

Cumulative Risk Assessment Research Theme



National Center for Computational Toxicology
BOSC Review
April 25-26, 2005

Research Issue

US EPA is being called on to:

- Assess cumulative risk resulting from exposures to complex mixtures
- Identify vulnerable populations
- Characterize life-stage risks
- Evaluate gene-environment interactions

To meet increasingly complex needs for cumulative risk assessment, the Agency requires sound scientific understanding of the systems being assessed and appropriate tools and approaches for characterizing these systems.

Mandate to Address Cumulative Risk

Food Quality Protection Act (1996) mandates consideration of “cumulative effects” from aggregate exposures to different pesticides with the same mode of action.

EPA’s Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures (2000) describes procedures for chemical mixture assessment using

- data on the mixture of concern,
- data on a toxicologically similar mixture
- data on the mixture component chemicals.

Mandate to Address Cumulative Risk

EPA's Framework for Cumulative Risk Assessment (2003) defines cumulative risk assessment as the "analysis, characterization, and possible quantification of the combined risks to health or the environment from multiple agents or stressors."

- Broad view expands cumulative risk assessment to include consideration of non-chemical stressors
- Increases emphasis on identifying and characterizing risks to vulnerable human and ecological receptors
- Shifts emphasis away from traditional environmental risk assessment to characterize environmentally related risks in the context of the larger public health paradigm

Research Needs

- Characterizing cumulative effects from exposures to complex mixtures
- Using biomonitoring data to assess cumulative risks
- Understanding the influence of prior exposures to one or more environmental contaminants on risks from subsequent exposures to additional stressors
- Understanding how to address non-chemical stressors in cumulative risk assessments.

NCCT Research Activities

Within the NCCT several activities are currently being conducted or are planned to address Agency needs for characterizing cumulative risk.

- Research focused on characterizing **effects** from exposures to multiple chemicals
 - Assumption of Dose-Additivity
 - Impacts of Temporal Patterns
 - Cumulative Assessment for Pyrethroid Pesticides
 - Molecular Interactions of Acetylcholine Esterase Inhibitors
- This research will improve quantitative risk assessment
- Research focused on characterizing **exposures** for cumulative risk assessment
 - A Framework for Assessing Risks From Exposures to Children
 - Using Biomonitoring Data to Assess Cumulative Risk
 - Incorporating Vulnerability Due to Social Factors
 - Frameworks for Cohort Studies of Children's Environmental Health
- This research will improve quantitative risk assessment as well as our understanding of source-to-outcome relationships

When is Dose-Additivity a Reasonable Assumption?

R. Woodrow Setzer, Jr

Modeling to Explore Toxicological Hypotheses

- Examine the received wisdom: “Toxicity of agents that act through a common mode of action should combine in a dose-additive fashion”.
- Demonstrate the value of quantitative models for developing and testing generalizations about toxicological outcomes -- “theoretical toxicology”.
- Collaboration with NHEERL/NTD

Approach

- Borrow/develop (emphasis on “borrow”!) PBPK/PD models for, e.g., Organophosphates, N-methyl-carbamate cumulative exposure.
- Two exposure scenarios to consider: continuous, long-term exposure, leading to steady-state inhibition of AChE; episodic but brief exposures (as in diet).
- Characterize interaction in terms of the behavior of isoboles (Berenbaum, 1989): Loci of points in “dose space” that have the same response in multi-chemical exposures.
 - Non-interaction coincides with linear isoboles.

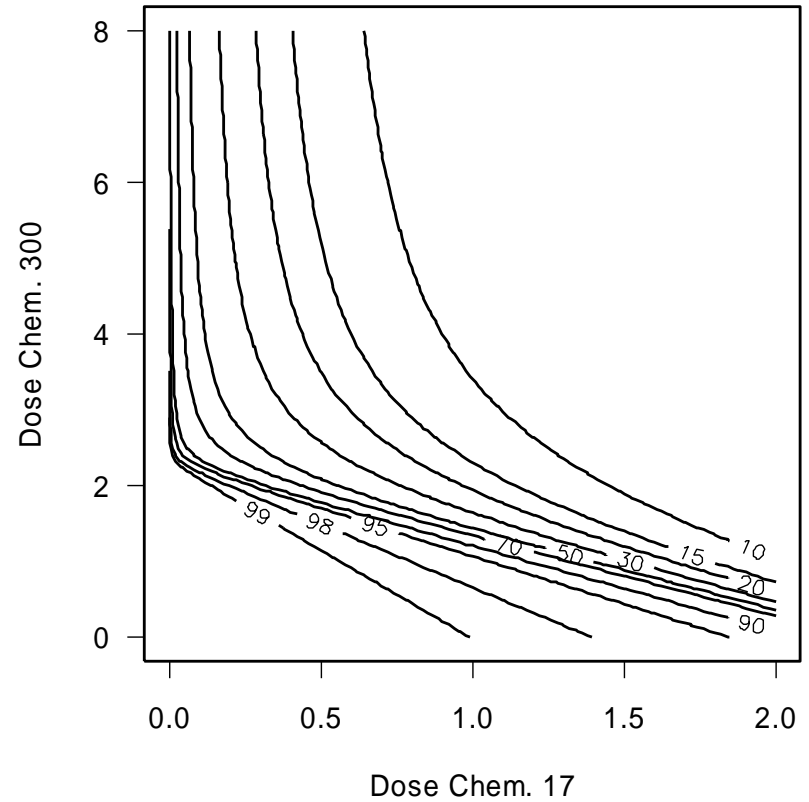
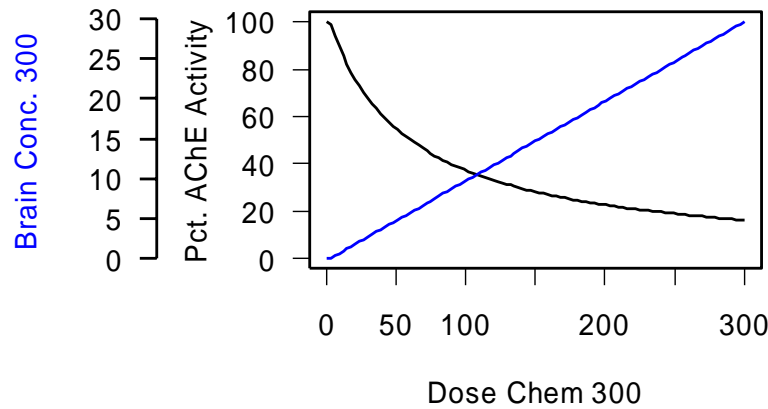
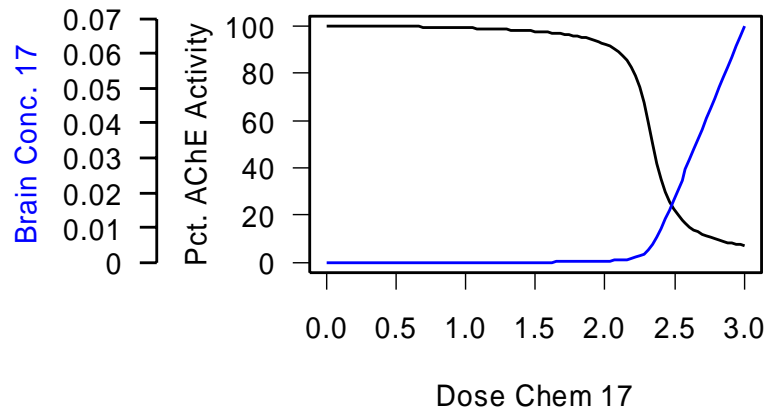
Example: A “Toy” OP Model

- Three compartments: brain, liver, everything else
- Constant infusion into the liver
- Metabolic clearance in the liver, Michaelis-Menten kinetics: (V_{max} , K_m)
- AChE inhibition in the brain uses same scheme as Timchalk, *et al.* (2002): K_i , K_r , K_a .
- Sample the 5-dimensional parameter space to make example “chemicals”.

In silico *Experiment*

- What happens when two chemicals that are identical except for K_i are combined?
 - Chem 17: $K_i = 11.04$
 - Chem 300: $K_i = 0.01$, other parameters the same
- Potency of 17 relative to 300 (ratios of BMD10) is ~ 4.25

Common Mode of Action?



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Impacts of Temporal Patterns of Exposure on Cumulative Risk

R. Woodrow Setzer, Jr

N-Methyl Carbamate Cumulative Risk Assessment

- Probabilistic risk assessment based on food, drinking water, and residential exposures: exposure probabilistic, health effects conventional.
- About 10 *N*-methyl carbamates included.
- Health effects via oral and dermal route combined using relative potency factors (RPFs).
- Collaboration with OPPTS and NHEERL

N-Methyl Carbamates

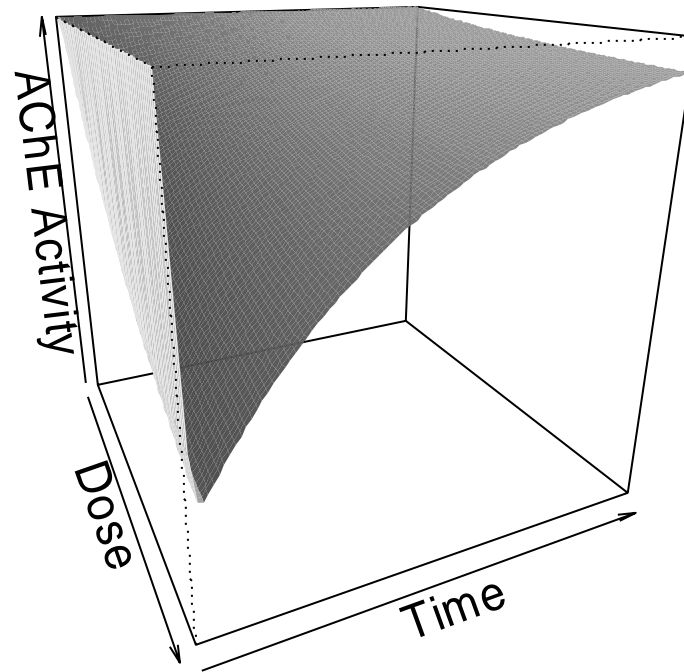
- We were so successful with the organophosphates, that we have returned to do the *N*-methyl carbamates. BUT...
- There is a big difference: the AChE inhibition of *N*-methyl carbamates is comparatively very short-lived (half lives of less than an hour to a few hours). The time course of inhibition matters.

Strategy

- Develop a single model that describes AChE activity as a function of dose and time post dosing. Parameters include:
 - $\log(\text{BMD})$ for 10% (or other specified) inhibition.
 - Time to peak effect.
 - Recovery half-life.
- Fit the model to all relevant data-sets, treating some of the variation among data-sets as random (*e.g.*, $\log(\text{BMD})$), others as fixed effects with specific values for each data-set and sex (*e.g.*, background levels). This gives a nonlinear mixed-effects model.
- Extrapolate animal dose-time response model to humans by scaling parameters.

Dose-Time-Response

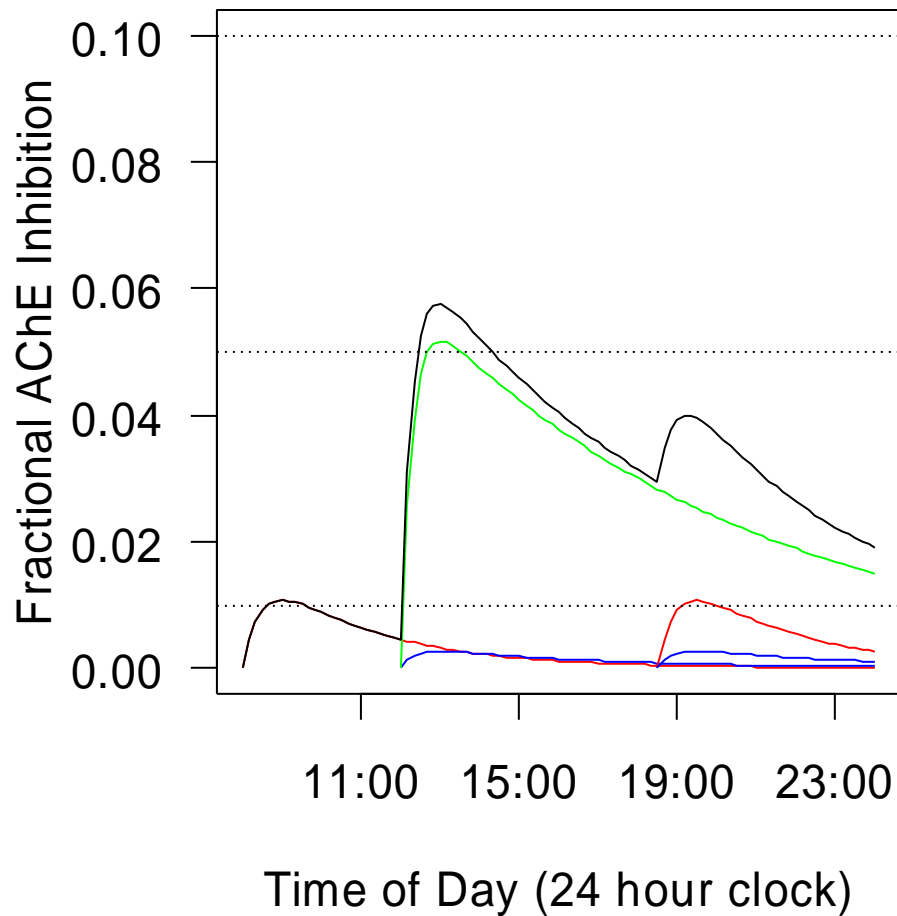
$$\begin{aligned} A &= 15 \\ T^* &= 0.5 \\ \alpha &= 70 \\ R &= 0.1 \\ P &= 0.1 \\ D_R &= 3 \\ \gamma &= 1 \end{aligned}$$



Outline of RA Approach

- Use approximate model of relationship between dose, time and AChE inhibition
- Use simulations of dietary exposure combined with the extrapolation model to produce estimates of human AChE inhibition time-courses
- At each new exposure “event” the *fraction of active* enzyme inhibited depends only on dose and time after dose (and chemical-specific parameters)
- The amount of enzyme inhibited at any given time is the sum of all enzyme still inhibited in all previous exposures

Result of Simplified PK Model



Example Response Metrics

Maximum inhibition: 5.8%

Fraction of time > 10%: 0%

Fraction of time > 5%: 7.6%

Fraction of time > 1%: 54%

Total Inhibition	—
X	—
Y	—
Z	—

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Computational Solutions in the Cumulative Assessment of Pyrethroid Pesticides

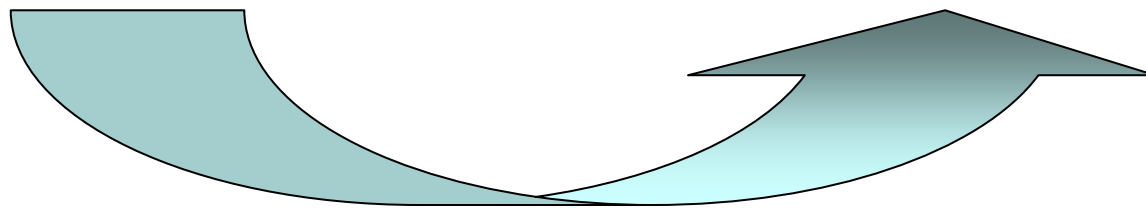
Mike Tornero

PBPK MODEL DEVELOPMENT

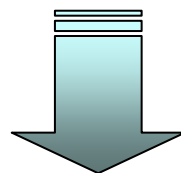
IN SILICO

Rodent *IN VITRO*

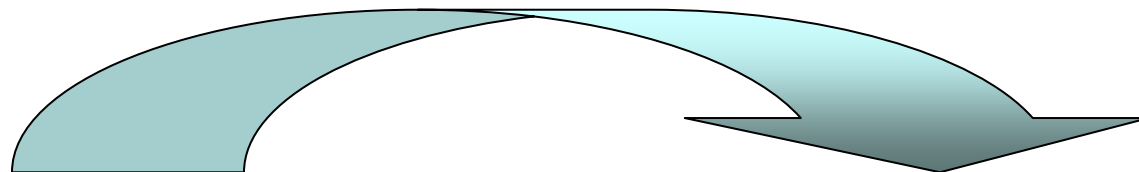
Rodent *IN VIVO*



Rodent PBPK MODEL



HUMAN PBPK MODEL



HUMAN *IN VITRO*

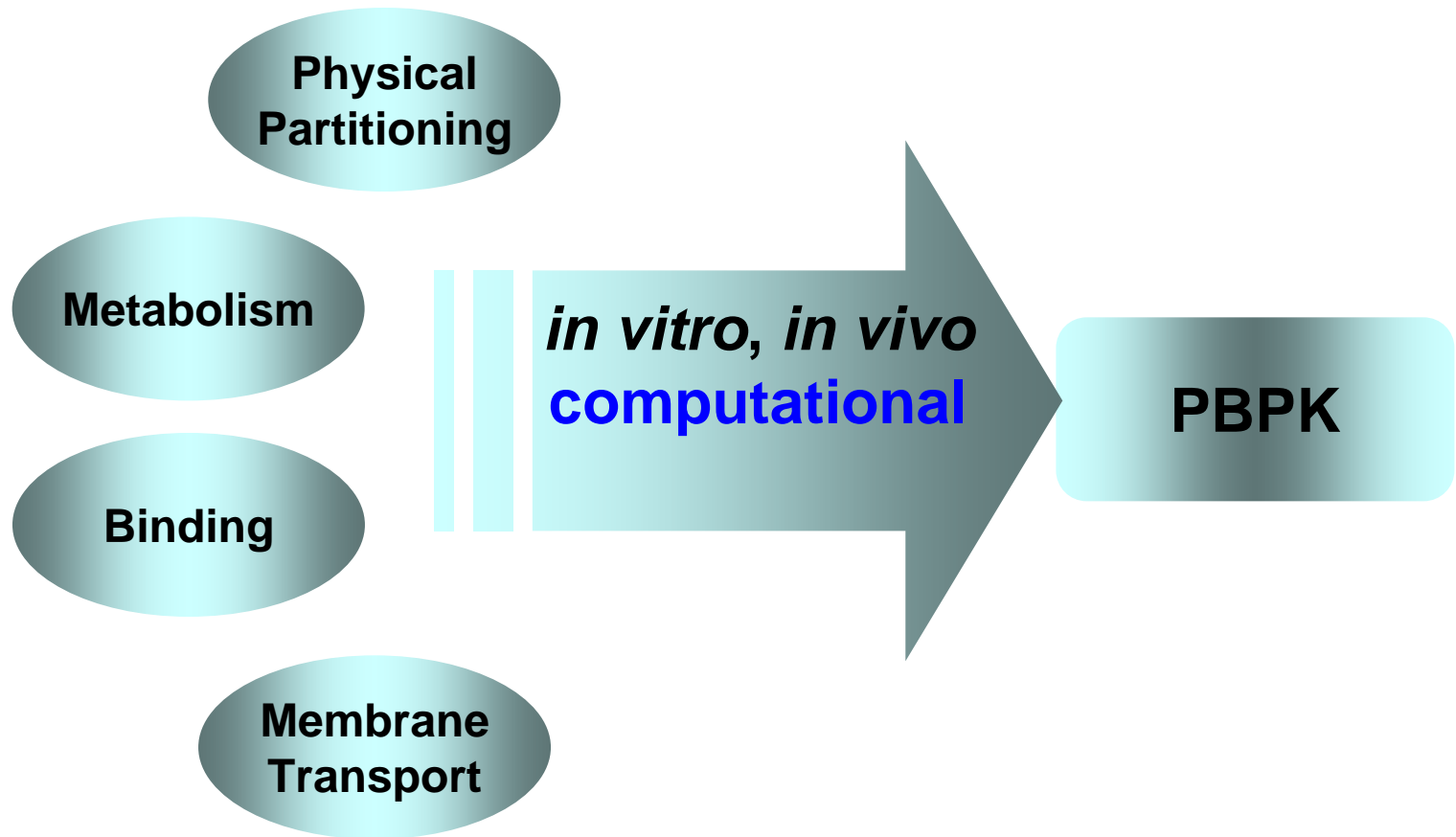
HUMAN *IN VIVO*

IN SILICO

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Model Parameterization



Computational approach: tissue:blood partition coefficients

Lipids, water, proteins

TISSUE



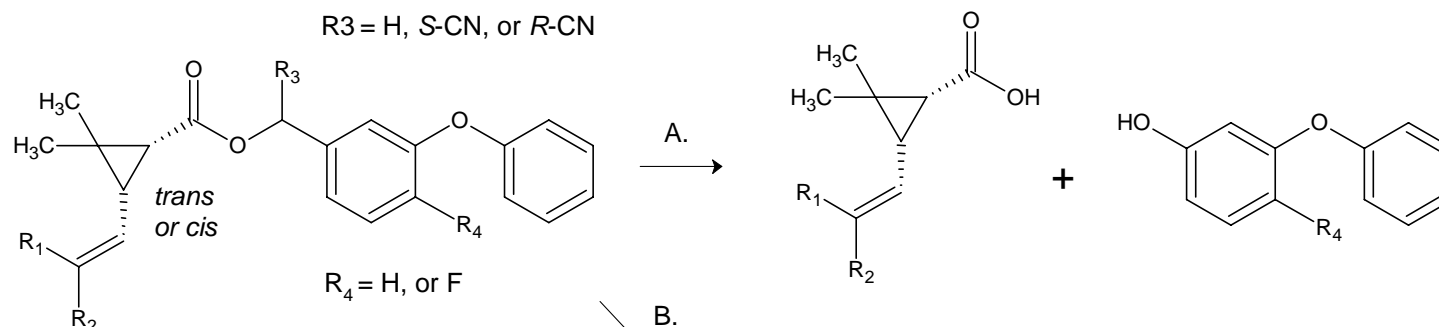
Blood

Lipids, water, proteins

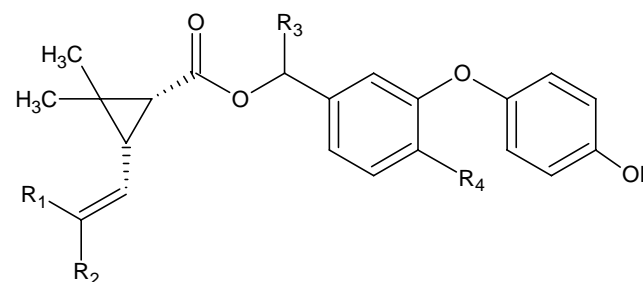
Equilibrium

- Based on $K_{o:w}$ (octanol:water)
- Based on distribution of lipids and water in tissues

Computational approach: Pyrethroid metabolism



Name	R1	R2	R3	R4
Permethrin:	Cl	Cl	H	H
Phenothrin:	CH ₃	CH ₃	H	H
Cypermethrin:	Cl	Cl	CN	H
Cyfluthrin:	Cl	Cl	CN	F
Cyphenothrin:	CH ₃	CH ₃	CN	H
Cyhalothrin	Cl	CF ₃	CN	H
Deltamethrin	Br	Br	CN	H



Quantum methods
QM/MM

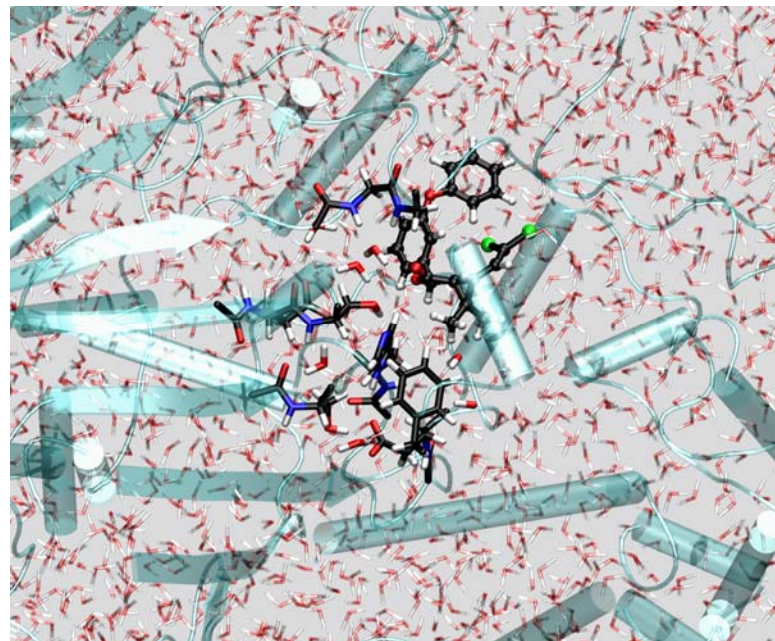
Ab initio Simulations of Metabolic Processes

Goals

General: Validate IBM quantum-classical (QM/MM) simulation methodology as a practical tool for predicting metabolic rates.

Specific: Estimate differential rate constants for the hydrolysis of the pyrethroid permethrin by human carboxylesterase in *trans* and *cis* configurations.

Model: ligand-protein complex embedded in water. “Quantum” subsystem highlighted.



PBPK Approaches in Cumulative Risk Assessment

- Develop *in Silico* approaches for model input; in particular, approaches which address uncertainties in biochemical inputs
- Cumulative assessments are fertile ground
- Methods can aid in interpretation of chemical-chemical interactions
- CompTox/NERL (Consultation with Molecular modelers)

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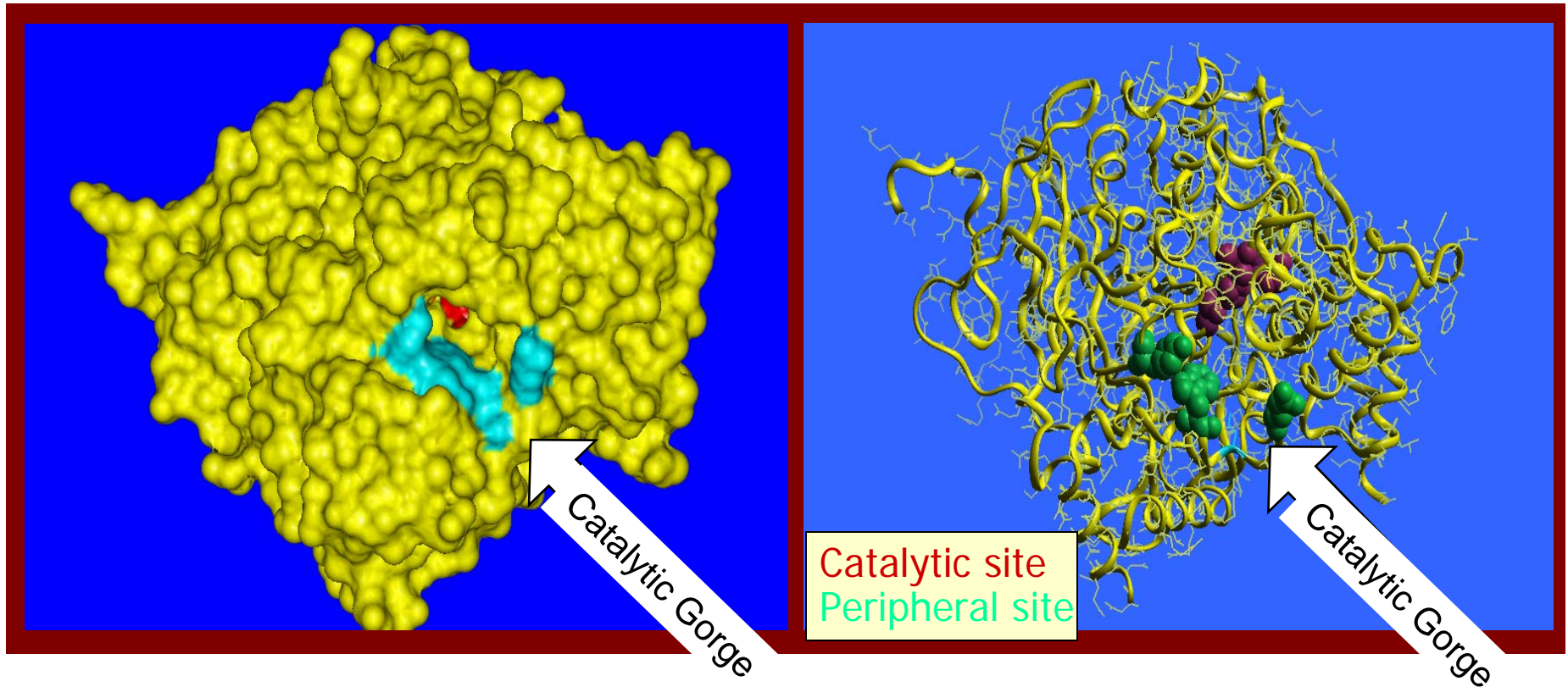
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Mixtures of Molecules Active Through Binding to Acetylcholine Esterase:

*Understanding Cumulative Effects Through
Modeling Key Steps in the Mechanism of Action*

James Rabinowitz

Crystal Structure Acetylcholinesterase



Binding to the catalytic site - inactivates the enzyme

Binding to the peripheral site - increases the specificity of the enzyme and decreases its activity

AChE Inhibitors - The Problem

- Exposures are often to mixtures of chemicals that are AChE inhibitors
- Data is almost all for single chemicals in this class
- For a single chemicals the difference in the effect due to the binding to the red site or the blue/green site is not apparent
- For mixtures the difference is critical

The activity after exposure to a single chemical is:

$$Z(\text{activity}) = C_E (E + D_x X \bullet E \bullet) = C_E E_{ap}$$

The Potency of a chemical: $P = Z / E_T = (E_T - E) / E_T$

Two chemicals (x,y) - a single site:

$$Z_{xy} = C_E E = E_T (1 - P_x) (1 - P_y)$$

Two chemicals (x,y) - both sites:

$$Z_{xy} = C_x C_y E + B_y D_x X \bullet E \bullet + B_x D_y X \bullet E \bullet$$

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- Collaboration with NHEERL/NTD

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Exposure Research

Elaine Cohen Hubal

Exposure Research Issue

- Characterizing cumulative risk and understanding exposure-outcome relationships requires collection and analysis of a wide range of data.
 - Characteristics of multiple stressors (chemical, physical, biological and psychosocial)
 - Characteristics of the human receptor (genetics, health status, life stage, behaviors, social factors, etc.) at multiple levels of organization (individual, community, population)
 - Temporal and spatial patterns of exposures and outcomes
- Multi-factorial analyses required to:
 - Conduct national-scale regulatory-based risk assessments
 - Conduct community-based risk screening and remediation
 - Support epidemiology studies investigating gene-environment interactions
 - Characterize exposure and risk for public health tracking

Approach

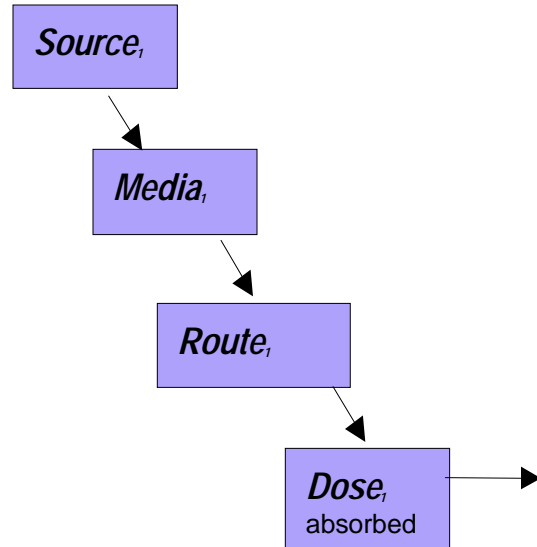
- To date, some preliminary (conceptual) research has been conducted to consider how to
 - Assess children's exposures (NCEA)
 - Use biomonitoring data to assess cumulative risk (EPA Risk Assessment Forum)
 - Incorporate psychosocial factors into cumulative risk assessments (EPA Risk Assessment Forum)
- As we move forward to address the significant challenges associate with characterizing cumulative risks, we will apply
 - Human-receptor-based framework
 - Systems approach
 - Visual analytic tools

A Framework for Assessing Health Risks Resulting From Exposures to Children

- Provides an overarching framework for a more complete assessment of health risks from exposures to children that examines the impact of potential exposures during all stages of development
- Takes a person/population oriented approach
- Suggests two levels (tiers) for exposure assessment; probabilistic methods may be required at screening level

Conceptual Model for Problem Formulation

Exposure



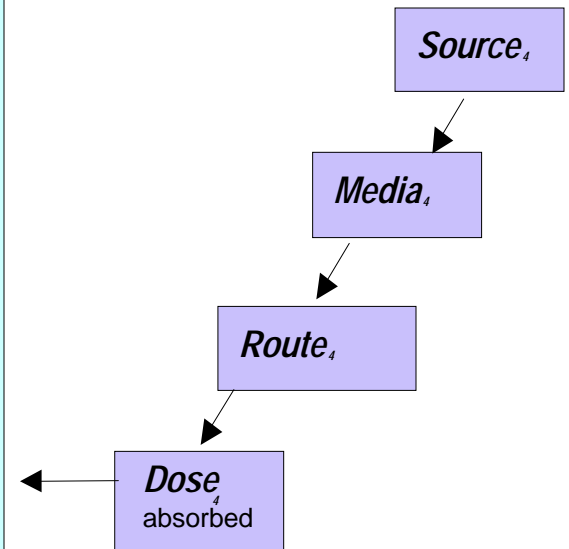
Child (child specific subpopulation)

Host factors

- Genetic Susceptibility
- Developmental Stage
- Behaviors
 - Activities
 - Locations
 - Product use
 - Diet
- Community and Other Factors

Outcomes

Exposure



Life-stage specific dose (e.g., mg/kg/d)

Health assessment values (e.g., RfV(s) for a specific duration(s))

Disaggregating Health and Biomonitoring Information

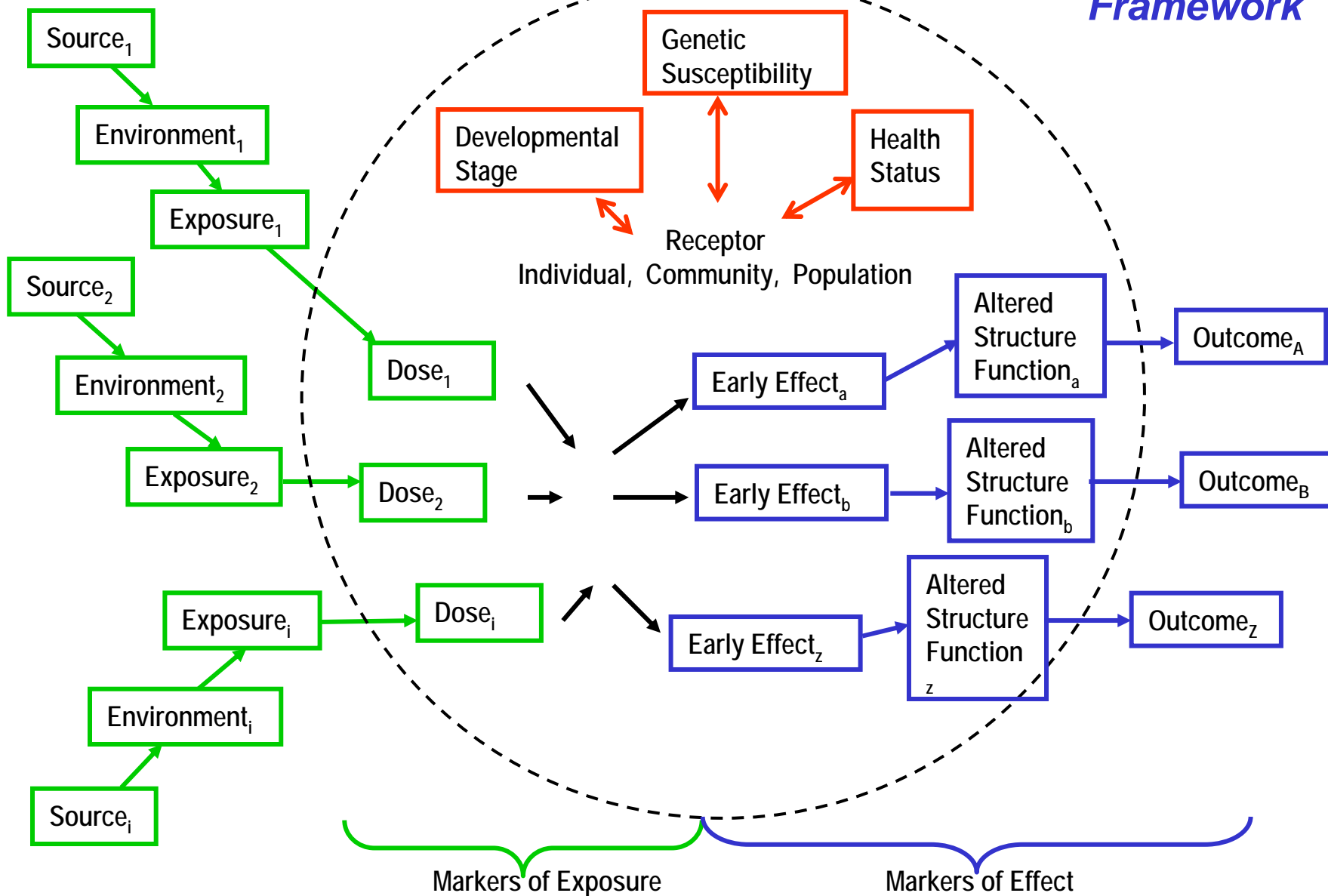
How can biomonitoring data be used to assess cumulative risk?

How do we do biomonitoring right for cumulative risk assessment?

- There is unlikely to be a single “Ideal” biomarker. All important characteristics are unlikely to exist in a single measure.
- Consider an array of biomarkers. (e.g., one might tell something about short-term exposures, another about long-term)
- Focus on what biomarkers tell us about disease in the community and risk to the population.
- Assess the utility of biomarkers in understanding risk to multifactorial diseases (e.g., asthma, neurodegenerative diseases, etc.)

Markers of Susceptibility

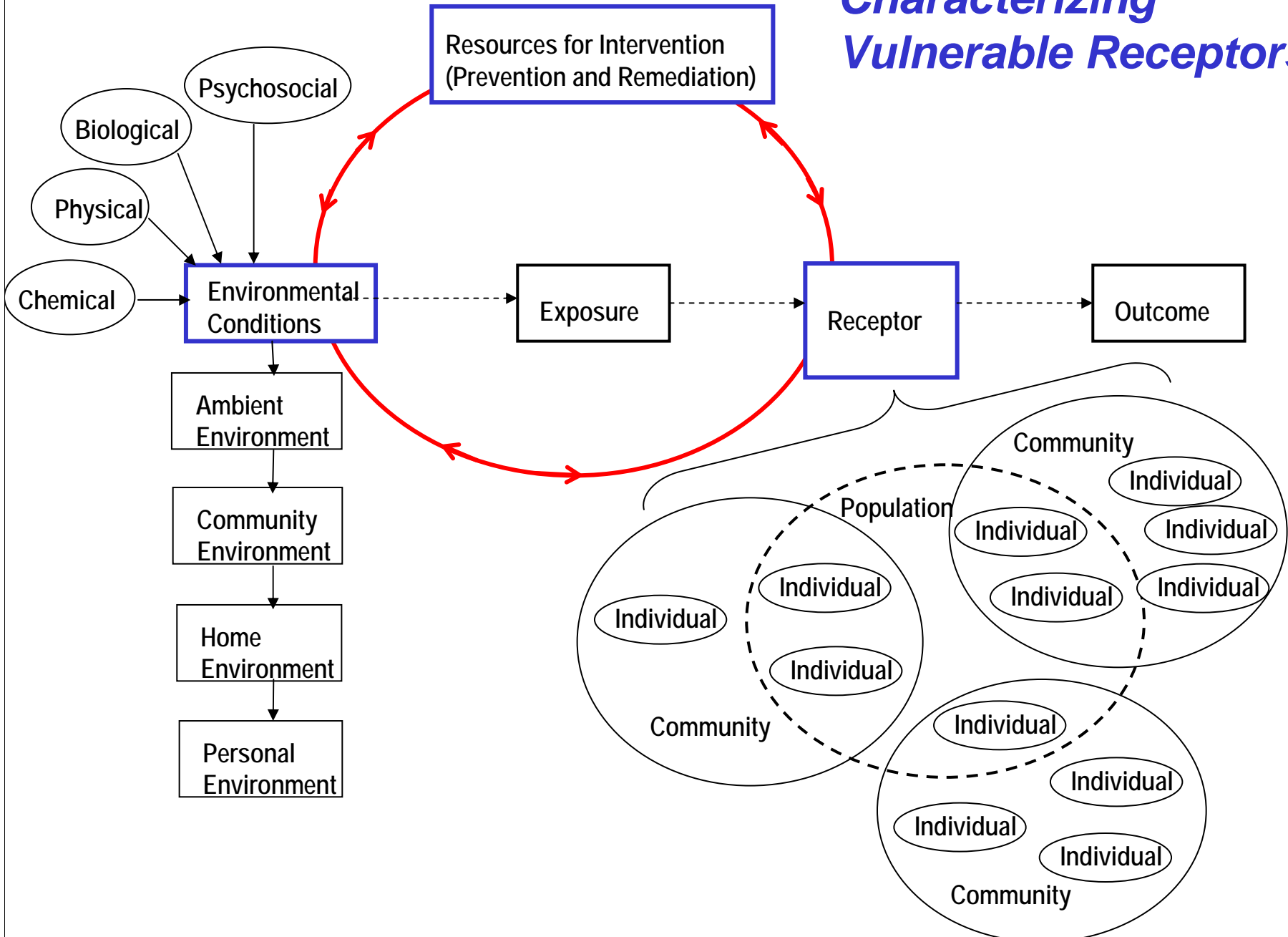
Biomonitoring Framework



Vulnerability Due to Social Factors

- How do we identify, characterize, and protect vulnerable individuals, communities, and populations?
- How can psycho-social factors be considered in estimating cumulative environmental risks? (Can a conceptual framework be developed and tested with case examples?)
- What information would need to be measured, collected, and tracked to insure that the full range of stressors and mediating influences are considered in a cumulative risk assessment?
- What research is needed to better determine the relationship between psycho-social conditions and environmental health?

Characterizing Vulnerable Receivers



Framework for Cohort Studies of Children's Environmental Health

Cohort studies of children's environmental health include

- Detroit Children's Study
- North Carolina Cohort Study
- National Children's Study

Science question

- Given multiple exposures, multiple outcomes, as children grow and develop across time, how do we understand the relationships in this multidimensional space?

Approach

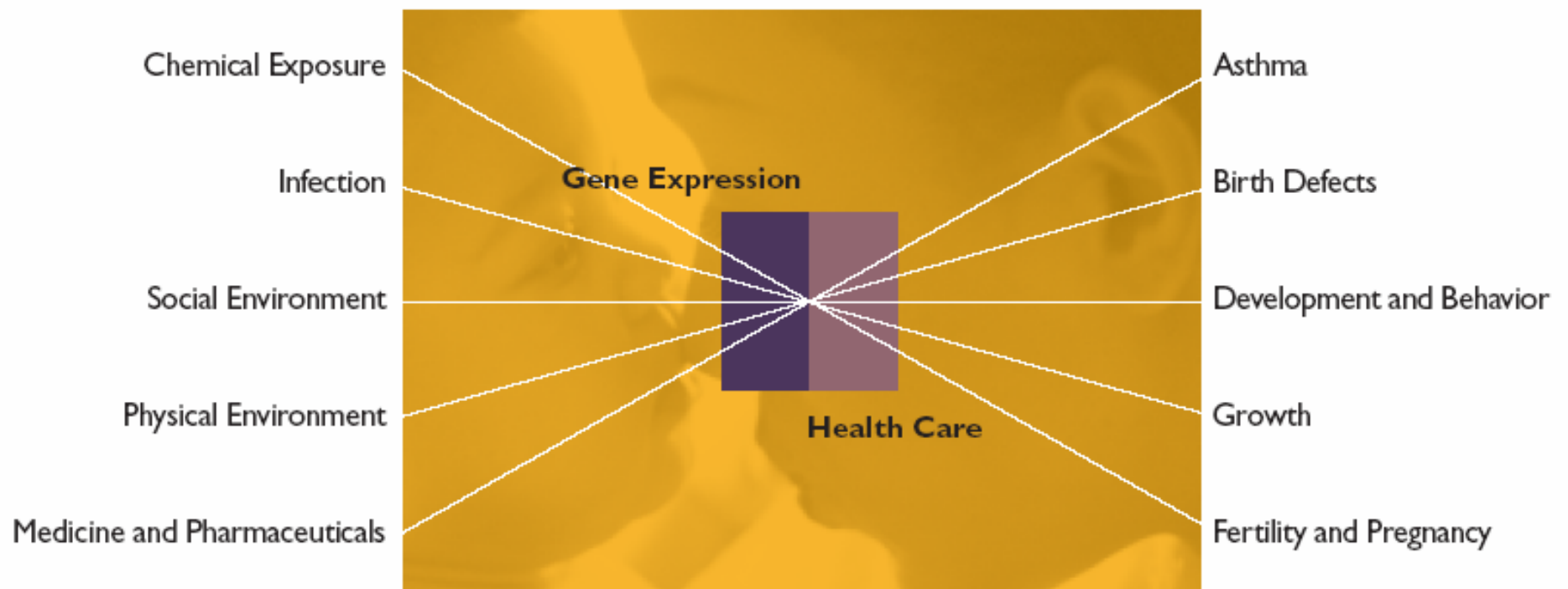
- Apply a systems approach to develop human-receptor based conceptual framework
- Design visual analytic tools based on conceptual framework to address analysis needs
- Develop and test VA tools using existing available data (e.g., STAR Children's Centers)

FROM EXPOSURE TO OUTCOME

Understanding Complex Interactions in a Child's Environment

POSSIBLE EXPOSURES

POTENTIAL OUTCOMES



From: Growing Up Healthy: An Overview of the National Children's Study

Visual Analytics

- Merges scientific and information visualization to represent complex multidimensional data
- Includes technologies from fields of information extraction, knowledge management, and statistical analysis
- Tools can be used to combine large, dynamic and complex data sets containing text, measurements, and images
- VA can be applied to reveal significant relationships and trends and to enhance discovery. Can be used:
 - for outcome analysis and visualization,
 - to find patterns and subtle relationships in data,
 - to infer rules that allow predictive analysis to prevent and mitigate environmental disease.
- The NCCT will take advantage of visual analytic capabilities that are being developed in the Scientific Visualization Center at the EPA National Environmental Scientific Computing Center.

Proof of Concept

- As a first step, we propose to establish collaborations with STAR Children's Center grantees. These centers have been studying large cohorts of pregnant women and young children for several years.
- Data collected by these researchers (that can be made available with appropriate human subjects clearance) will be combined with additional publicly available data and used to explore the potential of visual analytics to facilitate evaluation of the effects of environmental exposures on child health and development.
- Results will then be used to develop concepts and tools for application to the Detroit Children's Study, the North Carolina Cohort, and the National Children's Study.