Biomarkers of Pesticide Exposure: Lessons for Children in Agricultural Communities

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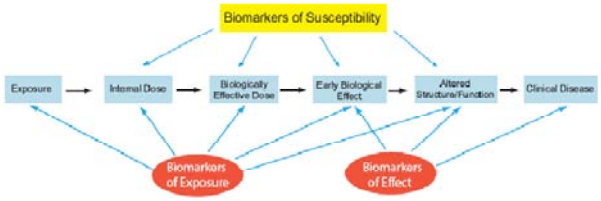
Gustav Klimt, *Baby (Cradle)*, 1917/1918.
National Gallery of Art. From www.nga.gov

Biomarkers for Monitoring Exposure and Effect in Populations



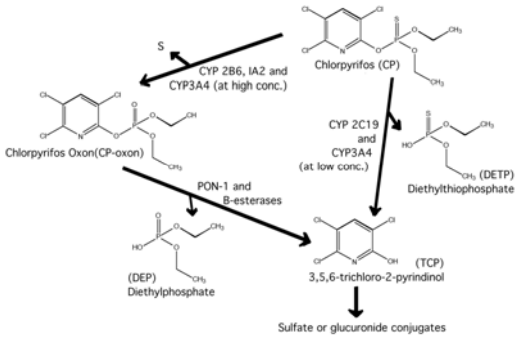
Examples of Chemicals Applied to Washington State Crops, 2001

Chemical class	crop	Chemical	Pounds applied
Organophosphates	Apples	Azinphos-methyl	241,000
		Chlorpyrifos	234,000
		Phosmet	138,000
	Potatoes	Ethoprop	119,000
		Metamidophos	143,000
N-Me Carbamates	Apples	carbaryl	202,000
	Potatoes	Aldicarb	153,000
Dithiocarbamate	Apples	Mancozeb	82,000
	Potatoes	Mancozeb	343,000

Source: "Agricultural Chemical Usage (PCU-BB)" National Agricultural Statistics Service, Agricultural Statistics Board, U.S. Department of Agriculture (http://jan.mannlib.cornell.edu/reports/nassr/other/pcubb Accessed 05/03)

Agricultural Pesticides: Contributions of Occupational Factors to Home Contamination

Metabolic Scheme for CP



Faustman et al. (2006)

Metabolites of Organophosphate Pesticides

- Biomarkers of exposure
- Nonspecific Diakyl Phosphate (DAP) metabolites
  - Six DAP Metabolites
  - Each metabolite can be produced by multiple OPs
  - Divided into two groups
    - Dimethyl metabolites
      - DMP, DMTP, DMDTP
    - Diethyl metabolites
      - DEP, DETP, DEDTP
- Specific metabolites
  - Chlorpyrifos metabolites
    - TCP, DEP, DETP
  - Chlorpyrifos-methyl metabolites
    - TCP, DMP, DMTP

Metabolites of Organophosphate Pesticides

Selected OPs and DAP metabolites

Diethyl OPs			
chlorpyrifos		DEP	DETP
diazinon		DEP	DETP
disulfoton	DEDTP	DEP	DETP
ethion	DEDTP	DEP	DETP
parathion		DEP	DETP
Dimethyl OPs			
azinophos methyl	DMDTP	DMP	DMTP
chlorpyrifos methyl		DMP	DMTP
dichlorvos (DDVP)		DMP	
malathion	DMDTP	DMP	DMTP
methyl parathion		DMP	DMTP
naled		DMP	
phosmet	DMDTP	DMP	DMTP
trichlorfon		DMP	

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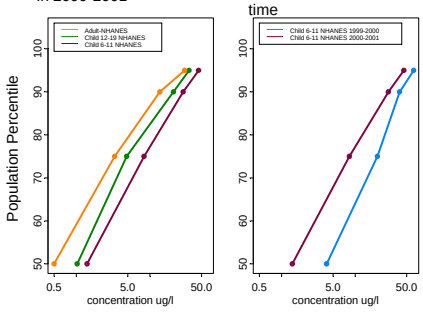
NHANES Data for DMTP in Urine

Random sample of US Population

Comparison across ages in 2000-2001

Comparison for children (6-11 years old) across time



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What do these values mean for my Children?

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Samples Collected in Studies of Farmworker Families

- Types of samples collected from individuals and their children in 3 seasons
  - Urine analyzed for metabolites of OPs—collected 3 times in 1 week
  - Blood analyzed for parent OPs, metabolites of OPs, AChE in RBCs and plasma, genotypes and phenotypes of metabolizing enzymes—collected once
  - Buccal Cells analyzed for gene expression—collected 2 times in 1 week
- Dust is collected from homes and autos in thinning and non-spray seasons season and analyzed for parent OPs

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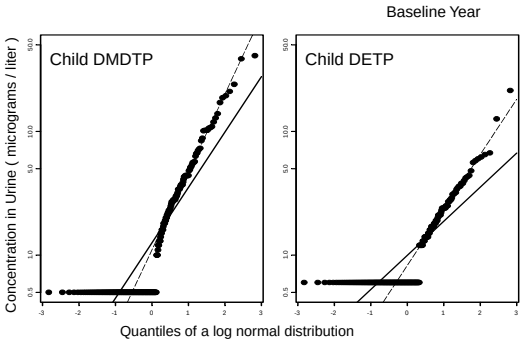
Many Values Are Below Limits of Detection



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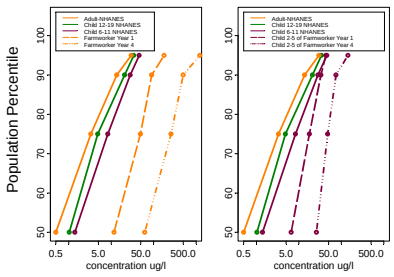
NHANES Compared to Farmworker Family Data for DMTP in Urine

Comparison to Adult Farmworkers

Comparison to Children of Farmworkers (2-5 years old)



Data for farmworkers and their children was collected in two different years

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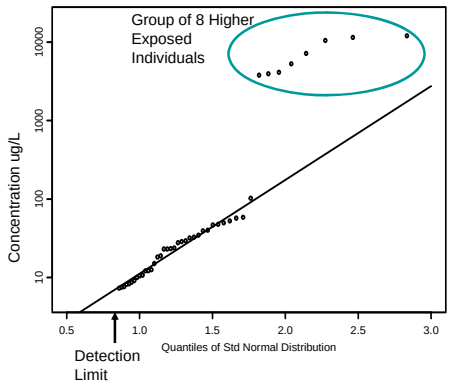
DMP in Adult Urine: QQ Plots to Estimate Population Distribution



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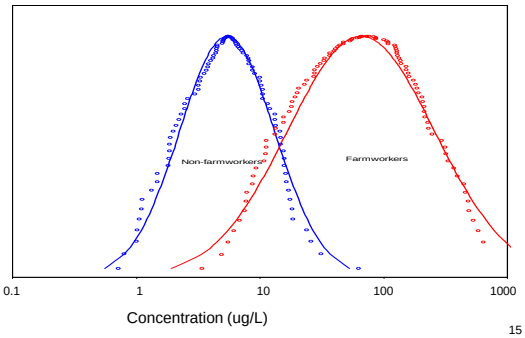
Distribution of Adult DMTP Metabolite Concentrations



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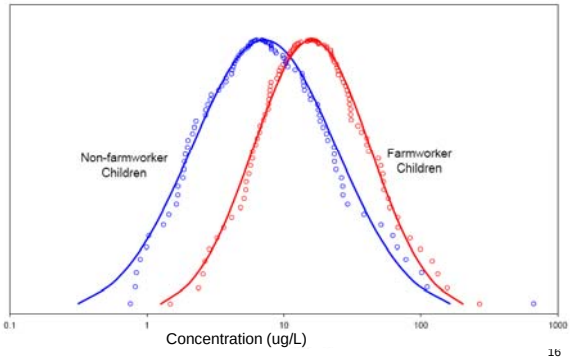
Distribution of Child Urinary DMTP Metabolite Concentrations



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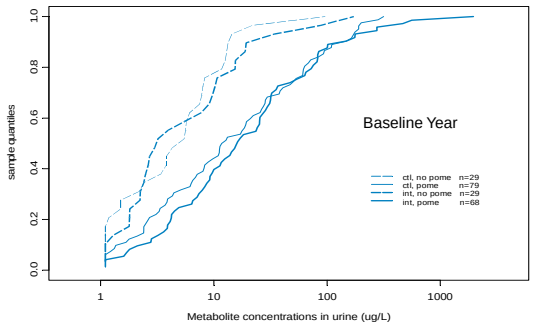
Distribution of Adult DMTP from year 1: Impact of Crop



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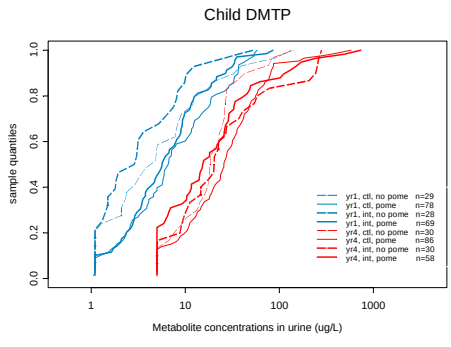
Distribution of Child DMTP from year 1 to year 4 of CHC study: Impacts of year to year variability



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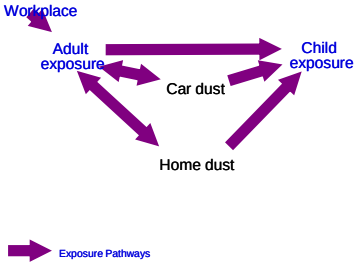
Assessing Children's Pesticide Exposure via the Take-home Pathway



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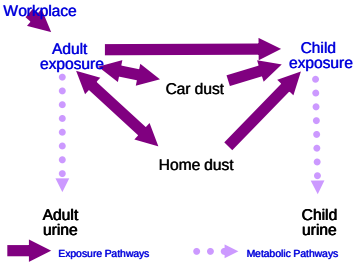
Assessing Children's Pesticide Exposure via the Take-home Pathway



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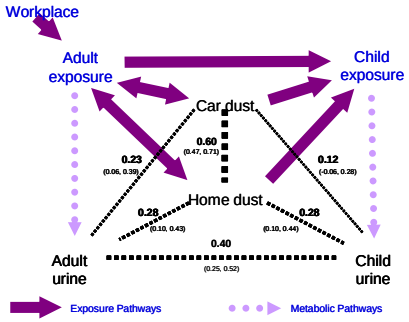
Azinphos-methyl Take-home Pathway



The dashed black lines that connect the samples illustrate the correlations between the sample concentrations. The lines are weighted according to the strengths of the correlations. The correlations are statistically significant if the 95% posterior probability intervals (in parentheses) do not include zero.

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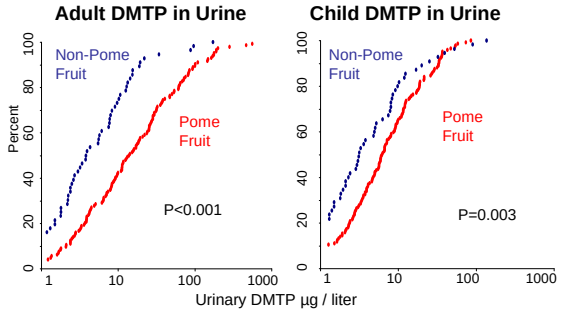
Urinary metabolites higher in adults who worked in pome fruit and their children



Coronado et al., Env. Hlth. Persp., 2004, 2006

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Two longitudinal studies of OP metabolites used to estimate within and between variability

- Multiple measurements in the same person across time permit estimation of both within and between person variability
  - Within and between person variability treated as a random effect and other variables such as age, gender ,residence, season treated as fixed effects
- TCP had a low percentage below limits of detection
- Measurements below limit of detection (LOD) were treated as being left censored in statistical analyses

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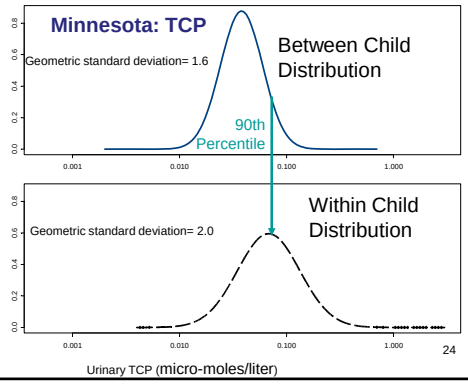
Within and Between Person Distributions for TCP

NHEXAS database

- Population based random sample collected at 3 times separated by 2 days
- 90 Children 3-14 yrs old and 263 samples
- Only 20 samples, 8%, below limit of detection
- Covariates of gender, age, residence were treated as fixed effects
- NHEXAS data Shared by John Quackenboss



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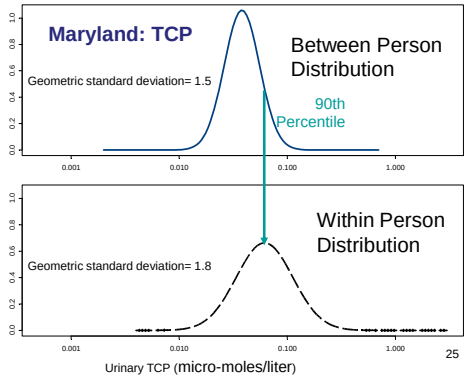
Within and Between Person Distributions for TCP

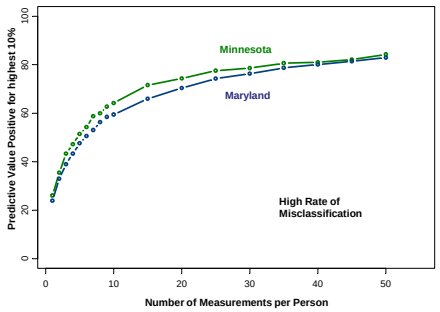
NHEXAS database

- Population based random sample collected over 1 year
- Up to 6 samples per person, samples separated by 2 months
- 79 individuals and 341 samples
- Only 14 samples, 4%, below limit of detection
- Covariates of gender, age, season were treated as fixed effects



Predictive Value Positive for Identifying Persons in the Upper 10% of the Population

The predictive value positive is the percent of the population assigned to a group that are correctly classified.



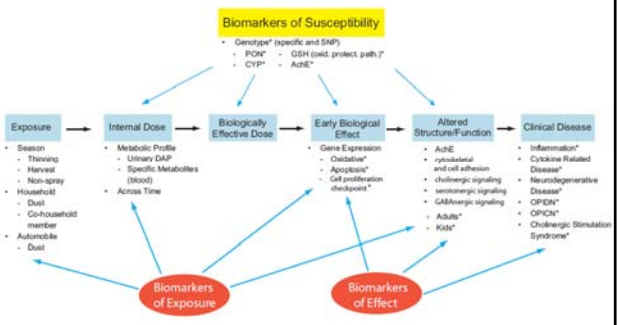
Based upon large within person variances it will require a large number of samples of urinary metabolites to correctly identify persons in a population who are more highly exposed to CP and CPM.

Sources of Uncertainty

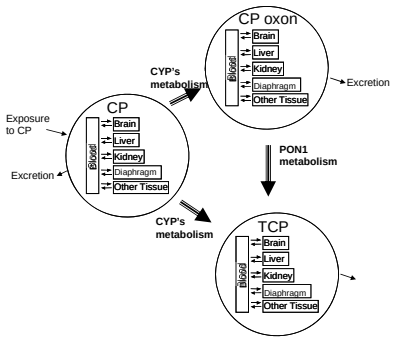
Stochasticity
- Characterization of Within and Between Person Variability

Parameter Uncertainty
- Year-to-Year Variability
- Observations below Limits of Detection (LOD)

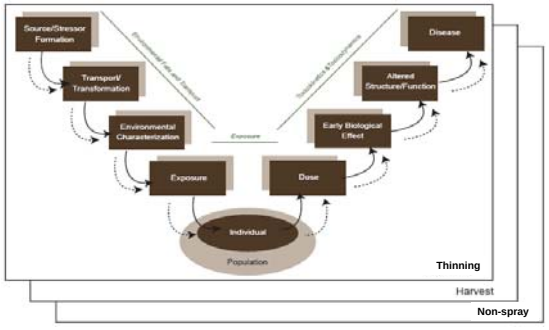
Model Uncertainty
- Crop vs. Agricultural Job Task
- Identification of Highly Exposed Individuals



Physiologic Based Toxicokinetic Models of CP Metabolism



Integrated Framework Tool



Methodology Underlying Integrated Framework Tool

- Bayesian Based Mixed Effects Model
  - Correlational structure of a multivariate distribution used to estimate correlations between pesticide concentrations, metabolites, gene expression levels, and other variables
  - Markov chain Monte Carlo methods used for parameter estimation

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Hypotheses to be Tested

1. Knowing the genotype/phenotype for key genes that metabolize CP (biomarkers of susceptibility) will improve prediction of
   - Exposure response
   - At risk individuals in agricultural communities
2. Knowing polymporphisms of oxidant responsive pathways will allow us to:
   - Better evaluate the potential for genomic biomarkers of early response with OP metabolites of exposure.
   - Better predict relationship of biomarkers of effect (AChE) to respond in dose-response manner to the OP exposures in adults and children.
   - Better predict whether "omic" biomarkers of disease are correlated with OP exposure.

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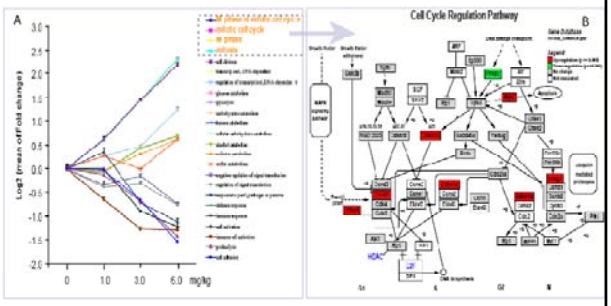
GO-Quant based quantitative pathway analysis



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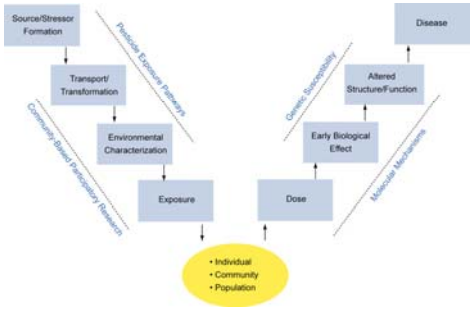

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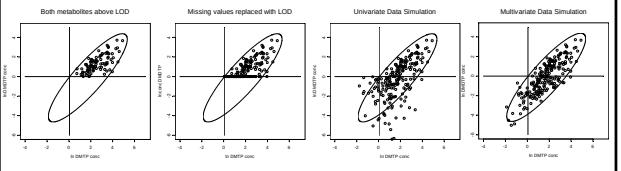
Using Markov Chain Monte Carlo Methods to Estimate Correlation Structure

Metabolites above LOD	Replace missing values by LOD	Univariate Data Simulation	Multivariate Data Simulation



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