The Application of Probabilistic Reverse Dosimetry for Interpreting Human Biomonitoring Data

Harvey Clewell

Director, Center for Human Health Assessment

The Hamner Institutes for Health Sciences

Linking Internal Dose to Health Outcomes
CDC Evaluation of Mercury in Blood

"… blood Hg levels in young children and women of childbearing age usually are below levels of concern. However, approximately 6% of childbearing-aged women had levels at or above a reference dose, an estimated level assumed to be without appreciable harm (≥5.8 μg/L)."

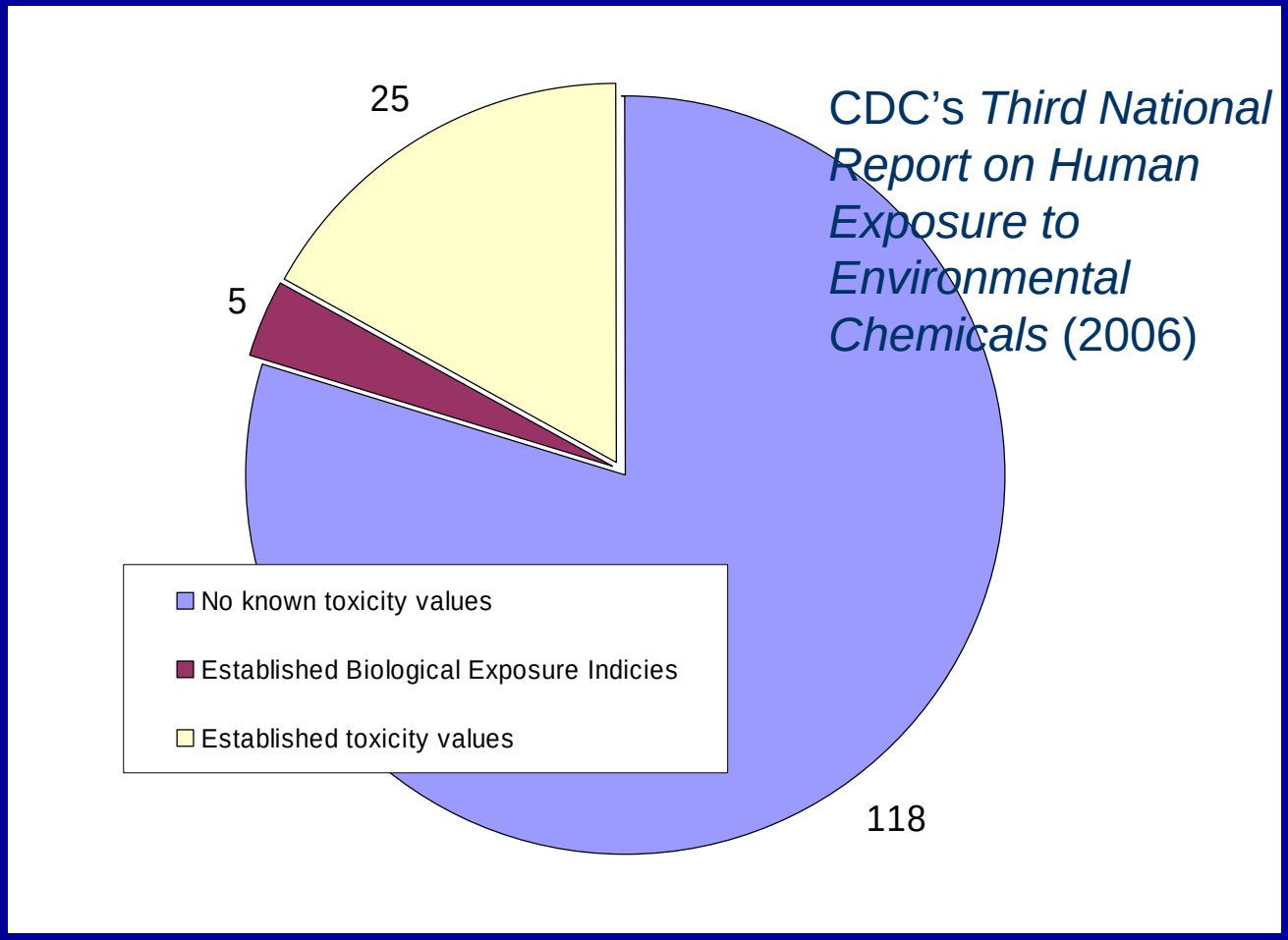
-- CDC MMWR (NHANES 1999-2002)

Types of Information Needed to Link Internal Dose to Health Outcomes

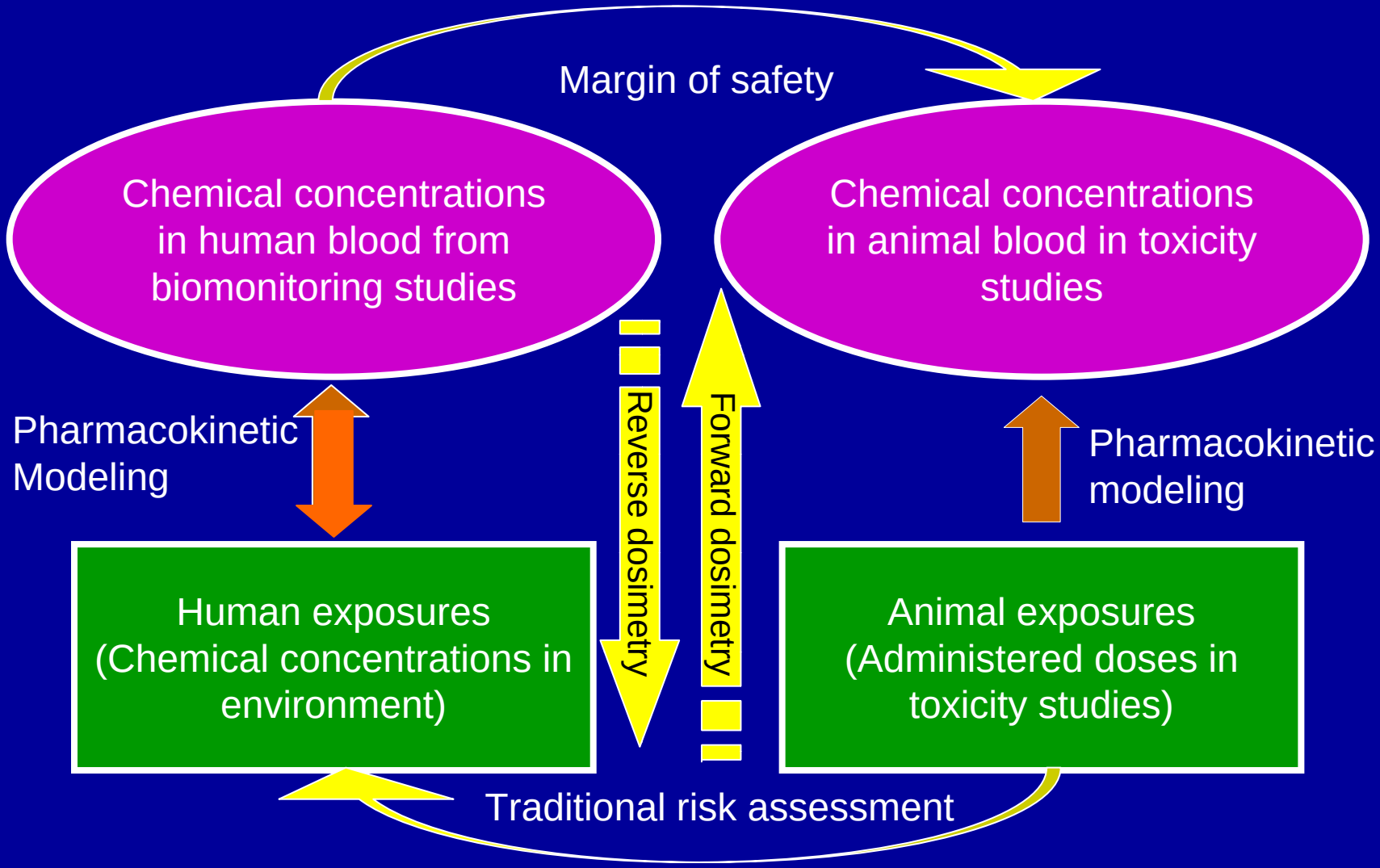
- Relationship to internal dose at health outcome in human studies
  - Lead in blood
  - Methylmercury in hair or blood
- Relationship to internal dose at health outcome in animal studies
  - Direct measurement (PFOA in blood)
  - Pharmacokinetic (PK) modeling (in experimental animal)
- Relationship to external dose at health outcome in animal or human studies
  - Most common situation
  - Need to link internal dose to external dose

Linking Internal Dose to Health Outcome

The Big Problem is Lack of Toxicity Data



Relationship of human biomonitoring to animal toxicity data



Alternative Approaches for Linking Biomonitoring Data to Health Outcomes

- **Animal Dosimetry:** Compare blood concentration in population with blood concentration at NOAEL/LOAEL in animal to obtain Margin of Exposure (MOE)
  - Requires: measurement of blood concentrations in toxicity studies or availability of PK model/data in animal to predict blood concentrations from external dose
  - Issue: how to determine adequacy of MOE
  - Complication: may also require data on relationship of human biomarker (e.g., urinary metabolite) to blood concentration

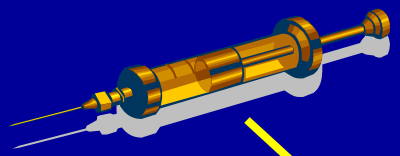
New toxicity studies that fail to characterize internal dose should no longer be accepted by journals or regulatory agencies

Alternative Approaches for Linking Biomonitoring Data to Health Outcomes

- **Forward Dosimetry:** Compare biomonitoring data with predicted biomarker at toxicity value (RfD, MCL, etc.)
  - Requires: human PK model
  - Complication: dealing with multiple-route exposures
  - Issue: Ignores temporal relationship of exposures and biomarker sampling
  - Appropriate use: initial screen

Challenge for Interpreting Biomonitoring Data

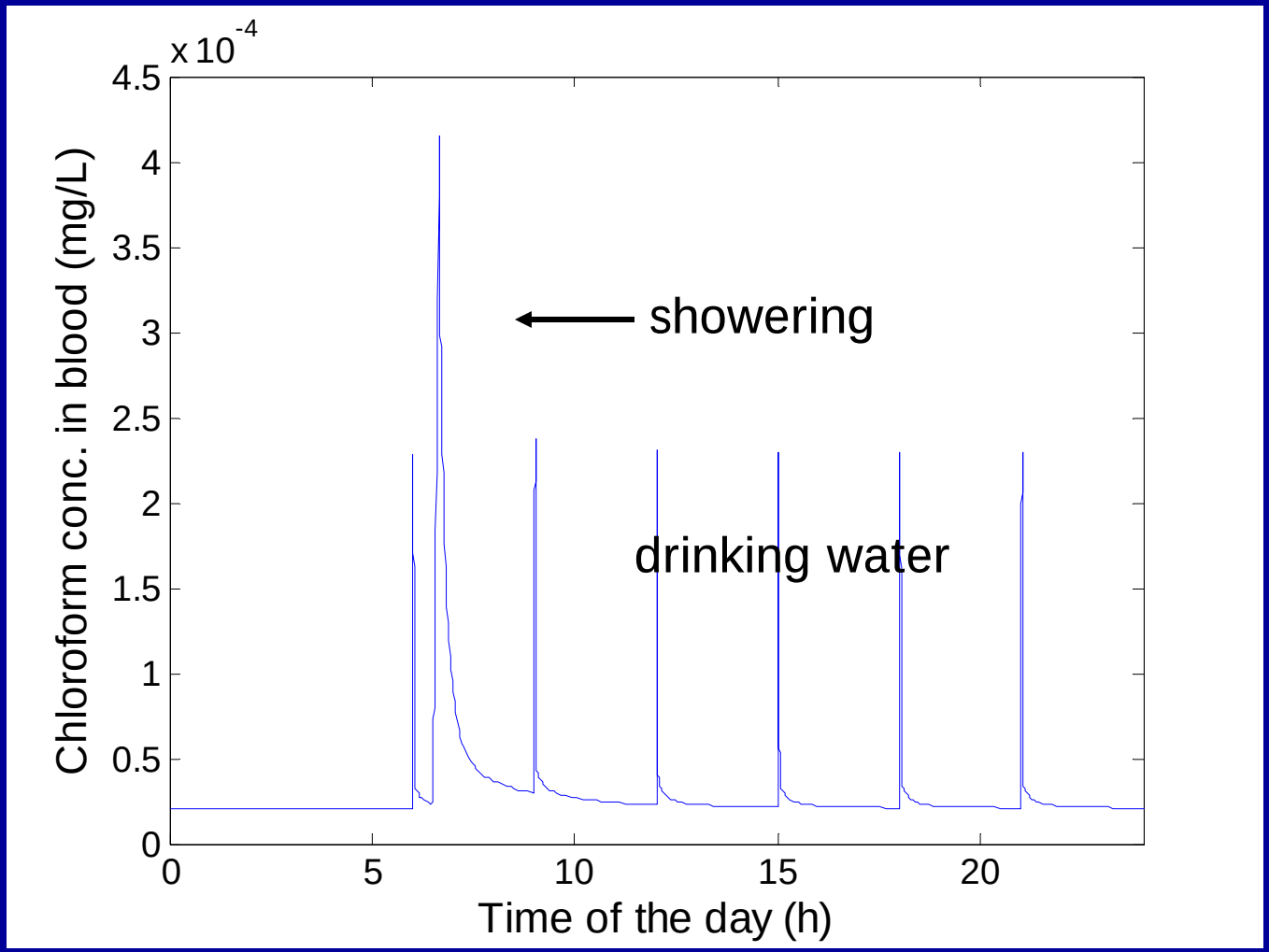
Variable Relationship of Exposures and Sampling



Time of the day

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24

Time-Course Simulations of Chloroform Blood Concentrations



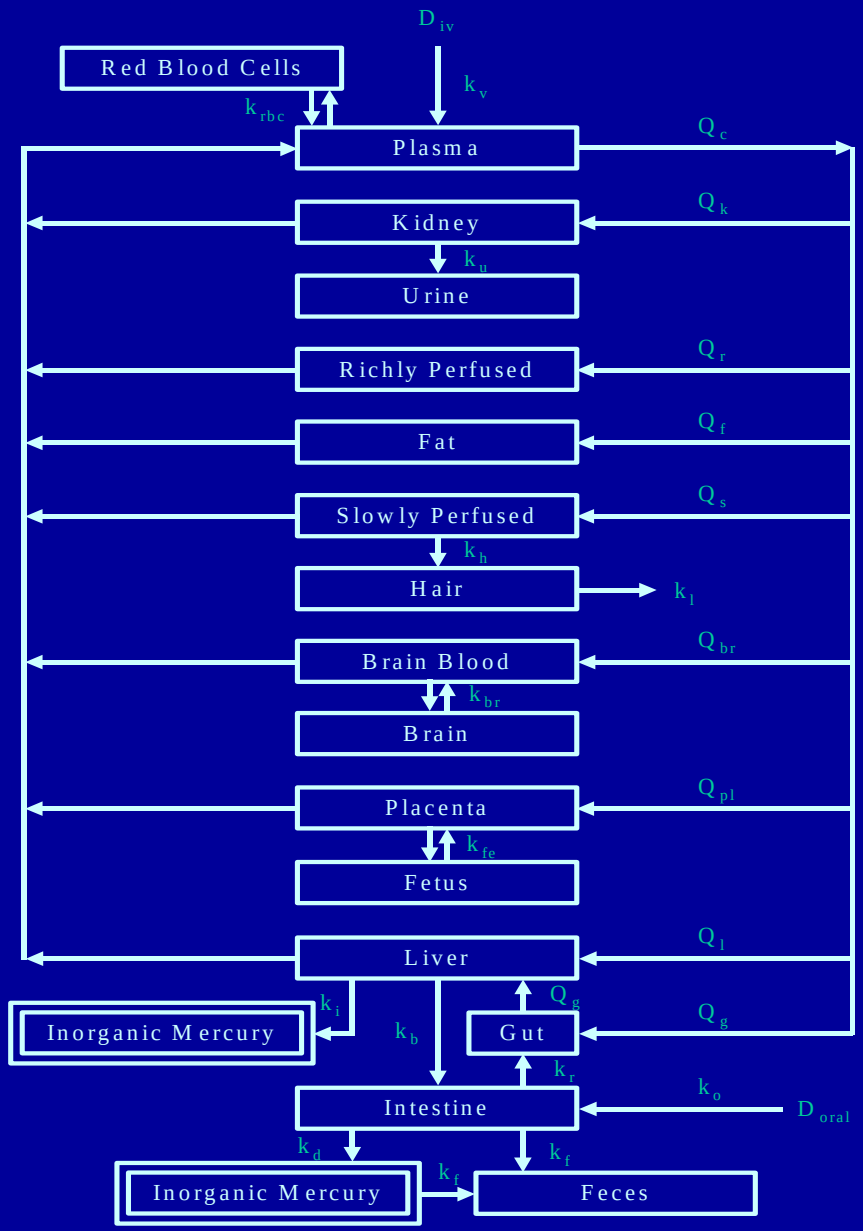
Alternative Approaches for Linking Biomonitoring Data to Health Outcomes

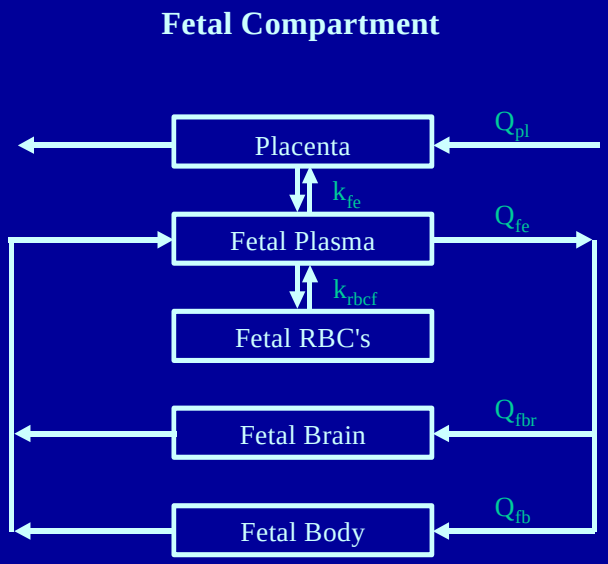
- **Reverse Dosimetry:** Estimate external exposure in population from biomonitoring data and compare with toxicity value (RfD, MCL, etc.)
  - Requires: human PK model to describe relationship of biomarker to external dose
  - Complication: may also require information on the nature (sources, frequency, duration, etc.) of potential exposures
  - Issue: dealing with uncertainty and variability in human exposures and pharmacokinetics
  - Appropriate Use: for chemicals of concern

Reconstructing Exposure with a PBPK Model: An Example with Methylmercury

- Accidental poisoning episode
  - Iraq – 1972
    - Seed grain, treated with methylmercury fungicide, inadvertently used to prepare bread
    - Exposures continued over 1- to 3-month period
    - Symptoms (late walking, late talking, neurological performance) observed in children of asymptomatic mothers exposed during pregnancy

PBPK Model for Gestational Exposure to Methylmercury

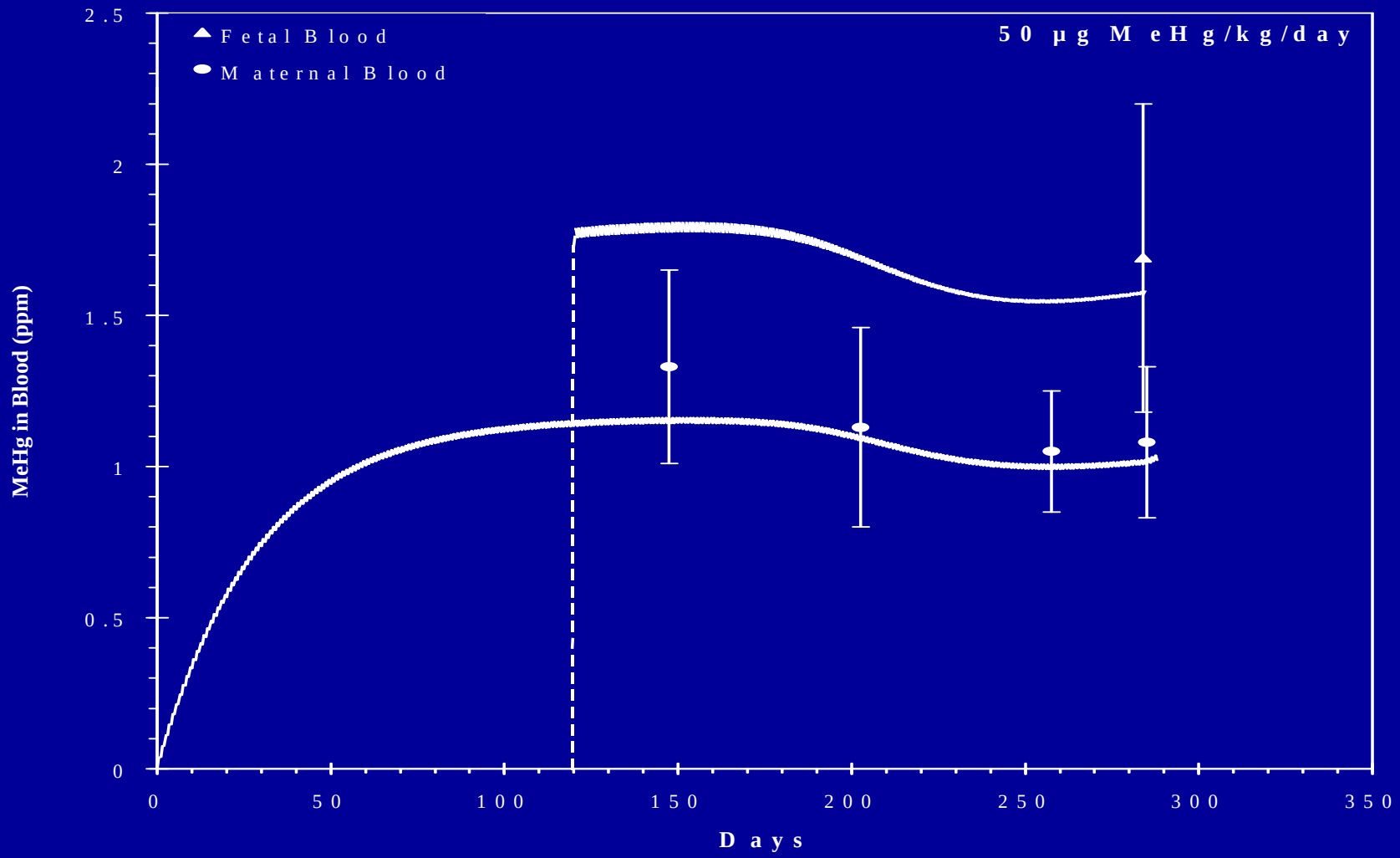




Clewell et al. 1999, *Risk Anal*
Shipp et al. 2000, *TIH*

Effect of Changes in Fetal and Maternal Physiology on Dosimetry

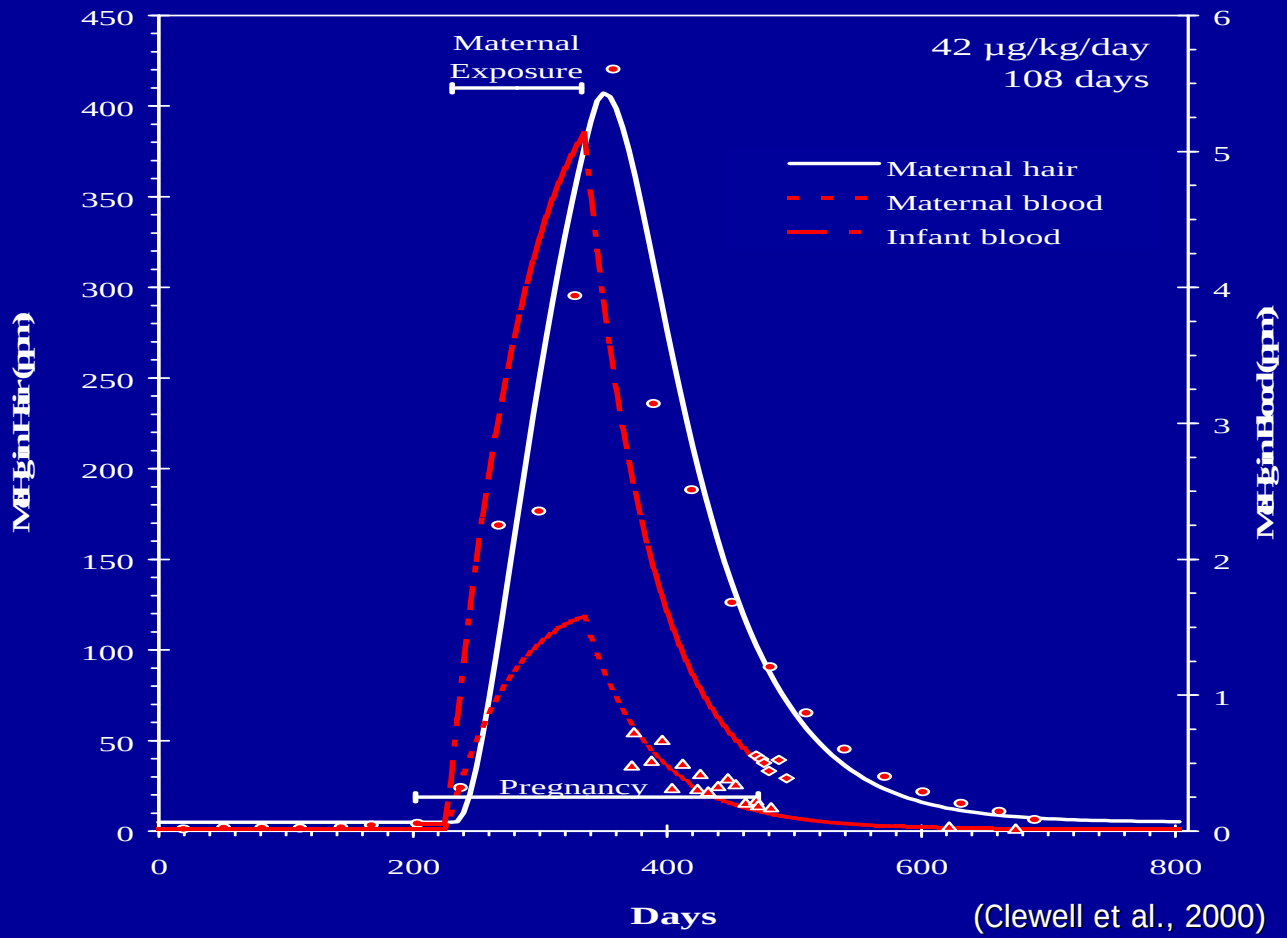
Non-human primates exposed to a constant daily dose of methylmercury during gestation



Linking Internal Dose to Health Outcome:

Exposure Reconstruction Using a PBPK Model

Iraqi woman exposed during pregnancy
to grain contaminated with methylmercury

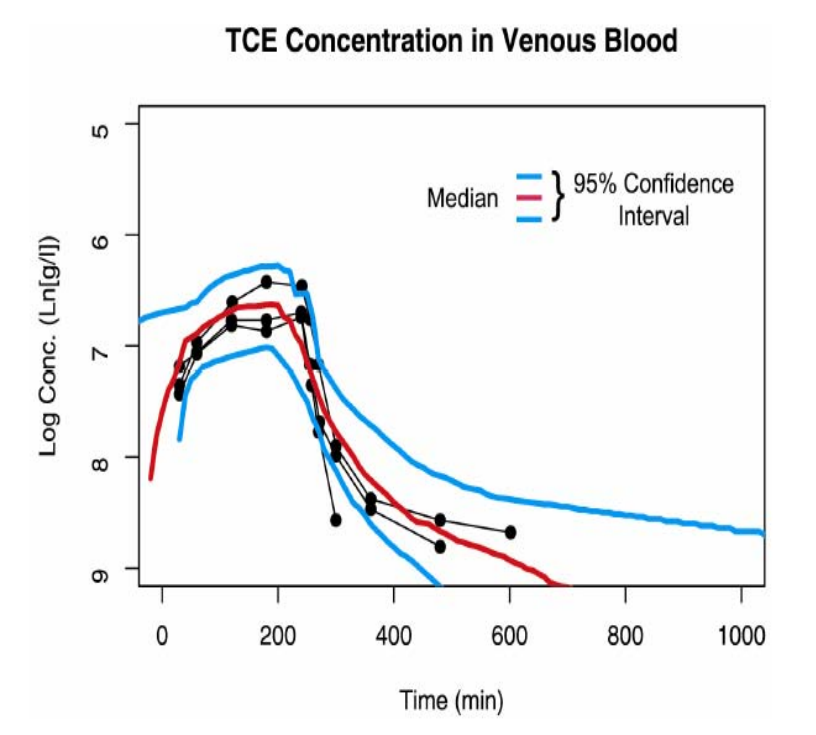


(Clewell et al., 2000)

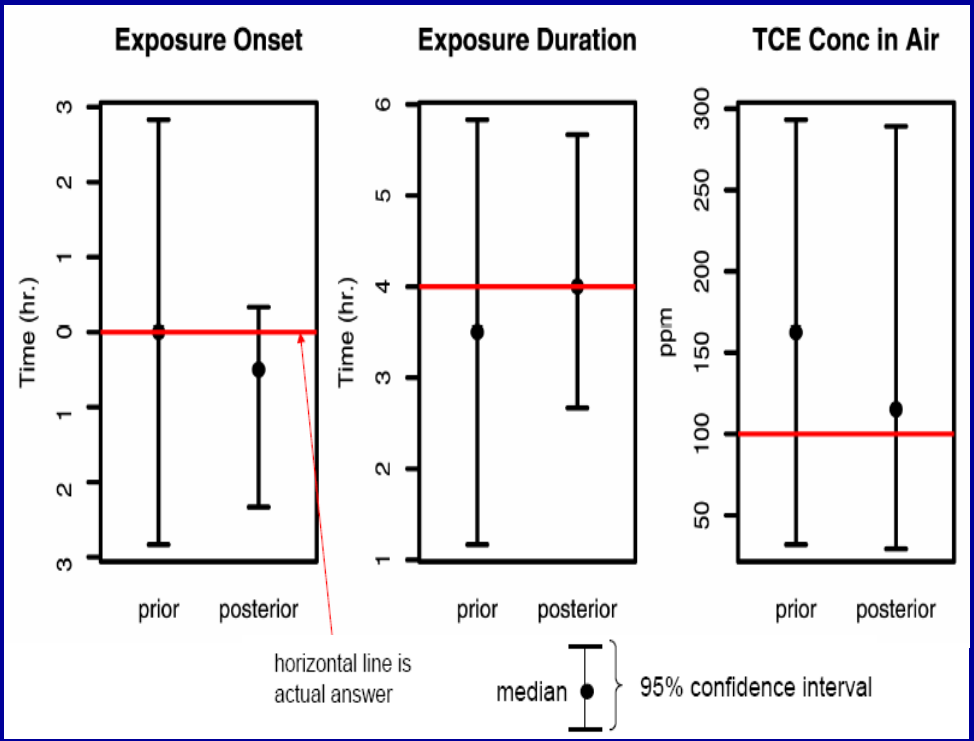
BUT: Exposure Reconstruction is an "Ill-Posed Problem"

(Many possible solutions)

Comparison of PBPK Predicted Blood Concentrations with Experimental Data



Comparison of Reconstructed Exposure Conditions with Actual Exposure Conditions



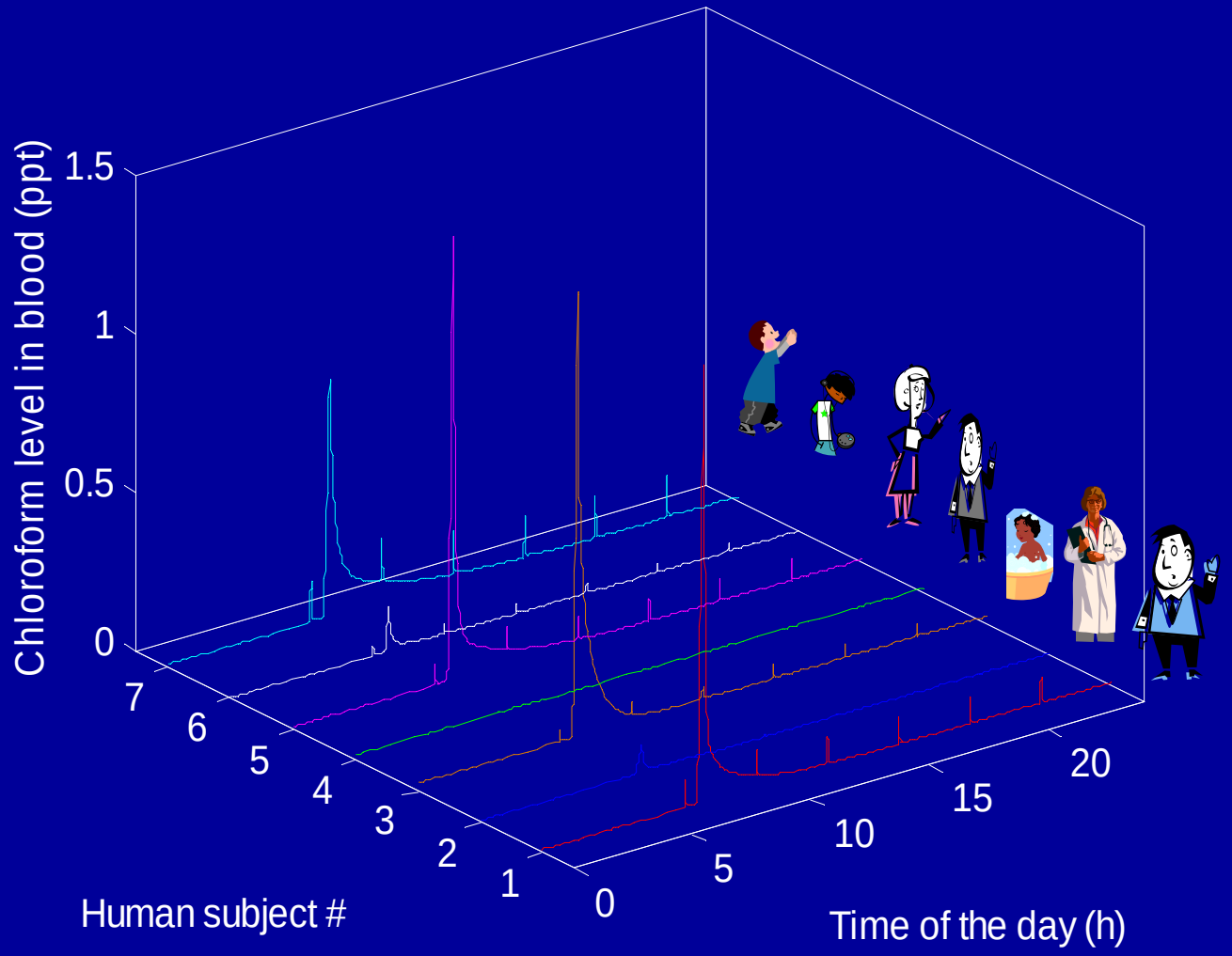
(Sohn et al., 2004)

Requires population-level, probabilistic approach

Solution: Probabilistic Reverse Dosimetry

(Tan et al., 2006, 2007)

Illustration of a Monte Carlo Analysis for the Time Course of Blood Concentrations from Household Exposures



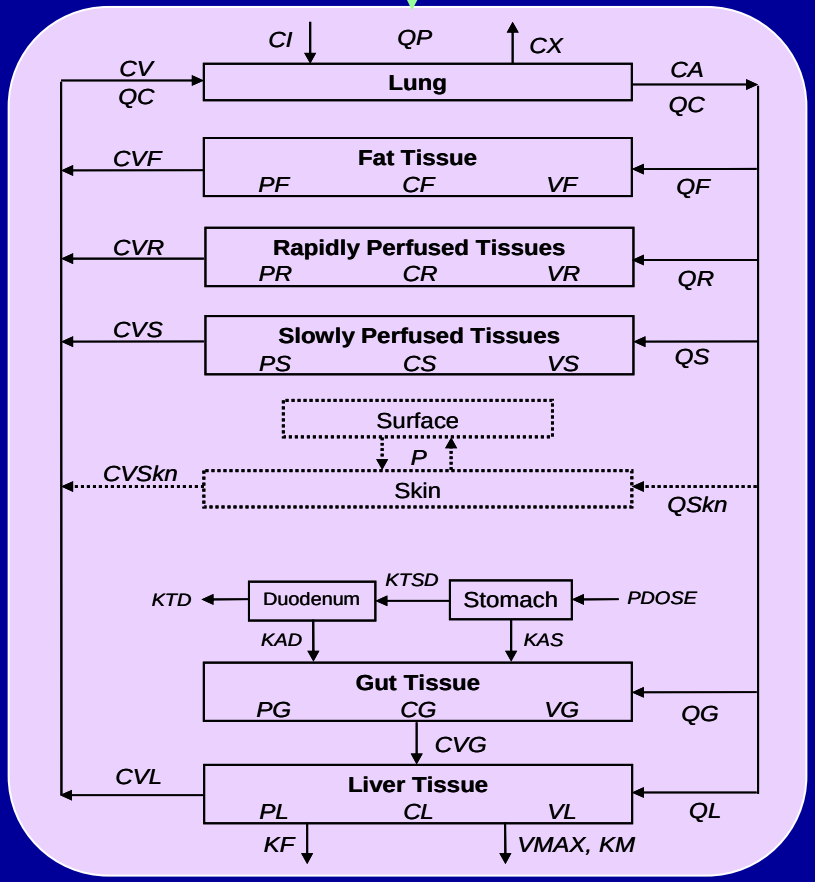
Linking Biomonitoring Data to External Dose Using Probabilistic Reverse Dosimetry

- Role of PBPK
  - Correct integration of exposure routes
    - pre-systemic clearance
    - flow-limited metabolism
  - Determine relationship of biomarker of internal exposure to target tissue dose for health effect (e.g., amount metabolized in the liver)

- Role of Monte Carlo Analysis
  - Reconstruct distribution of likely exposures across the population, not just average or worst-case
  - Consider variability and uncertainty in exposure and sampling

Linking Biomonitoring Data to External Exposure
Physiologically Based Pharmacokinetic (PBPK) Modeling
(Tan et al., 2006)

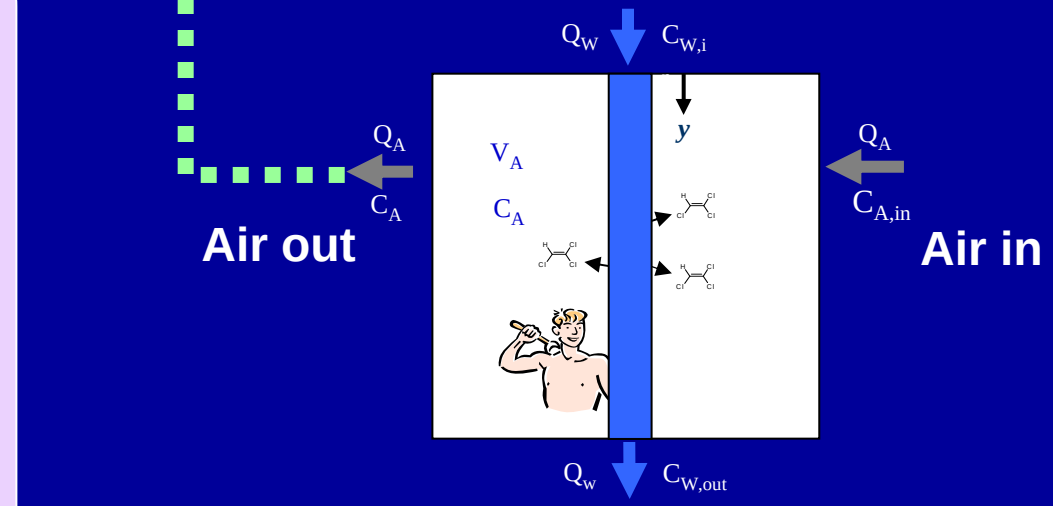
PBPK Model for Chloroform



(Corley et al. 2000)

Mass Transfer of VOC from Shower Water to Air

Hot water in

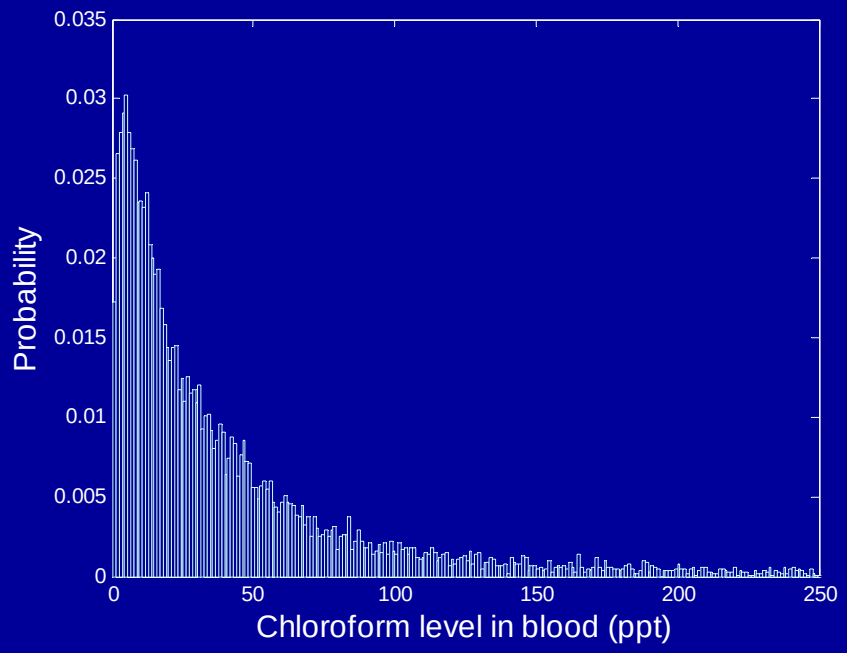


Water out

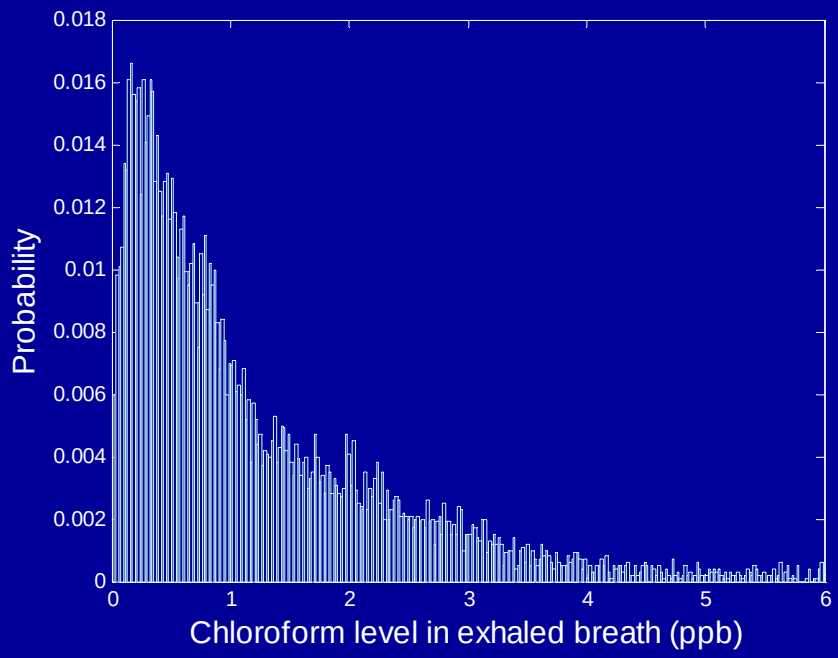
(Weisel et al. 1999)

Predicted Distribution of Chloroform Levels at 8:30 am

Blood



Exhaled breath



Comparison of Measured Distribution of Blood Concentrations of Chloroform (from NHANES III) with PBPK/MC Predictions Based on Measured Distribution of Tap Water Concentrations of Chloroform (from TEAM)

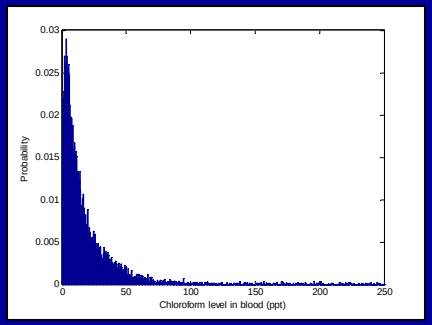
Measured distributions of chloroform concentrations in blood (pg/mL)							
Percentile	*5%*	*10%*	*25%*	*50%*	*75%*	*90%*	*95%*
NHANES III data	--	--	--	23	41	77	127
Predicted distributions of chloroform concentrations in blood (pg/mL)							
Assuming chloroform concentration in household air is independent of chloroform concentration in tap water							
Blood (pg/mL)	3.3	4.8	9.3	19	42	79	135
Assuming chloroform concentration in household air = 0.0179 × chloroform concentration in tap water							
Blood (pg/mL)	1.1	1.7	5.9	17	28	54	95

Probabilistic Reverse Dosimetry Approach

(Tan et al., 2006, 2007)

ppb of chemical in air
or
µg/L of chemical in water

Monte Carlo analysis



Estimated distribution of
chemical in blood

÷

Invert Distribution

"Exposure Conversion Factor" distribution

Convolute Distributions

×

Estimated population
exposure distribution

Distribution of measured blood concentrations

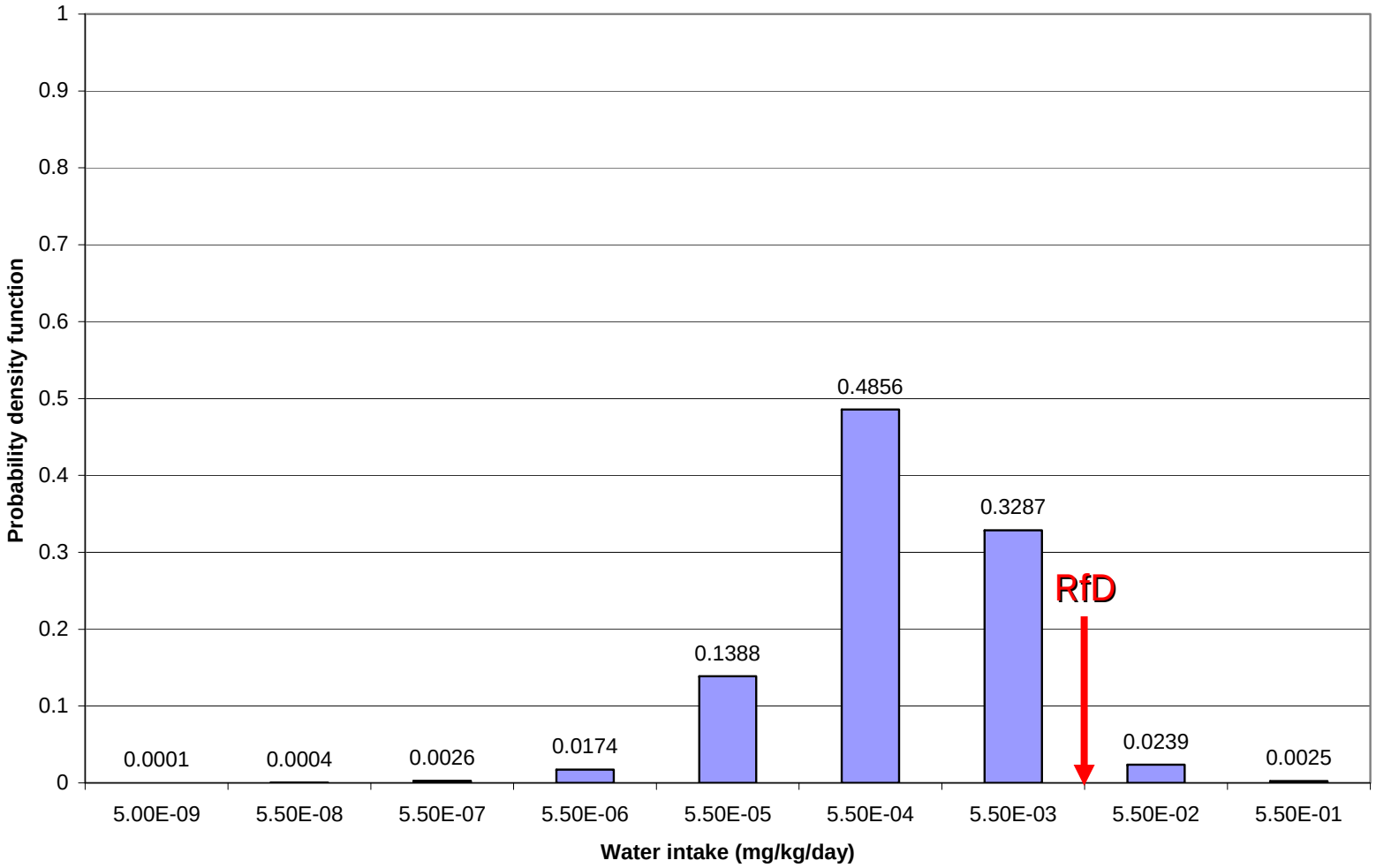
Exposure Conversion Factor Distribution

The distribution of exposure concentrations that could yield a unit blood concentration of chloroform:

Percentile	*5%*	*10%*	*25%*	*50%*	*75%*	*90%*	*95%*
ECF (µg/L in water per pg/mL in blood)	4.52	4.11	3.42	2.65	1.73	0.877	0.506

e.g., If Mr. X has a blood concentration of 0.5 pg/mL, the concentration of chloroform in his water has a median estimate of 2.65×0.5 = 1.33 µg/L, but could range from 0.25 to 2.26 µg/L with 90% confidence.

Predicted Distribution of Exposures to Chloroform in the Population Reported in NHANES III (mg/kg/day)



Approaches for describing the health implications of an estimated distribution of exposure

Assume that the estimated 95th percentile of the population exposure distribution is 0.0094 mg/kg/day

Margin of Exposure

Cancer: LED_{10} = 23 mg/kg/day
MOE = 23/0.0094 = 2460

Non-cancer: NOAEL = 12.86 mg/kg/day
MOE = 12.98/0.0094 = 1375

Comparison with RfD

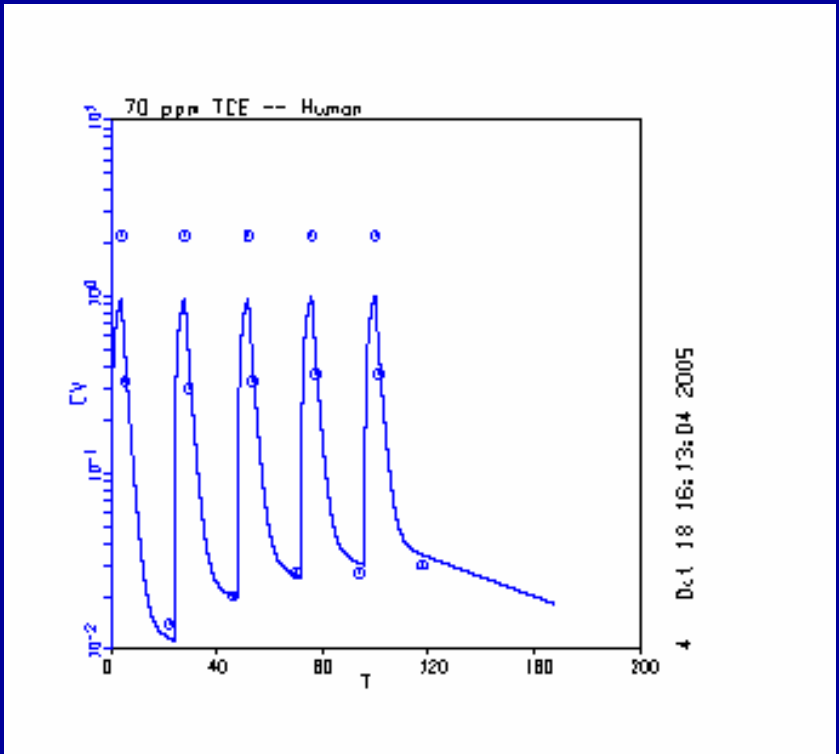
RfD = 0.01 mg/kg/day
→ < 5% of the population is above RfD

Model Simulations based on Partition Coefficients and Metabolic Constants Estimated using QSAR*

Trichloroethylene

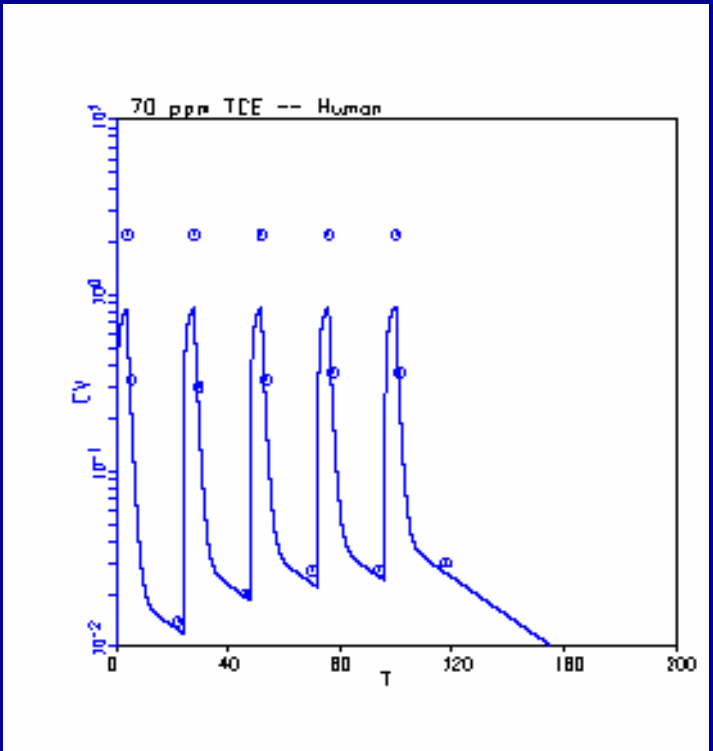
Published:

Vmaxc = 10.0
Km = 1.5



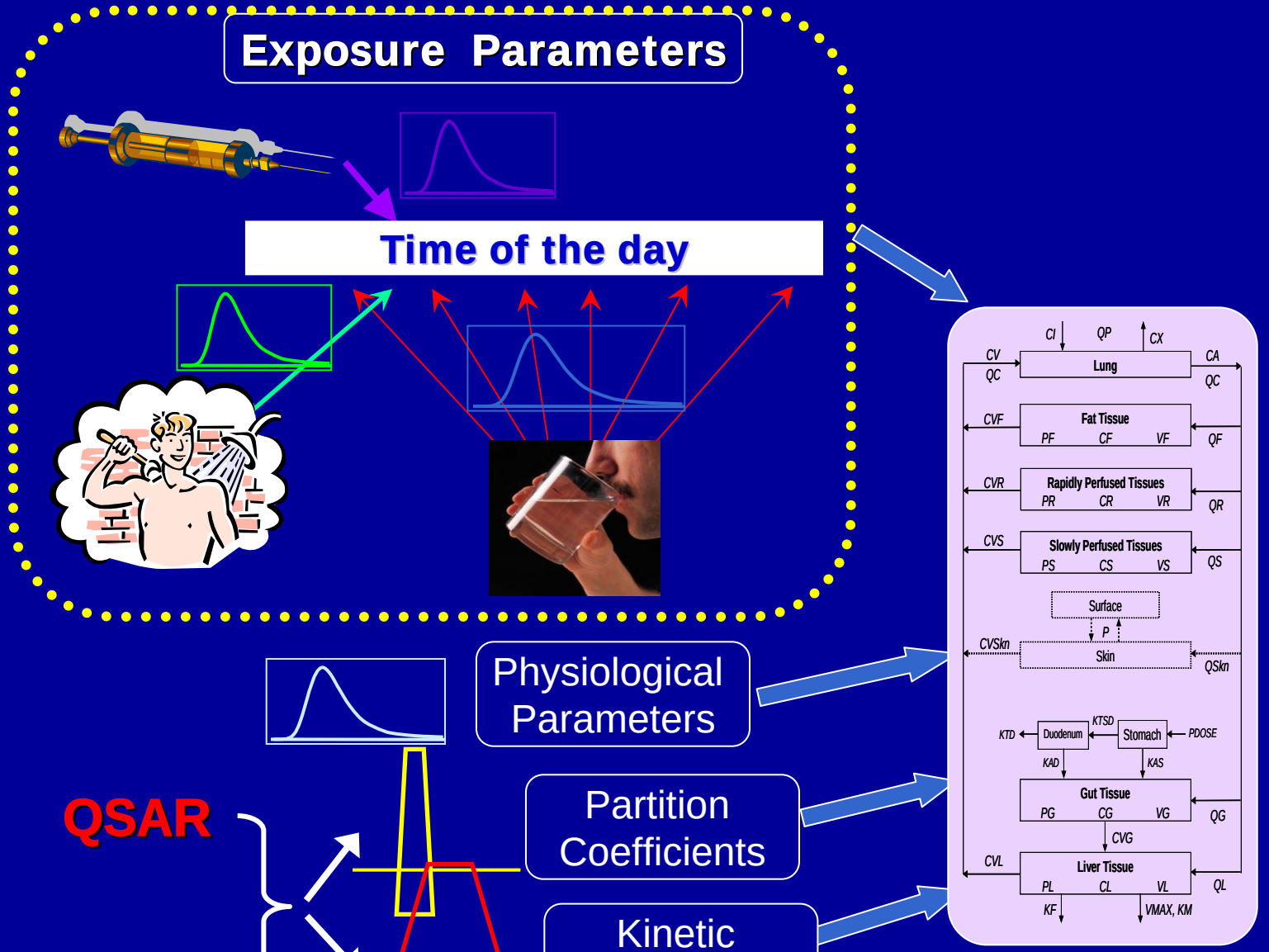
QSAR:

Vmaxc=64.7
Km = 1.0



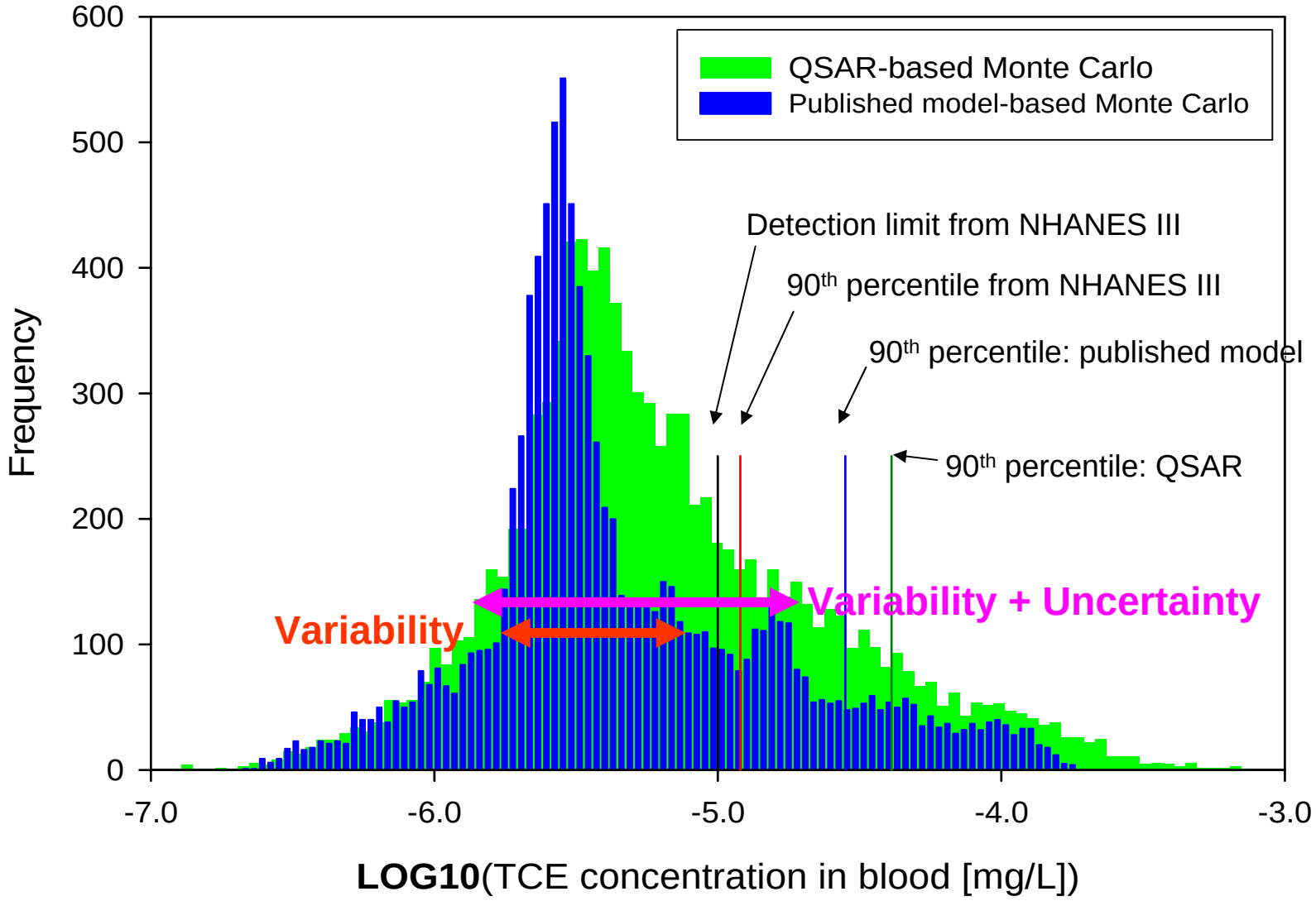
* Beliveau, M; Lipscomb, J; Tardif, R; Krishnan, K. *Chem Res Toxicol.* **2005**, *18*, 475-485.

Monte Carlo Analysis with QSAR-Estimated Partition Coefficients and Kinetic Parameters (Liao et al. 2007)



Monte Carlo Simulation for TCE Concentrations in Blood Across a Population (Liao et al., 2007)

Impact of Uncertainty in QSAR-derived PBPK Model

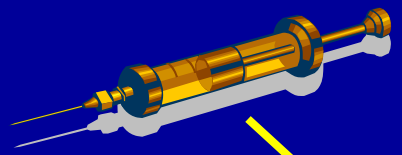


Linking Human Biomonitoring Data to Exposure

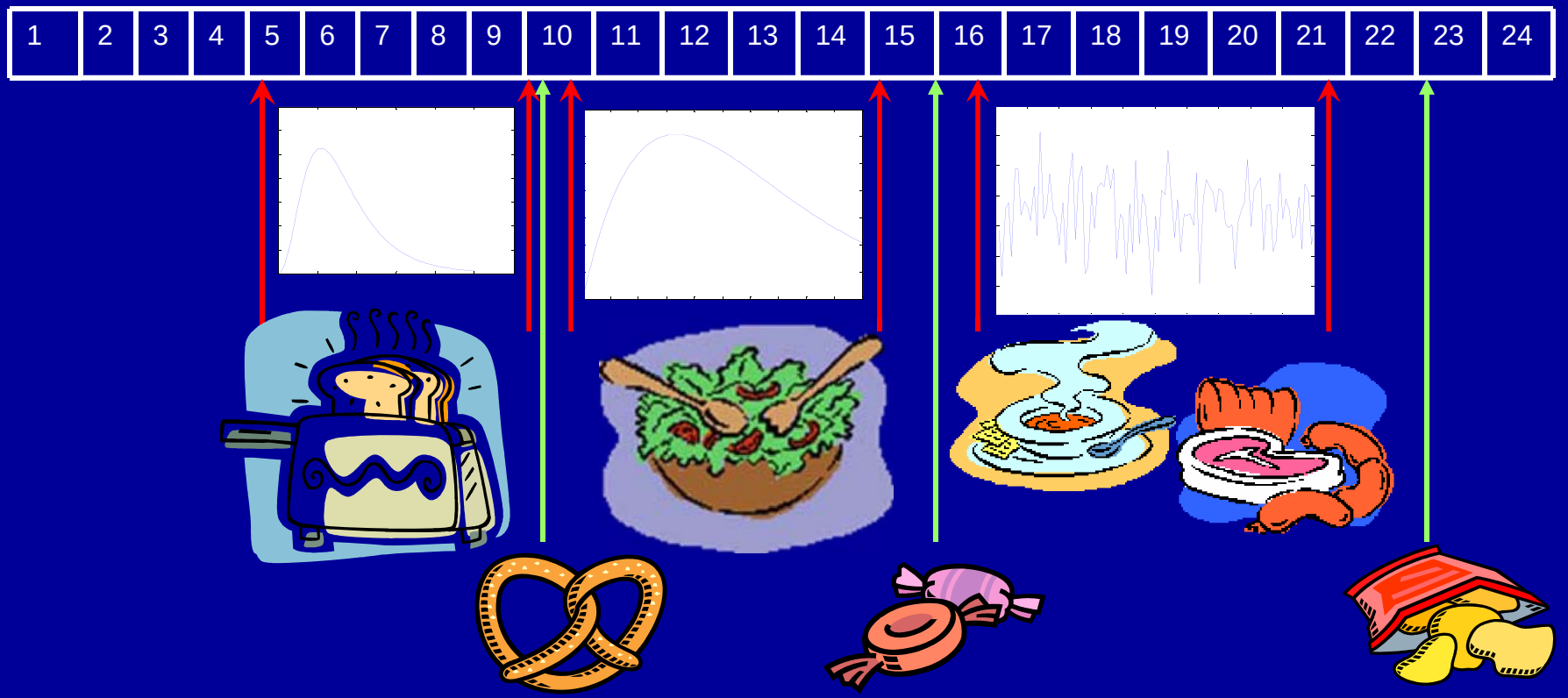
Problems Vary with the Nature of the Chemical

- Volatiles
  - Complex household exposures
  - Rapid clearance
    - Blood levels highly sensitive to transient exposures
- Intermediate persistence compounds
  - Interpretation depends on rate of clearance
    - Need to consider timing of exposures vs. sampling
  - May need to deal with multiple metabolites
- Highly persistent compounds
  - Slow approach to steady state
  - Apparent clearance confounded by changes in body weight, fat content

Complications in the interpretation of biomonitoring data on non-persistent chemicals: Timing of Exposure vs. Sampling



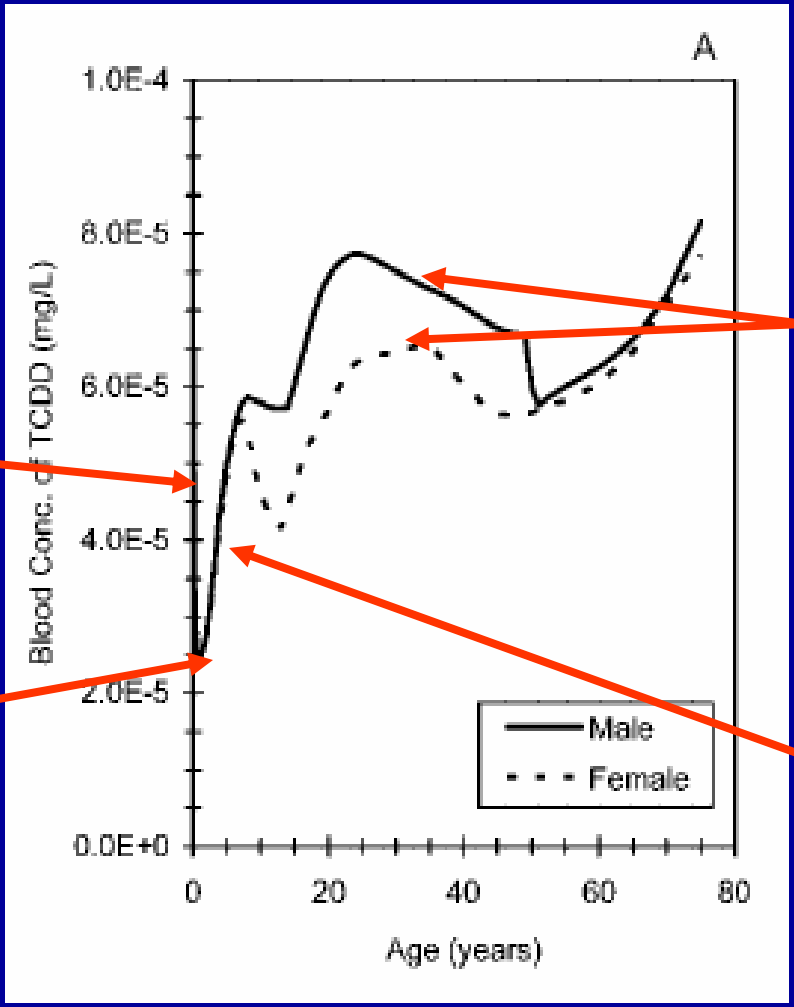
Time of the day



Complications in the interpretation of biomonitoring data on persistent chemicals: Age- and composition-dependent kinetics

Transplacental exposure to maternal stores of TCDD

Dilution of TCDD stores by the rapid growth of neonate



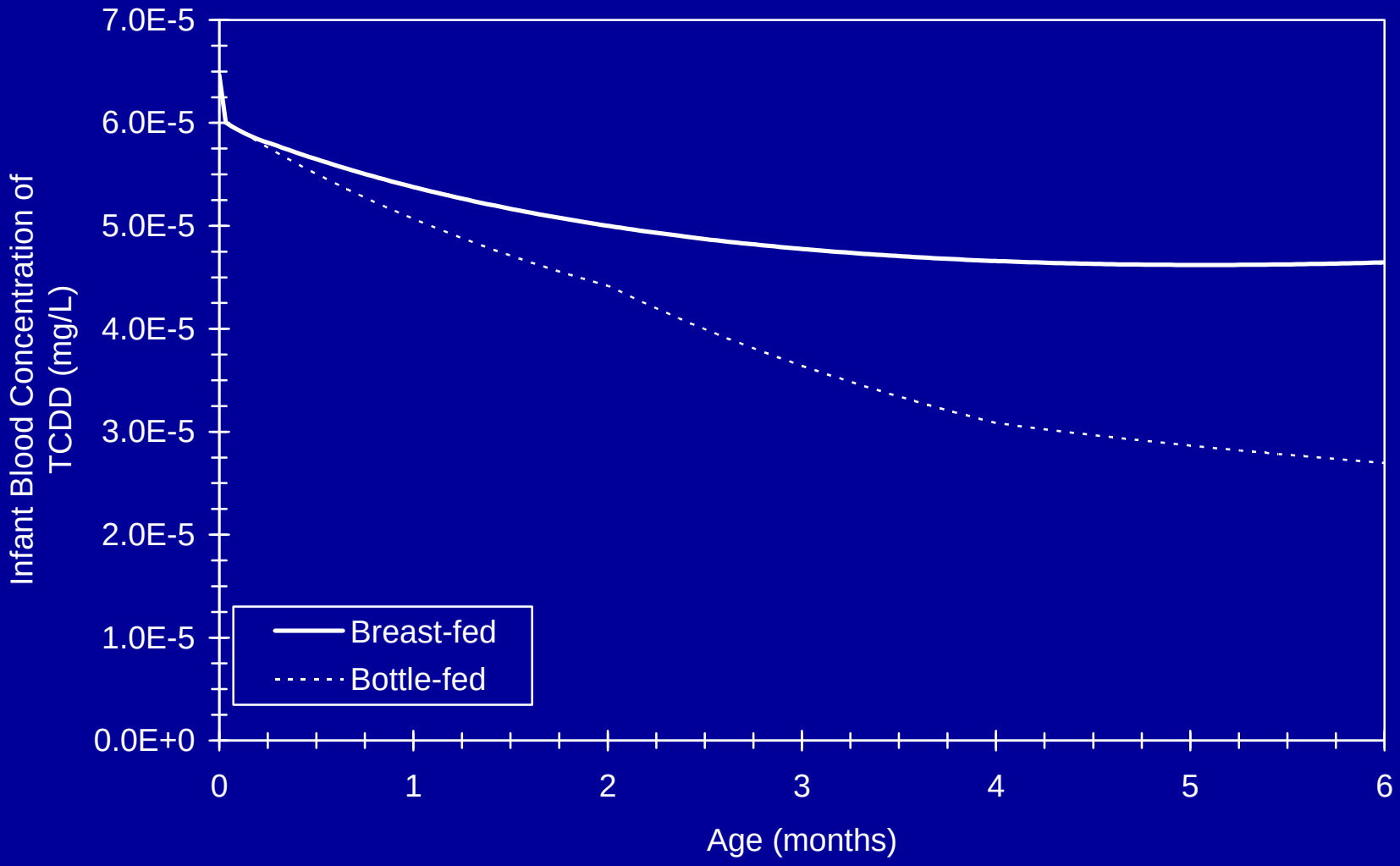
Different fractional volume of fat between male and female

Continuous exposure

(Clewell et al., 2004)

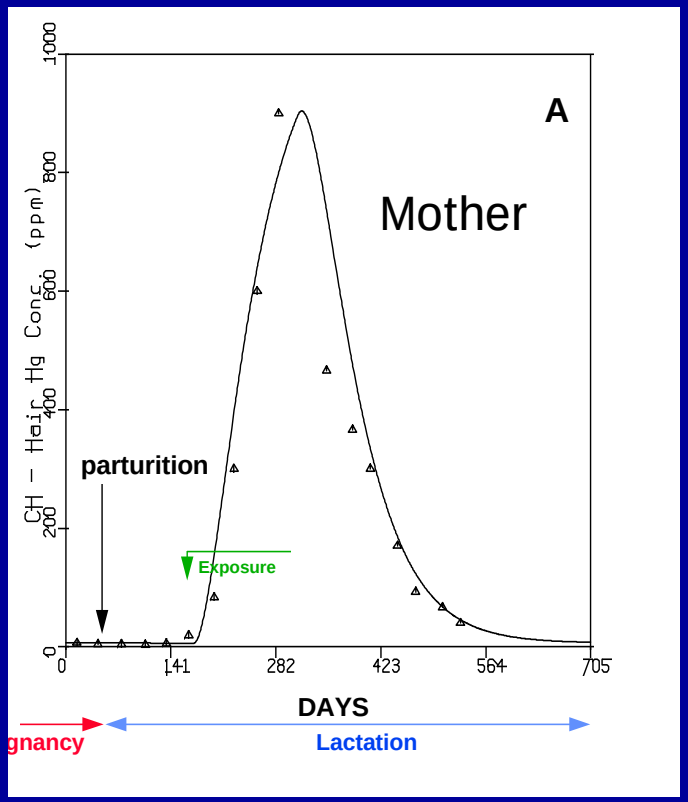
Complication in the interpretation of biomonitoring data on persistent chemicals:

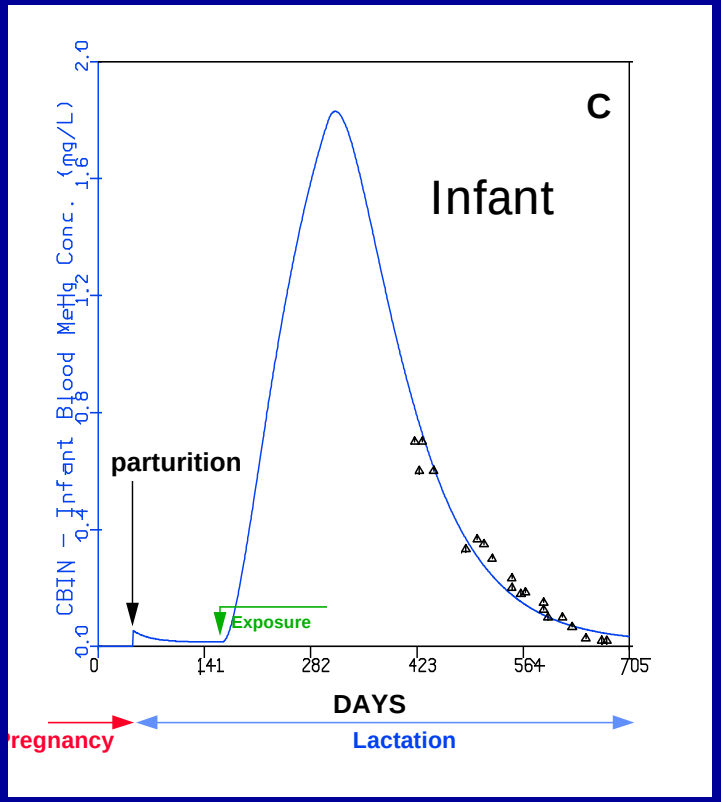
Lactation Transfer



(Gentry et al., 2003)

Reconstructing a Perinatal Exposure:
Iraqi woman exposed during lactation to grain contaminated with methylmercury





(Byczkowski & Lipscomb, 2001)

Linking biomarkers to exposure and health outcome

Problems vary with the nature of the biomarker

- Parent chemical / active metabolite in blood
  - Often a good surrogate for target tissue dose
  - Directly comparable to animal blood levels at NOAEL/LOAEL
  - Use to estimate exposure requires PK information
- Inactive metabolite in Blood
  - Use requires PK information
  - Not directly comparable to animal blood levels
- Parent chemical or metabolite in urine
  - More easily related to exposure (uptake) rather than internal (target tissue) dose
  - Use of metabolite for exposure reconstruction requires information on fractional yield

Summary

- Reverse dosimetry
  - Probabilistic dose reconstruction at the population level
  - Links biomarkers of internal dose to likely external exposures
  - Useful in absence of direct link between biomarker and health outcomes
  - Critically dependent on population exposure characterization

Acknowledgements

CIIT at the Hamner

Cecilia Tan
Ken Liao
Mel Andersen

EPA

Rory Conolly

ACC

Rick Becker

Funding

Chlorine Chemistry Council
American Chemistry Council