Importance of Pharmacokinetics, Distributional Analyses, and Early Effect Biomarkers for Understanding Biomonitoring Results

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Outline

- Problem#1—Risk at the RfD/RfC and Therefore the BE is Undefined
- Problem#2—Biomonitoring Focused Exclusively on Levels of Environmental Chemicals Will Miss Opportunities to Discover Relationships to Early Effect Biomarkers of Public Health Importance
- Possible Program Modifications That May Improve Contributions to Public Health Protection/Promotion

The current RfD/RfC System—a Reminder

- Original 100 fold factor between NOEL and permitted level—later decomposed to 10 fold each for interspecies differences and human interindividual variability in susceptibility
- Additional factors added for inadequacies of testing—absence of full chronic study and/or reproductive/developmental studies
- Original empirical bases for these factors, if they ever existed, are lost in the mists of time.

The System for Defining RfDs/RfCs Can Be Greatly Improved

- Hopeless to represent the compounding effects of different sources of uncertainties with single-point “factors”. Far better: Use available empirical data to define distributions representing specific uncertainties.
- Using empirically based distributions allows restatement of should be able RfD goals in terms of a finite incidence of effect (or less) with a given degree of confidence.
- The current system is based on a universal assumption of population thresholds for non-cancer effects that is likely to be wrong both because of appreciable human variability in susceptibility and interactions with background pathologies.
- By failing to provide a basis for derivation of some, albeit highly uncertain finite estimates of risk, the current system does not allow development of inputs needed for comparison of potential impacts of different policy options.
- After considering the fundamental difficulties in RfDs/RfCs—the difficulties posed by the “Biological Equivalent” translations are not major, although there are some problems.

Definition from Aylward et al. 2009

- “A Biomonitoring Equivalent (BE) is defined as the concentration or range of concentrations of an environmental chemical (or metabolite) in a biological medium (blood, urine, or other medium) that is consistent with an existing health-based exposure guidance value such as a reference dose (RfD) or tolerable daily intake (TDI).”

Goal of BE's

- "BEs are intended to be used as screening tools to allow an assessment of biomonitoring data to evaluate which chemicals have large, small, or no margins of safety compared to existing risk assessments and exposure guidance values."
- Comment: "margin of safety" or "margin of exposure analyses beg many questions including the population exposure percentile to be compared with the "point of departure" inferred from the small-group animal studies, and the internal dose metric assumed to produce "equivalent" risk of effects across species.

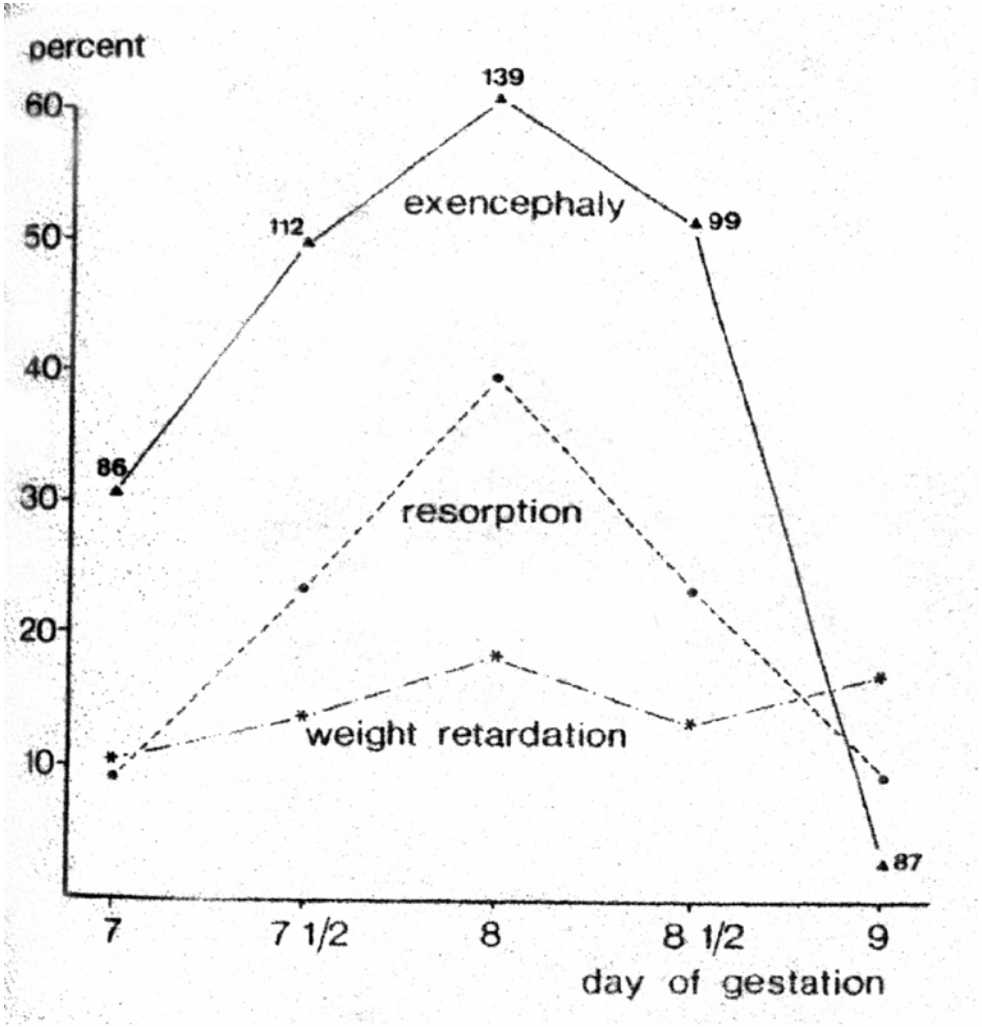
Aylward (2009) Procedure for BE Derivation for Some Phthalates

- Identify the POD used as the basis for the derivation of the TDI or RfD.
- Apply any uncertainty factors (UFs) used in the TDI or RfD derivation to account for exposure duration, severity of endpoint, and interspecies extrapolation to identify the human-equivalent POD.
- Estimate the total daily urinary excretion of mono-ester on a molar and mass basis per unit dose of parent compound. Divide the estimated daily excretion per unit dose of parent compound by 24-h average urine volume and average creatinine excretion. This factor allows estimation of average urinary concentrations associated with steady-state chronic intake of any dose of parent compound.
- Apply the urinary excretion factor to the human-equivalent POD from step 2 to estimate the urinary BEPOD.
- Apply the intraspecies uncertainty factor to the BEPOD to derive the BE.

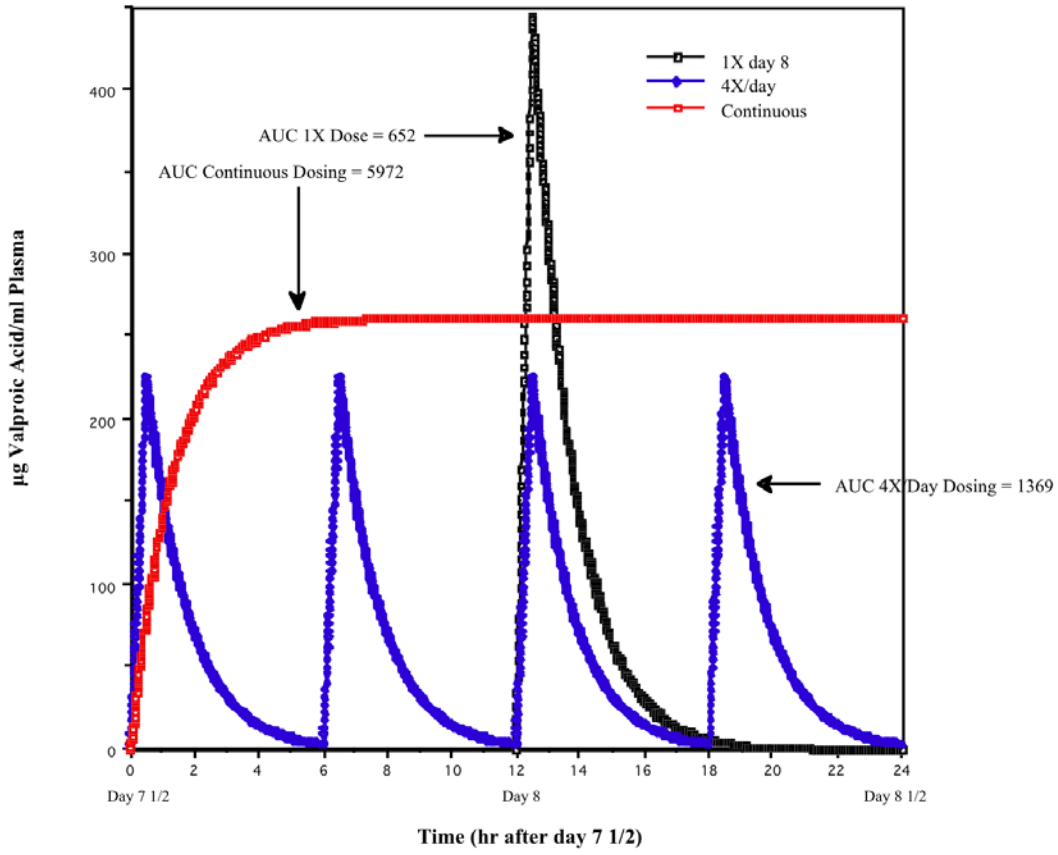
Some Difficulties/Issues

- Chronic Long Term Average Biological Equivalent Exposure Value vs Acute Measurement vs Uncertain Causally Relevant Dose Metric—The latter may be particularly important for time-sensitive exposures causing reproductive-developmental effects.
- Limitations in Toxicological Testing for Most Substances Included in Biomonitoring Studies—Even where some testing is available:
  - Limitations to a single age (e.g. young adults)
  - Absence of the potential for interactions with background exposures and pathological processes important for public health in free-ranging humans
- Effects of Measurement Uncertainty in Spreading Observations from True Variability Distribution—Comparisons are mainly recommended to population averages, rather than extreme values; However detection of the incidence of likely high exposure rates is important for risk assessment in cases where nonlinearities in dose response are suspected.
- No direct interpretation of BEs in terms of risks is currently suggested.

Potential Importance of Dynamics---—Time Dependence of Responses to Single Doses of Valproic Acid Given During Development (from Nau, 1985)



Time Patterns of Valproic Acid Plasma Concentrations for Three Different Administration Regimens That All Are Expected to Result in a 10% Incidence of Exencephaly in Mouse Experiments Nau (1985)



Conclusions

- Quantitative dynamic theories of toxicants' action(s) needed for meaningful risk evaluation/quantification—and these theories will not be uniform across different modes of actions for different toxicants.
- Significant effort may be needed to develop appropriate preliminary risk-related interpretations of biomonitoring data.
- Creative development and testing of risk related hypotheses from the data will generally be needed in order to make reasonable inferences about the sources of current exposures, and potential benefits of different options for intervention.

Current Official California Biomonitoring Program Goals

- Determine baseline levels of environmental contaminants in a representative sample of Californians
- Establish time trends in chemical levels
- Assess the effectiveness of current regulatory programs. Comment: two possible definitions:
  - "effectiveness" in preventing exposures over current regulatory guidelines
  - "effectiveness" of the guidelines themselves in best protecting/promoting public health

Some Candidate Early-Effect Biomarkers that Might Be Usefully Evaluated in Relation to Biomonitoring Exposure Indicators

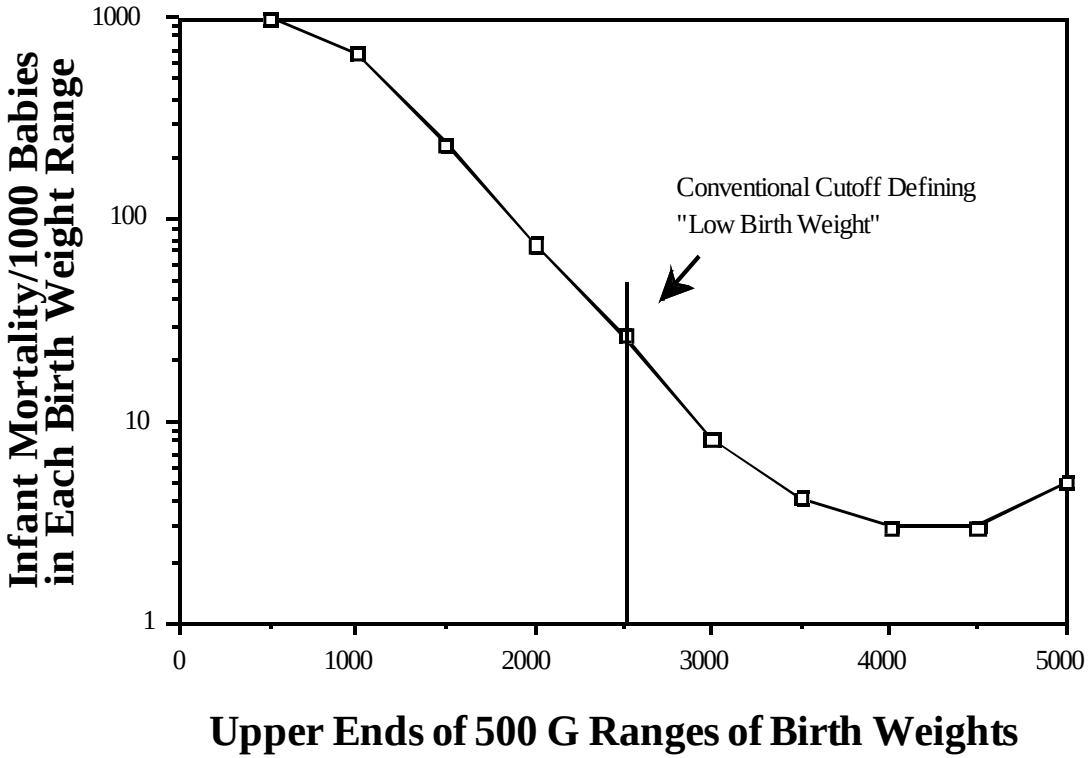
- Repro/Developmental--Birth Weight, Gestational Age, Thyroid Hormone, Viable Sperm Counts
- Cardiovascular
  - Inflammatory indicators of atherosclerosis
  - Traditional risk factors--Blood pressures, LDL, HDL (e.g. recent findings of blood pressures in relation to ortho-PCBs)
  - Heart rate variability
  - Measures of acute damage (e.g. heart-specific creatinine kinase)
- Respiratory
  - Traditional lung function (FEV1; FVC)
  - Indicators of structural protein destruction (e.g. elastin excretion)
- Cancer--somatic mutation/chromosome anomaly indicators
- Renal—Beta-2 microglobulin
- Neurological
  - New brain activity imaging measurements?
  - Hearing levels, controlling for noise exposure history
  - Measures of today's deaths of specific types of neurons (e.g., analogous to heart-specific creatinine kinase as an indicator of heart muscle death)

The Promise of Early Effect Biomarkers for Two-Step Assessments of Risks

(Continuous Parameter, Statistically Powerful)

(Rare Quantal Effect, Important but Statistically Noisy; Hard to Measure)

Relationship Between Weight at Birth (in 500 Gram Increments) and Infant Mortality



Differences In Birth Weight Have Appreciable Implications for Infant Mortality Both Above and Below the Conventional Clinical Criterion for "Low Birth Weight"

Relationship Between Reported Cigarettes/Day Smoked, Average Birthweight, and Infant Mortality

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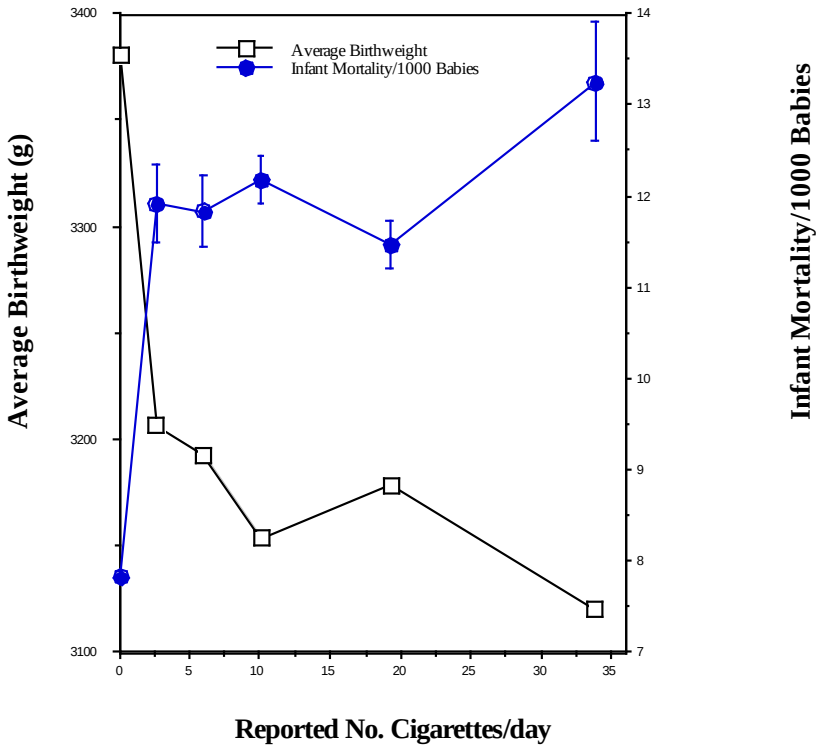
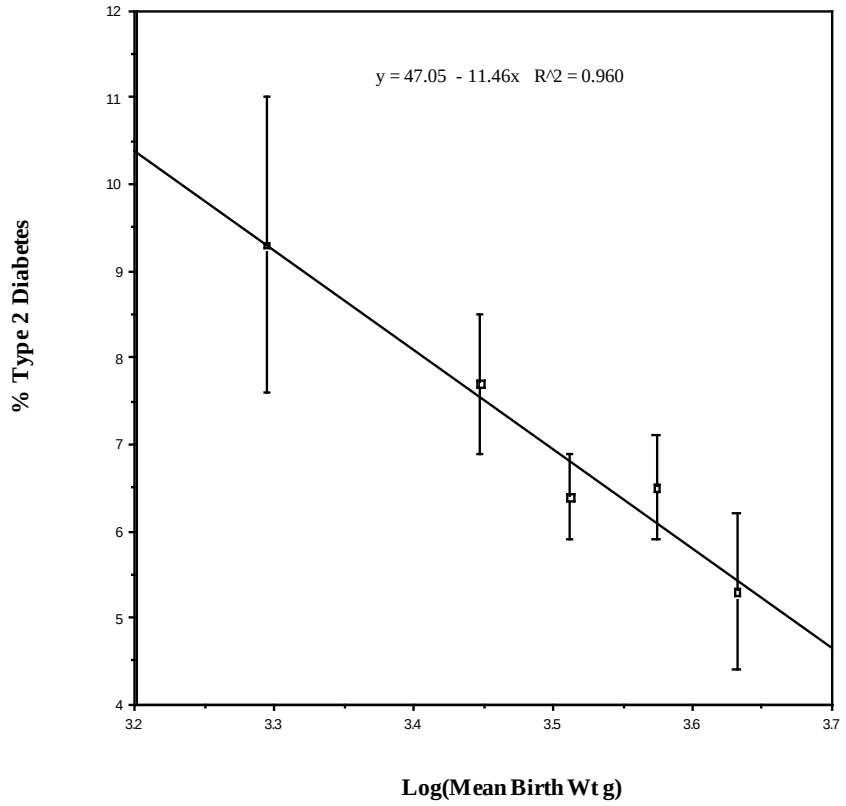


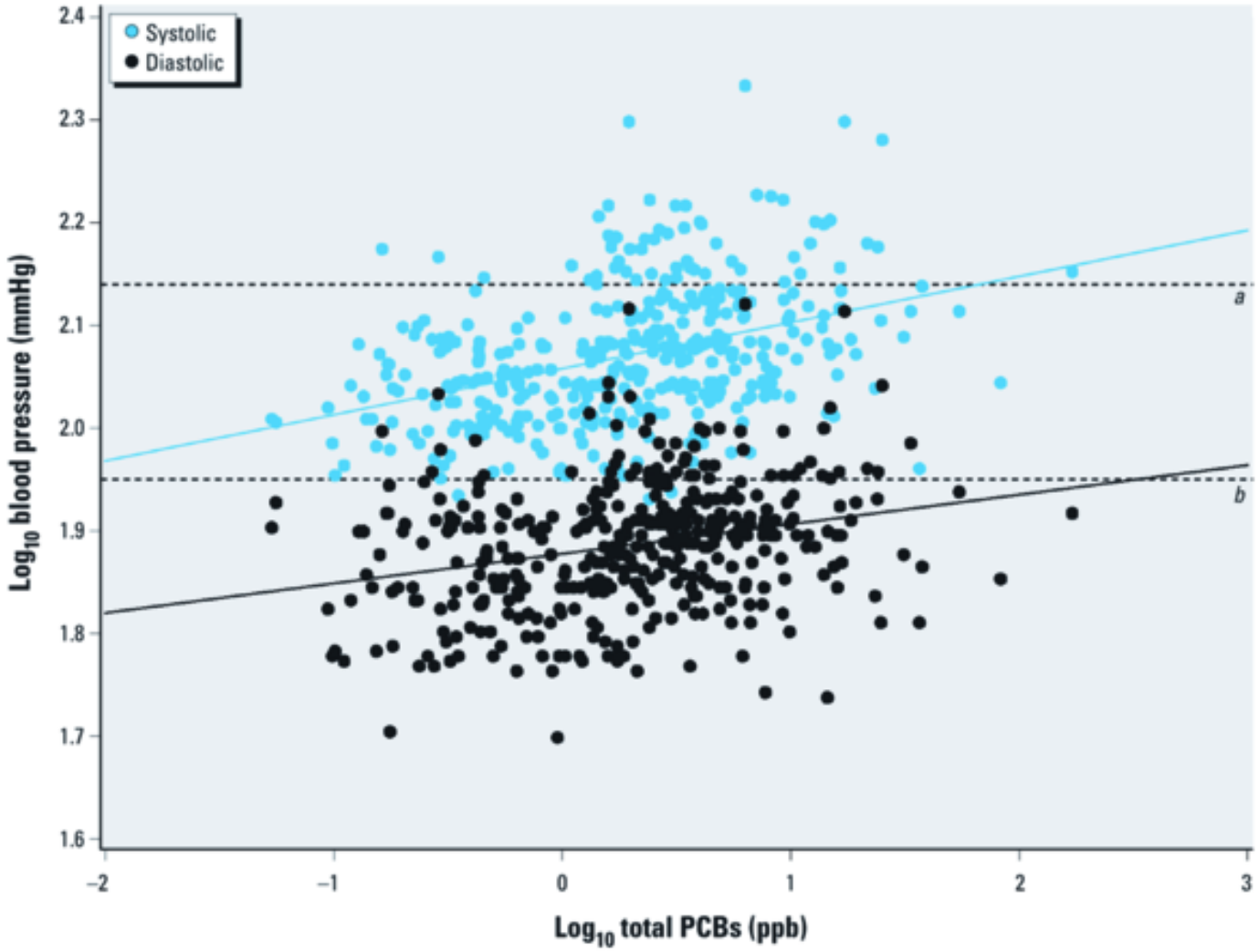
Similar "Saturating" Patterns of Dose Response for Relationships of Both Birth Weight and Infant Mortality to Reported Direct Smoking--U.S. National Center for Health Statistics 1990 Data

Plot of the Incidence of Type 2 Diabetes in Relation to Log (Mean Birth Weight) – Data of Forsen et al., 2000



Birth Weights are Correlated with Some Important Imperfections of Homeostatic Control in Later Life

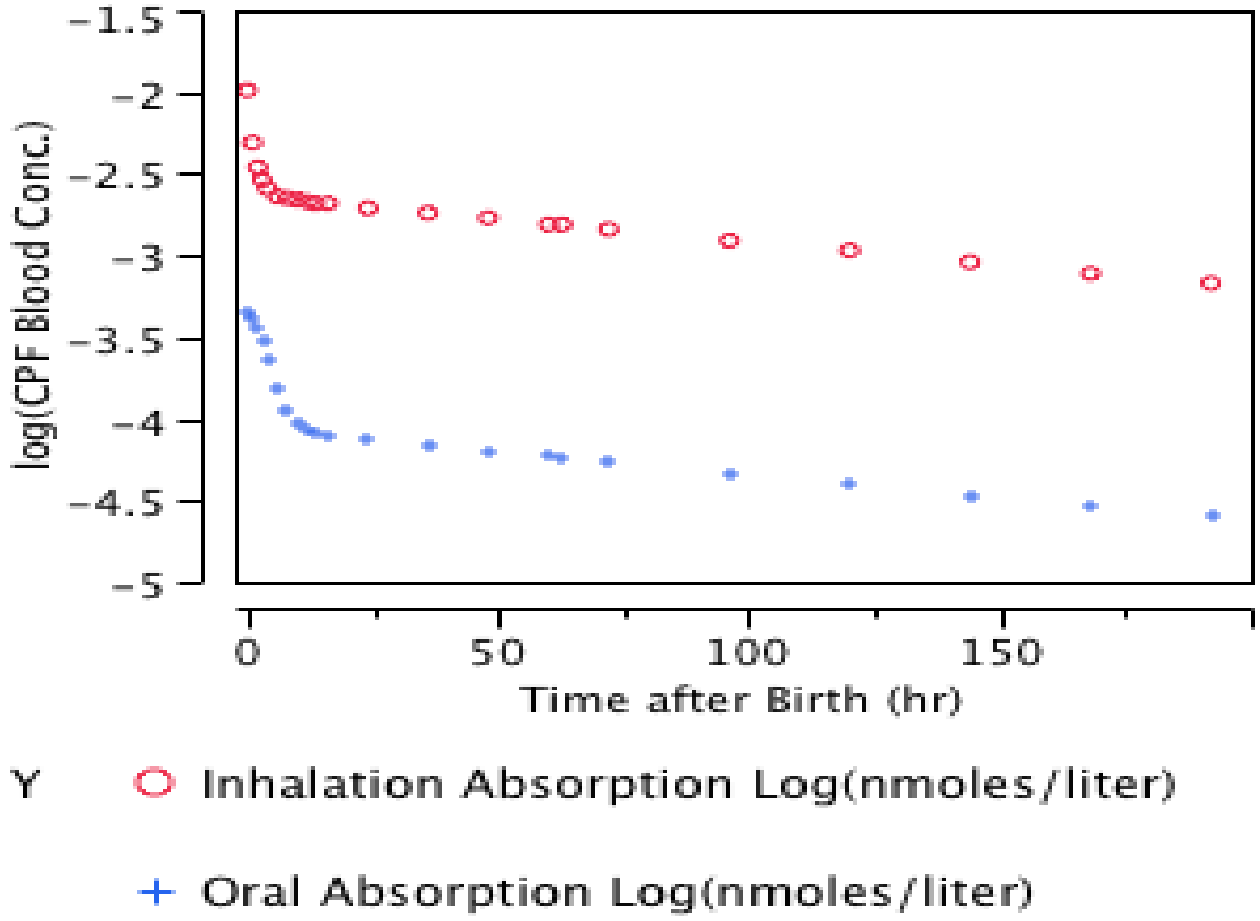
Blood Pressures In Relation to PCBs in a Recent Study (source: Goncharov et al. EHP 119(3), March 2011)



Importance of Exposure Measurement Proximate to Sampling—Current Struggles to Do Reverse Dosimetry from Chlorpyrifos Blood Levels from Perinatal Samples

- Maternal and cord blood levels available from about 400 women and their babies
- Reconstruction of likely exposures in women's homes requires data/assumptions about the time lags and exposure levels between the times they left their apartments, delivery, and maternal blood sampling
- Expected rapid initial fall in blood levels in the first few hours means that there must be appreciable adjustments between steady state and observed blood levels at the times of sampling.

Expected Falls in Maternal Blood Chlorpyrifos After Birth, Assuming No In-Hospital Exposures (assuming continuous inhalation or oral exposures in the mothers' apartments)



Take-Home Lessons

- Biomonitoring measurements have considerable potential to lead to new epidemiological/toxicological understanding
- Getting the most of the data in terms of both science and public health protection depends critically on
  - Obtaining collateral data on early effect biomarkers and exposure information proximate in time to the biomarker measurements.
  - Creative mechanism-based modeling to relate the distributions of observed chemical measurements to distributions of individual risks of pathological processes of public health important (especially chronic cumulative and reproductive/developmental processes).
  - Time and budget constraints are likely to make this even more challenging than it otherwise might be.