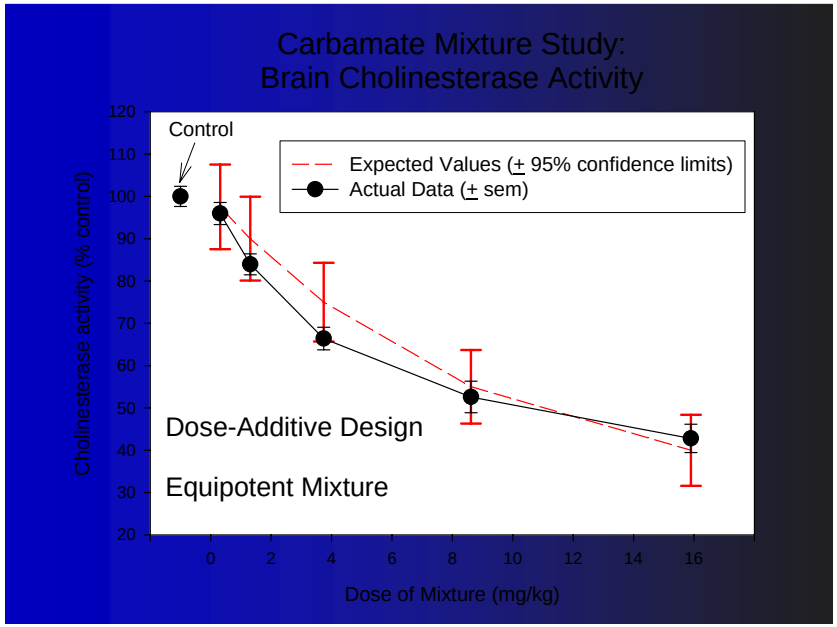
Example: Oxamyl Dose-Time Response



Relative Potency Factors from Preliminary **NMC** Cumulative Risk Assessment





Exposure Assessment and Probabilistic Techniques

- Probablistic exposure techniques are routinely applied by OPP for virtually all its pesticide risk assessments
  - More accurate estimate of the entire range of exposures and their associated probabilities
- OPP's Cumulative Risk Assessments rely on probabilistic (Monte-Carlo) techniques to evaluate exposure
  - Food, drinking water, residential uses, multi-pathway

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Exposure Assessment Software & Modeling

- Development of probabilistic models that permit time-based integration of residential, food, and water exposures to pesticides
  - "Time-Based Integration" = Calendar-based approach
  - Allow probabilistic combining of exposures through multiple pathways and routes
    - Single chemical or Multi-chemical
    - Food, Drinking Water, Residential
    - Ingestion, Inhalation, Dermal absorption
- *Key concept:* Must track potentially exposed persons on a daily basis in a way that preserves all appropriate linkages and appropriately allows for co-occurring exposures
  - Age, sex, behavior, region, etc.

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Exposure Assessment Software & Modeling

- OPP has used several software models to perform its risk assessments
- Presented to FIFRA SAP by OPP along with model development teams

LifeLine™

CARES
LSI Research Foundation

Dietary **E**xposure **E**valuation **M**odel
/**C**alendex

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Exposure Assessment Software & Modeling

- All three probablistic exposure models:

  1) conform to EPA & OPP guidance
  2) have undergone peer review
  3) publicly available

  http://www.exponent.com/practices/foodchemical/deem.html
  http://www.thelifelinegroup.org/
  http://cares.ilsi.org/

- ORD SHEDS/Pesticides under development
  - "Stochastic Human Exposure & Dose Simulation" Model

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Exposure Assessment Software & Modeling

- Inputs include
  - Toxicity information (e.g RfD, BMD, NOAEL)
  - Exposure information
    - Residues
    - Food consumption (from USDA's CSFII)
    - Behavior information (e.g., hand to mouth behavior)
- Output includes
  - Exposure levels (mg/kg bwt/day)
  - Risk metric (% RfD occupied, Margin of Exposure)
  - Risk "drivers"
    - chemical(s), commodities, or residential uses which contribute significantly to risk

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Exposure Assessment Software & Modeling

- Use data from well-known surveys to generate and evaluate specific daily exposures for individuals
  - Use available databases to address each component of simulation
  - Incorporates seasonal and other aspects

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Software Inputs: CSFII 1994-96/1998 Food Consumption Survey

- Nationally Representative/Statistically-Based
  - Intakes of individuals residing in 50 states and D.C.
  - 21,662 individual participants interviewed over the period
- 1998 Supplemental Children's Survey
  - ~5000 children
  - birth through 9 years old
  - integrated into 1994-96 CSFII
- Consisted of:
  - 2 non-consecutive days using in-person 24 hour recalls (ca. 3-10 days apart)
- Covers all seasons of year and all days of week

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Software Inputs: USDA Pesticide Data Program (PDP) Residue Data

- Statistically-reliable sampling procedure designed to be representative of US food supply
  - Approximately 600 samples per commodity per year
- Samples collected at terminal markets and distribution centers
  - Samples prepared as if for consumption
- PDP has tested more than 50 different commodities and more than 300 pesticides/metabolites
  - Fresh/frozen/canned fruits & vegetables, fruit juices, milk, grains, meat/poultry/pork, corn syrup, etc.
  - Emphasis on children's foods
- Reliable analytical methods with low limits of detection

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Drinking Water Assessment

- Regional (watershed) approach
  - Location-specific environmental data (soil/site, weather, crops)
  - Major crop combinations within that area
- Daily distributions of residues in water employed
  - PRZM/EXAMS modeling
  - Account for variations in time

    (daily, seasonally, yearly)

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Residential Exposure Assessment

- Extensive use of survey data and other pesticide use information
- Use of distributions for residues and behavior/activity elements
  - Hand-to-mouth activities
  - Choreographed adult activities/Non-scripted play
  - Transfer Coefficients/Dislodgeable Foliar Residue
- Use of a calendar based model to address the temporal use of residential uses
- Region-specific analyses

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Residential Exposure Assessment

- Assessment performed for the following uses:
  - Indoor Uses
  - Pet Uses
  - Home Lawn and Garden
  - Golf Course
  - Public Health Uses

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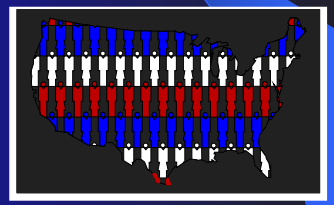
Populations Groups Assessed

- Separate assessments were based on survey information on the following age groups:
  - Infants <1
  - Children 1 - 2 years old
  - Children 3 - 5 years old
  - Children 6 - 12 years old
  - Youths 13 - 19 years old
  - Adults 20 - 49 years old
  - Adults 50+ years old
  - Females 13 - 49



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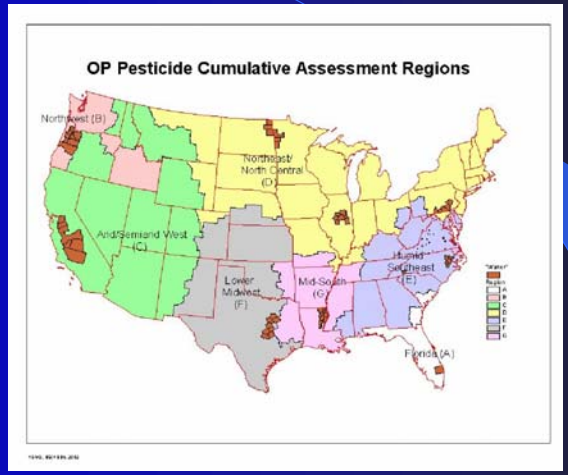
Regions Assessed



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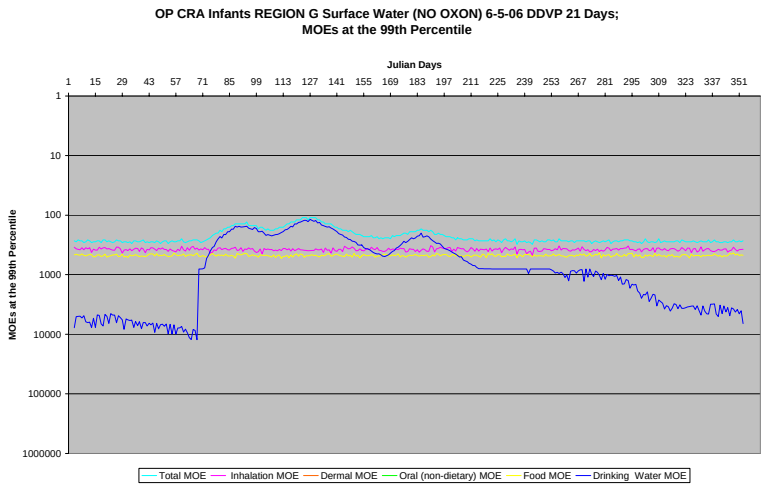

Consideration of Life Stage Sensitivities: Infants & Children

- Evaluated comparative cholinesterase studies.
  - Rat toxicity studies designed to compare sensitivity of adult and juvenile rats
- CSFII Supplemental Children's Survey (1998)
  - Age groupings
- Residential Exposures
  - Hand to mouth, child behaviors, etc.

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What's Next?

- Release of Revised NMC Cumulative Risk Assessment
- Pursue PBPK/BBDR modeling for future cumulative risk assessments
- Linkage between probabilistic exposure assessment and PBPK models
- Comparison of model outputs & predictions with biomonitoring and other studies

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Conclusions

- Risk assessments which consider the cumulative effects of pesticides are required by the Food Quality Protection Act of 1996
- EPA's Office of Pesticide Programs routinely performs probabilistic exposure assessments using a variety of exposures software models
- OPP has released a number of Cumulative Risk Assessments which incorporate state-of-the-art exposure assessment methods
  - Reflects realistic pesticide use based on pest pressures, weather, activity patterns, etc.
  - Demographic Temporal and spatial characteristics were preserved and maintained to produce realistic assessments

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Thank You!
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