Approaches to Pesticide Cumulative Risk Assessment: Policy, Practice, Experimentation

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Outline: Policy & Practice

1. Introduction: regulatory context, guidance documents, key principles
2. Hazard Assessment: relative potency factor approach
3. Exposure Assessment: food, water, residential
4. Cumulative assessment & ‘Track Back’
5. Summary

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Introduction

- EPA's Office of Pesticide Programs is a licensing program regulating pesticide products in the U.S.
  - Review effects of pesticides on human and ecological health
- Food Quality Protection Act (FQPA, 1996)
  - 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 <u>*common mechanism of toxicity*</u>."

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Introduction

- Under FQPA (1996), cumulative risk is defined as:
  - The risk associated with a group of chemicals that are toxic by a common mechanism from all pathways
  - Multi-chemical & Multi-pathway
    - Food, drinking water, consumer uses
    - Routes of exposure (oral, dermal, inhalation)

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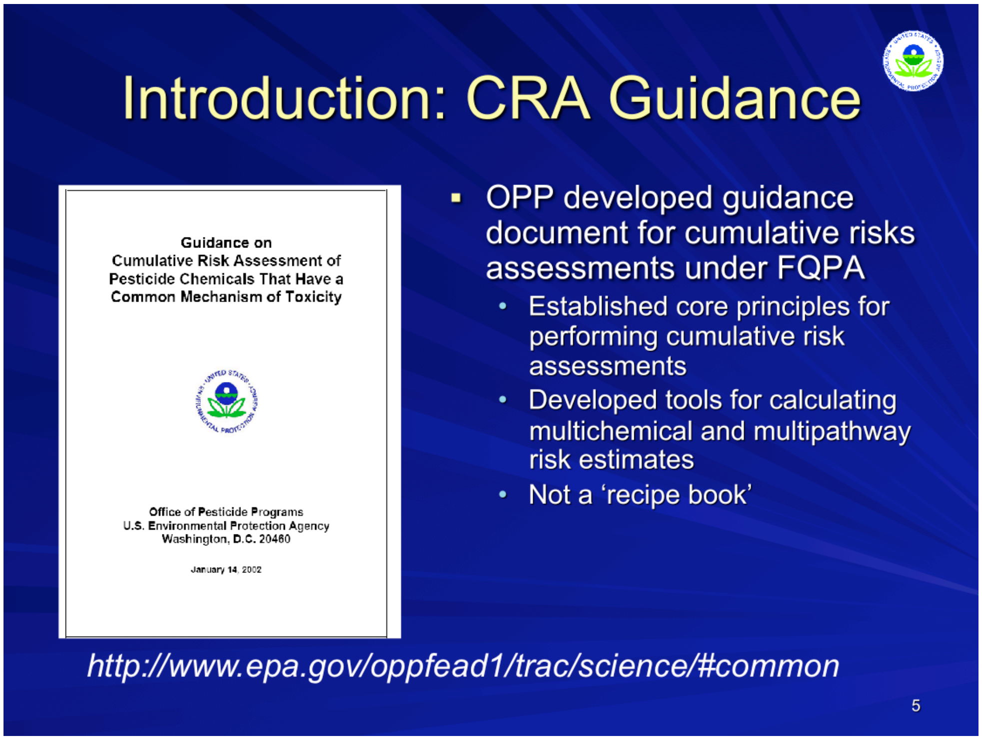
Introduction: CRA Guidance
Guidance on
Cumulative Risk Assessment of
Pesticide Chemicals That Have a
Common Mechanism of Toxicity
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, D.C. 20460
January 14, 2002
OPP developed guidance document for cumulative risks assessments under FQPA
Established core principles for performing cumulative risk assessments
Developed tools for calculating multichemical and multipathway risk estimates
Not a 'recipe book'
http://www.epa.gov/oppfead1/trac/science/#common
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Introduction: Key Principles

- Appropriately Integrate Toxicology & Exposure Data
  - Time-Frame Considerations
    - Time to peak effect? Time to recovery?
    - When does the exposure occur? What is the duration of exposure?
- Strive for Realistic & Accurate Assessments
  - Use Representative Data
  - Avoid Compounding Conservatisms
- Preserve and Maintain Geographic, Temporal & Demographic Specificity
  - Calendar-Base Approach

Emphasis of presentation at CRA Workshop

- Be Able to “Track Back” Sources of Exposures & Perform Sensitivity Analyses
  - Major Risk Contributors

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Basic Steps in a Pesticide Cumulative Risk Assessment

- Identify common mechanism group (CMG)
- Determine relevant exposure scenarios/pathways
- Identify cumulative assessment group (CAG)
- Consider appropriate method(s) & data sources
- Conduct assessment
  - Characterize & select common mechanism endpoint(s), determine chemical potency & select index chemical
  - Convert pesticide residues to equivalents of the index chemical
  - Combine/integrate food, water, & residential exposures on an internally consistent manner which incorporates demographic & temporal-spatial factors

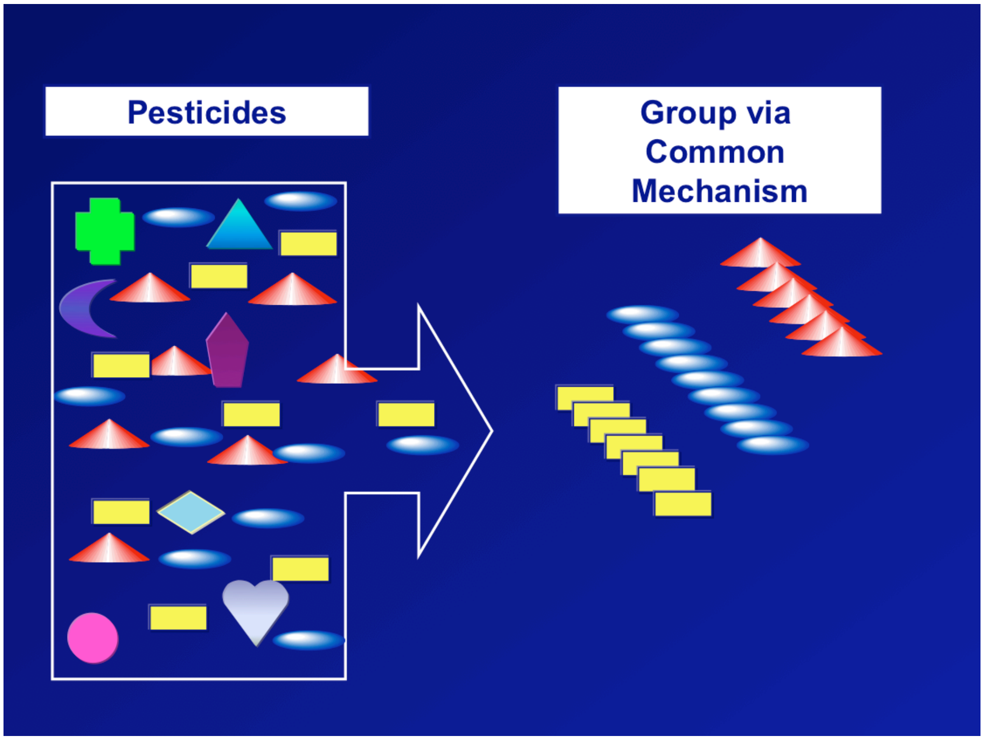
Introduction: CMG Guidance

GUIDANCE FOR IDENTIFYING PESTICIDE CHEMICALS AND OTHER SUBSTANCES THAT HAVE A COMMON MECHANISM OF TOXICITY

(January 29, 1999)

- *Mechanism of Toxicity*--Major steps leading to an adverse health effect following interaction of a pesticide with biological targets. All steps leading to an effect do not need to be specifically understood
- *Common Mechanism*--Two or more pesticide chemicals that cause a common toxic effect…by the same, or essentially the same, sequence of major biochemical events

http://www.epa.gov/fedrgstr/EPA-PEST/1999/February/Day-05/6055.pdf


Pesticides
Group via Common Mechanism

□

Common Mechanism of Toxicity?

- Three general principles to guide common mechanism determinations:
  - Act on the same molecular target at the same target tissue,
  - Act by the same biochemical mechanism of action, possibly sharing a common toxic intermediate
  - Cause the same critical toxic effect
    - Called the common toxic effect

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Common Mechanism of Toxicity?

- Is there concordance in dose response and timing between the major steps and the toxic effect?
- Is it biologically/chemically plausible?
- What are strengths & uncertainties of the available data?
- Could there be other an alternative mechanism(s) of action?

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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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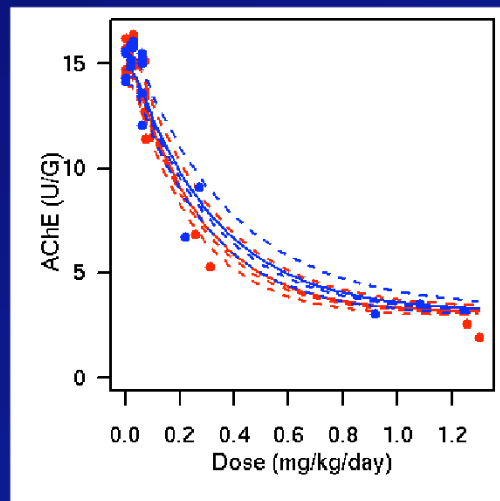
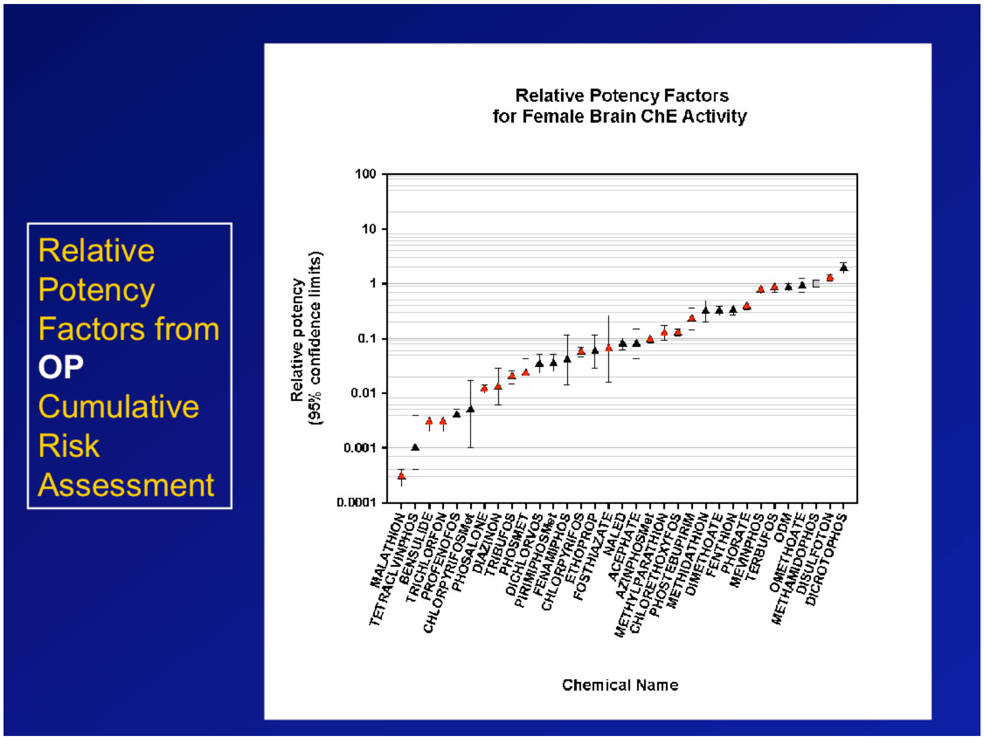
OP CRA Hazard & Dose Response

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



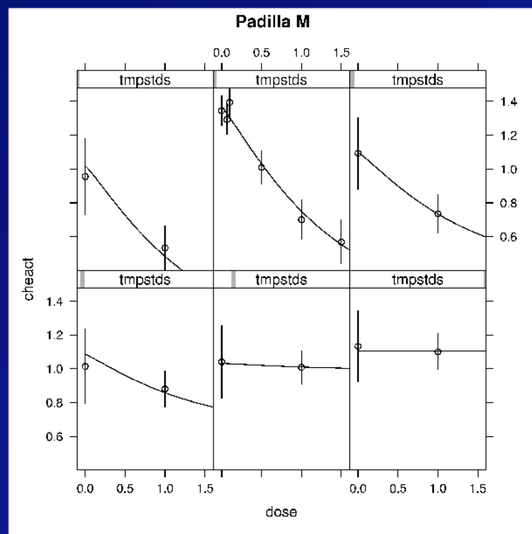


Relative Potency Factors from OP Cumulative Risk Assessment
Relative Potency Factors
for Female Brain ChE Activity
Relative potency
(95% confidence limits)
100
10
1
0.1
0.01
0.001
0.0001
MALATHION
TETRACLVINPHOS
BENSULIDE
TRICHLORFON
PROFENOFOS
CHLORPYRIFOSMet
PHOSALONE
DIAZINON
TRIBUFOS
PHOSMET
DICHLORVOS
PIRIMIPHOSMet
FENAMIPHOS
CHLORPYRIFOS
ETHOPROP
FOSTHIAZATE
NALED
ACEPHATE
AZINPHOSMet
METHYLPARATHION
CHLORETHOXYFOS
PHOSTEBUPIRIM
METHIDATHION
DIMETHOATE
FENTHION
PHORATE
MEVINPHOS
TERBUFOS
ODM
OMETHOATE
METHAMIDOPHOS
DISULFOTON
DICROTOPHOS
Chemical Name

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
- Rapid nature of NMC toxicity----Exposure assessment on single day exposures only

Example: Oxamyl Dose-Time Response



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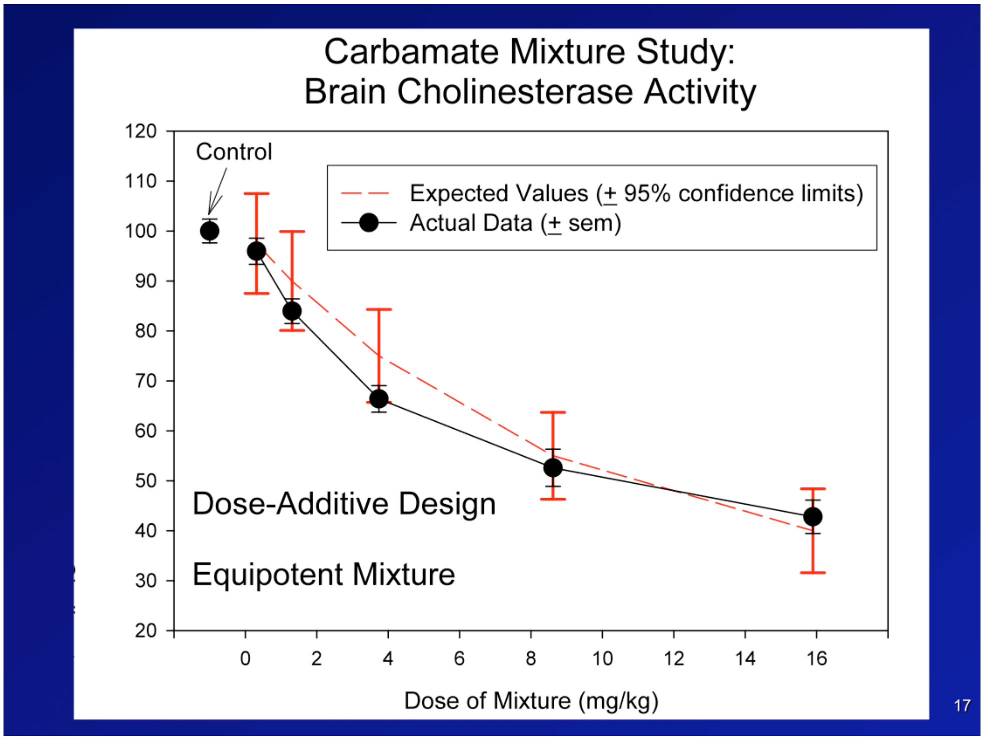

Carbamate Mixture Study:
Brain Cholinesterase Activity
Control
Expected Values (+ 95% confidence limits)
Actual Data (+ sem)
Dose-Additive Design
Equipotent Mixture
120
110
100
90
80
70
60
50
40
30
20
0
2
4
6
8
10
12
14
16
Dose of Mixture (mg/kg)
17

Exposure Assessment & 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

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Exposure Assessment Software & Modeling

- 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

- OPP has used several software models to perform its risk assessments
- Presented to FIFRA SAP by OPP along with model development teams
  - Lifeline
  - CARES
  - DEEM/Calendex
  - SHEDS
- All four models
  - conform to EPA & OPP guidance
  - have undergone peer review
  - are publicly available

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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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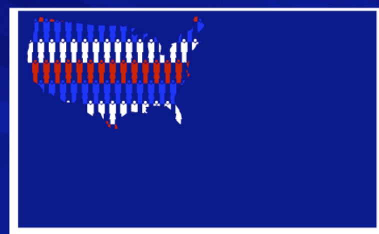
Populations Groups Assessed

- 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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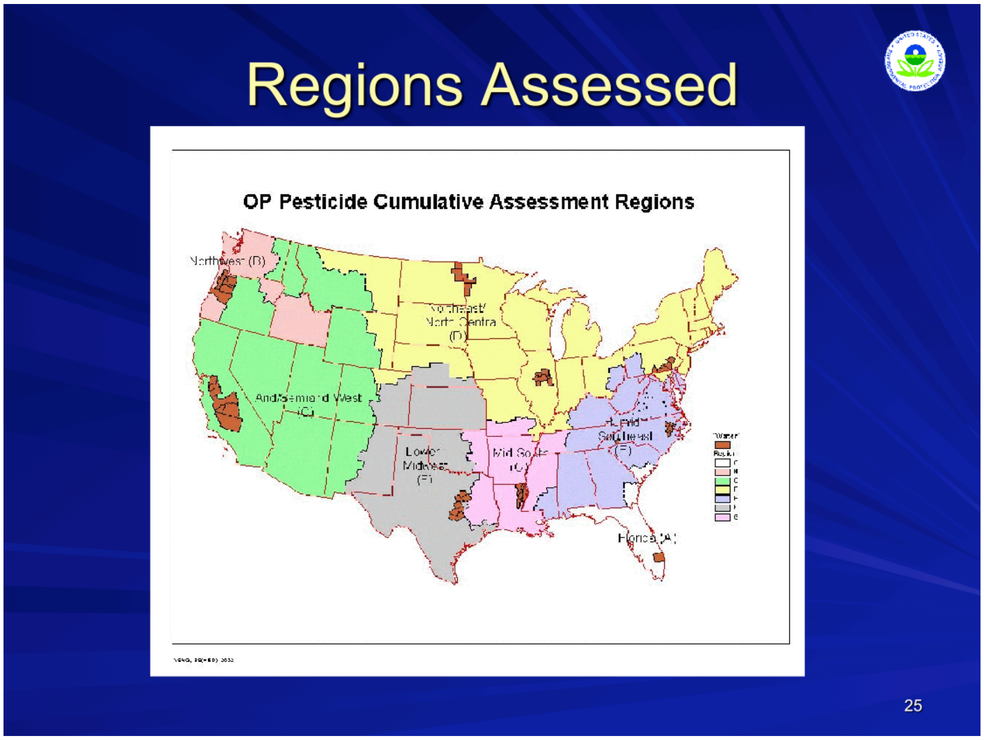
Regions Assessed
OP Pesticide Cumulative Assessment Regions
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Software Inputs: CSFII 1994-96/1998 Food Consumption Survey

- 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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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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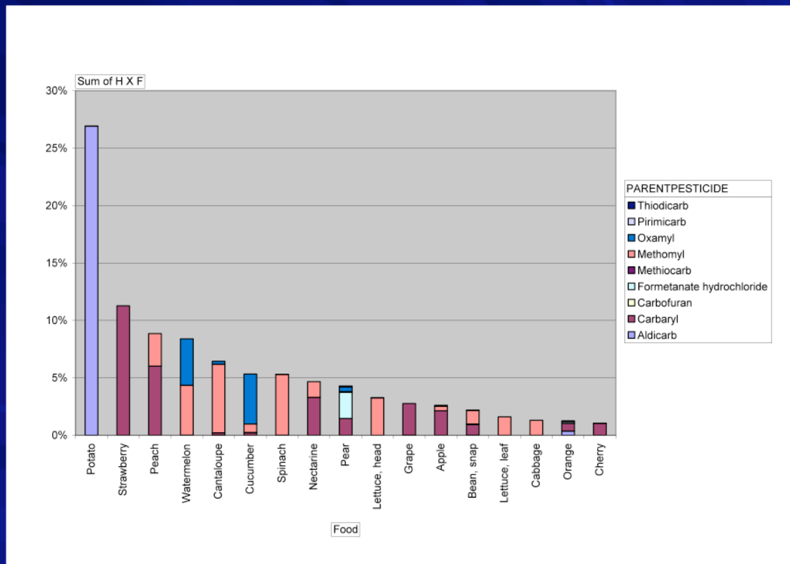
"Track Back" in Food Exposure



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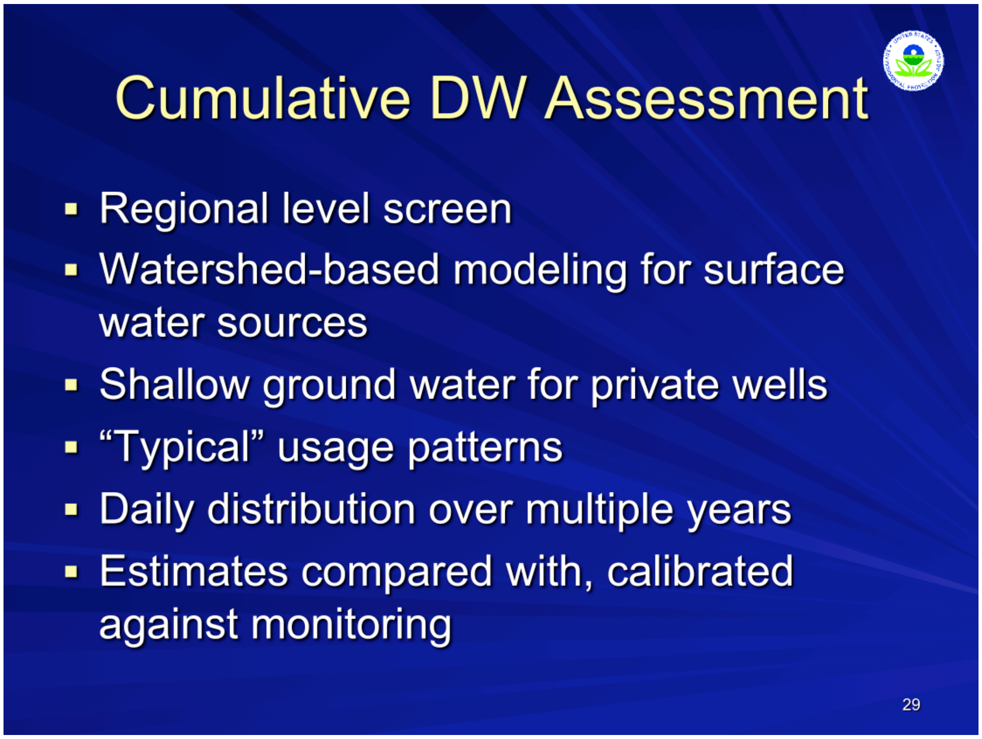
Cumulative DW Assessment
Regional level screen
Watershed-based modeling for surface water sources
Shallow ground water for private wells
“Typical” usage patterns
Daily distribution over multiple years
Estimates compared with, calibrated against monitoring
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For DW, Each Regional Location Reflects …

- Geographic area with high potential for combined (cumulative) exposure
  - Influenced by both use and relative toxicities
- Location-specific conditions
  - environmental data (soil/site, weather, crops)
  - Major crop-pesticide combinations within that area
- Vulnerable drinking water sources within the region

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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

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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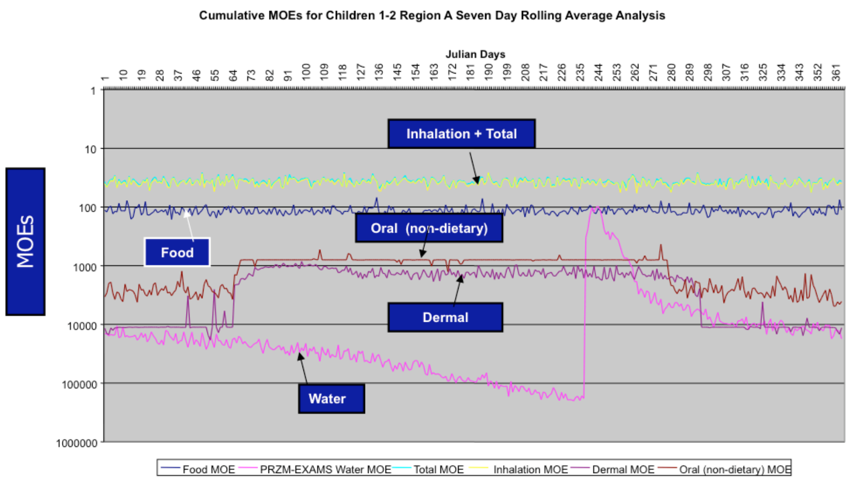
Example of Time based exposure profile: Organophosphates



Day of the Year

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Public Participation Process

- Numerous Public Technical Briefings on methods and approaches for cumulative risk assessment and results
- FIFRA Science Advisory Panel meetings on methods and approaches
  - More than 20
- Preliminary assessment –public comment and Science Advisory Panel meetings
- Revised assessment(s)–public comment
- Website dedicated to cumulative risk assessment http://www.epa.gov/pesticides/cumulative/

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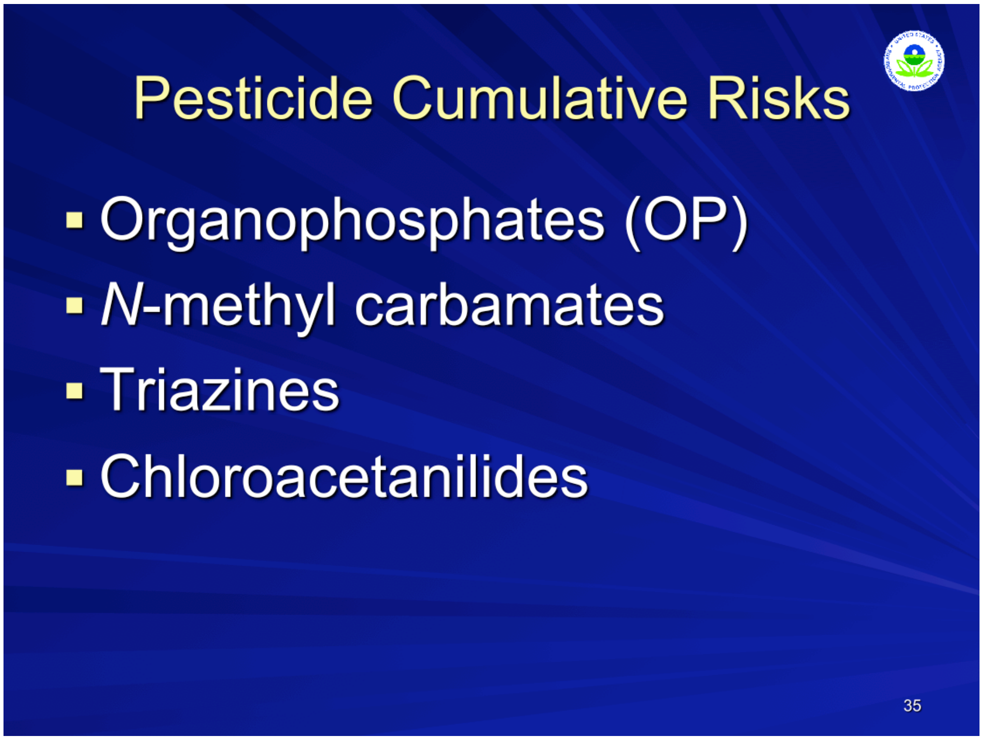
Pesticide Cumulative Risks
▪ Organophosphates (OP)
▪ *N*-methyl carbamates
▪ Triazines
▪ Chloroacetanilides
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Pesticide Cumulative Risks

- Pyrethroids—Work has only just begun
  - Draft common mechanism grouping reviewed & supported by SAP, June 2009
  - OPP & ORD developing PBPK models for use in the pyrethroid cumulative risk assessment
  - Linkage between probabilistic exposure assessment (SHEDS) and PBPK models


Key Principles
Appropriately Integrate Toxicology & Exposure Data
Time-Frame Considerations
Time to peak effect? Time to recovery?
When does the exposure occur? What is the duration of exposure?
Strive for Realistic & Accurate Assessments
Use Representative Data
Avoid Compounding Conservatisms
Preserve and Maintain Geographic, Temporal & Demographic Specificity
Calendar-Base Approach
Be Able to "Track Back" Sources of Exposures & Perform Sensitivity Analyses
Major Risk Contributors
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Thank You!
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Approaches to Pesticide Cumulative Risk Assessment: Policy, Practice, **Experimentation**

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Acknowledgements

- Statistical expertise: Virginia Commonwealth University
  - Drs. Chris Gennings, Hans Carter, Jr.
  - Graduate students including but not limited to Michelle Casey, Adam Hamm
- Technical collaborations: US EPA
  - Drs. Dave Herr, Stephanie Padilla, Anna Lowit, Jane Ellen Simmons
  - Pam Phillips, Kathy McDaniel, Renée Marshall

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Background

- Humans are exposed to multiple chemicals
- Effects of chemical mixtures may not be adequately predicted by studying individual chemicals
- Component-based mixtures risk assessment is aided by experimental design combining:
  - exposure evaluations
  - quantitative chemical information
  - appropriate statistical analyses

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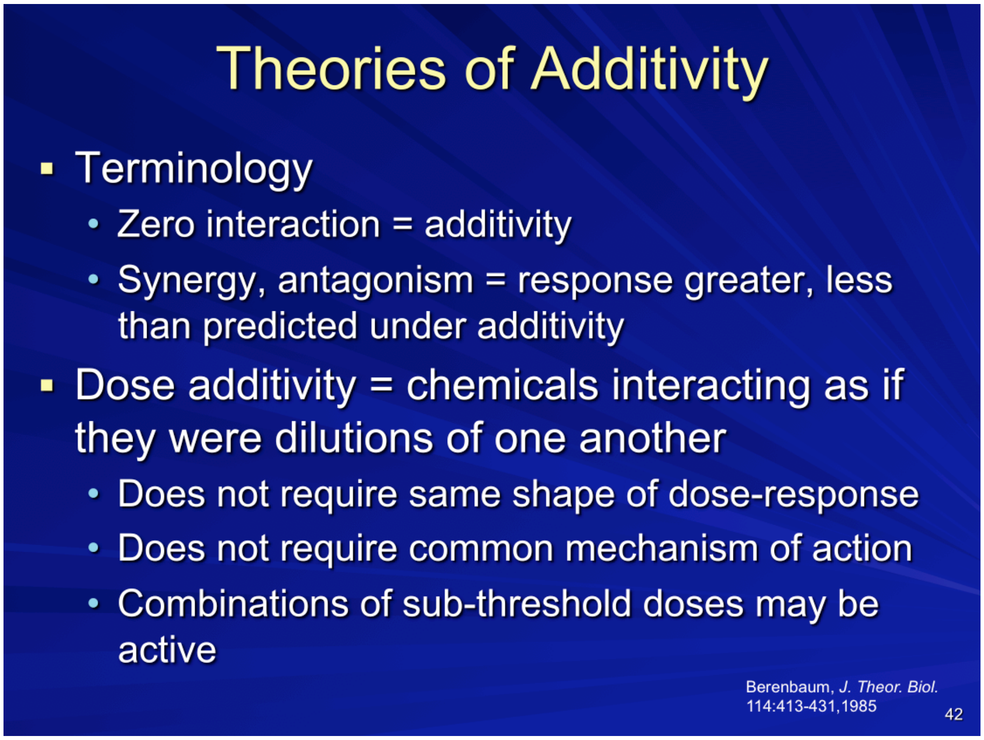
Theories of Additivity
Terminology
Zero interaction = additivity
Synergy, antagonism = response greater, less than predicted under additivity
Dose additivity = chemicals interacting as if they were dilutions of one another
Does not require same shape of dose-response
Does not require common mechanism of action
Combinations of sub-threshold doses may be active
Berenbaum, J. Theor. Biol. 114:413-431,1985
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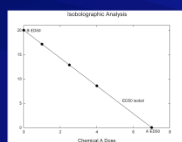
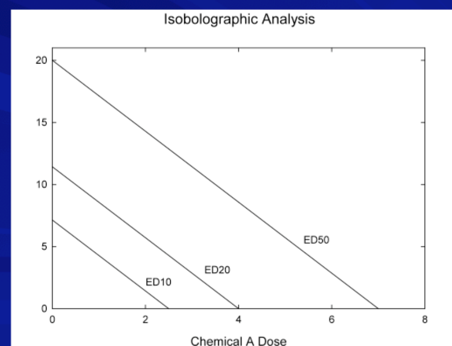
Isobolographic Approach

- Classic method of describing dose-additivity
  - Isobols of equi-effective doses
  - Requires multiple dose-response determinations with different dose combinations of each chemical
  - Data intensive





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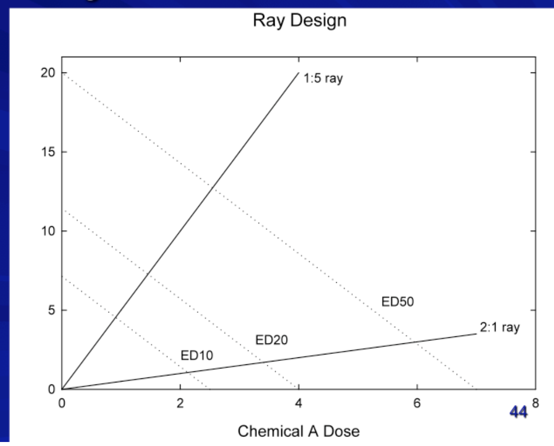
Ray Approach

- Dose-response along ray of mixture with fixed proportions of components
- Uses individual chemical dose-response curves plus mixture curve
- Inferences limited to mixing ratio tested

Isobol = curve fitted to points with fixed response
Ray = curve fitted to points with fixed ratios



Advantages of Ray Designs

- Useful for any number of chemicals
- Economical and efficient design to test for interactions
- Provides statistical test of additivity
- Mixture of study can be tailored to address experimental question(s)
- Hypothesis-testing as well as -generating

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General Methodology for Additivity Analysis using Ray Designs

- Dose-response model is fit to single chemical data
- Additivity model (predicted) along fixed ray is generated based on single-chemical data and mixing ratio of each chemical
- Dose-response model (observed) is fit to experimental mixture data
- Fitted models (predicted vs observed) are tested for departure from additivity, *e.g.*,
  - Equality of parameters for experimental and additivity model
  - Experimental model fits within confidence limits of predicted model
  - Equality of statistically derived thresholds

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Considerations Using Ray Designs

- Adequately characterize shape of individual and mixture dose response
- Dose-response characteristics
  - Maximal responses
  - Slopes
- **Focus on chemical selections, combinations, and mixing ratios of interest**
- Also important: dose-rate, sequence and route of administration

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Mixture of 5 Organophosphorus Pesticides

- Why OPs?
  - Widely used pesticides, still
  - Potential for human exposure to multiple OPs through use on foods and other commercial crops, pets, garden, home
  - Common mode of action (inhibition of acetylcholinesterase)
  - Epidemiological studies implicate OPs for neurological adverse effects not predicted by individual chemicals
- Why 5 OPs?
  - Monitoring data show 99% of food products have ≤5 pesticide residues (USDA Pesticide Data Program)

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Mixture of 5 Organophosphorus Pesticides

- Which OPs?
  - Relevance based on potential human exposures, usage patterns, food residues
  - Overlapping geographical usage
  - Chlorpyrifos, diazinon, malathion, acephate, dimethoate
    - These were among top 10 OPs in use in US
- What ratios?
  - Proportions based on predicted dietary exposures estimated by Dietary Exposure Estimate Model (DEEM™)

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Environmentally Relevant Proportions (Ratios)

- Dose ratios

0.031 (chloryprifos)
0.825 (malathion)
0.102 (dimethoate)
0.002 (diazinon)
0.04 (acephate)

Chlorpyrifos DEEM values

POPULATION	95% EXPOSURE		99% EXPOSURE		99.9% EXPOSURE	
	mgs/kg/day	percent of aPAD	mgs/kg/day	percent of aPAD	mgs/kg/day	Percent of aPAD
U. S. Population	0.000019	0.4	0.000112	2.3	0.000790	15.8
All Infants	0.000013	2.5	0.000065	13.0	0.000645	129
Nursing Infants	0.000010	2.0	0.000068	13.7	0.001148	230
Non-nursing Infants	0.000014	2.7	0.000065	13.1	0.000482	96.4
Children 1 - 6 years old	0.000048	9.6	0.000240	48.1	0.001808	362
Children 7 - 12 years old	0.000034	6.9	0.000194	38.9	0.001357	272

Acute Population Adjusted Dose – based on RfD

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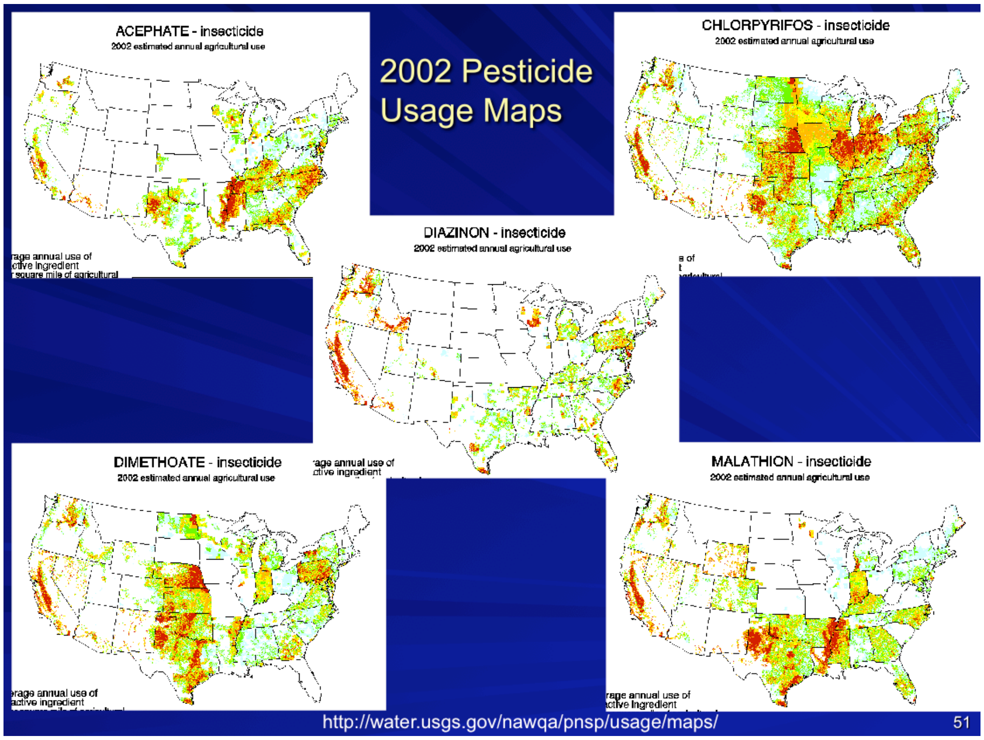
2002 Pesticide Usage Maps
ACEPHATE - insecticide
2002 estimated annual agricultural use
CHLORPYRIFOS - insecticide
2002 estimated annual agricultural use
DIAZINON - insecticide
2002 estimated annual agricultural use
DIMETHOATE - insecticide
2002 estimated annual agricultural use
MALATHION - insecticide
2002 estimated annual agricultural use
http://water.usgs.gov/nawqa/pnsp/usage/maps/
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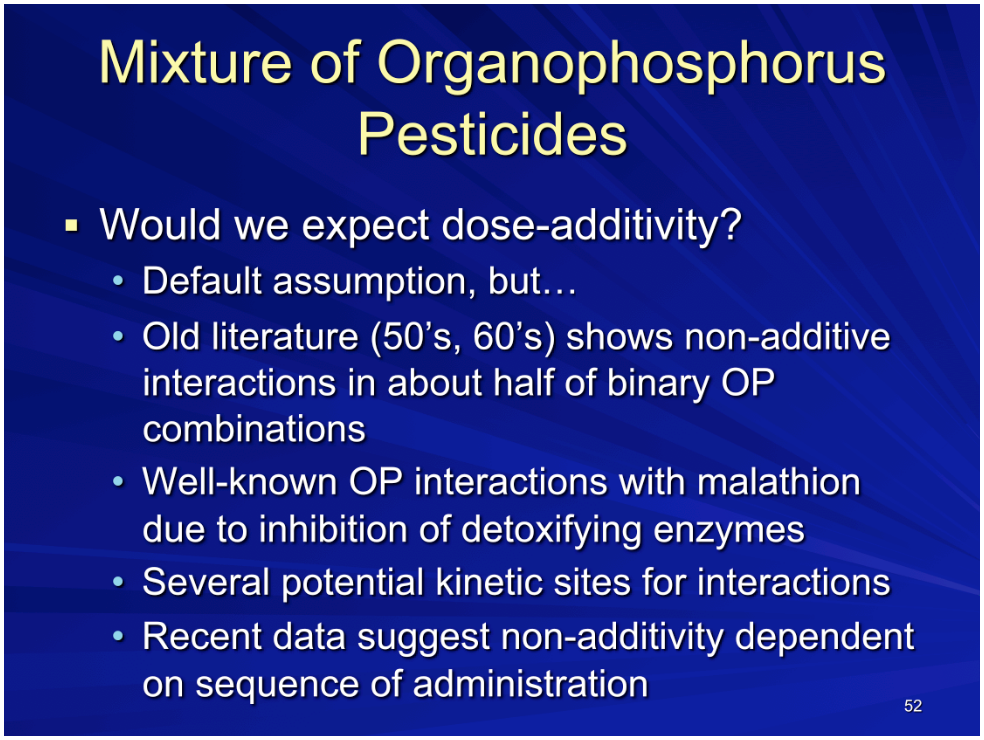
Mixture of Organophosphorus Pesticides
Would we expect dose-additivity?
Default assumption, but…
Old literature (50's, 60's) shows non-additive interactions in about half of binary OP combinations
Well-known OP interactions with malathion due to inhibition of detoxifying enzymes
Several potential kinetic sites for interactions
Recent data suggest non-additivity dependent on sequence of administration
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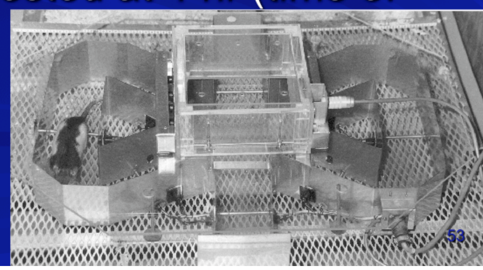
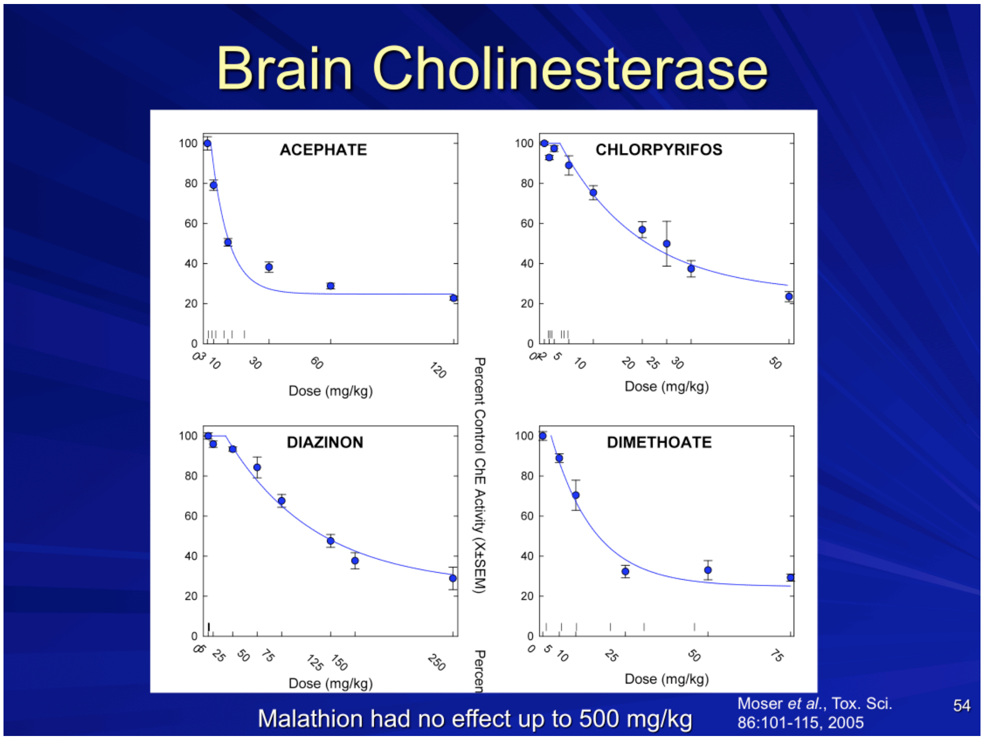
Approach

- Use multiple endpoints to fully characterize interactions
  - Brain and blood ChE inhibition, motor activity, gait score, tail pinch response
- Evaluate influence of malathion in the mixture by removing it (reduced ray)
- Acute oral dosing, tested at 4 hr (time of peak effect), male Long-Evans rats, n=10/dose
  Adult, PND17





Brain Cholinesterase
ACEPHATE
CHLORPYRIFOS
DIAZINON
DIMETHOATE
Dose (mg/kg)
Percent Control ChE Activity (X±SEM)
Malathion had no effect up to 500 mg/kg
Moser et al., Tox. Sci. 86:101-115, 2005
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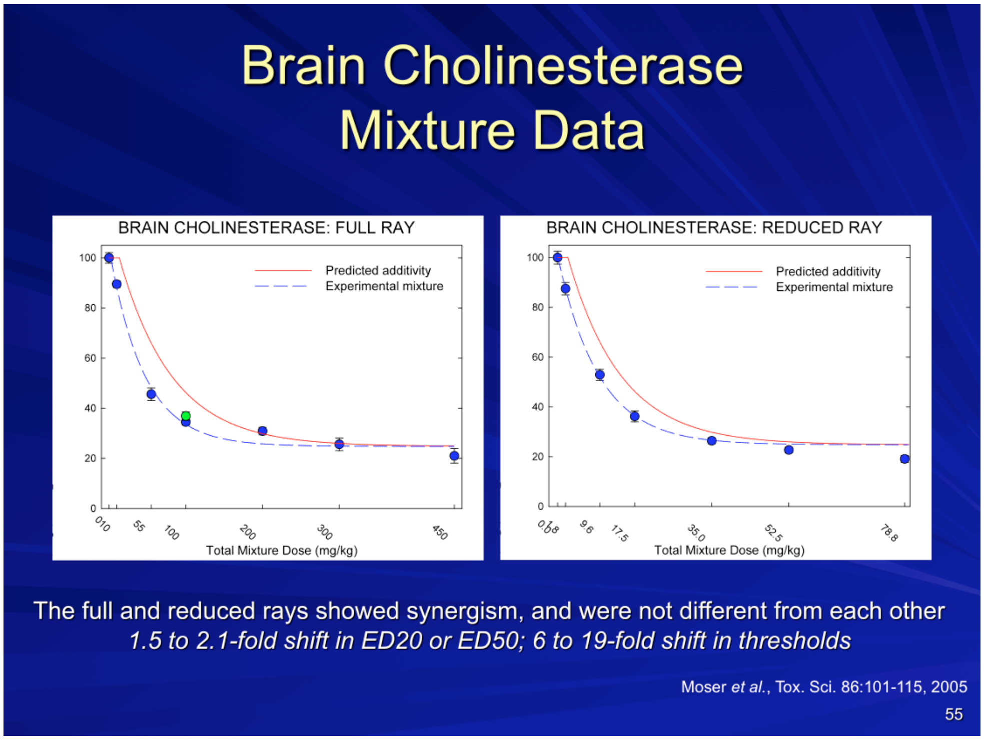
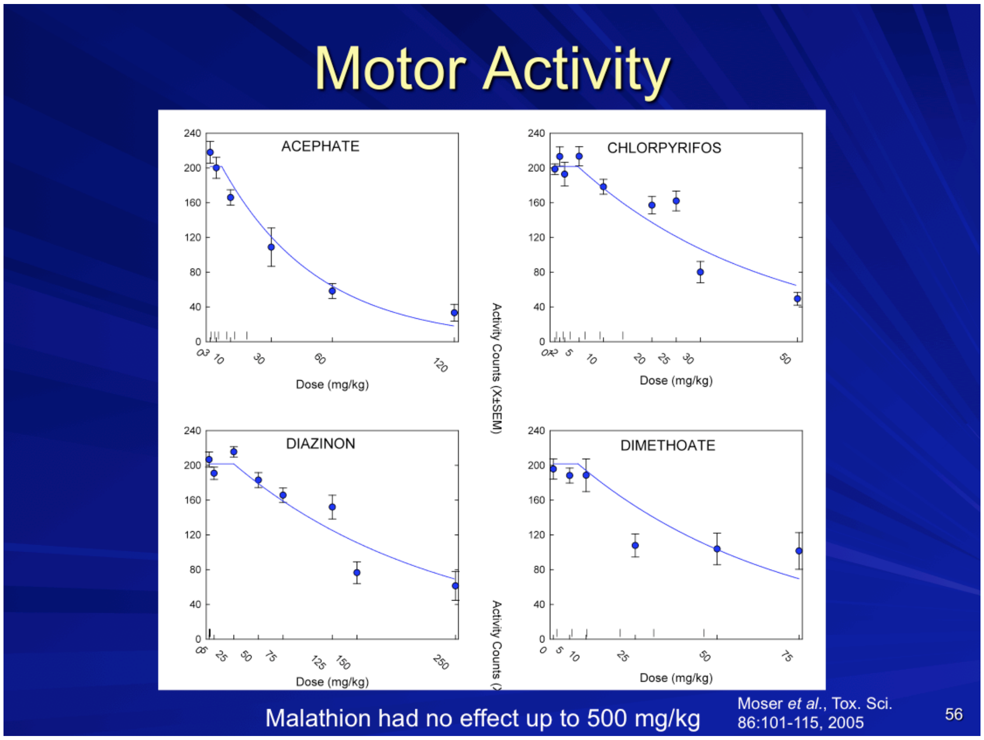

Brain Cholinesterase
Mixture Data
BRAIN CHOLINESTERASE: FULL RAY
Predicted additivity
Experimental mixture
100
80
60
40
20
0
55
100
200
300
450
Total Mixture Dose (mg/kg)
BRAIN CHOLINESTERASE: REDUCED RAY
Predicted additivity
Experimental mixture
100
80
60
40
20
0
9.6
17.5
35.0
52.5
78.8
Total Mixture Dose (mg/kg)
The full and reduced rays showed synergism, and were not different from each other
1.5 to 2.1-fold shift in ED20 or ED50; 6 to 19-fold shift in thresholds
Moser et al., Tox. Sci. 86:101-115, 2005
55


Motor Activity
ACEPHATE
CHLORPYRIFOS
DIAZINON
DIMETHOATE
Dose (mg/kg)
Activity Counts (X±SEM)
Malathion had no effect up to 500 mg/kg
Moser et al., Tox. Sci. 86:101-115, 2005
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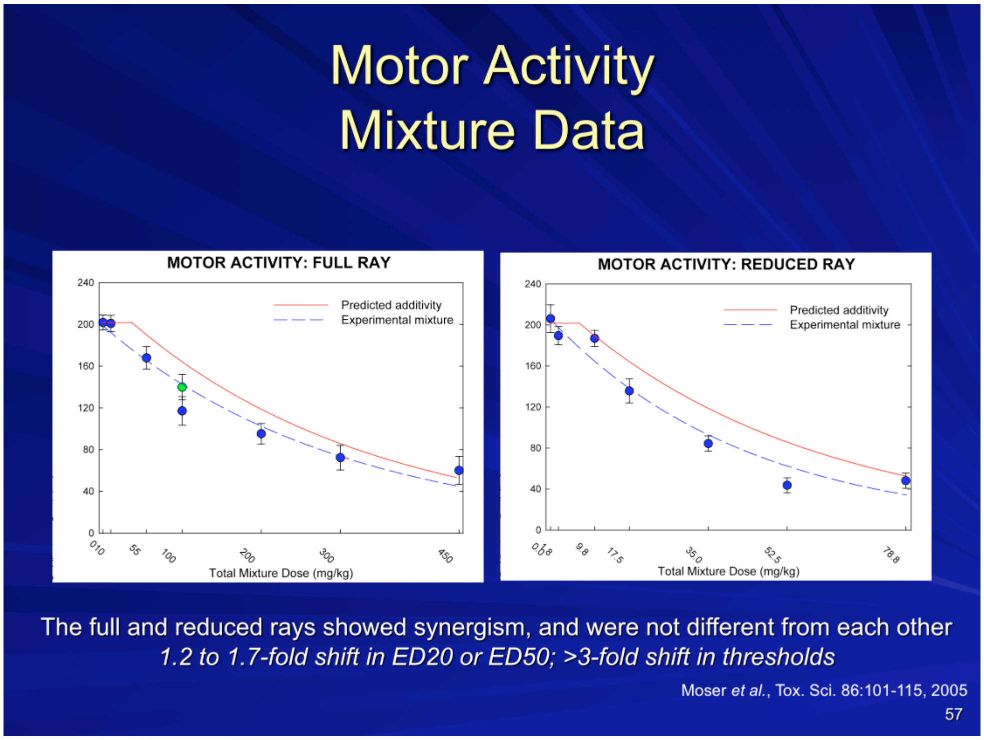
Motor Activity
Mixture Data
MOTOR ACTIVITY: FULL RAY
Predicted additivity
Experimental mixture
Total Mixture Dose (mg/kg)
MOTOR ACTIVITY: REDUCED RAY
Predicted additivity
Experimental mixture
Total Mixture Dose (mg/kg)
The full and reduced rays showed synergism, and were not different from each other
1.2 to 1.7-fold shift in ED20 or ED50; >3-fold shift in thresholds
Moser et al., Tox. Sci. 86:101-115, 2005
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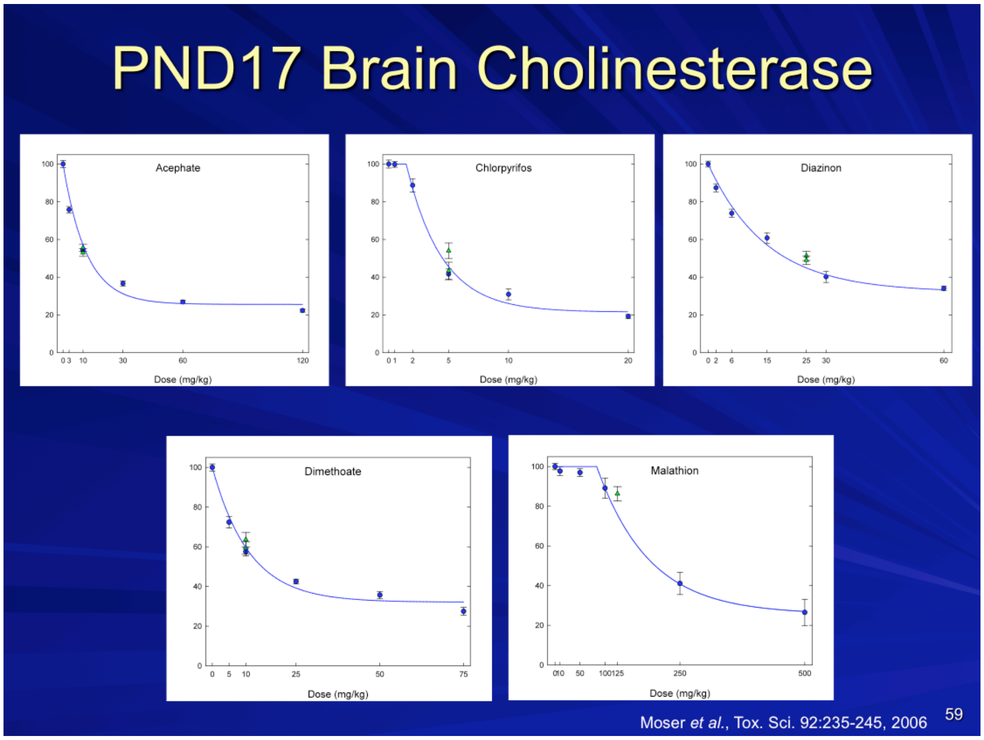
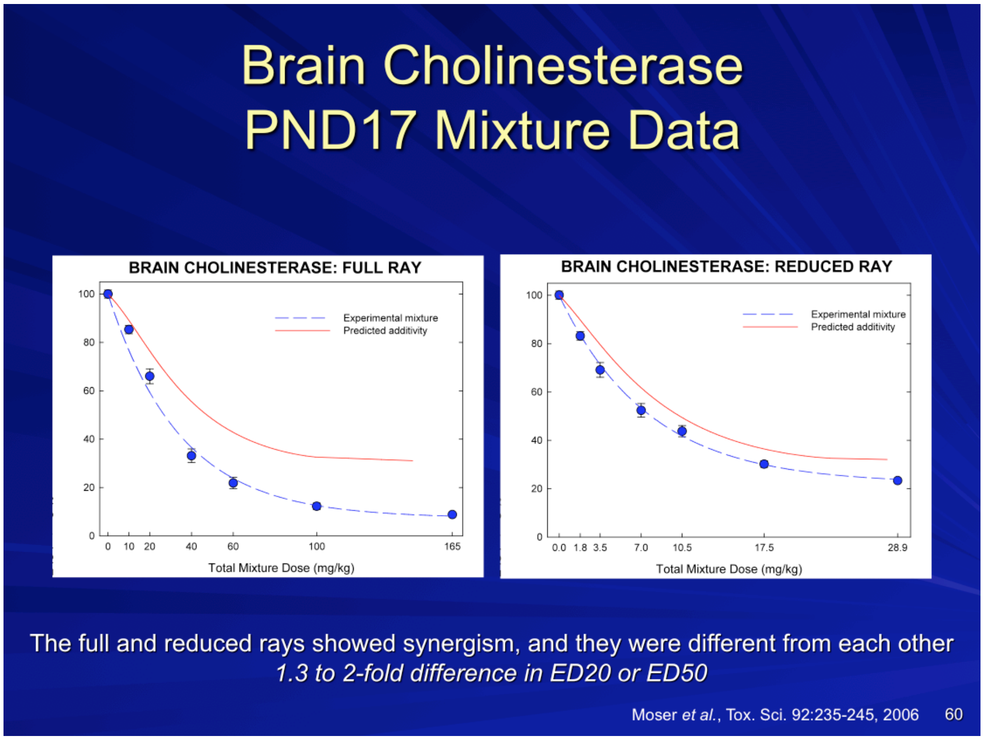
Adult Mixture Summary

Endpoint	Full Ray*	Reduced Ray*	Full vs. Reduced**	ED20/50 Difference
Brain ChE	Yes	Yes	No	1.5-2.1X 6-19X threshold shift
Blood ChE	Yes	Yes	Yes	1.2-1.9X
Motor Activity	Yes	Yes	No	1.2-1.7X >3X threshold shift
Gait Score	Yes	No	Yes	1.6-1.7X
Tail Pinch Response	No	No	--	--

* significantly different from additivity, greater-than-additive (synergism)
** significant difference between full and reduced rays

Moser *et al.*, Tox. Sci. 86:101-115, 2005 58


PND17 Brain Cholinesterase
Acephate
Dose (mg/kg)
Chlorpyrifos
Dose (mg/kg)
Diazinon
Dose (mg/kg)
Dimethoate
Dose (mg/kg)
Malathion
Dose (mg/kg)
Moser et al., Tox. Sci. 92:235-245, 2006
59


Brain Cholinesterase
PND17 Mixture Data
BRAIN CHOLINESTERASE: FULL RAY
Experimental mixture
Predicted additivity
Total Mixture Dose (mg/kg)
BRAIN CHOLINESTERASE: REDUCED RAY
Experimental mixture
Predicted additivity
Total Mixture Dose (mg/kg)
The full and reduced rays showed synergism, and they were different from each other
1.3 to 2-fold difference in ED20 or ED50
Moser et al., Tox. Sci. 92:235-245, 2006
60

PND17 Mixture Summary

Endpoint	Full Ray*	Reduced Ray*	Full vs. Reduced**	ED20/50 Difference
Brain ChE	Yes	Yes	Yes	1.5-2.1X
Blood ChE	Yes	Yes	Yes	1.7-2.3X
Motor Activity	Yes	No	Yes	1.3-2.6X
Gait Score	Yes	Yes	Yes	2.2-3X
Tail Pinch Response	Yes	No	Yes	3.5X

* significantly different from additivity, greater-than-additive (synergism)
** significant difference between full and reduced rays

Moser *et al.*, Tox. Sci. 92:235-245, 2006 61

Summary of OP Mixtures

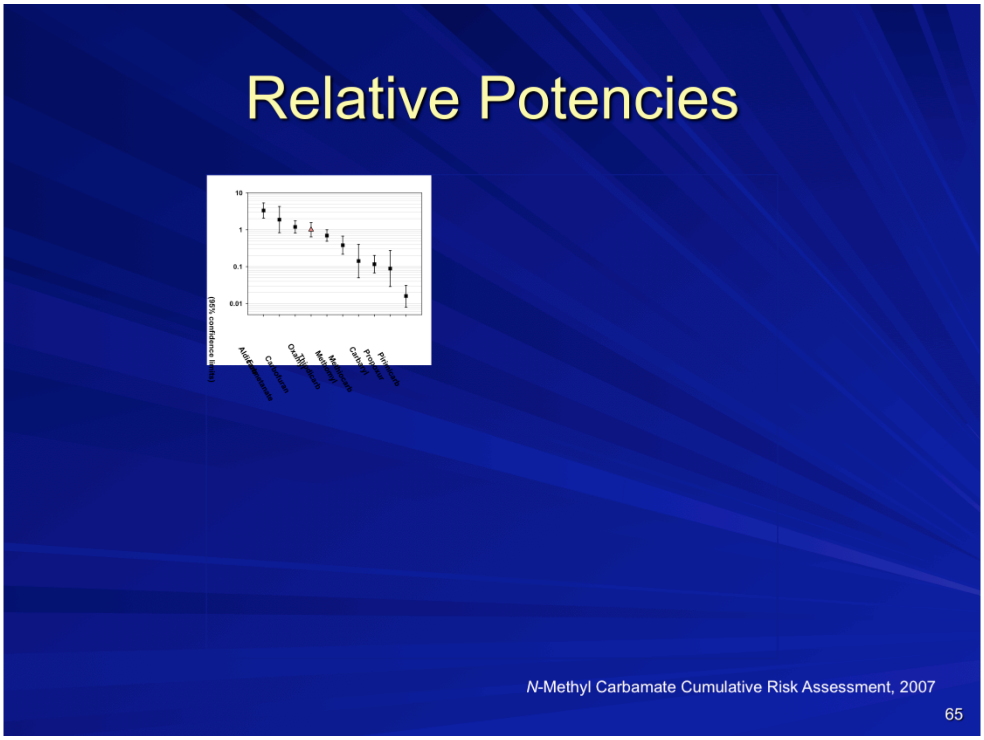
- Greater-than-additive interactions (*i.e.*, synergism) detected with both mixtures at both ages
  - Interactions depended on endpoint
  - Significant differences at low end of dose-response (threshold)
  - Comparing the reduced to the full ray indicated an influence of malathion on most endpoints
    - Degree of influence depended on endpoint

Mixture of 7 *N*-Methyl Carbamate Pesticides

- Why carbamates?
  - Broad agricultural and residential uses
  - Exposures from food residues, drinking water, and home – dermal, inhalation, oral
  - Common mode of action (inhibition of acetylcholinesterase)
- Why 7 carbamates?
  - Of 10 carbamates being regulated, these 7 had high contribution to cumulative risk assessment

Mixture of 7 *N*-Methyl Carbamate Pesticides

- Which carbamates?
  - High usage and contribution to cumulative risk assessment
  - Carbaryl, carbofuran, formetanate HCl, methiocarb, methomyl, oxamyl, propoxur
- What ratios?
  - Proportions based on relative potencies using BMD10 (10% brain ChE inhibition)
  - Proportions based on California database of tonnage sold in 2005
    - Surrogate for total (aggregate) exposures


Relative Potencies
10
1
0.1
0.01
(95% confidence limits)
Carbofuran
Methomyl
Methiocarb
Carbaryl
Propoxur
Pirimicarb
N-Methyl Carbamate Cumulative Risk Assessment, 2007
65

Pesticide Use Reporting (PUR)

Back to Home Page

California's pesticide use reporting program is recognized as the most comprehensive in the world. In 1990, California became the first state to require full reporting of agricultural pesticide use in response to demands for more realistic and comprehensive pesticide use data. Under the program, all agricultural pesticide use must be reported monthly to the county agricultural commissioner, who in turn, reports the data to DPR.

California has a broad legal definition of "agricultural use," so the reporting requirements include pesticide applications to parks, golf courses, cemeteries, rangeland, pastures, and along roadside and railroad rights-of-way. In addition, all postharvest pesticide treatments of agricultural commodities must be reported, along with all pesticide treatments in poultry and fish production, as well as some livestock applications. The primary exceptions to the full use reporting requirements are home and garden use and most industrial and institutional uses.

- Laws governing pesticide use reporting (Scroll to Food and Agricultural Code section 14011.5 et seq)
- Pesticide use reporting regulations (3 CCR sections 6624 – 6628)
- Pesticide use reporting of field fumigant applications
- Forms for pesticide use reporting

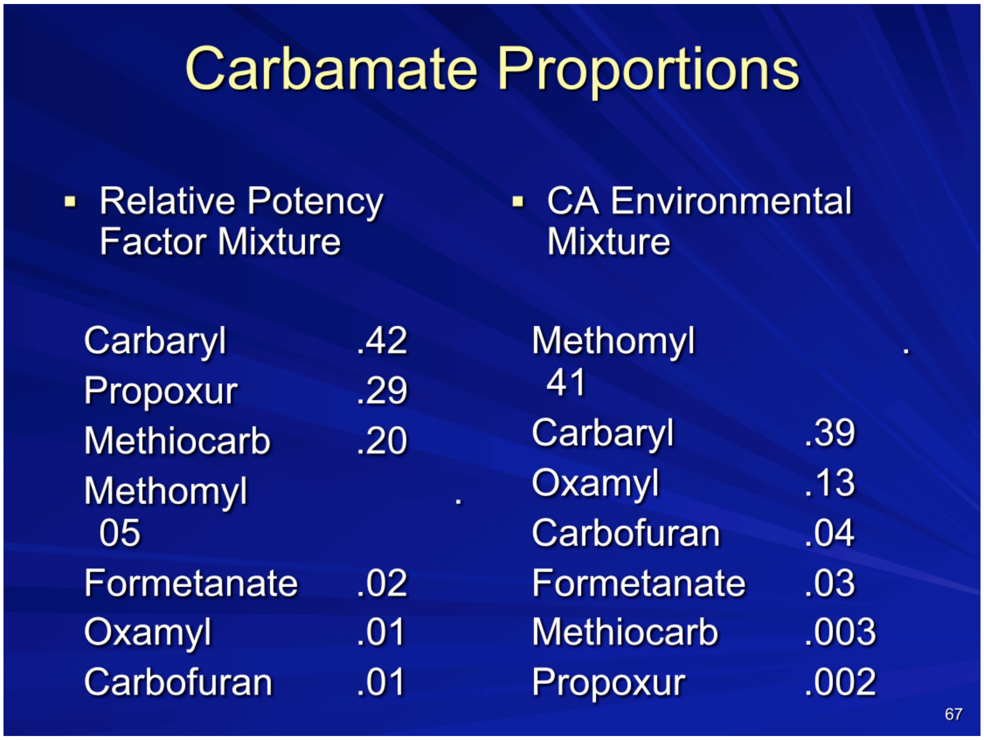
California Pesticide Information Portal (CalPIP)

- California Pesticide Information Portal – Generate customized information from DPR's Pesticide Use Report Database

Summaries of Pesticide Use Data (1989 to present - note that in 1989, full use reporting requirements were not in effect)

Click arrow to select year.

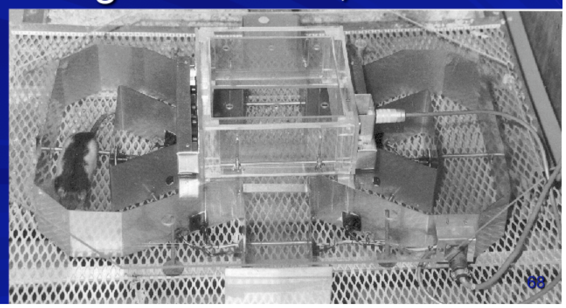
Use DPR's Publication Order Form (PDF, 170 kb) to order copies of the printed version of the annual *Summaries of Pesticide Use Data* or CDs of the complete database.

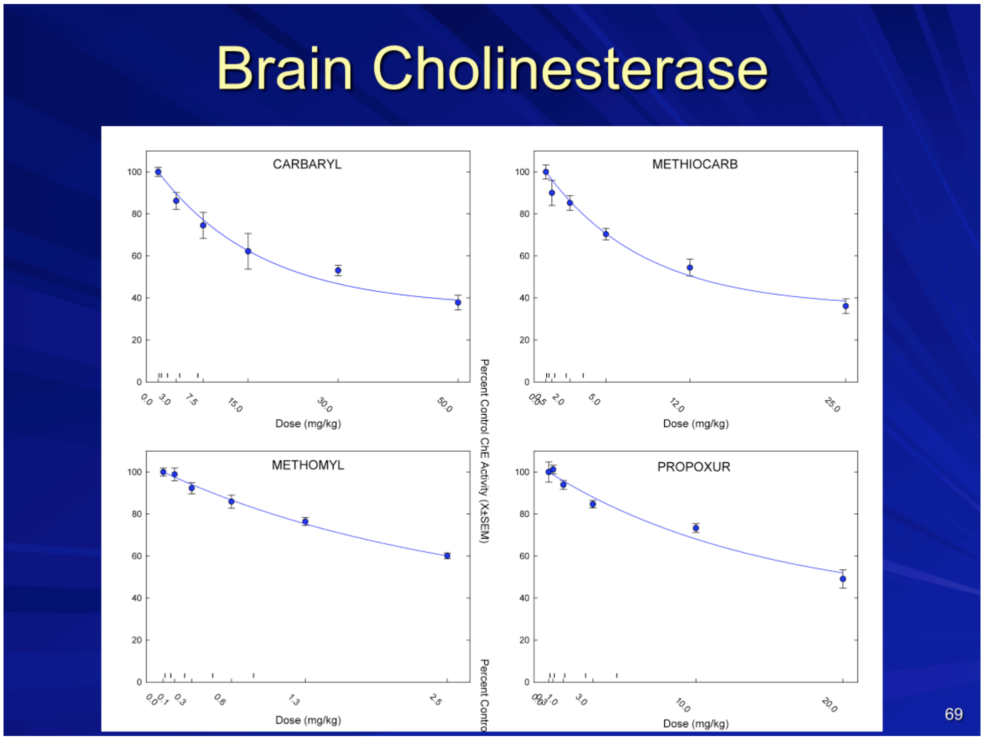

Carbamate Proportions
Relative Potency Factor Mixture
CA Environmental Mixture
Carbaryl .42
Propoxur .29
Methiocarb .20
Methomyl .
05
Formetanate .02
Oxamyl .01
Carbofuran .01
Methomyl .
41
Carbaryl .39
Oxamyl .13
Carbofuran .04
Formetanate .03
Methiocarb .003
Propoxur .002
67

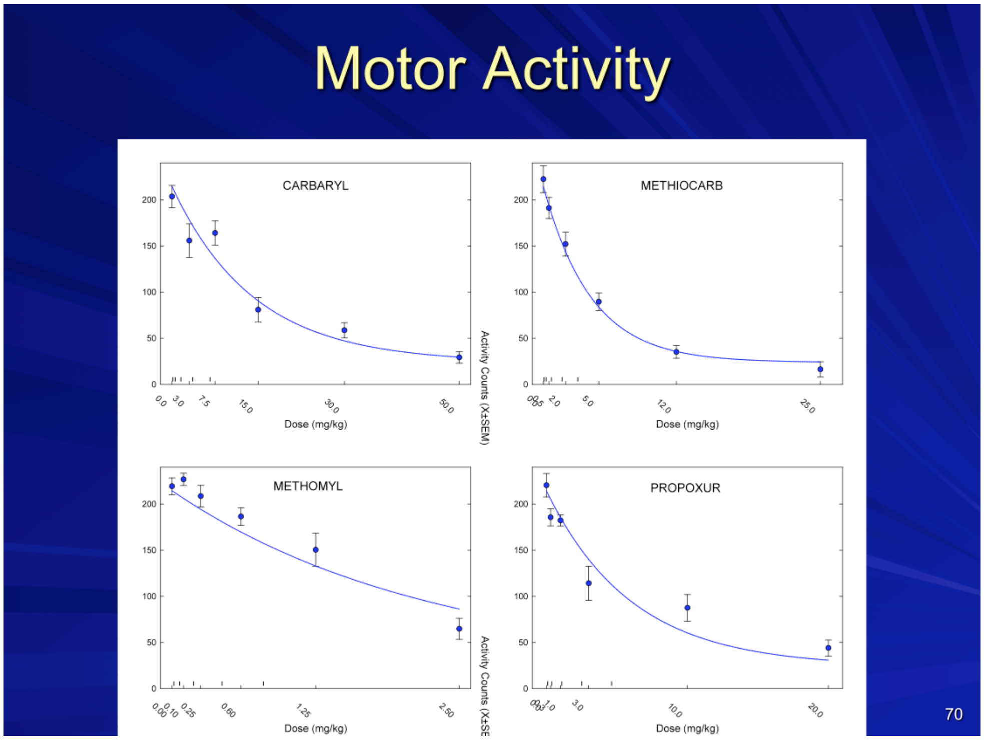
Approach

- Use several endpoints to characterize interactions
  - Brain and RBC ChE inhibition, motor activity
- Evaluate influence of mixing ratios
- Acute oral dosing, tested at 40 min (time of peak effect), male Long-Evans rats, n=10/dose

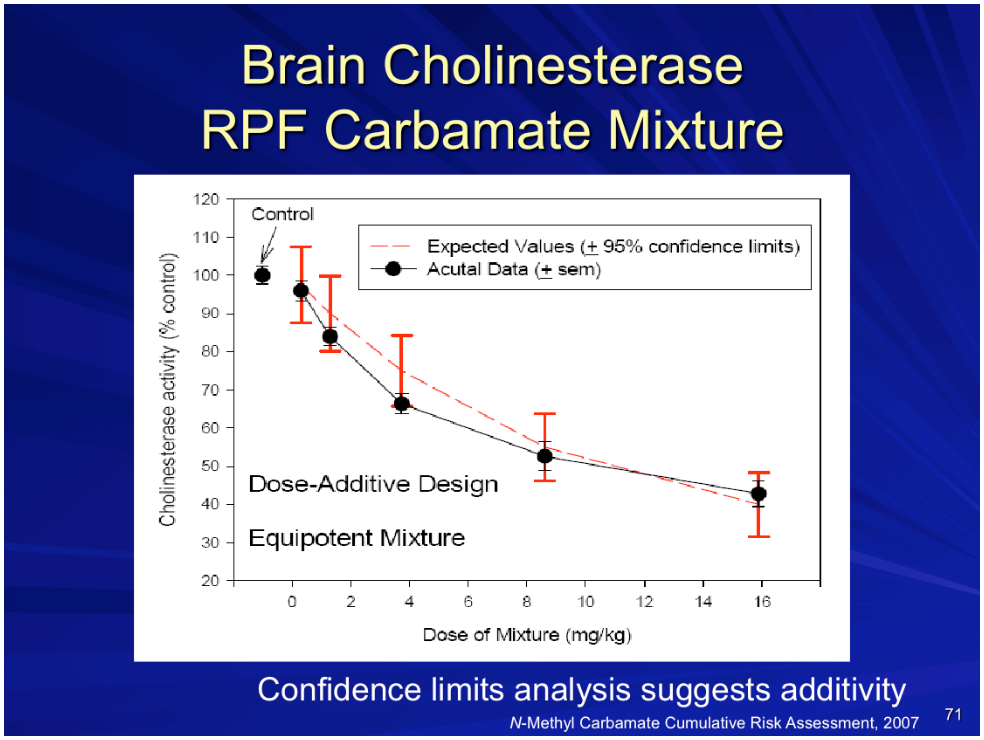
  Adult, (PND17)



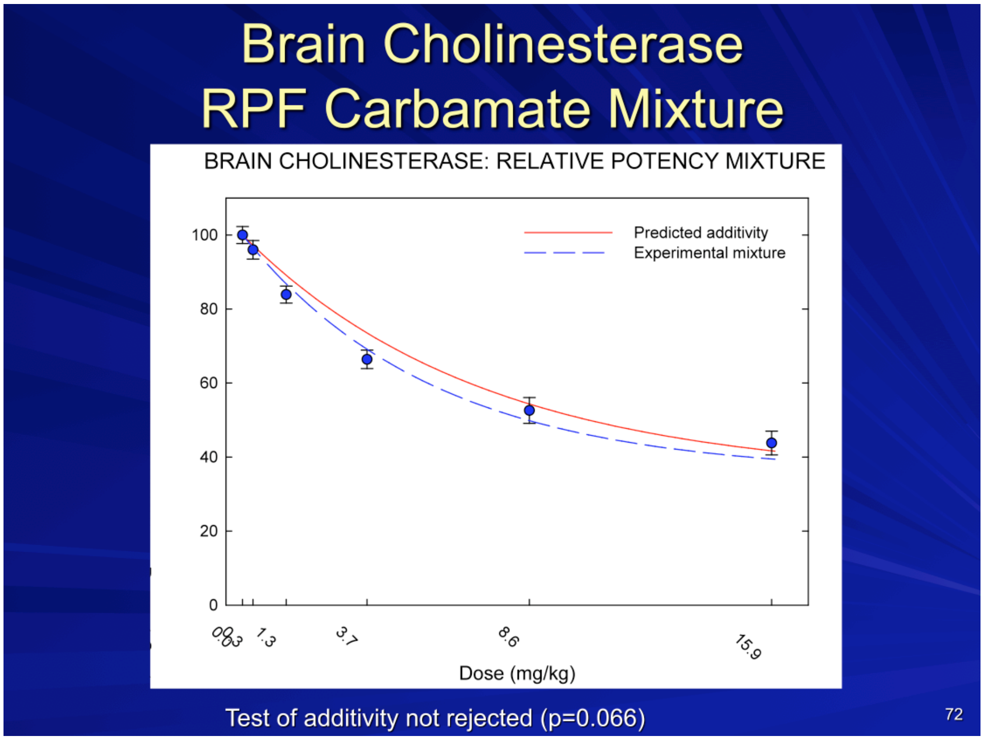

Brain Cholinesterase
CARBARYL
METHIOCARB
METHOMYL
PROPOXUR
Dose (mg/kg)
Percent Control ChE Activity (X±SEM)
69

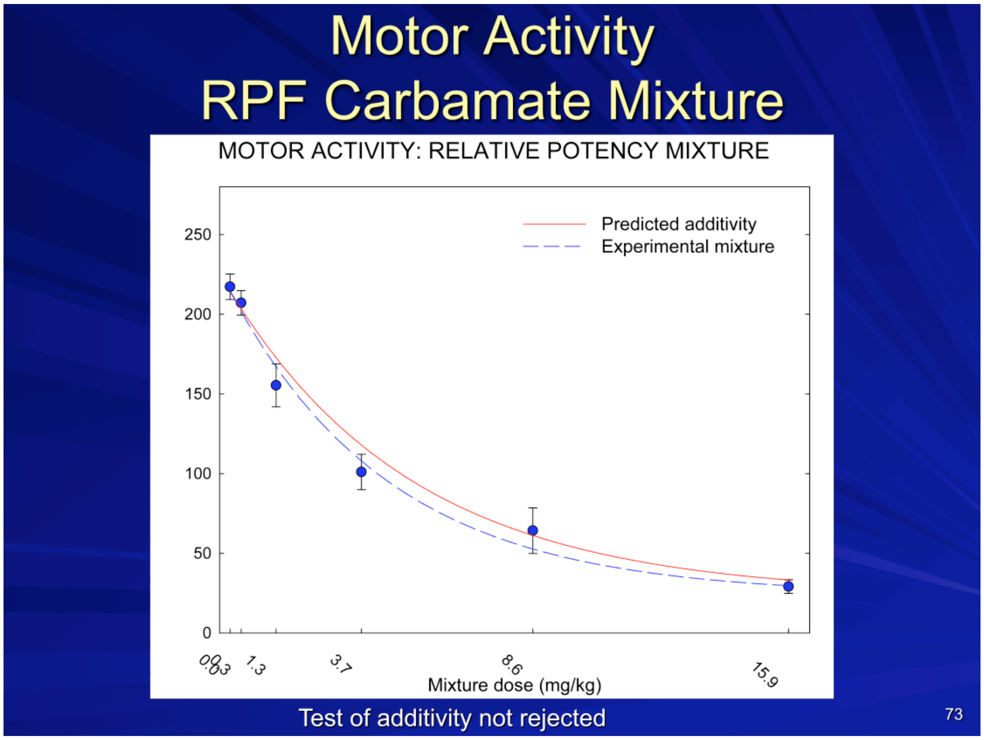

Motor Activity
CARBARYL
METHIOCARB
METHOMYL
PROPOXUR
Activity Counts (X±SEM)
Dose (mg/kg)
70

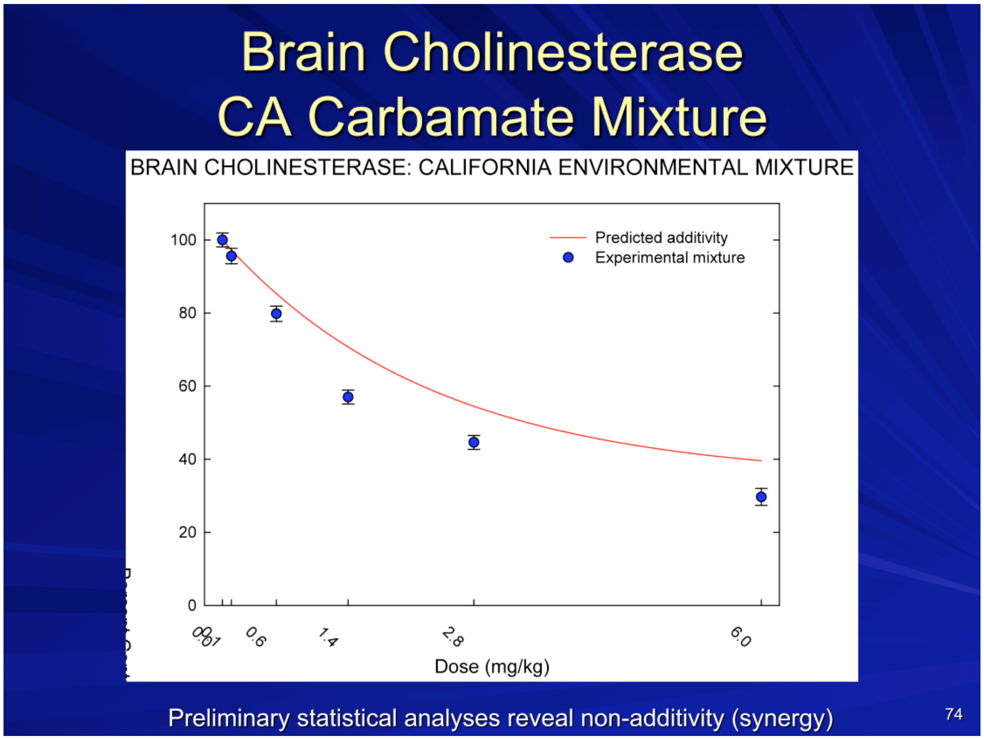
▫

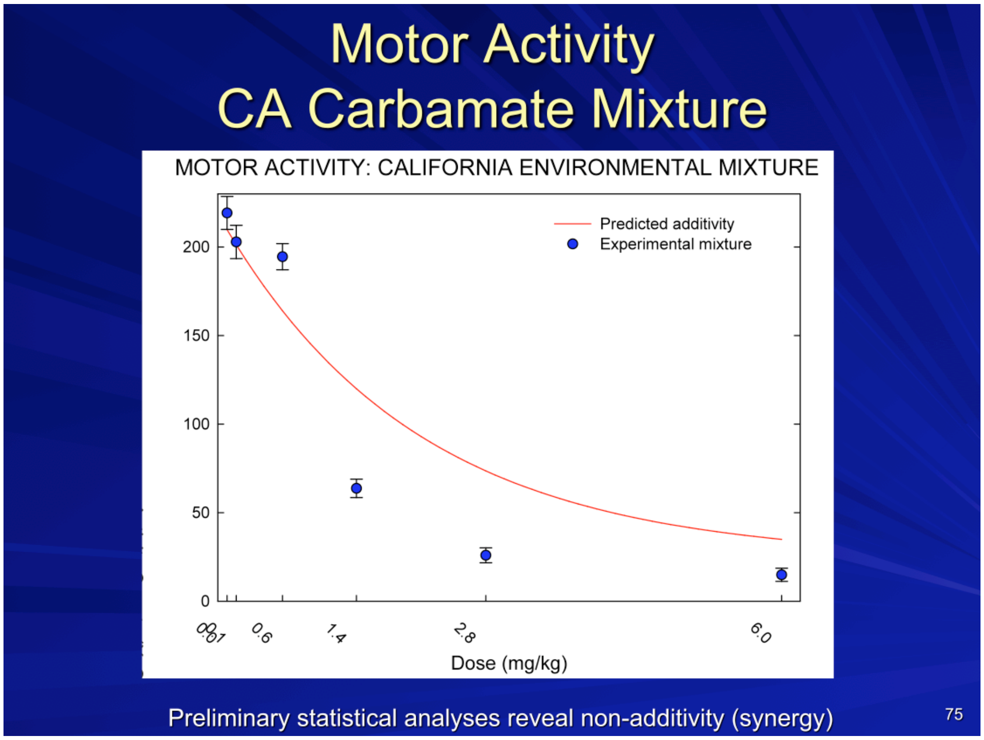


Brain Cholinesterase
RPF Carbamate Mixture
Control
Expected Values (± 95% confidence limits)
Acutal Data (± sem)
Cholinesterase activity (% control)
120
110
100
90
80
70
60
50
40
30
20
Dose-Additive Design
Equipotent Mixture
0
2
4
6
8
10
12
14
16
Dose of Mixture (mg/kg)
Confidence limits analysis suggests additivity
N-Methyl Carbamate Cumulative Risk Assessment, 2007
71


Brain Cholinesterase
RPF Carbamate Mixture
BRAIN CHOLINESTERASE: RELATIVE POTENCY MIXTURE
Predicted additivity
Experimental mixture
100
80
60
40
20
0
0
0.3
1.3
3.7
8.6
15.9
Dose (mg/kg)
Test of additivity not rejected (p=0.066)
72


Motor Activity
RPF Carbamate Mixture
MOTOR ACTIVITY: RELATIVE POTENCY MIXTURE
Predicted additivity
Experimental mixture
250
200
150
100
50
0
1.3
3.7
8.6
15.9
Mixture dose (mg/kg)
Test of additivity not rejected
73


Brain Cholinesterase
CA Carbamate Mixture
BRAIN CHOLINESTERASE: CALIFORNIA ENVIRONMENTAL MIXTURE
Predicted additivity
Experimental mixture
100
80
60
40
20
0
0.01
0.6
1.4
2.8
6.0
Dose (mg/kg)
Preliminary statistical analyses reveal non-additivity (synergy)
74



Motor Activity
CA Carbamate Mixture
MOTOR ACTIVITY: CALIFORNIA ENVIRONMENTAL MIXTURE
Predicted additivity
Experimental mixture
200
150
100
50
0
0.6
1.4
2.8
6.0
Dose (mg/kg)
Preliminary statistical analyses reveal non-additivity (synergy)
75

Summary of 7-Carbamate Mixtures

- Additivity (zero interaction) with mixture ratios based on relative potency factors
- Greater-than-additive interactions (*e.g.*, synergy) with mixture ratios based on amounts sold in California
- Differences in outcome based on mixing ratios of components

Other Studies, Similar Methodology

- 4 DBPs producing hepatotoxicity (mice)[1]
  - Ratio based on average seasonal proportion of 35 water treatment facilities
  - No departure from additivity
- 18 PHAHs decreasing serum T4 (rats)[2]
  - Ratio based on average concentrations found in human breast milk and food sources
  - Concentrations in range of human body burdens
  - Synergy emerged as dose increased
- 6 synthetic estrogens producing estrogenic actions (*in vitro* ER-α reporter gene and *in vivo* uterotrophic assays)[3]
  - With and without phytoestrogens
  - Ratios based on relative potencies
  - Interactions depended on concentrations and components of mixture

[1] Gennings et al., J Agr Biol Environ Stat, 2:198-211, 1997
[2] Crofton et al., Env Health Perspec 113:1549-1554, 2005
[3] Charles et al., Tox Appl Pharm 218:280-288, 2007

Considerations for Environmentally Relevant Mixture Research

- Appropriate experimental design and statistical analyses
  - Specify dose- or response-additivity hypotheses, design and analyze experiment appropriately
- Strategically select specific exposure scenarios
  - Potentially worrisome chemicals, *e.g.*, high-use, environmentally persistent
  - Rational mixing ratios, *e.g.*, reflecting potential or known human exposure
  - Site-specific combinations and ratios
- Use of fixed-ratio ray designs can provide efficient and focused research of mixtures

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Cadillac of Mixture Assessments

- Quantitative component-based mixtures risk assessment that includes:
  - Exposure scenarios reflective of human exposures
  - Environmental relevance in composition of mixture
  - Defined dose-response data addressing common toxic pathway
  - Experimental data on actual mixtures
  - Evaluation of additional influences, *e.g.*, age, gender, *etc.*
  - Biologically based modeling (*e.g.*, PBPK) to describe interactions

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Volkswagen of Mixture Assessments

- Less data-intensive approaches for (partially) defined mixtures
- Given exposure data and some measure of acceptable level (*e.g.*, RfD/C)
  - Hazard quotient (HQ) or index (HI)
  - Target organ toxicity dose (TTD)
  - Toxicity equivalence factor (TEF)
- Given only composition
  - Analysis of sufficiently similar mixtures

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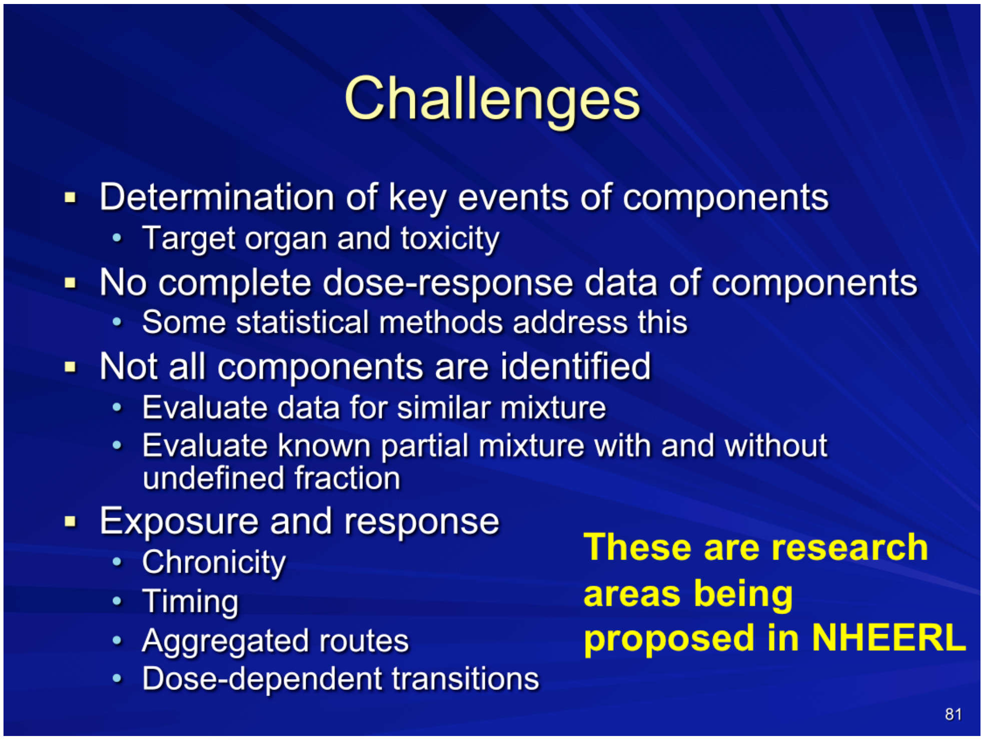
Challenges
Determination of key events of components
Target organ and toxicity
No complete dose-response data of components
Some statistical methods address this
Not all components are identified
Evaluate data for similar mixture
Evaluate known partial mixture with and without undefined fraction
Exposure and response
Chronicity
Timing
Aggregated routes
Dose-dependent transitions
These are research areas being proposed in NHEERL
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Thank you!

US Environmental Protection Agency, Research Triangle Park, NC

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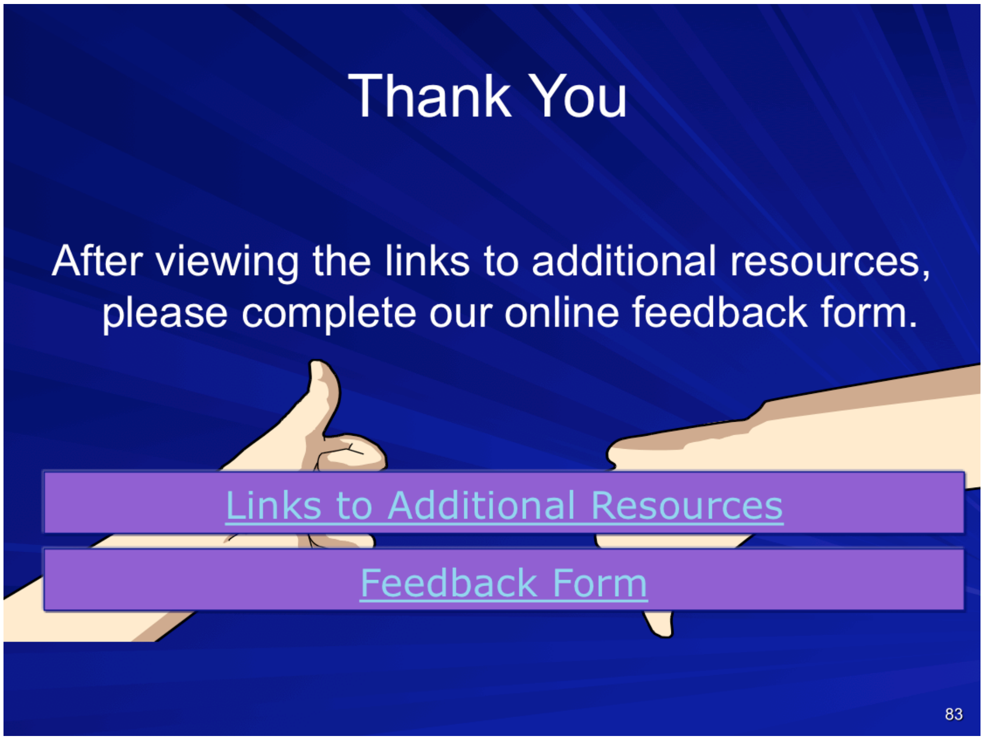
Thank You
After viewing the links to additional resources, please complete our online feedback form.
Links to Additional Resources
Feedback Form
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