Connecting Environment, Biology, and Behavior for Human Exposure and Risk Assessment:

Integrative Modeling Approaches

by Panos G. Georgopoulos

Presented at Exposure Science Community of Practice Meeting

USEPA - May 5, 2009

CCL Computational Chemodynamics Laboratory

Environmental and Occupational Health Sciences Institute (EOHSI) - Exposure Science Division

EOHSI is a joint institute of UMDNJ-RWJ Medical School and Rutgers University

the Center for Exposure and Risk Modeling → CERM

ebCTC environmental bioinformatics and Computational Toxicology Center

CERM and ebCTC are primarily funded by USEPA; additional funding and resources are provided by NIEHS, CDC and USFDA

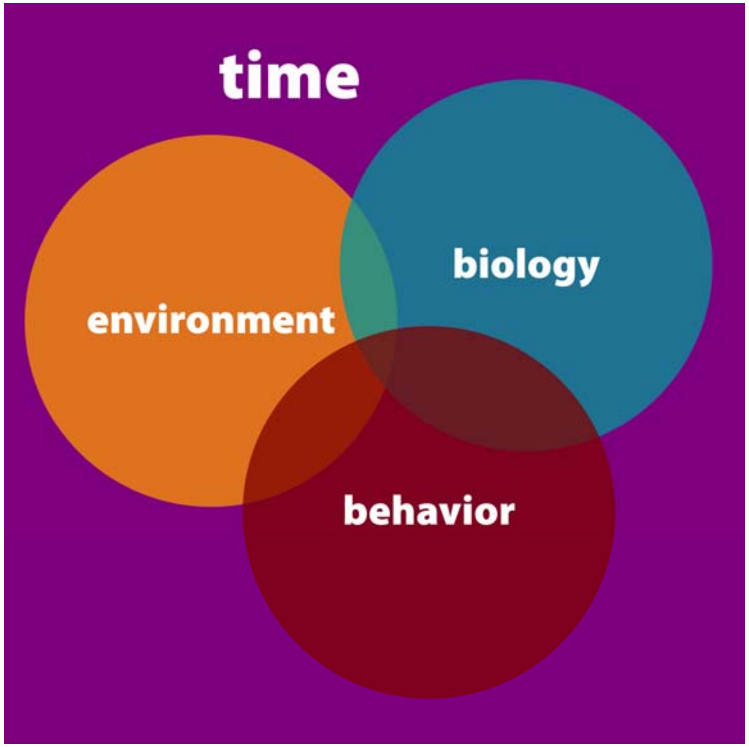
General objective of research at CCL:
integrative frameworks for exposure, dosimetry and toxicity that "translate" into mathematical terms and subsequently into computational code the statement:

"Genetics loads the gun, but environment pulls the trigger"

Judith Stern, University of California at Davis

Aims: develop and apply mathematical/computational tools to:

- **Characterize aggregate/cumulative exposures to environmental stressors (by source, route, and pathway) for individuals and populations**
- **Interpret biomarkers of exposure and effect through biologically based toxicokinetic and toxicodynamic models**



… for any particular person, the risk of developing environmentally caused disease depends on many factors, including **how** they are exposed to a toxicant, the **length** and **intensity** of the exposure, and the person's **genetic makeup**...

paraphrased from the web site of the American Cancer Society

"Integrative" consideration of environmental, biological and behavioral factors is critical

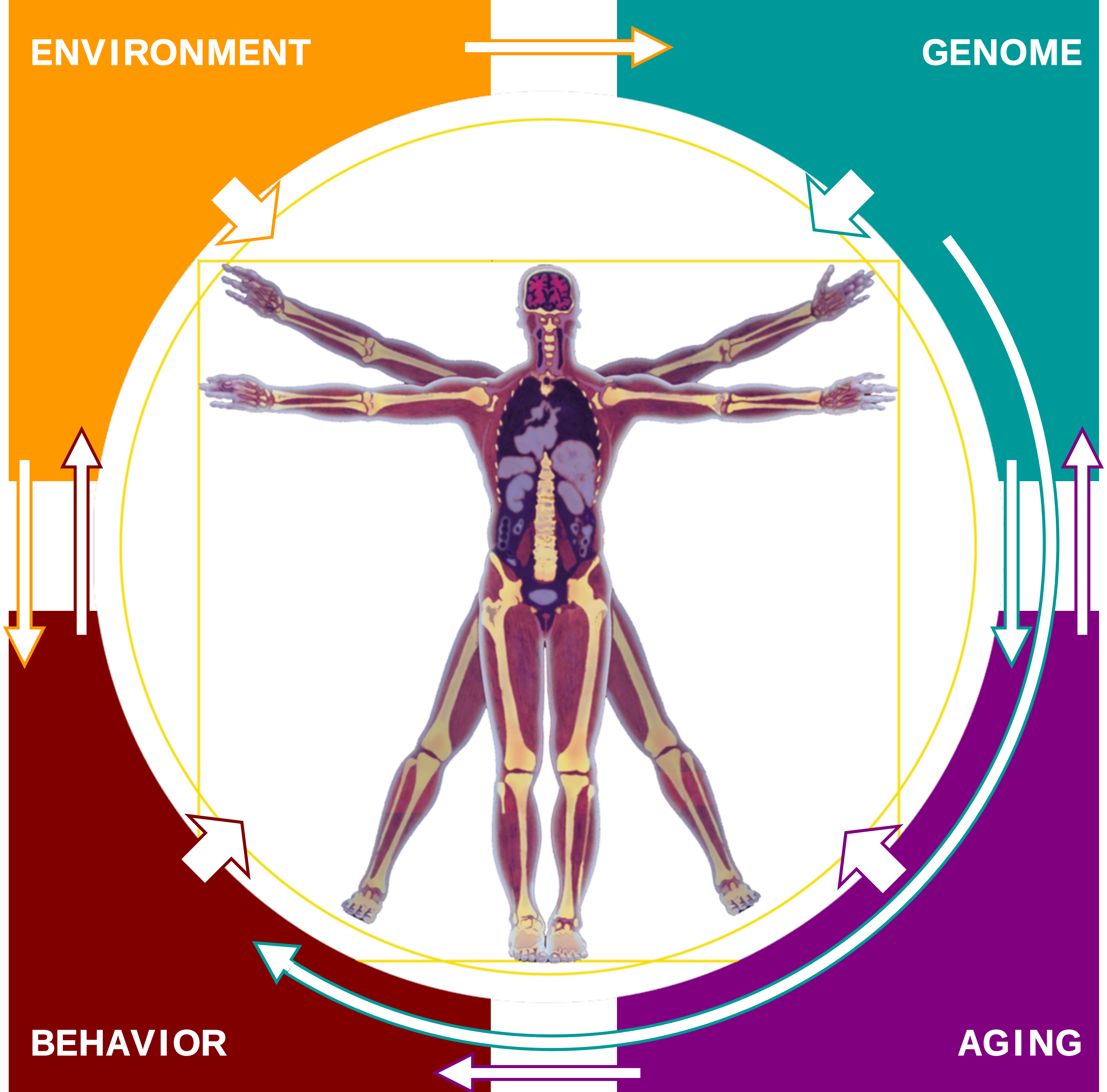
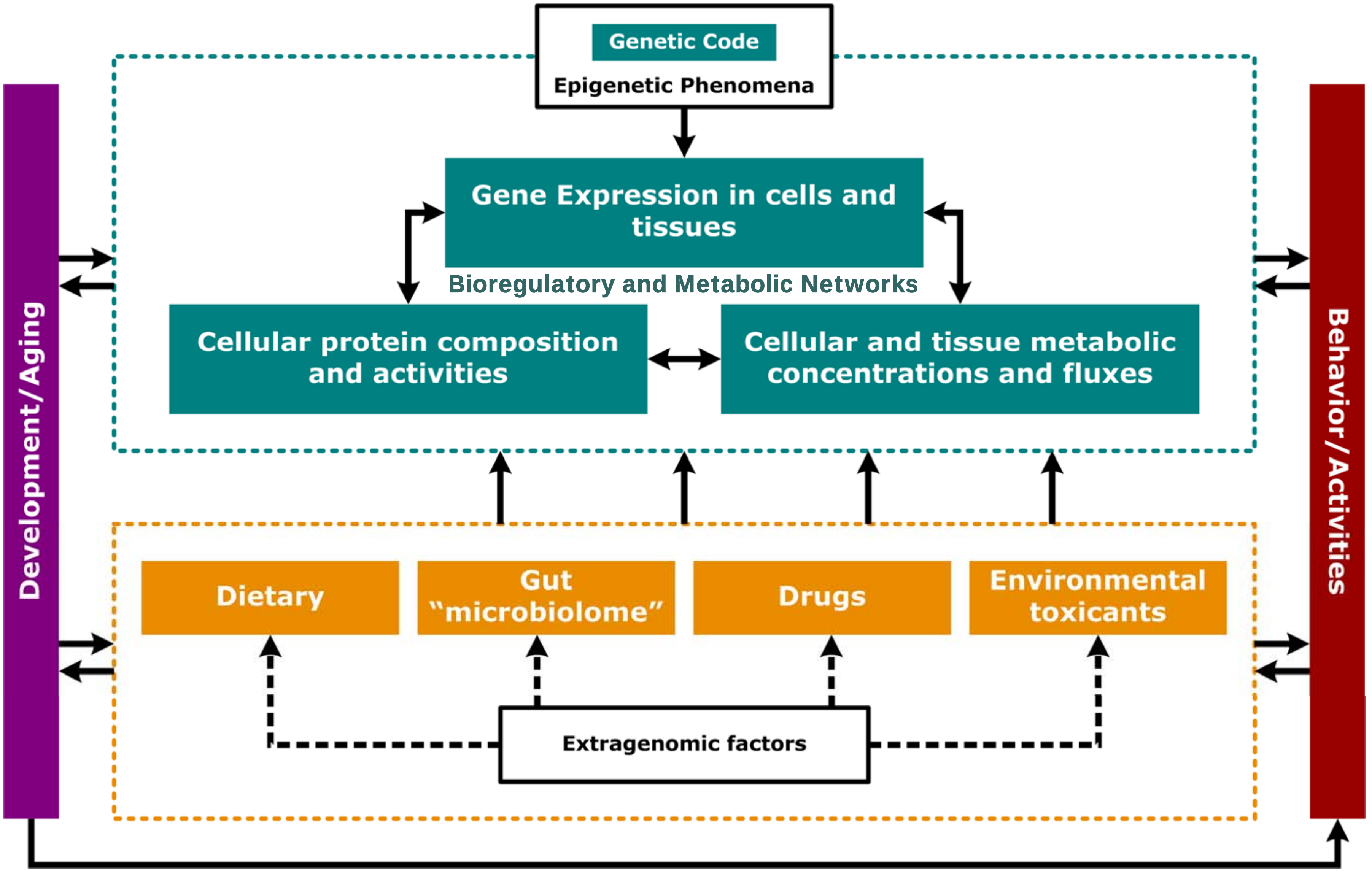
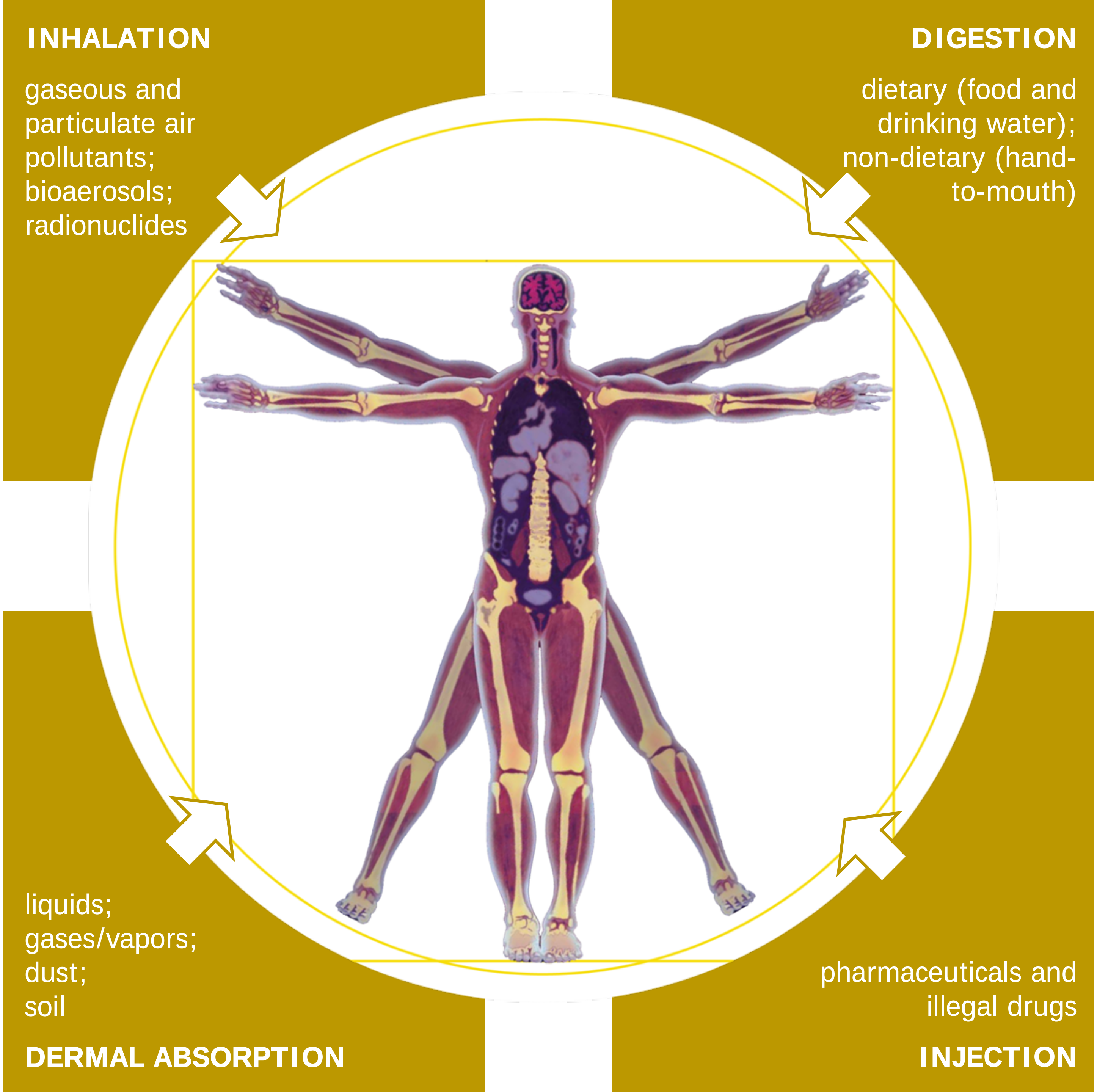


Image in the center has been adapted from *Science* 26 May 2006: Vol. 312. no. 5777, p. 1162

A general mathematical framework for environmental health risk analysis must consider multiscale bionetwork dynamics (spanning the genome, transcriptome, proteome, metabolome, cytome, physiome) linked with the dynamics of environmental ("extragenomic") stressor networks





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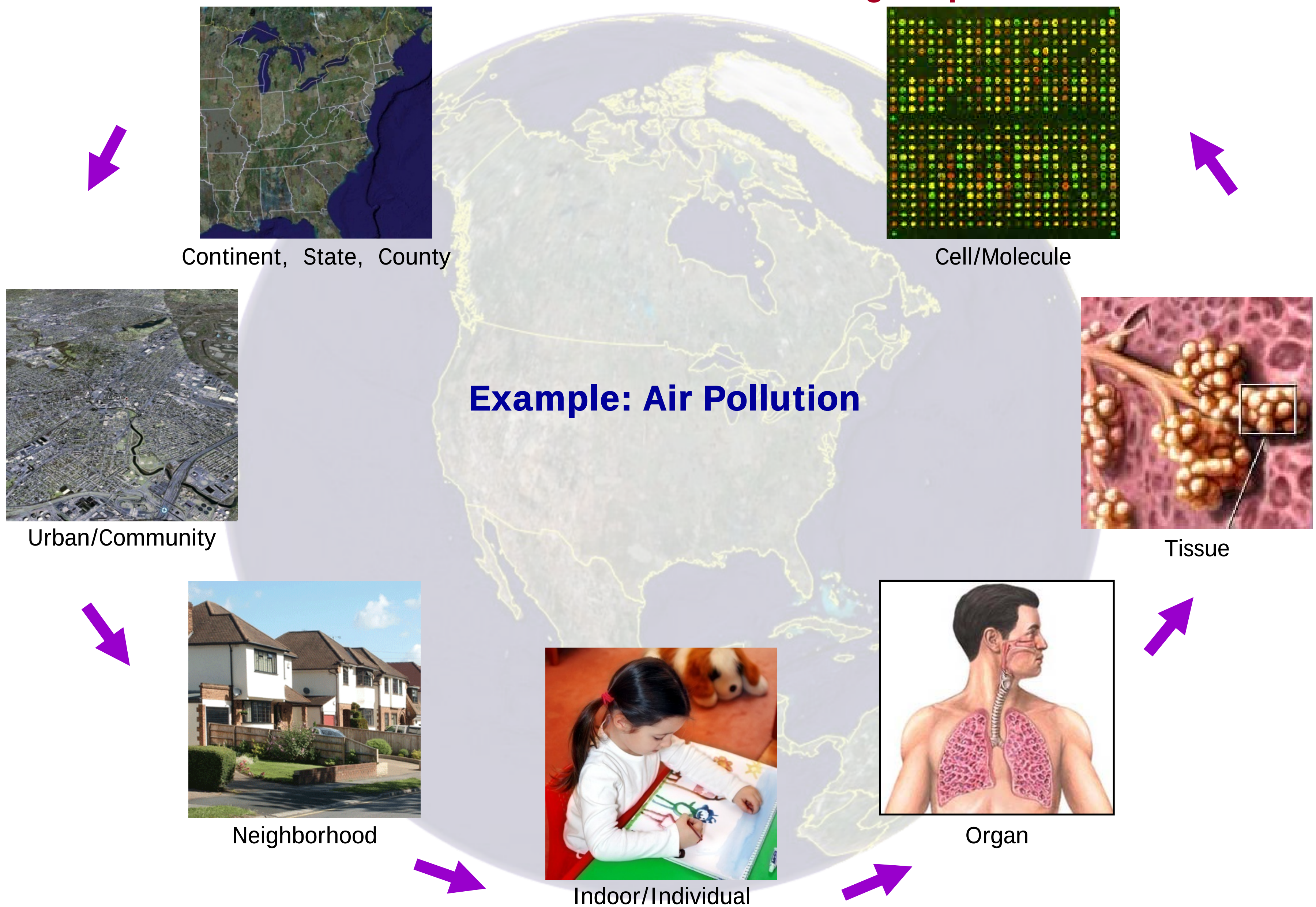
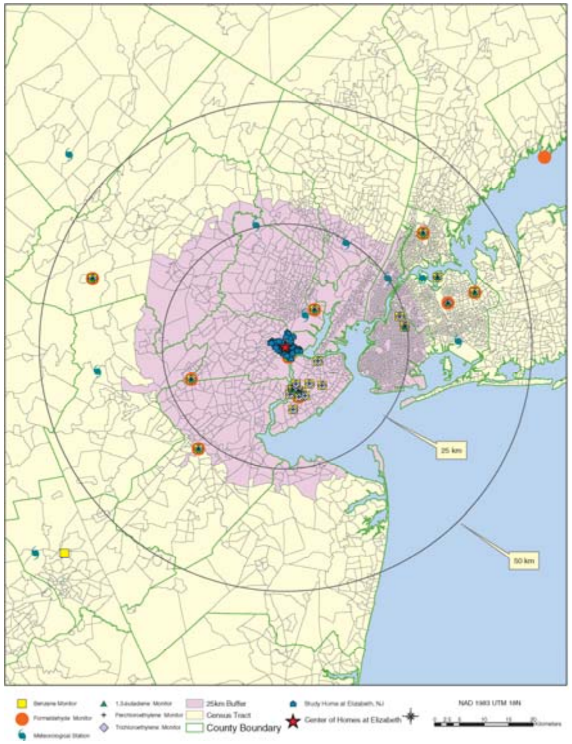
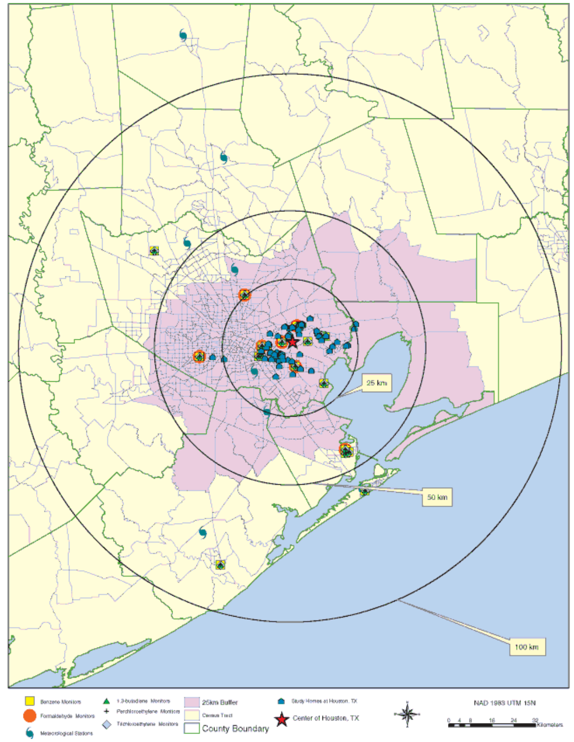
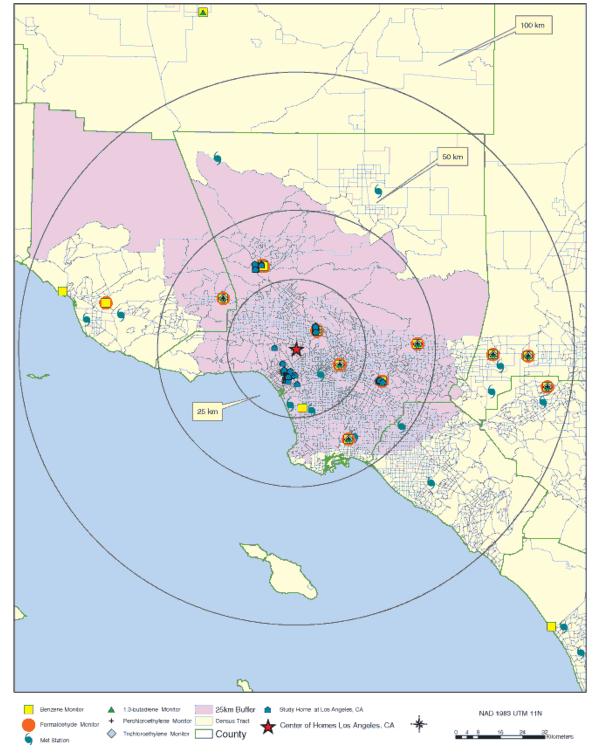
Analysis of exposures to environmental contaminants, and of subsequent doses and effects is typically a complex multiscale problem in terms of both the environmental / microenvironmental and the biological processes involved

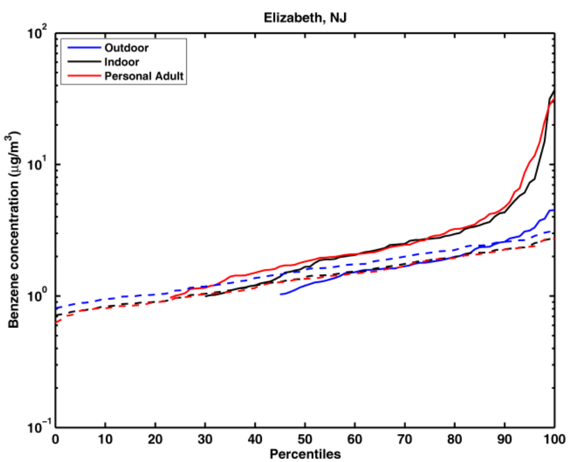


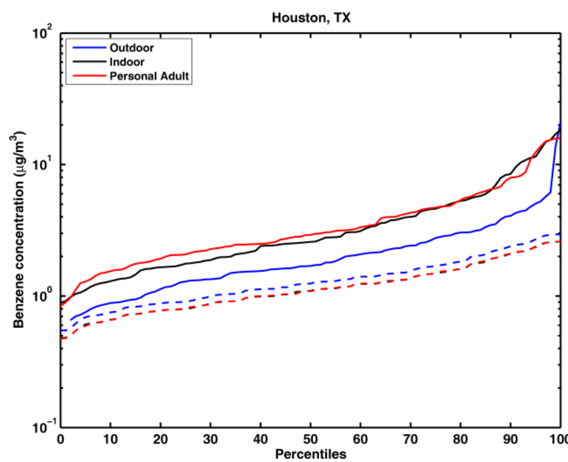
Comparison of outdoor, indoor and personal air concentrations RIOPA studies (Elizabeth, NJ; Houston, TX; and Los Angeles, CA): Cumulative distributions of benzene measurements and “simple” predictions

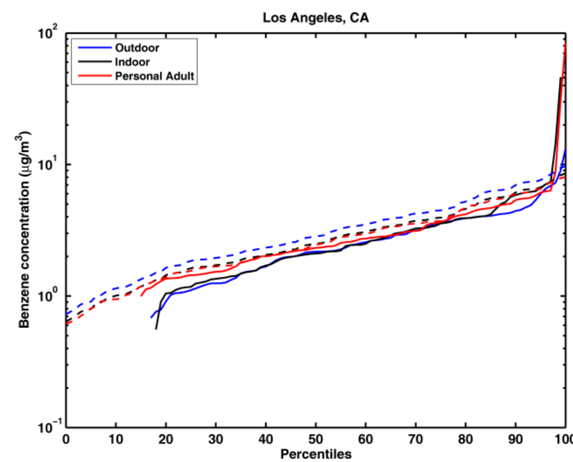




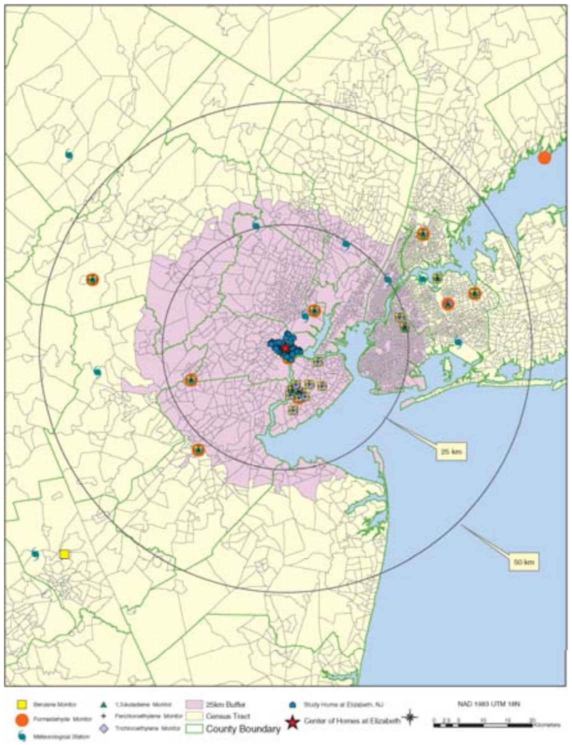


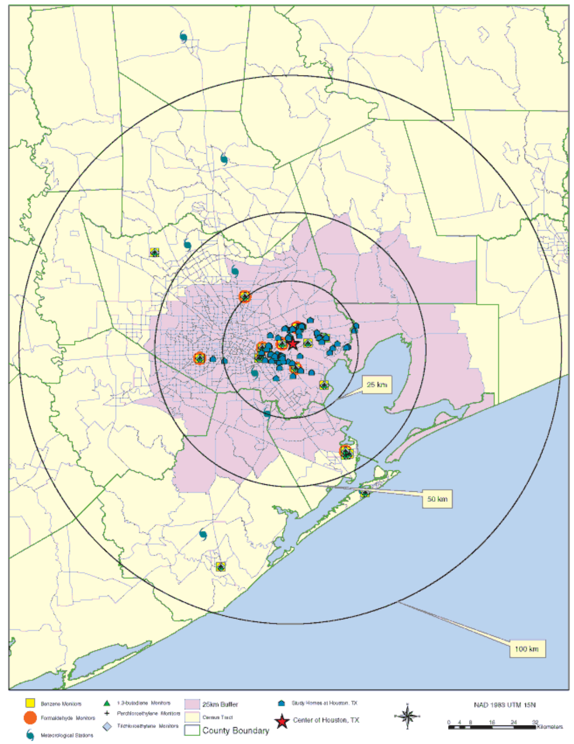


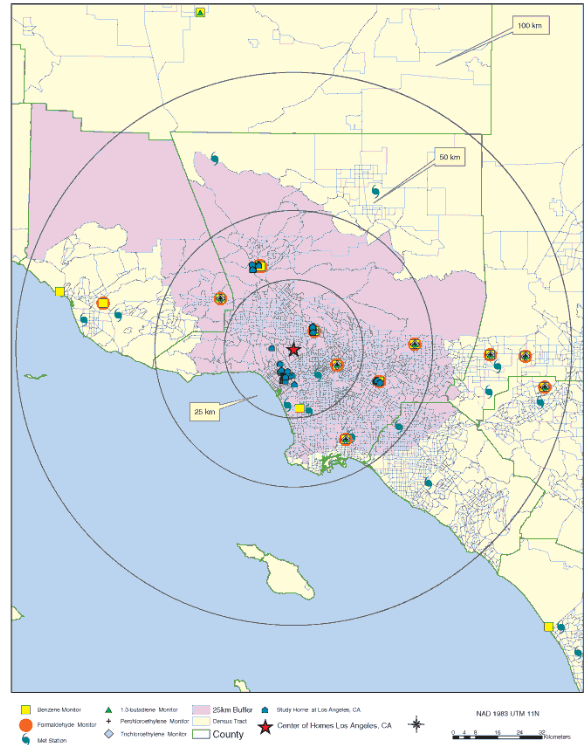


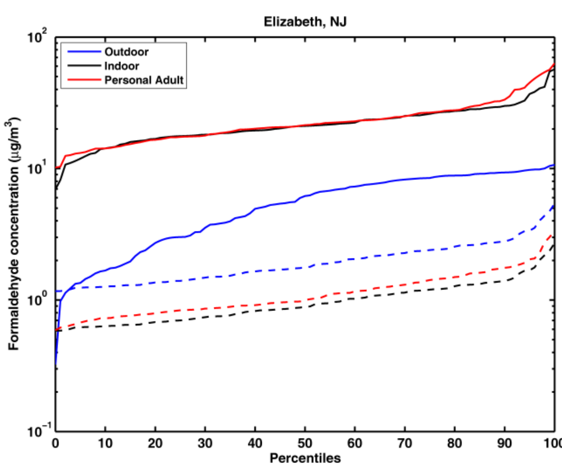


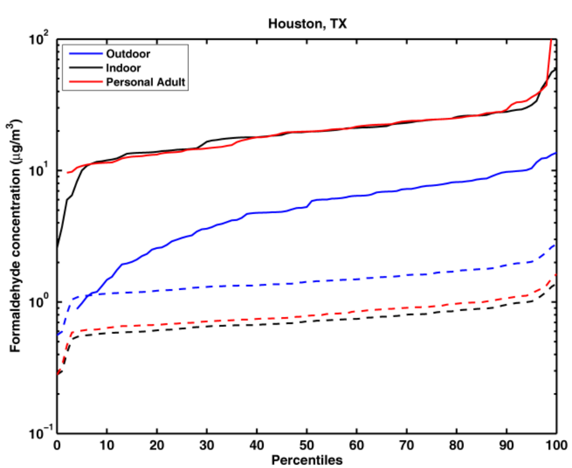
Comparison of outdoor, indoor and personal air concentrations RIOPA studies (Elizabeth, NJ; Houston, TX; and Los Angeles, CA): Cumulative distributions of formaldehyde measurements and “simple” predictions

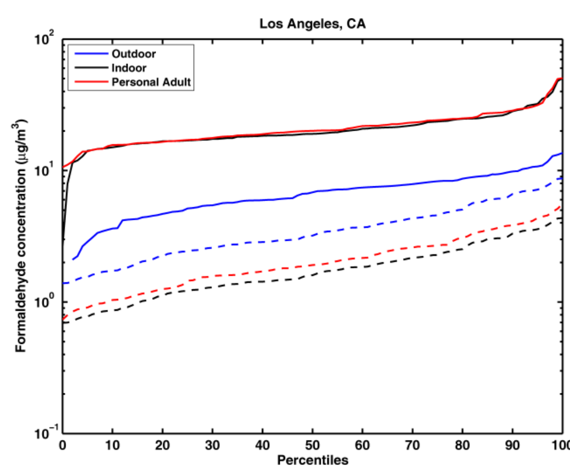




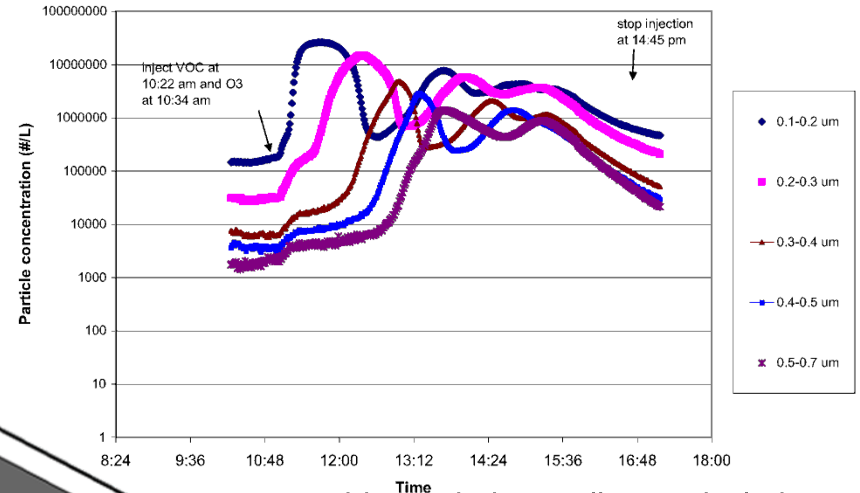




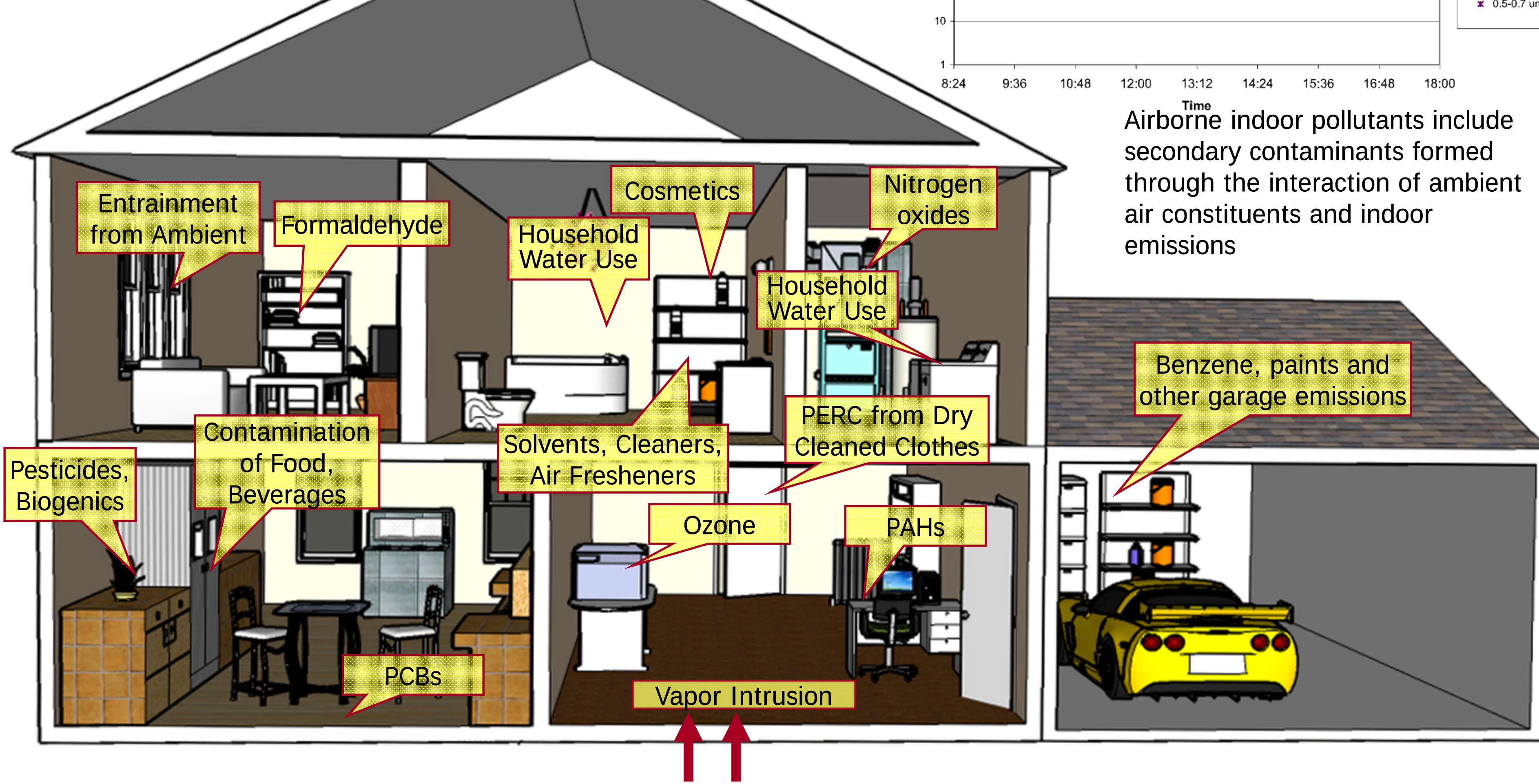




For most people the majority of exposures to contaminants takes place through ingestion of foods and beverages and through contact and inhalation of chemicalsin indoor (residential or occupational) microenvironments

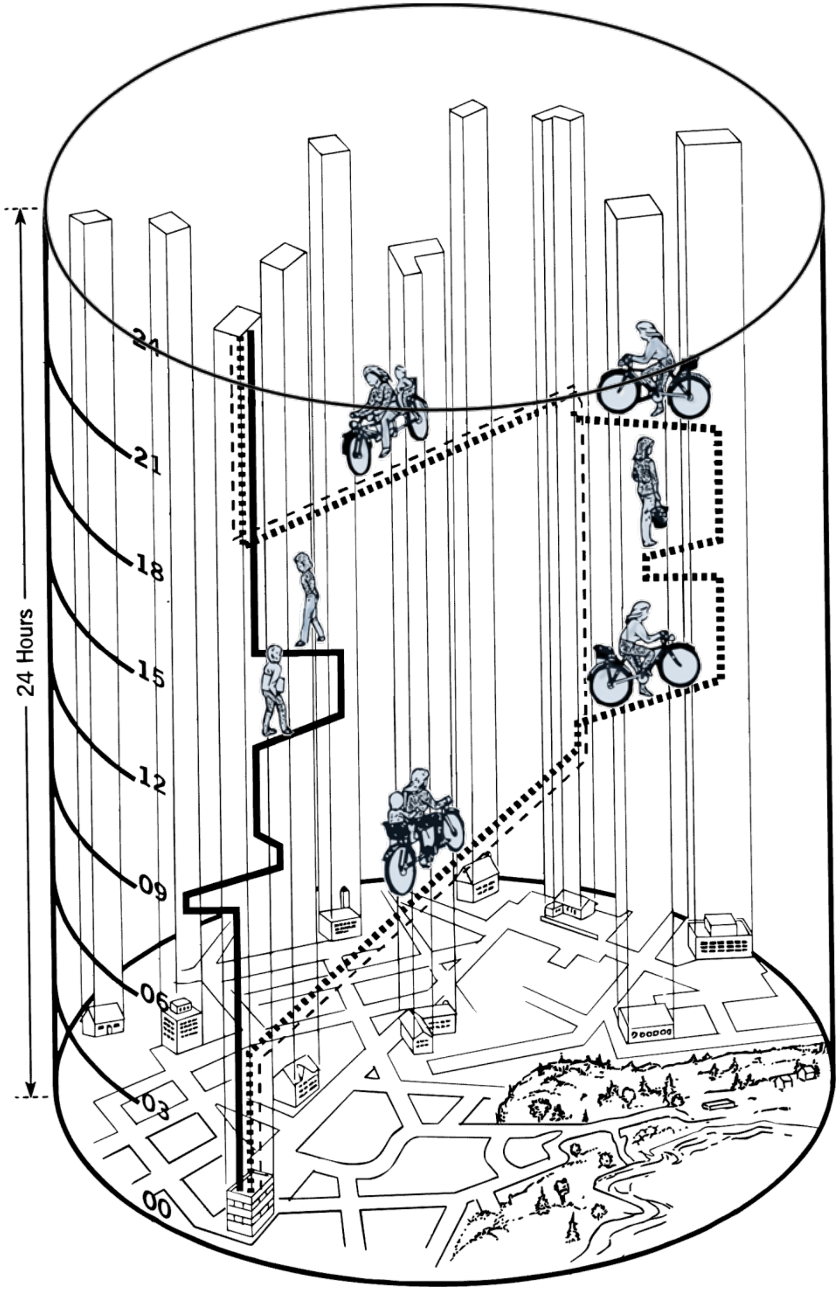


Airborne indoor pollutants include secondary contaminants formed through the interaction of ambient air constituents and indoor emissions

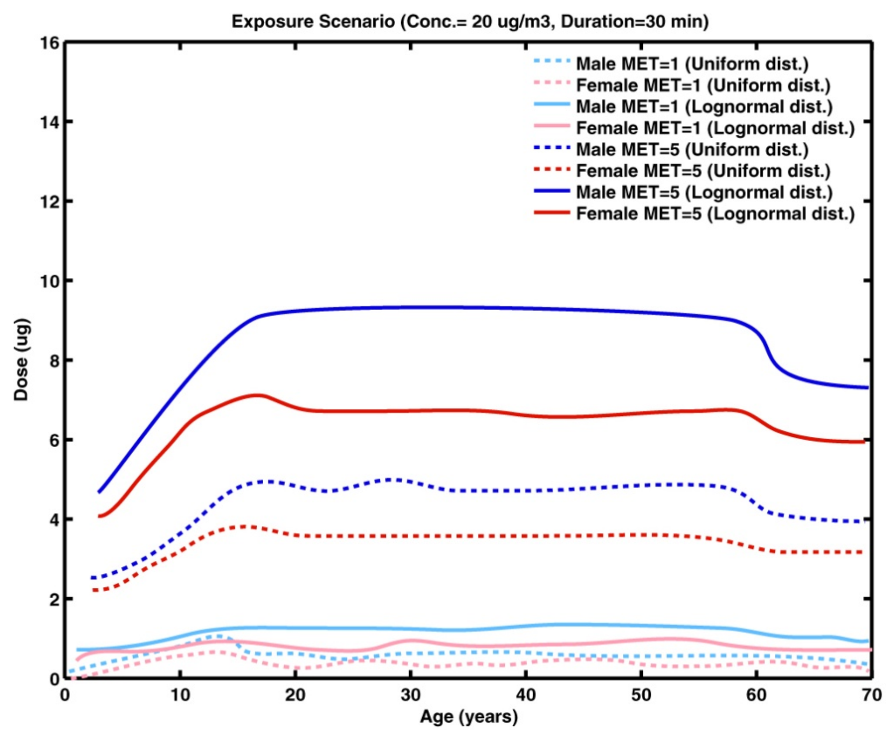


Exposure Factors and Exposure Biology: In addition to time and geographic location, factors such as: **dynamic microenvironmental attributes, demographics, behavior/activity, biological (physiological) characteristics,** etc. differentiate significantly the exposures and doses of individuals (and of selected subpopulations) that result from environmental (or emergency) events

Challenge: All relevant information must be integrated in a consistent/unifying framework (Spatiotemporal Exposure Information System)



People/Time/Space: Adapted from Parkes & Thrift (1980)



Example: Dependence of inhaled fine PM dose on gender, age, and activity (MET= Metabolic Equivalent of Tasks)

Interpretation of health outcomes requires consideration of individual susceptibility and population variability: There arises the need to couple Exposure Biology with Genomics

Sir Winston Churchill

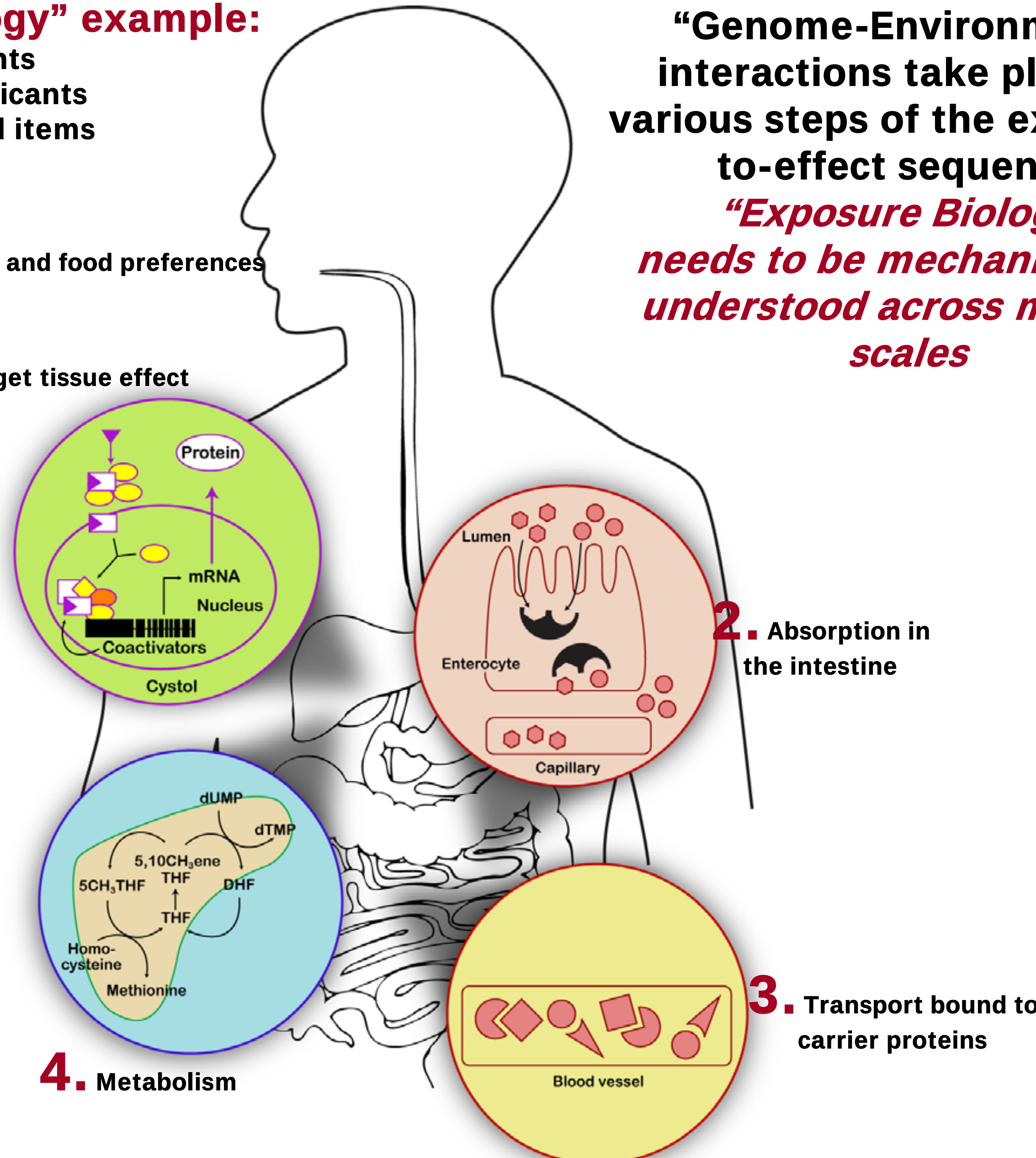
Dr. Jim Fixx

A general "Exposure Biology" example:

digestion of nutrients and environmental toxicants that are present in food items

"Genome-Environment" interactions take place at various steps of the exposure-to-effect sequence:

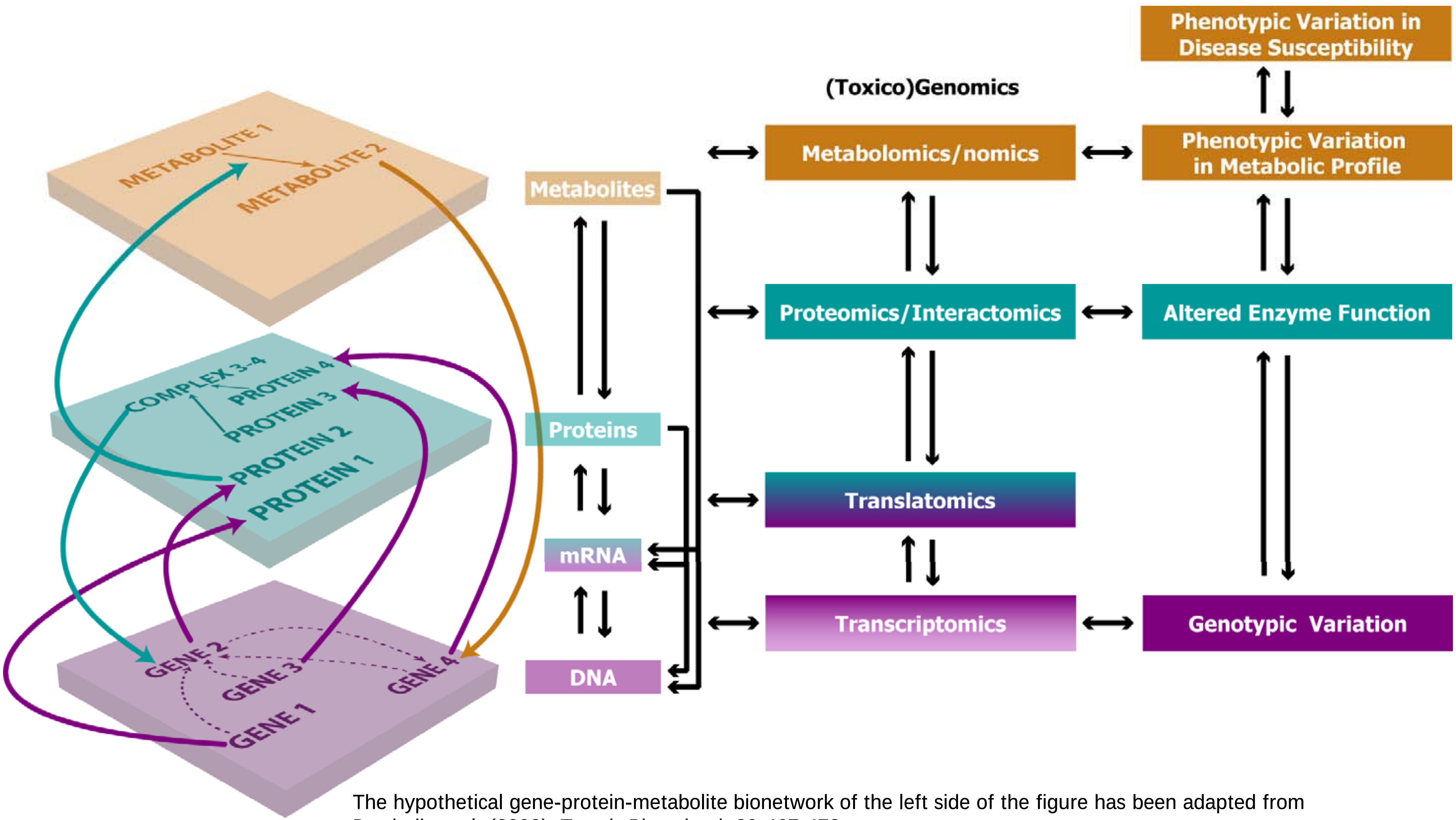
"Exposure Biology" needs to be mechanistically understood across multiple scales



Genes control processes affecting exposure, dose, toxicokinetics and toxicodynamics; however, extragenomic factors and development/aging may control genome dynamics

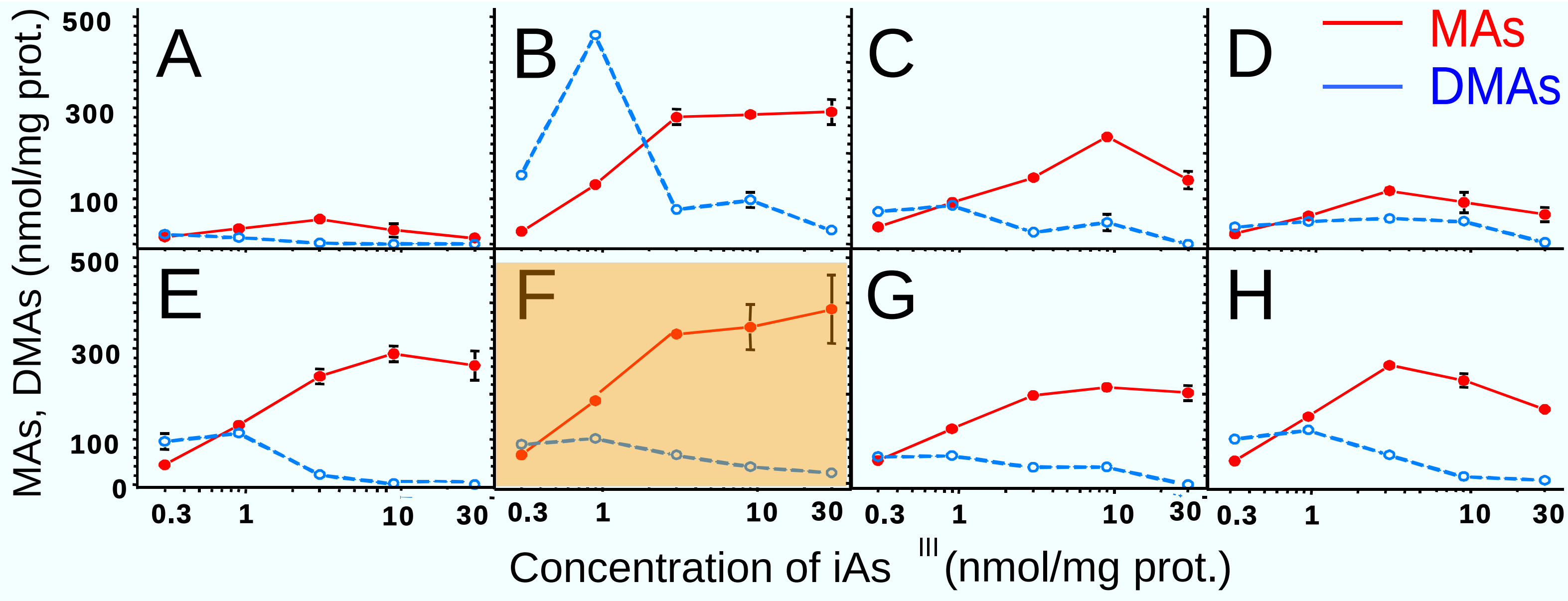
Schematic adapted from: Costa and Eaton (eds.) 2006 *Gene-Environment Interactions*

Connecting genotypes with phenotypes to assess toxicokinetic and toxicodynamic variability - and associated disease susceptibility - to environmental agents requires integrating data/information across multiple biological levels



The hypothetical gene-protein-metabolite bionetwork of the left side of the figure has been adapted from Brazhnik et al. (2002) *Trends Biotechnol*, *20*, 467-472

Human CYT19 (AS3MT) genotype and inter-individual variability in arsenic metabolism



Hepatocytes from 8 donors cultured in the presence of arsenite for 24 hours and metabolites determined in cells and medium.

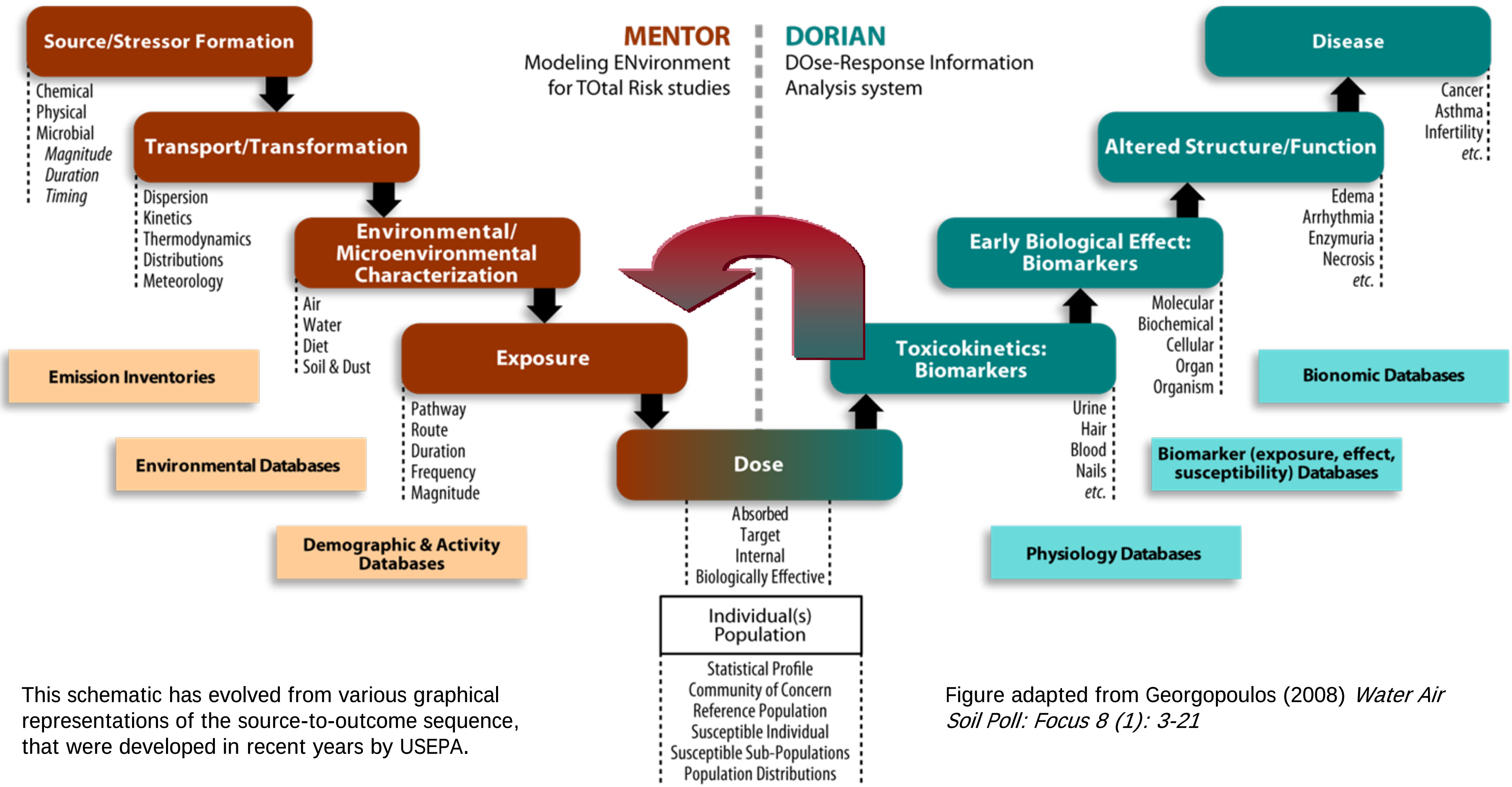
AS3MT is developmentally regulated and encodes a protein that functions both as an As^{III} methyltransferase and as an As^{V} reductase. Variation in this gene may translate to an altered methylation & reduction pathway, and therefore altered toxicity.

In-vitro studies like this one, and in-vivo data of arsenic metabolites in urine, are combined to construct “modeling hypotheses” of toxicokinetics, inter-individual variability, and toxicity.

Data from Drobna et al. (2004) *Toxicol Appl Pharmacol 201* (2): 166-177

Research to address the toxicant "Source-to-Effect Continuum" through development of an integrated, modular, computational framework

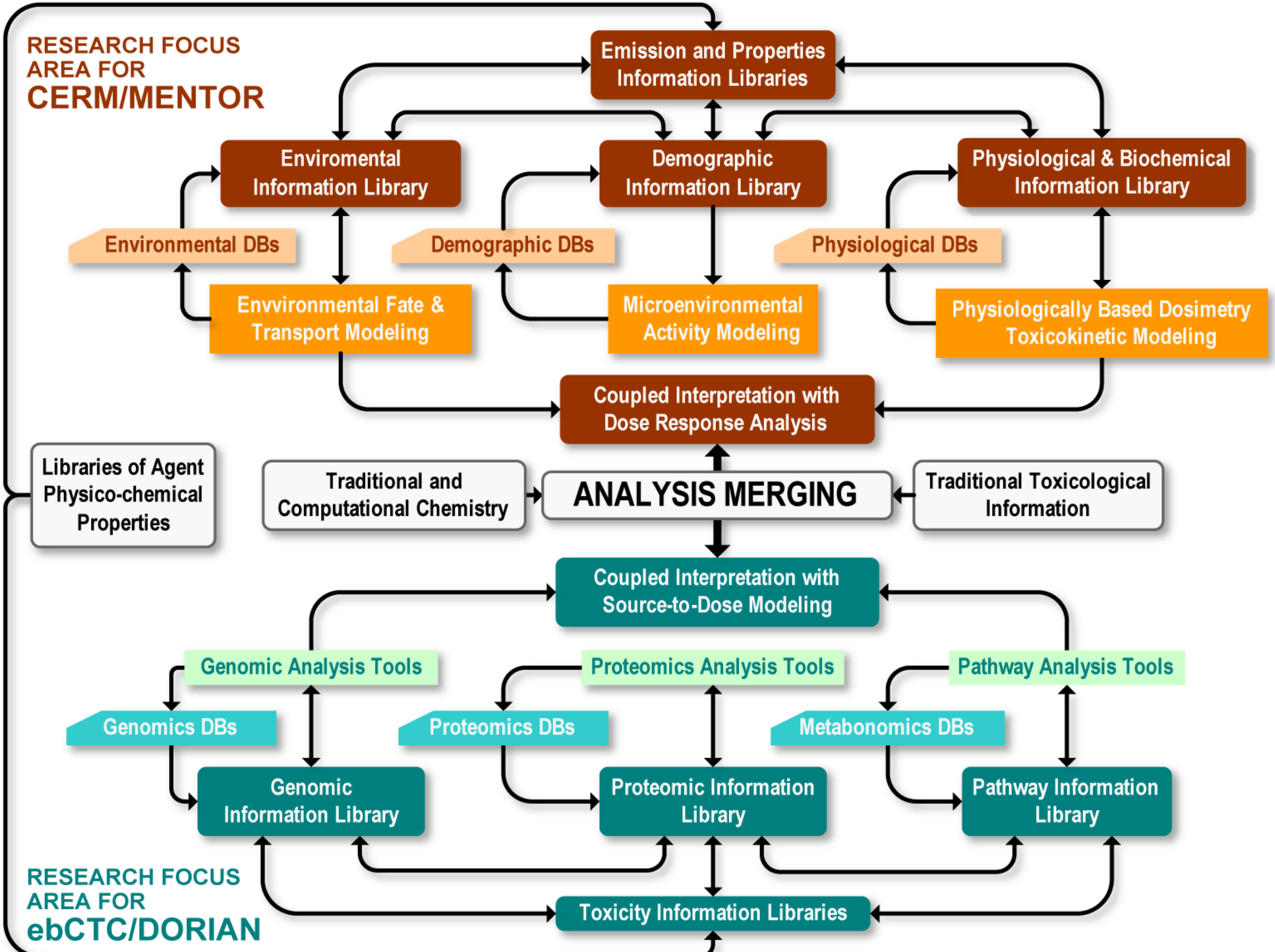
(CERM – development of MENTOR; ebCTC – development of DORIAN)



This schematic has evolved from various graphical representations of the source-to-outcome sequence, that were developed in recent years by USEPA.

Figure adapted from Georgopoulos (2008) *Water Air Soil Poll: Focus 8 (1): 3-21*

CERM: Center for Exposure and Risk Modeling
MENTOR: Modeling ENvironment for TOtal Risk studies (development started in 1993 with CDC funding; USEPA funding commenced in 1998)
ebCTC: environmental bioinformatics and Computational Toxicology Center
DORIAN: DOse-Response Information Analysis system (development started in 2006 with USEPA STAR funding; consortium of UMDNJ-RWJMS with Rutgers, Princeton and USFDA)

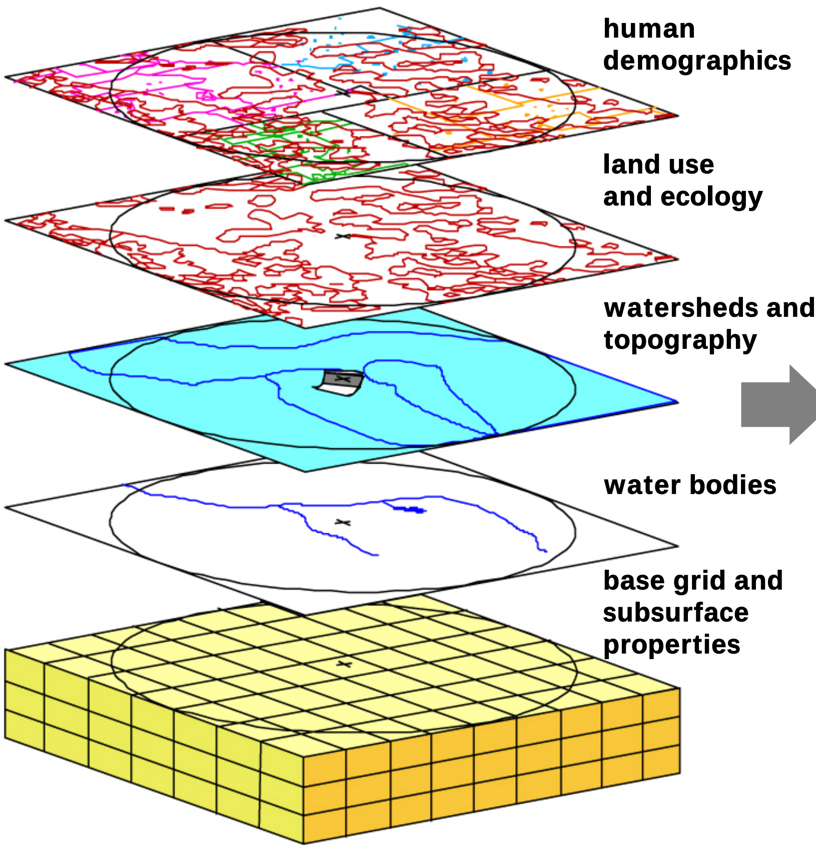


From Georgopoulos (2008) *Water Air Soil Poll: Focus 8 (1): 3-21*

A “sample” of on-going applications of MENTOR and DORIAN

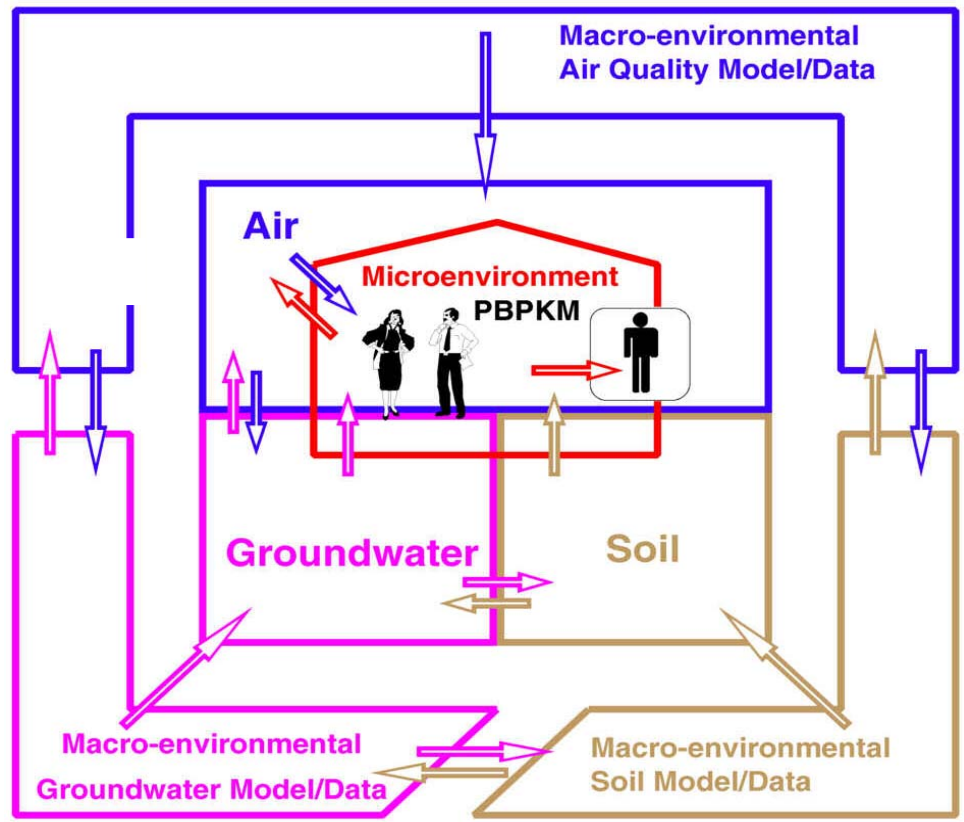
Air Contaminant Applications	Multimedia Applications
▪ regional/multiscale ozone and particulate matter (PM) control, ▪ urban/local/personal scale inhalation exposures to complex mixtures of co-occurring ozone, PM, other criteria pollutants, and air toxics, ▪ exposures to contaminant releases from forest and urban fires, ▪ exposures to contaminant releases from chemical facility accidents, ▪ exposures to bioaerosols (ranging from anthrax spores to birch and ragweed pollen), ▪ etc.	▪ exposures to mixtures of metals and metalloids (Hg, Cd, Cu, As, etc.) and their compounds, ▪ exposures to pesticides (organophosphates, pyrethroids, conazoles), ▪ exposures to organic solvents, ▪ exposures to water chlorination by-products, ▪ exposures to phthalates, ▪ exposures to PCBs and dioxin-like compounds, ▪ exposures to CWAs, ▪ etc.

MENTOR employs an "anthropocentric" (person-oriented) approach, linking multiple scales of macroenvironmental and local models and information with microenvironmental conditions and human activities in time / space



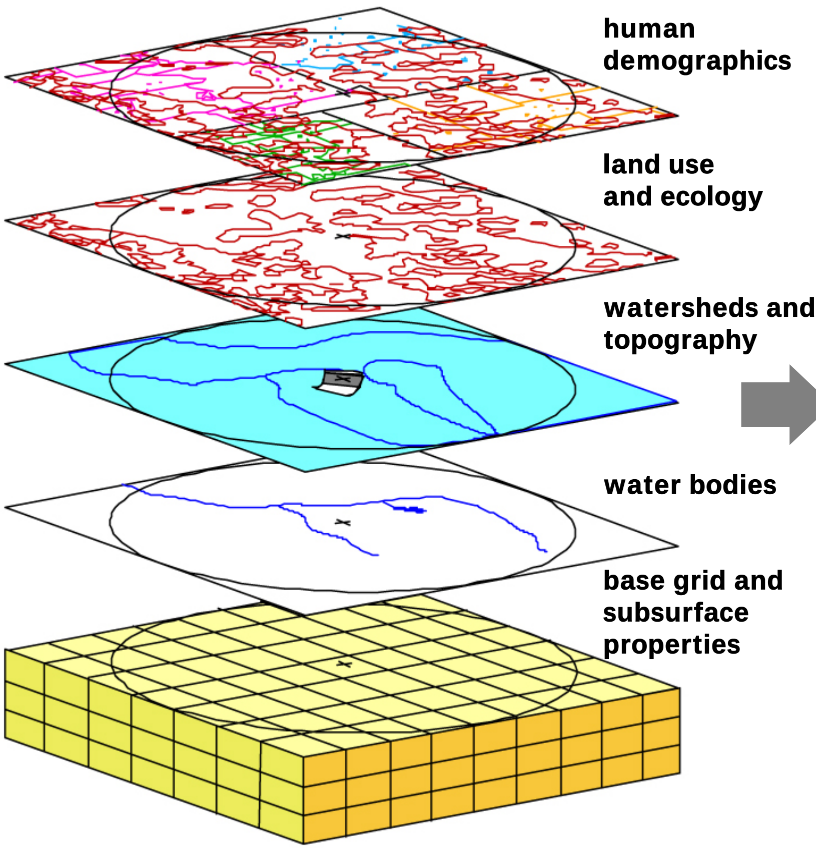
Source: 3MRA User Guide 2002

Microenvironmental / exposure / dose modeling system



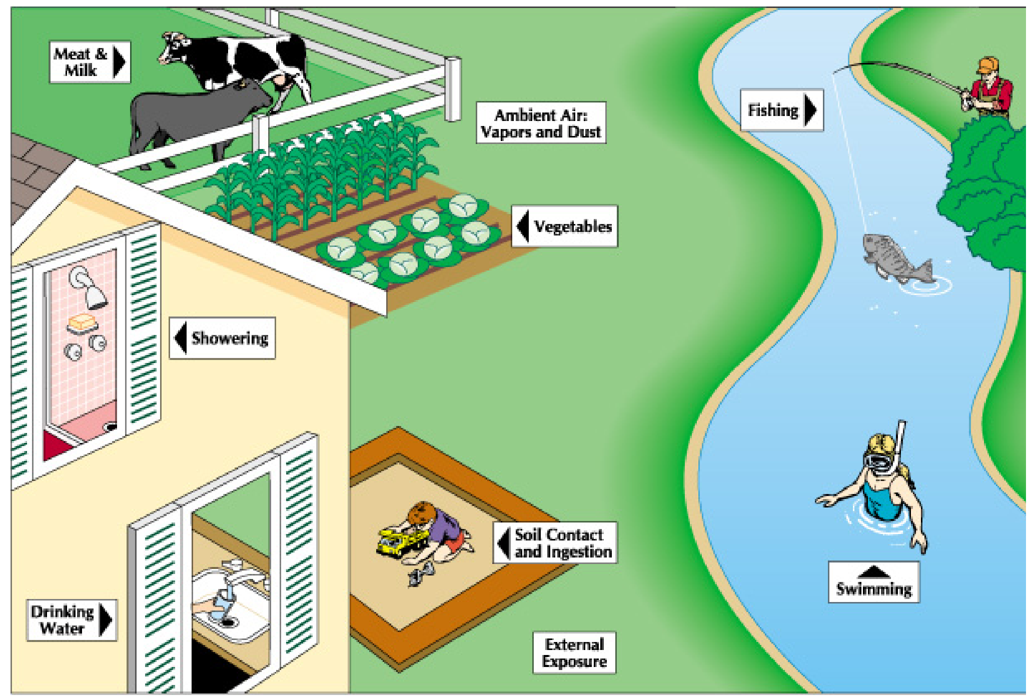
Source: Georgopoulos et al., ES&T, 1997, 31(1)

MENTOR employs an “anthropocentric” (person-oriented) approach, linking multiple scales of macroenvironmental and local models and information with microenvironmental conditions and human activities in time / space



Source: 3MRA User Guide 2002

Human activities determine pathways of exposure



Source: http://rivrisk.tetratech.com/inf_radionuclides.htm

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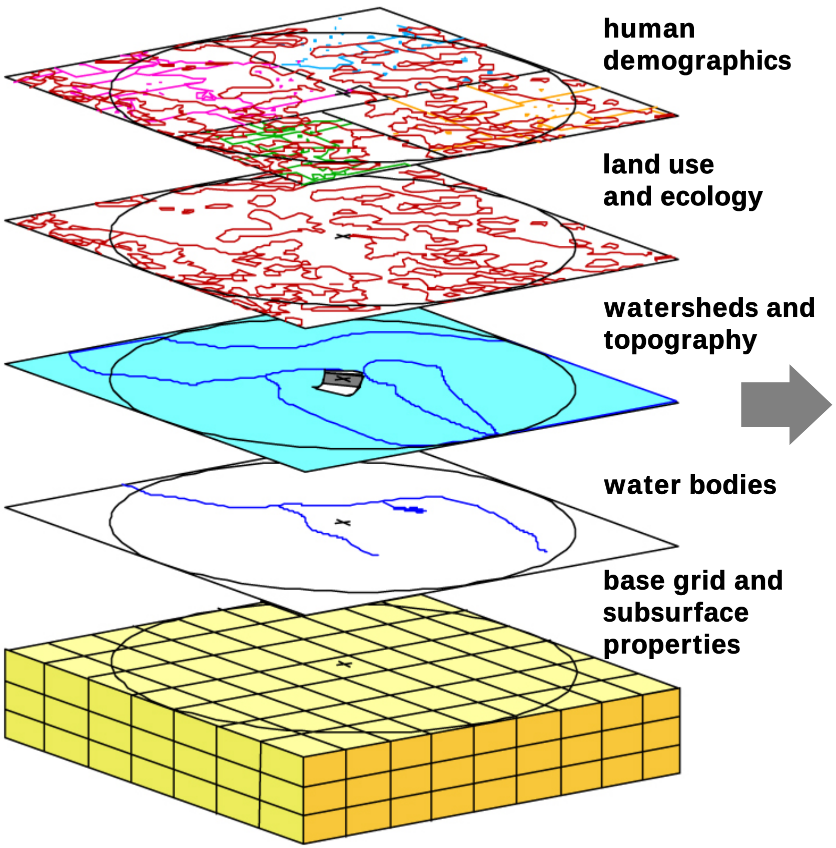


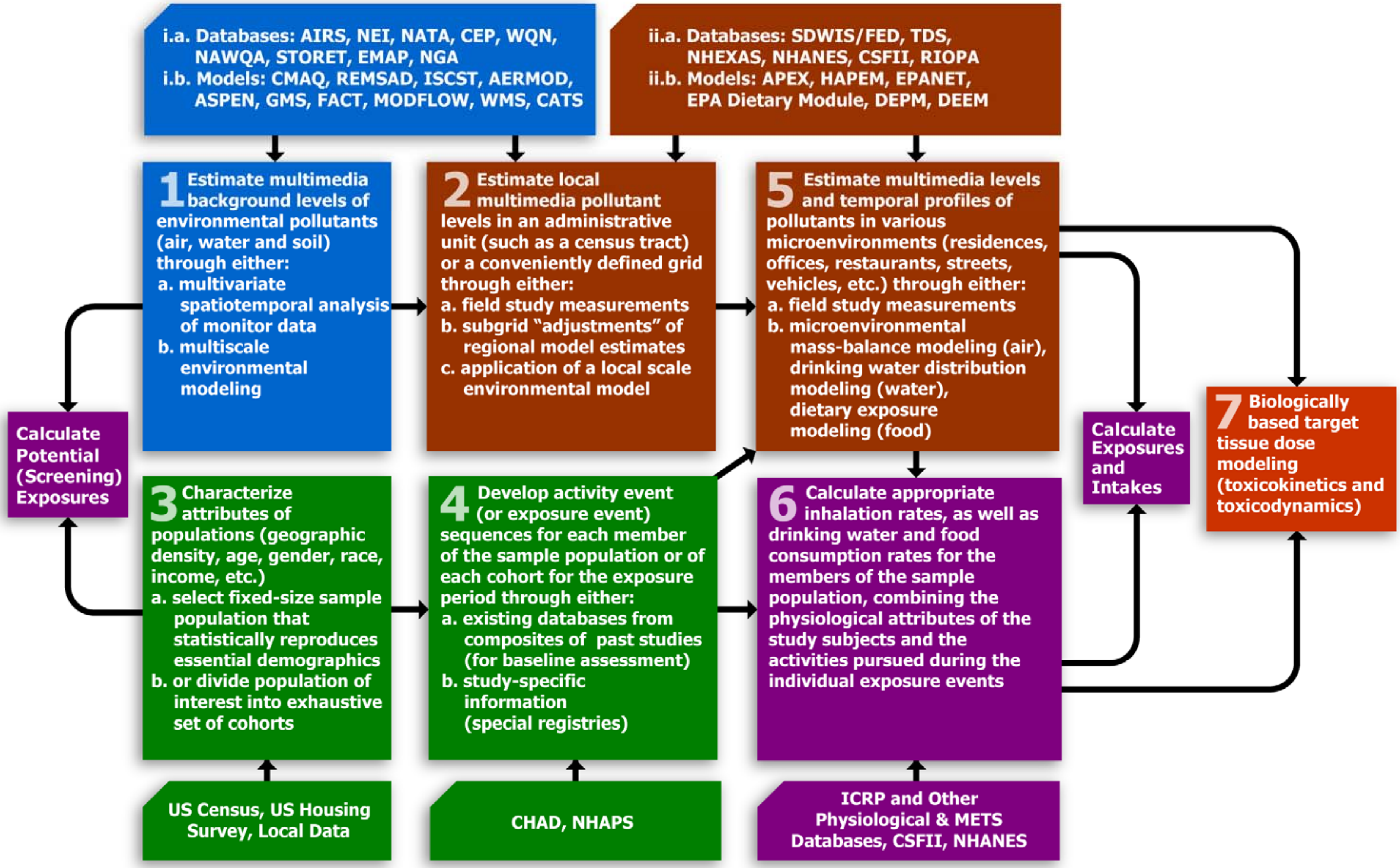
Source: 3MRA User Guide 2002

Human activities determine pathways of exposure

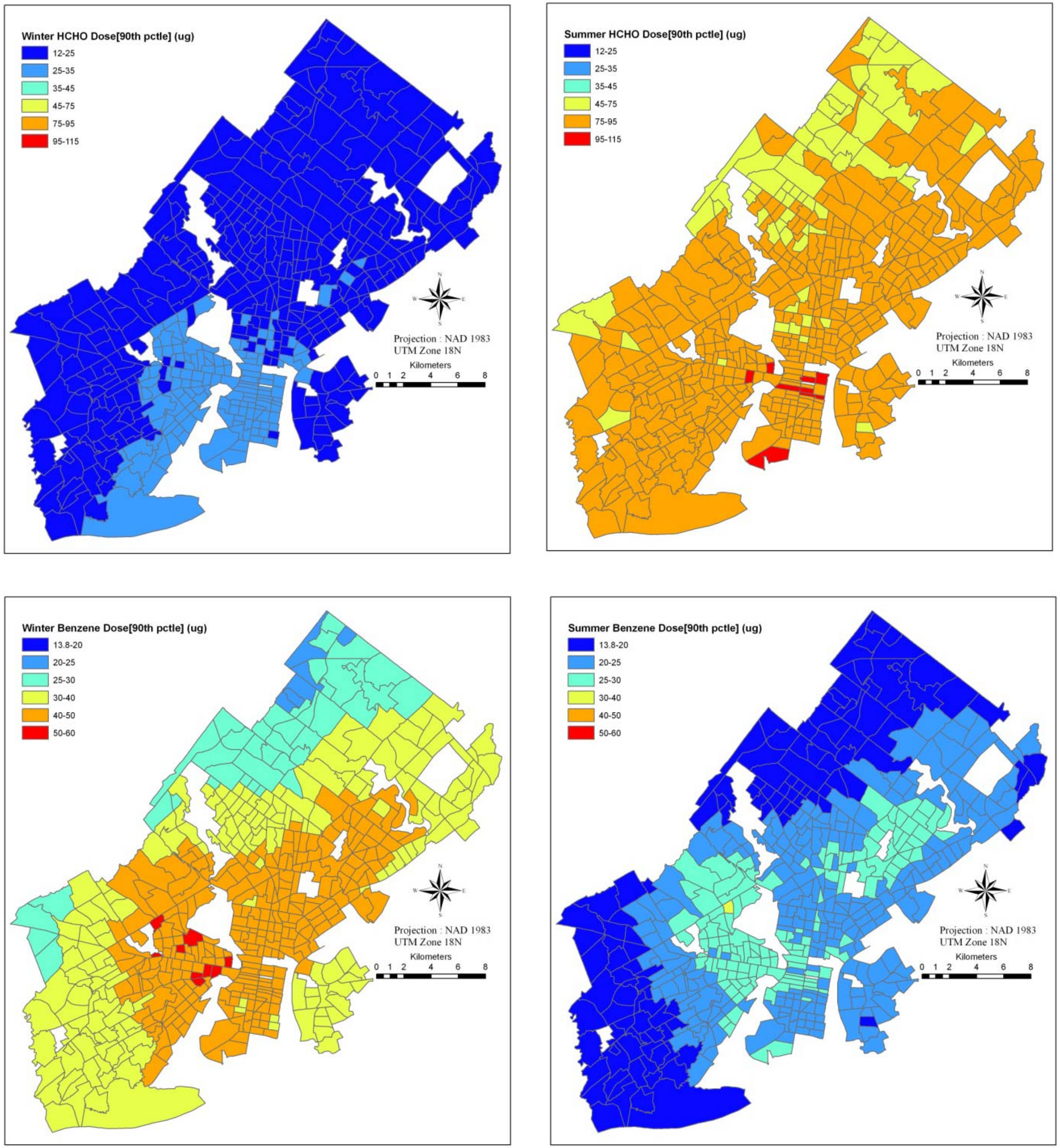
Please click to animate ^

Animation source: EA Games - The Sims™

The MENTOR modular framework for assessing cumulative/aggregate exposures and doses for multiple contaminants: it relies on a wide range of existing models and databases (environmental, demographic, behavioral, physiological, biomarker, etc.)



MENTOR-1A estimates of the 90th percentile of seasonal averages of daily personal formaldehyde (top) and benzene (bottom) intake ("dose") (μg) due to outdoor air for Winter and Summer of 2001



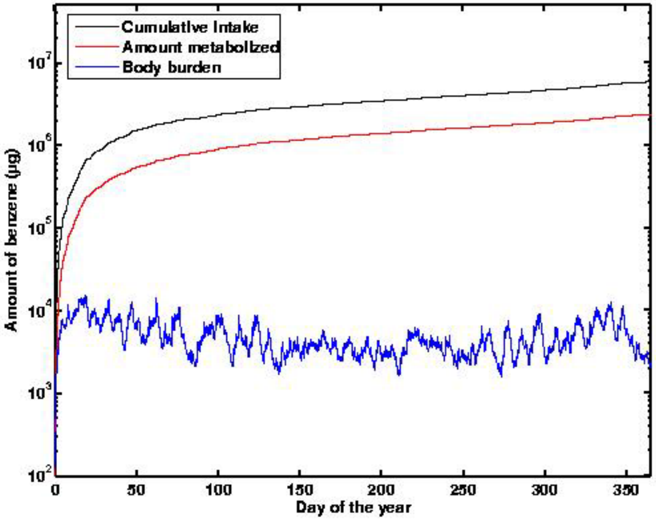
Formaldehyde

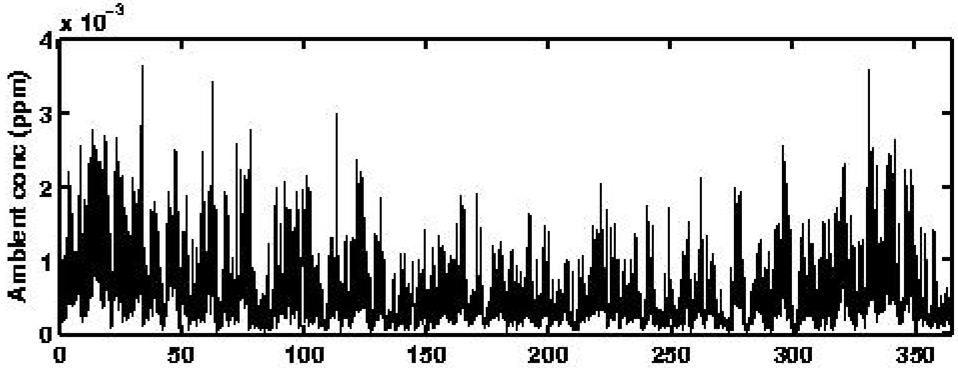
Benzene

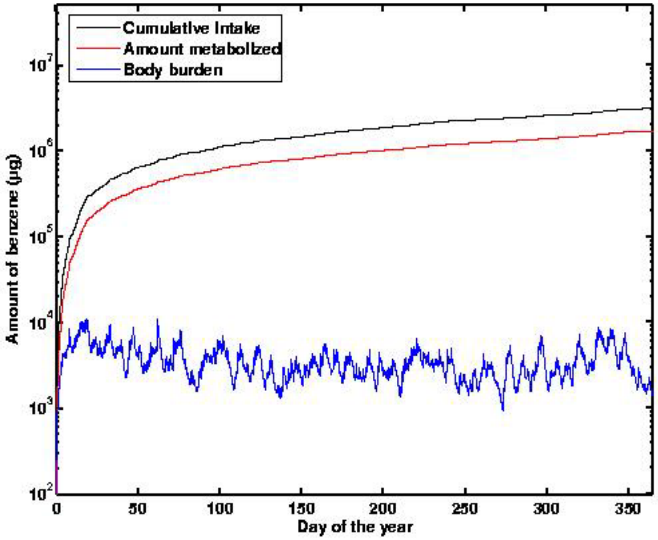
Winter

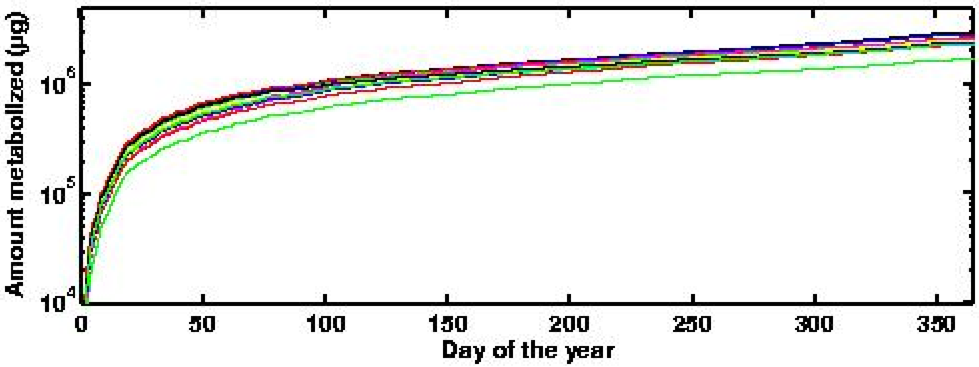
Summer

Example application of the PBTK modules of MENTOR: year-long benzene intake, body burden time series, and biologically effective dose for "virtual individuals" sharing location and similar physiological attributes (variability due to activities sequences)

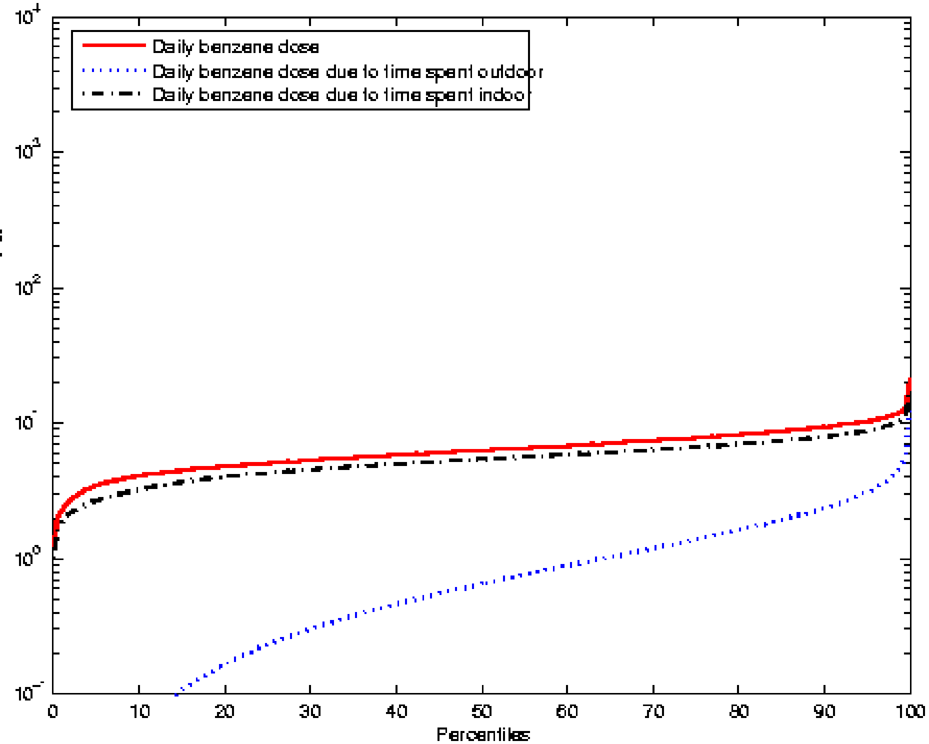




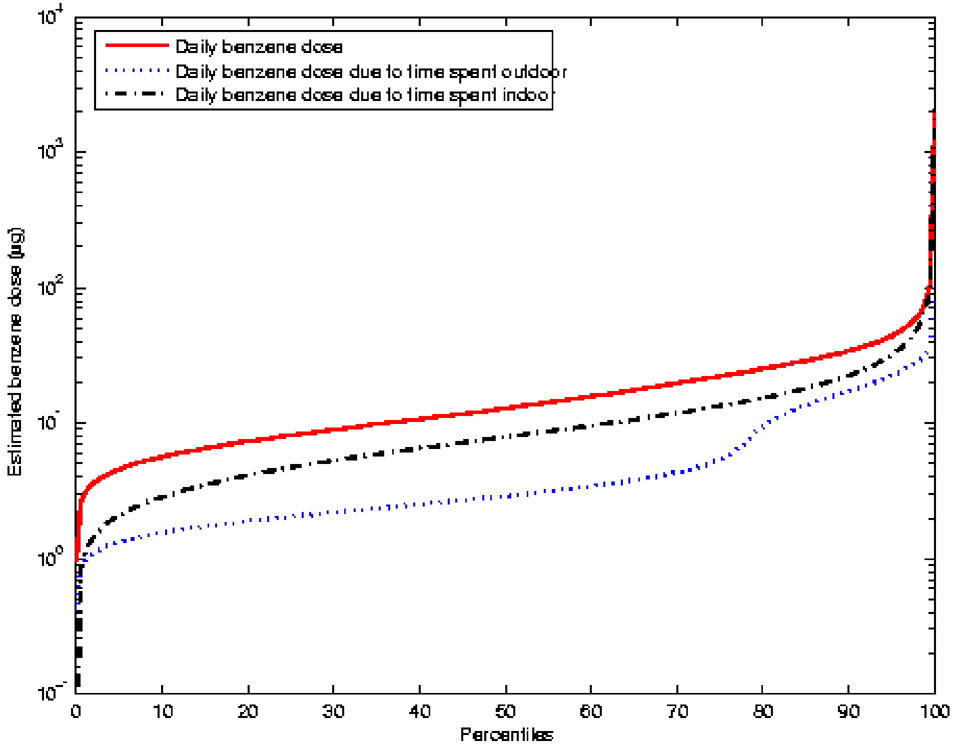




Example "diagnostic" simulations: Comparison of population benzene doses with/without roadway adjustments, commuting and indoor sources (cigarettes, garage emissions, wood parquet)

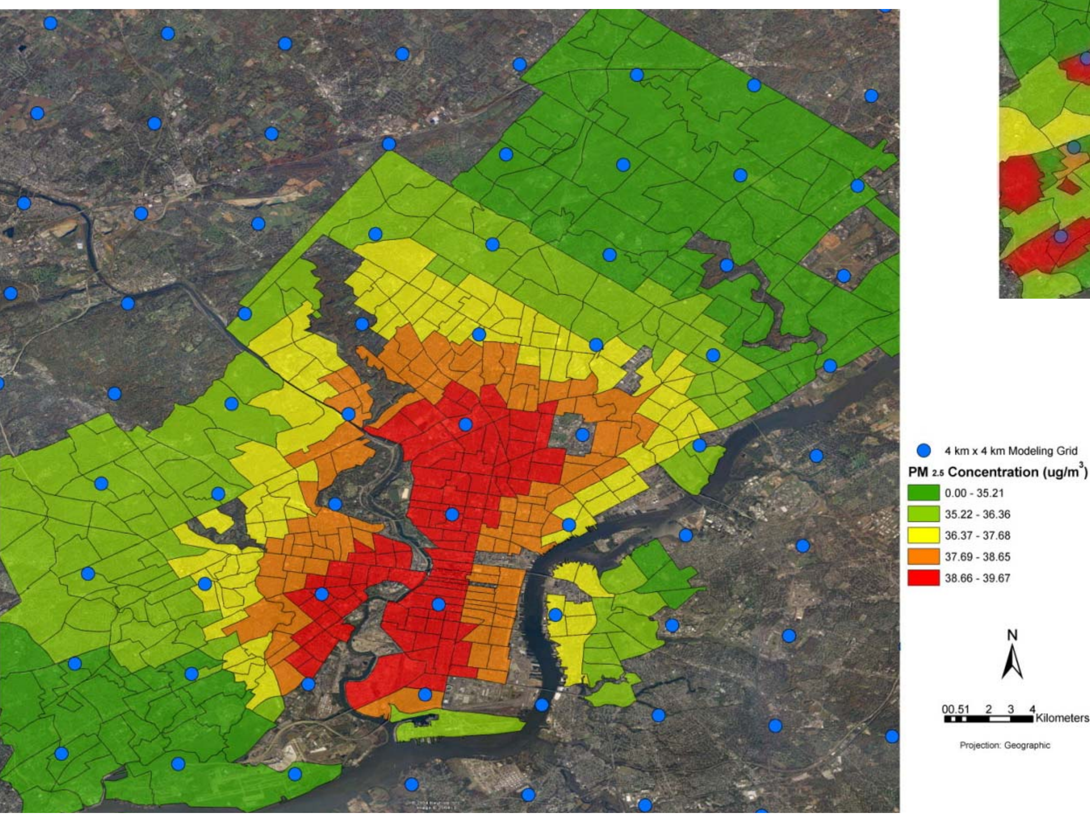


No commuting, no indoor sources, no roadway adjustments



Commuting population, indoor sources, and roadway adjustments

Example of urban/local scale results from a MENTOR-1A application employing CMAQ and "data fusion": comparison of PM 2.5 outdoor concentrations with the 95th percentiles of 24-hour PM 2.5 total dose for 7/19/1999 across the Philadelphia, PA and Camden, NJ area

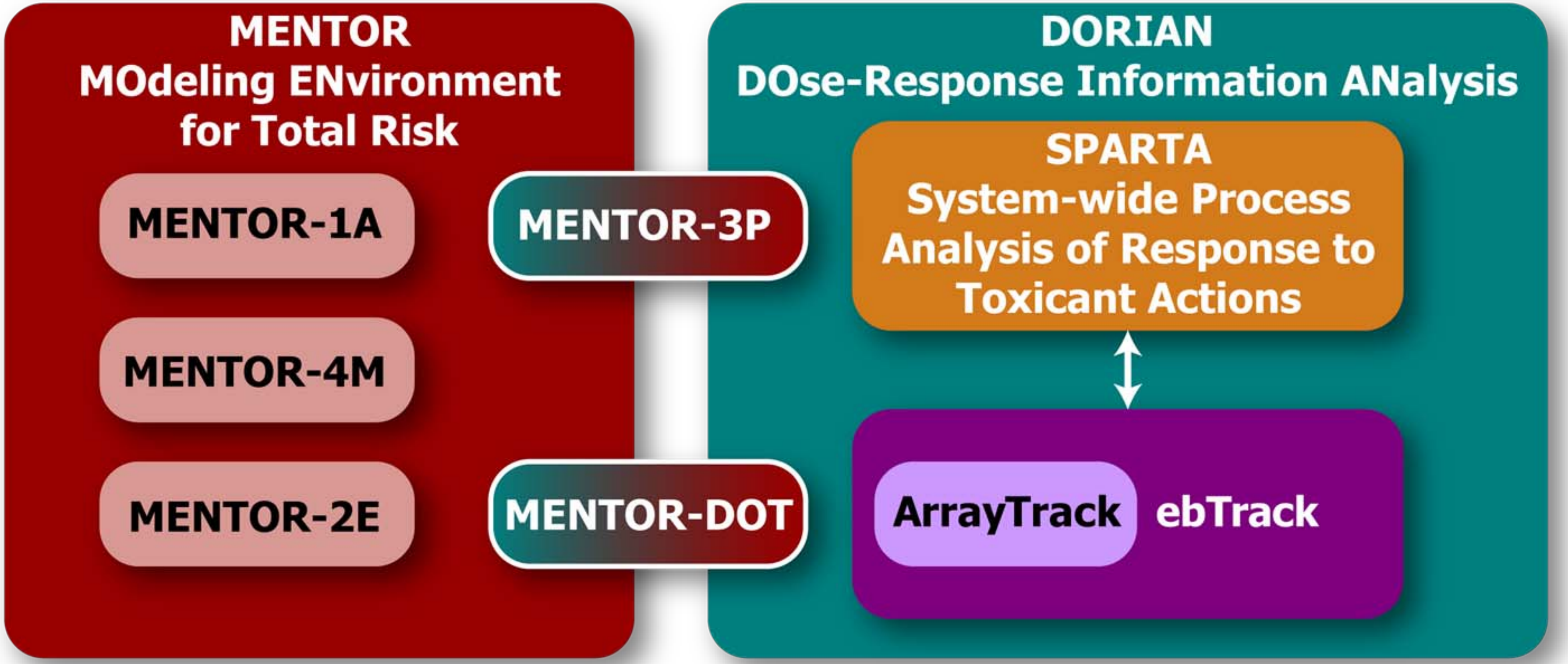


MENTOR-1A: MENTOR-"One Atmosphere"

CMAQ: Community Multiscale Air Quality Model

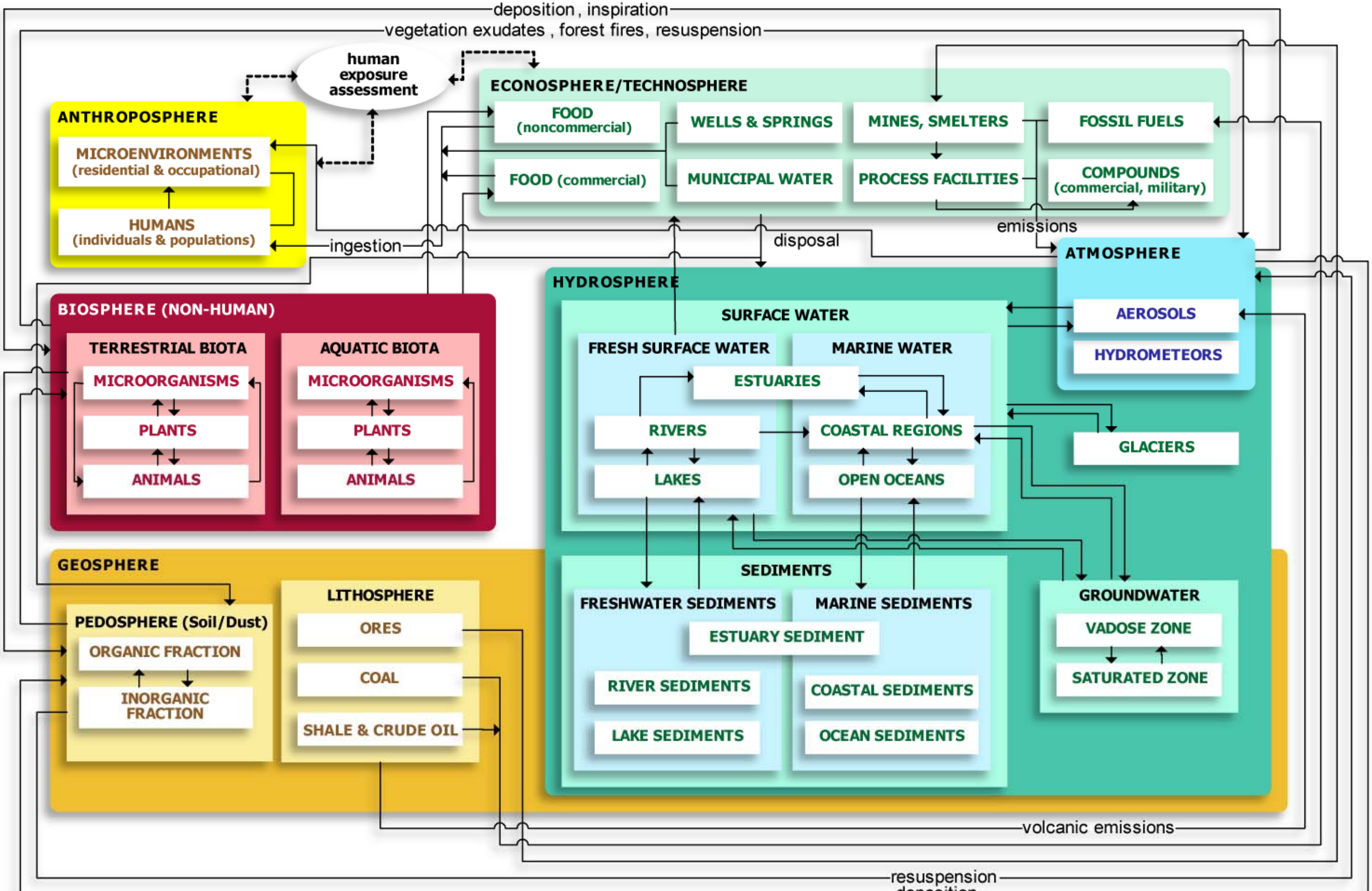
From Georgopoulos (2008) *Water Air Soil Poll: Focus 8 (1):* 3-21

Outcomes of the parallel MENTOR and DORIAN development efforts are "research-oriented" computational toolboxes that provide modules supporting consistent environmental / biological modeling



3P: physiological population pharmacokinetics
DOT: diagnostic and optimization tools
1A: "one atmosphere"
4M: multimedia, multiroute, multipathway, multicontaminant

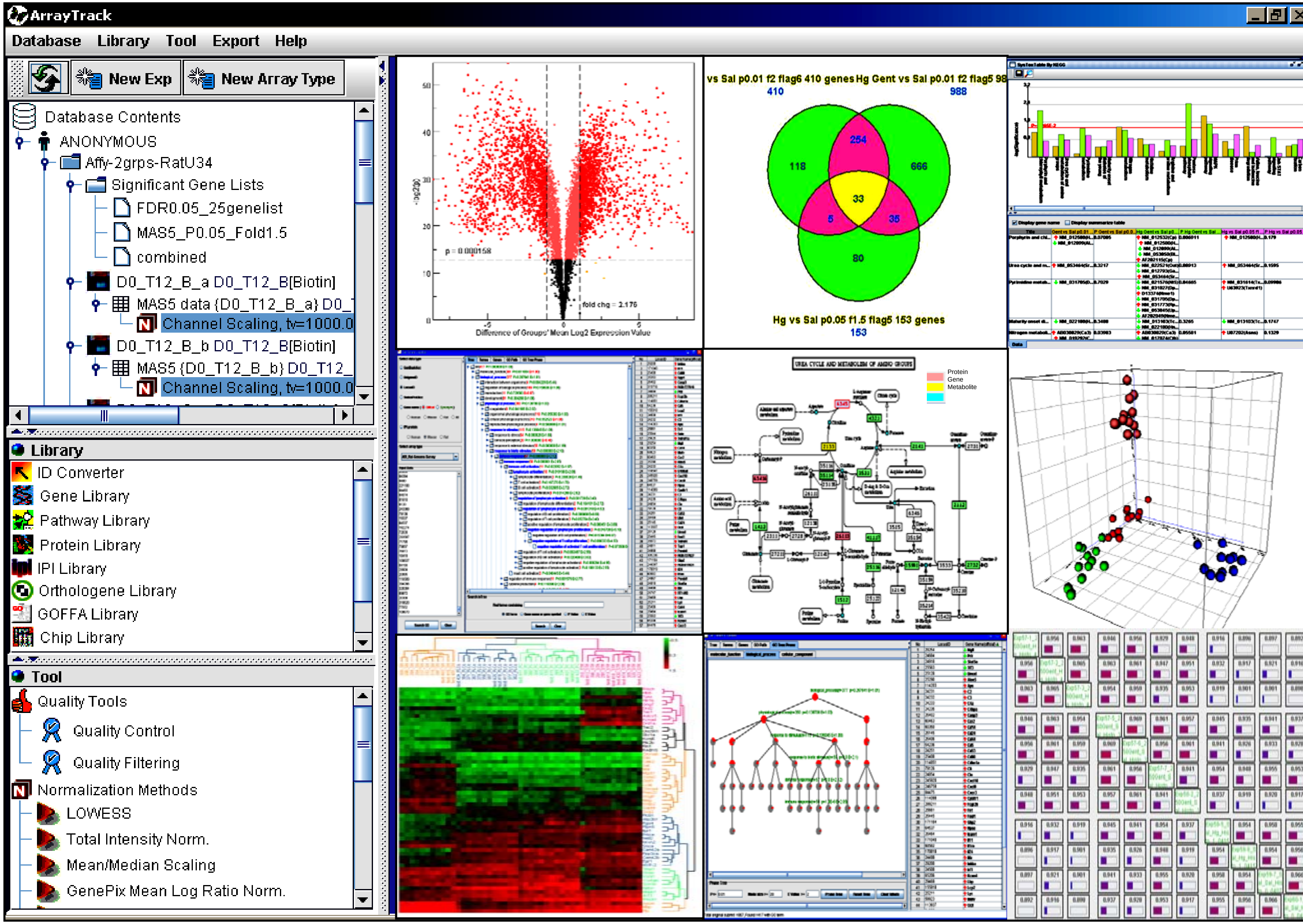
MENTOR-4M provides a unified multimedia / multiscale / multipathway modeling approach to support aggregate / cumulative exposure assessments



From Georgopoulos (2008) *Water Air Soil Poll: Focus 8 (1):* 3-21

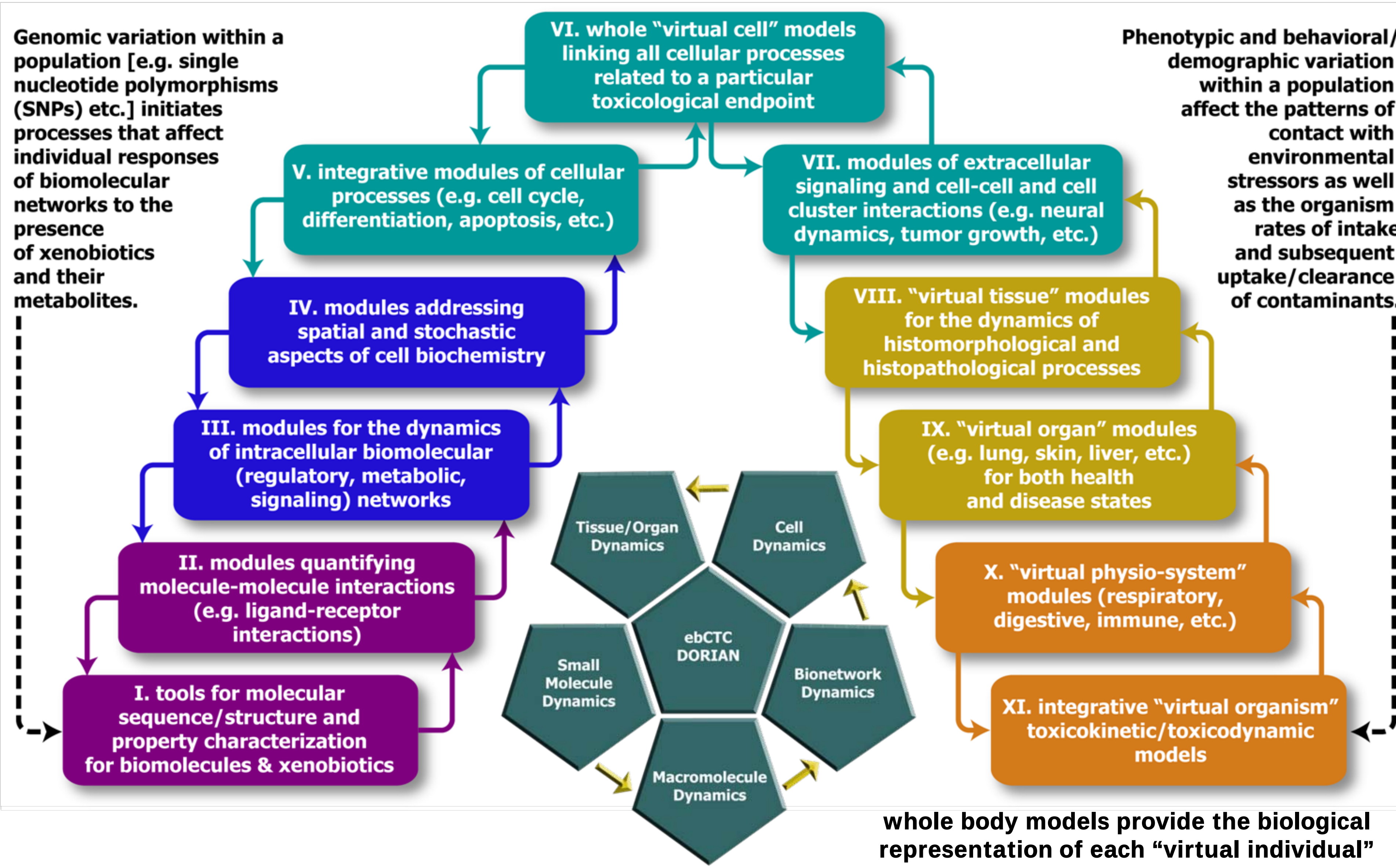
ebTrack* is a "research platform" that expands FDA ArrayTrack's features with tools for the analysis of "bionetwork perturbation data"

www.fda.gov/nctr/science/centers/toxicoinformatics/ArrayTrack/



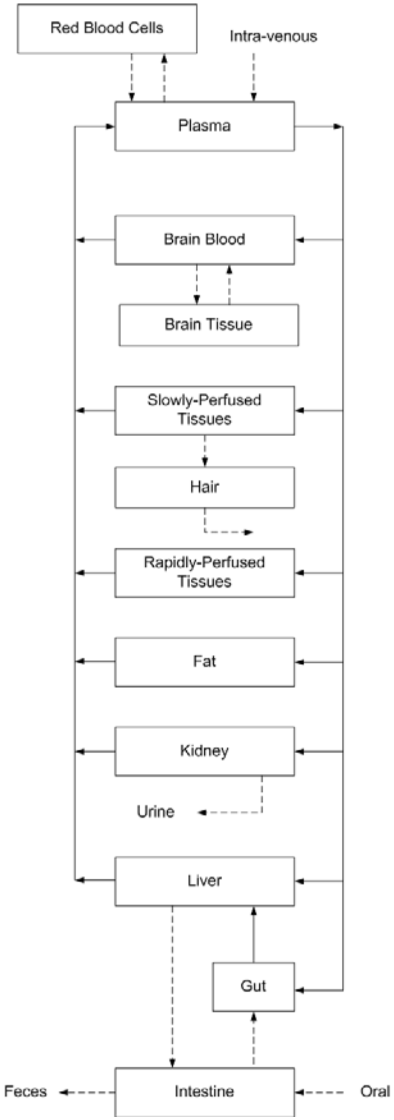
*Chen et al. (2009) ebTrack: an environmental bioinformatics system built upon ArrayTrack. *BMC Proceedings 3 (Suppl 2): S5.*

The Systemwide Process Analysis of Response to Toxicant Action (SPARTA) project aims to provide in the long-term a general, modular, framework supporting multiscale Biologically-Based Dose-Response (BBDR) Modeling

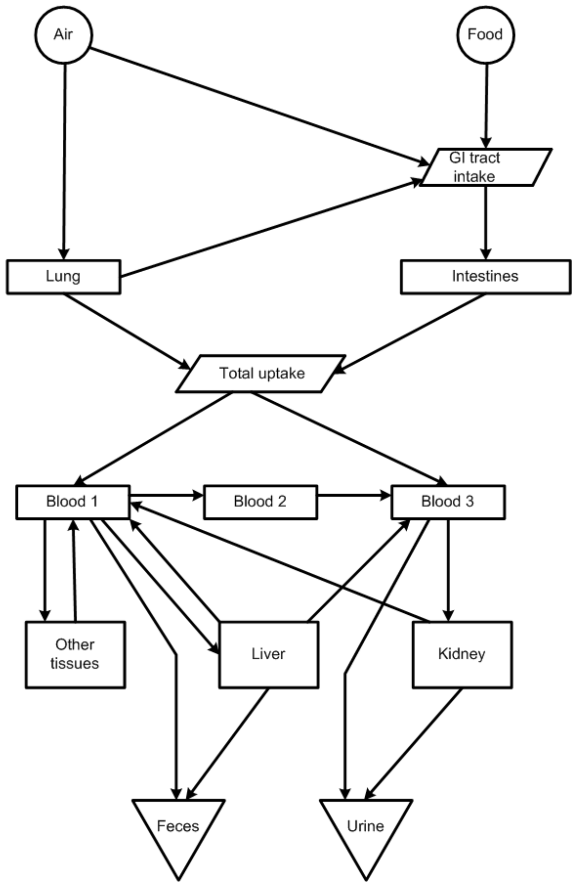


whole body models provide the biological representation of each "virtual individual" in the exposure and risk analysis

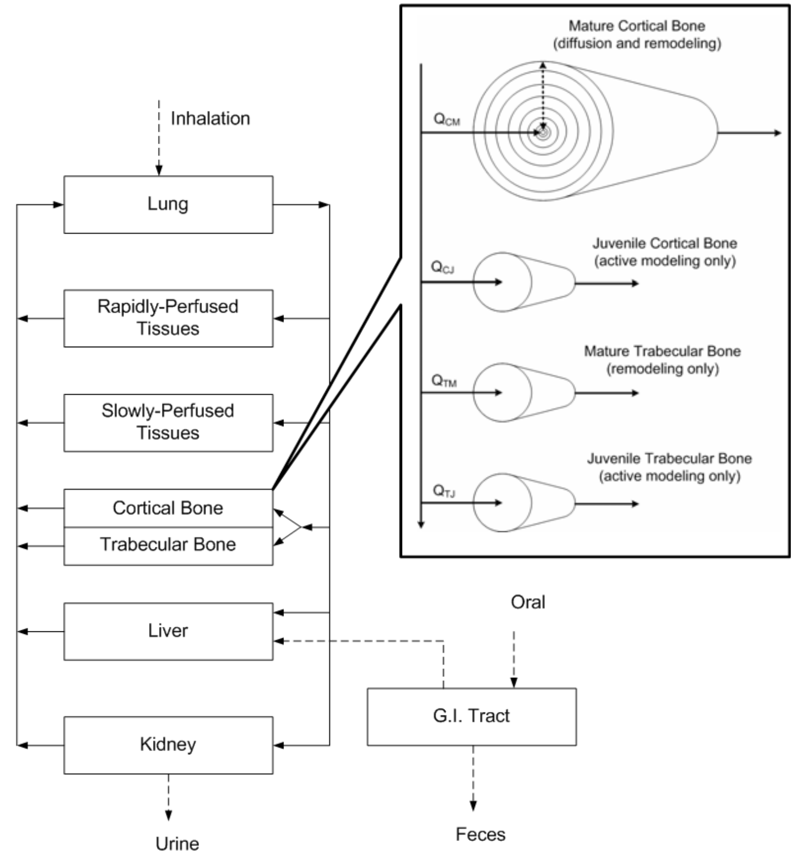
“Real world” environmental health risks involve exposures to multiple co-occurring contaminants via a variety of routes and pathways; however “traditional” PBTK models are designed for single contaminants and their structure and organ/tissue representations are “contaminant-specific”



Methylmercury
Shipp, et al. (2000) *Toxicol Ind Health 16*, 335-438

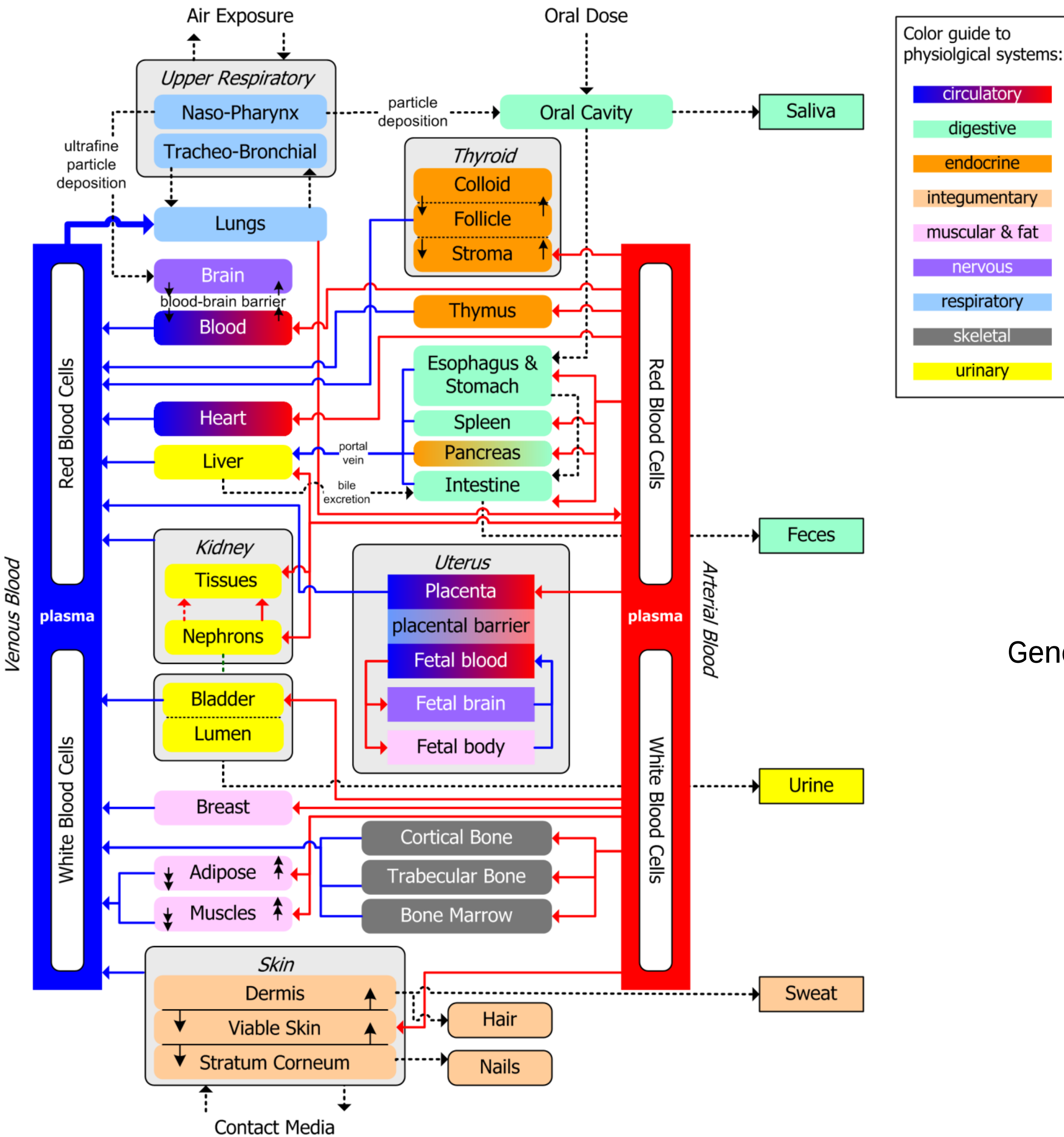


Cadmium
Kjellstrom and Nordberg (1978) *Environ Res 16*, 248-69)



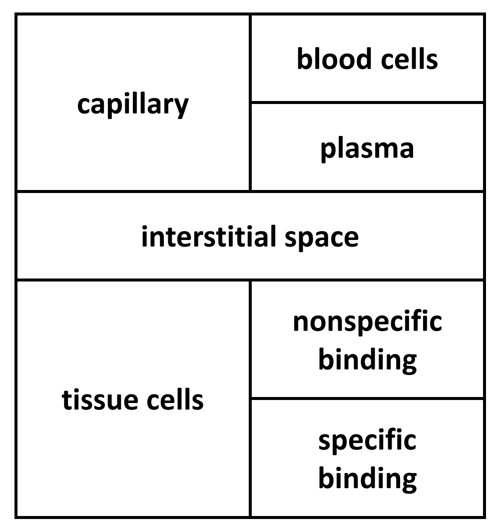
Lead
O'Flaherty (1993) *Toxicol Appl Pharmacol 118*, 16-29

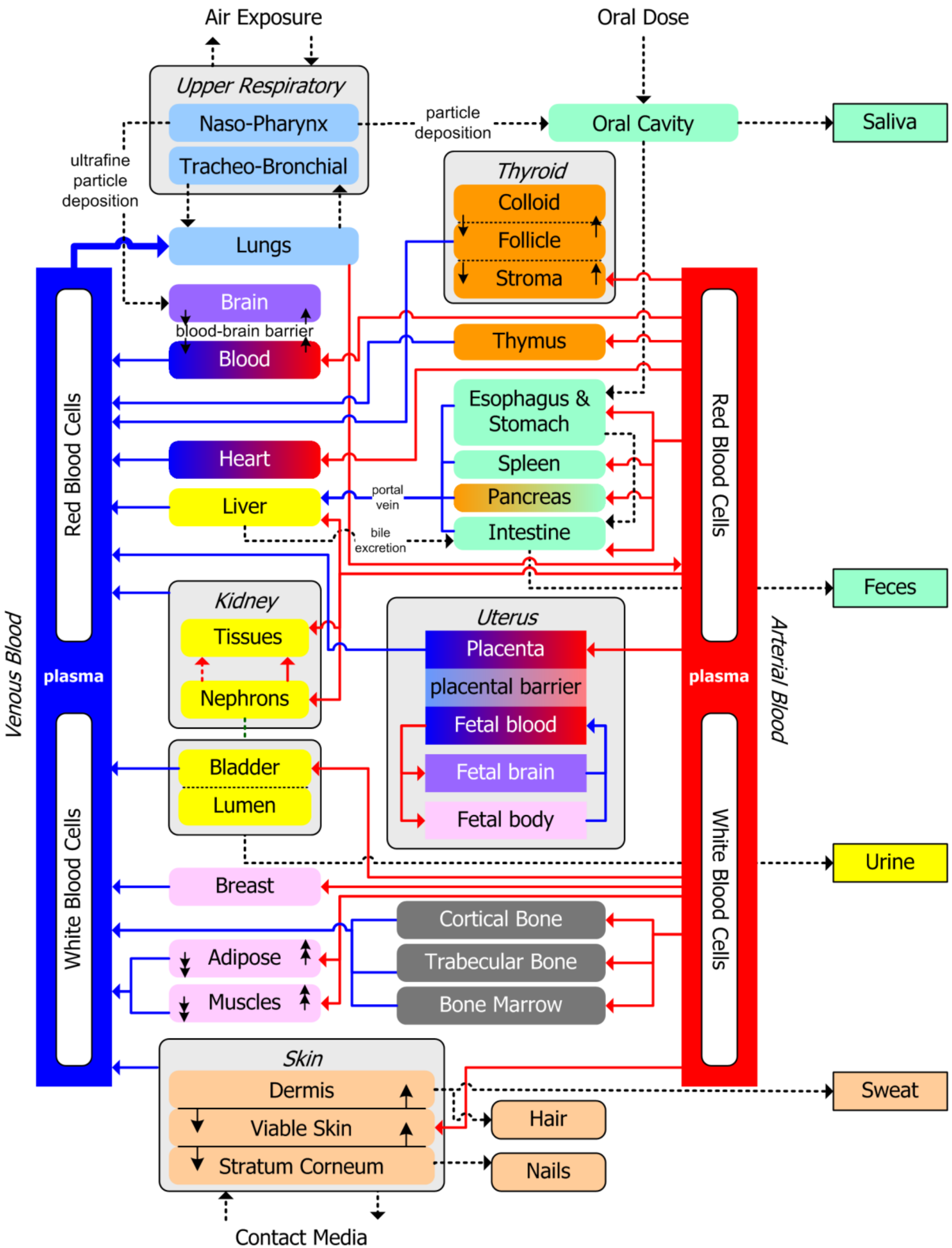
Example: Existing PBTK models for metals have different mechanistic structures due to differences in dominant transport processes. These structures are often inconsistent with each other. Nevertheless, the "multi-component" nature of exposures to metals and their compounds, and the presence of potentially significant metal-metal interactions, highlight the need for simultaneous and consistent toxicokinetic modeling of these chemicals.



MENTOR-3P / DORIAN provide a new modular "whole body" platform for consistent characterization of multicontaminant toxicokinetic and toxicodynamic processes in individuals and populations; it provides links with physiology databases to account for intra- and interindividual variation and variability

Generic compartmental substructure

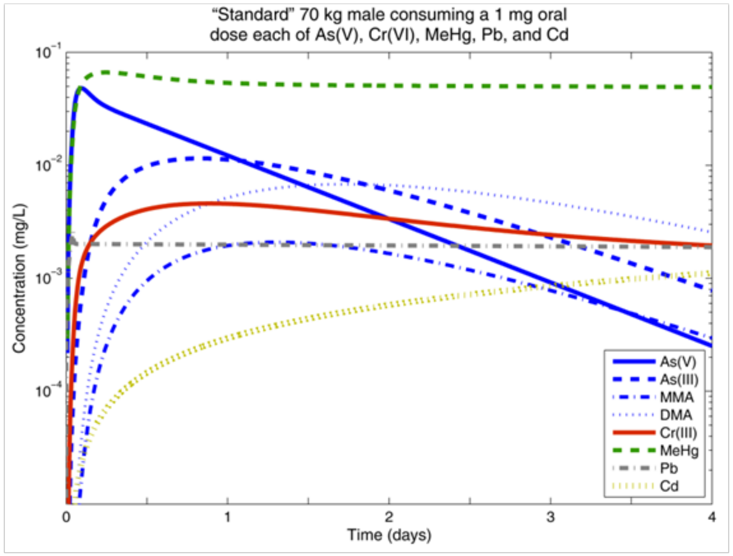




Color guide to physiolgical systems:

- circulatory
- digestive
- endocrine
- integumentary
- muscular & fat
- nervous
- respiratory
- skeletal
- urinary

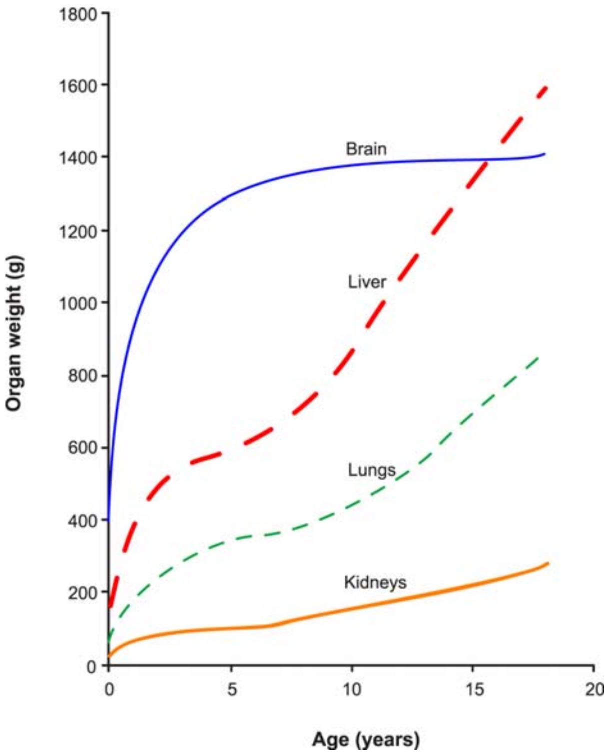
MENTOR-3P/DORIAN provide a new modular "whole body" platform for consistent characterization of multicontaminant toxicokinetic and toxicodynamic processes in individuals and populations; it provides links with physiology databases to account for intra- and interindividual variation and variability



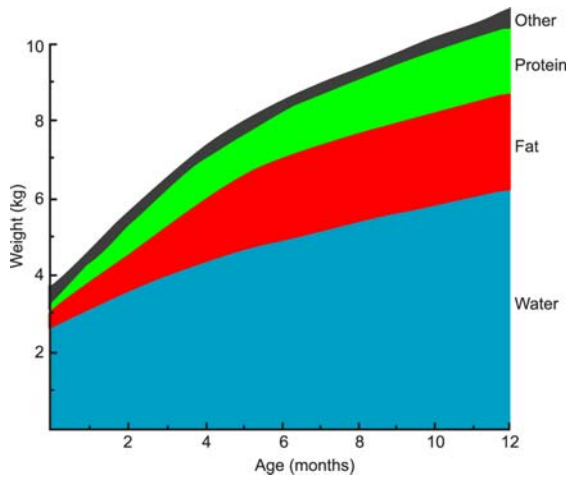
Simulated concentration profile of chemicals and metabolites in the liver of a standard reference male ingesting a mixture of metals.

Source: Georgopoulos (2008) *Water Air Soil Poll Focus 8:* 3-21

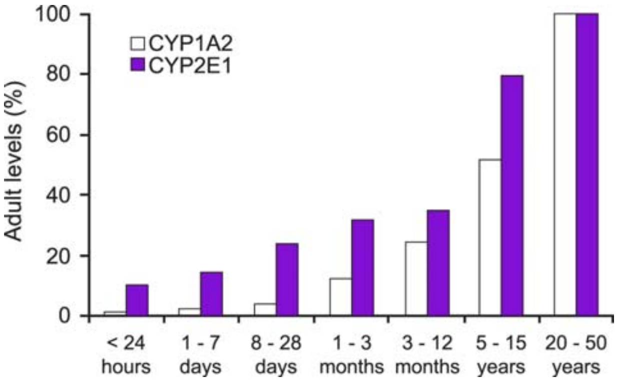
Individual and population human biology (physiology and biochemistry) changes non-uniformly with development, aging, disease, drug treatment, diet, environmental exposures, etc.



Organ weight from birth to adolescence in boys (based on Haddad et al. 2001)



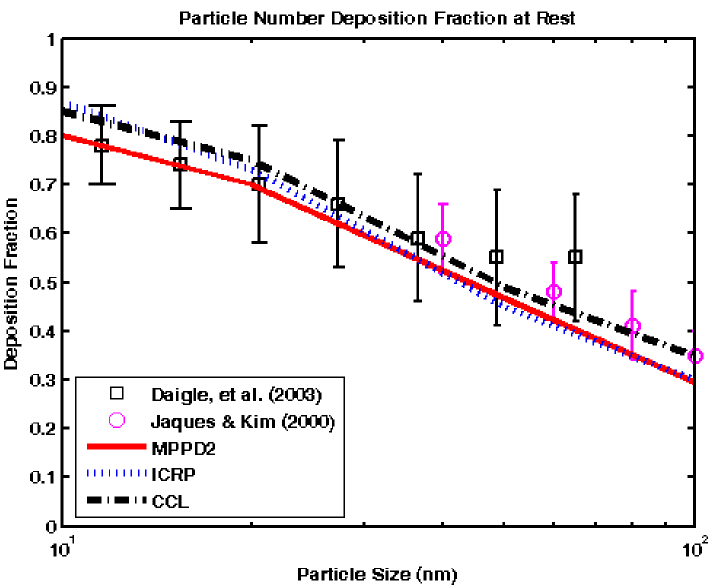
Weights of water, fat, protein, and other components as a function of age, from birth to one year of age. [Figure reproduced from Fomon (1966) with permission from W.B. Saunders Co.]



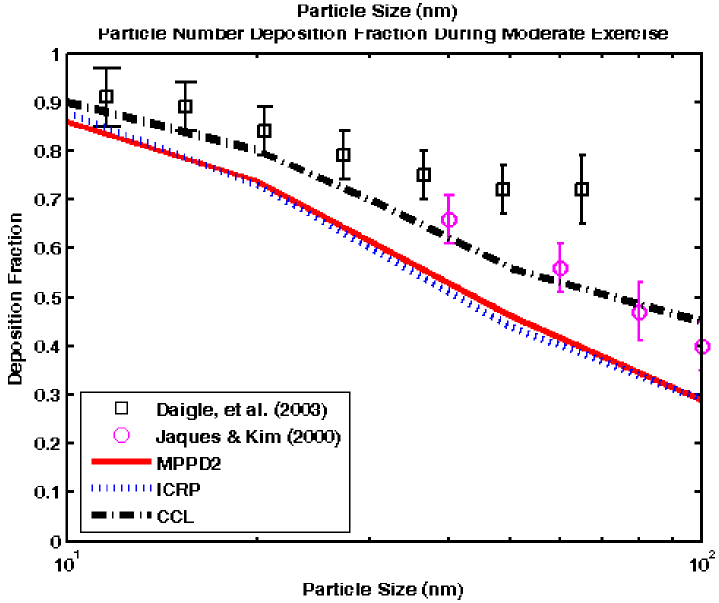
Hepatic cytochrome CYP1A2 and CYP2E1 in children of various age groups as a percentage of adult weights (from Cresteil, 1998).

from: WHO (2006). Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals. World Health Organization. Environmental Health Criteria 237

MENTOR-3P offers a “whole organism” modular platform for incorporating organ/tissue representations at various levels of detail (on-going projects focus on lung, skin and liver)

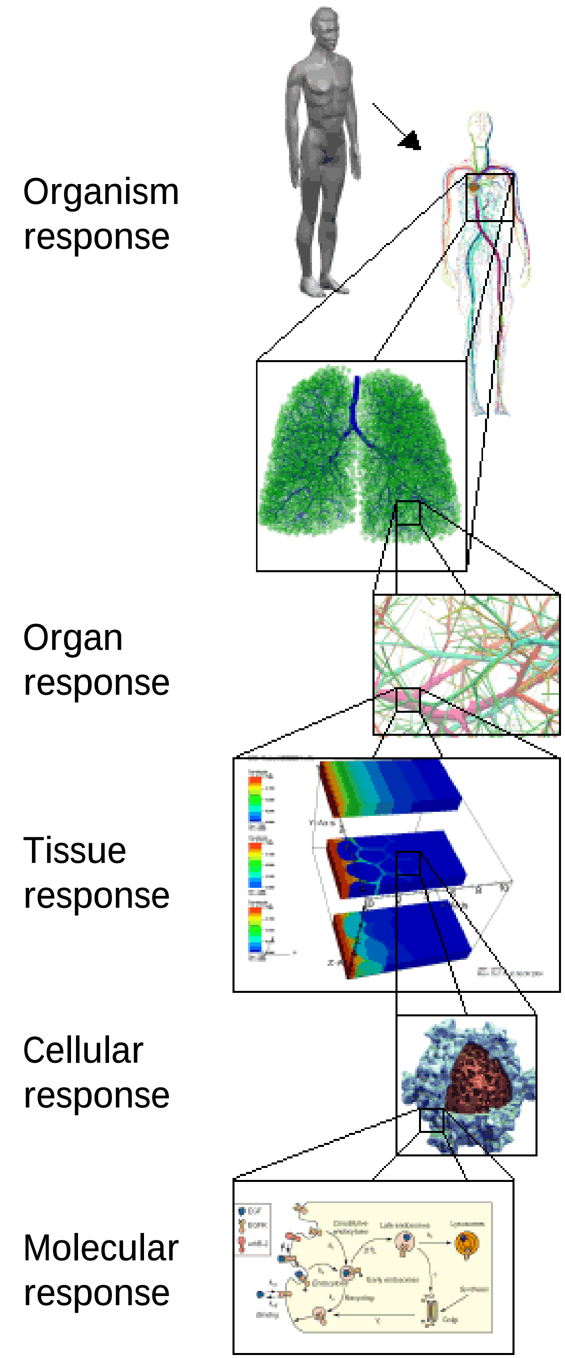


- Data from Jaques & Kim (2000) and Daigle, et al. (2003) studies at rest and during moderate exercise
- Experimental data compared to model predictions using MPPD2, ICRP, and (HUMTRN-derived) module of MENTOR-3P; experimental conditions used as model inputs



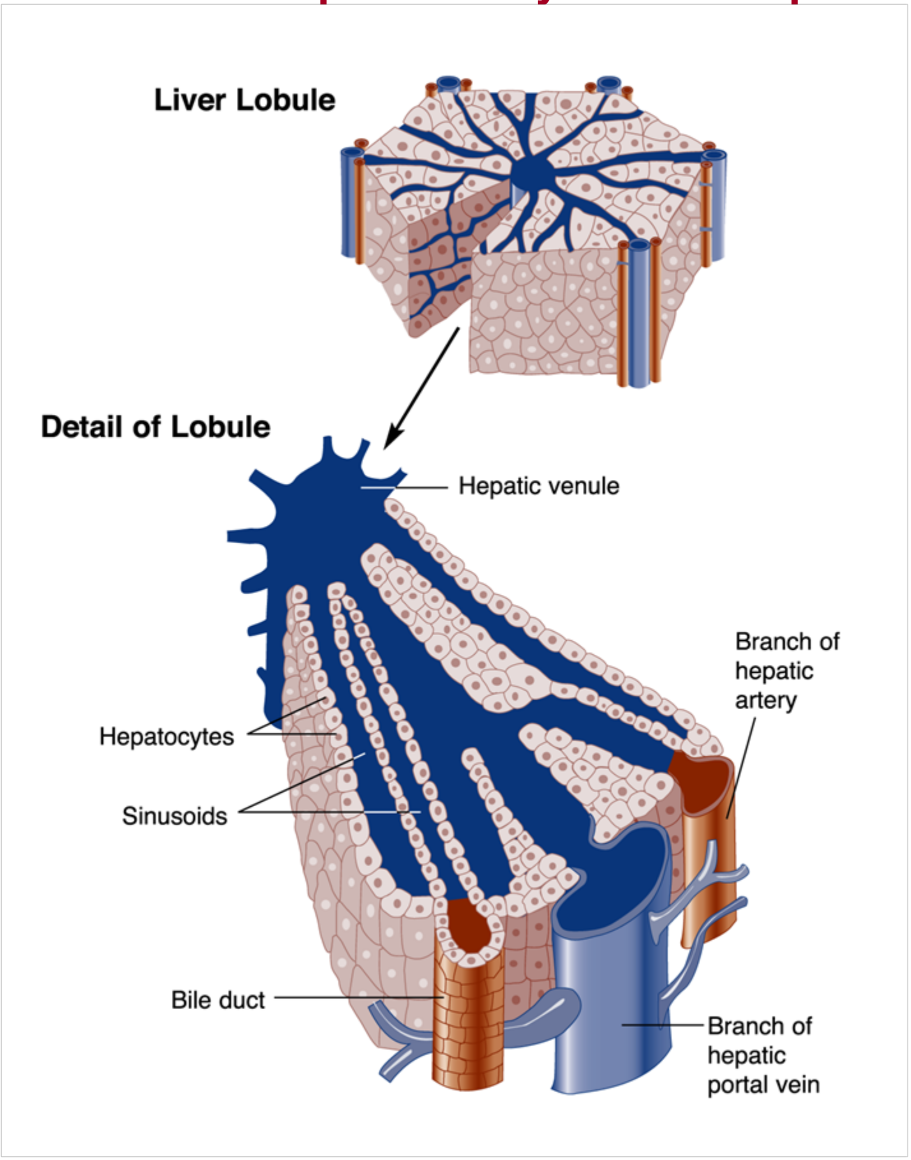
- Incorporation of “virtual organs” in MENTOR-3P will support the **evolution from Physiologically Based Pharmacokinetic models to integrative Physiologically Based Pharmacokinetic/ Pharmacodynamic models**

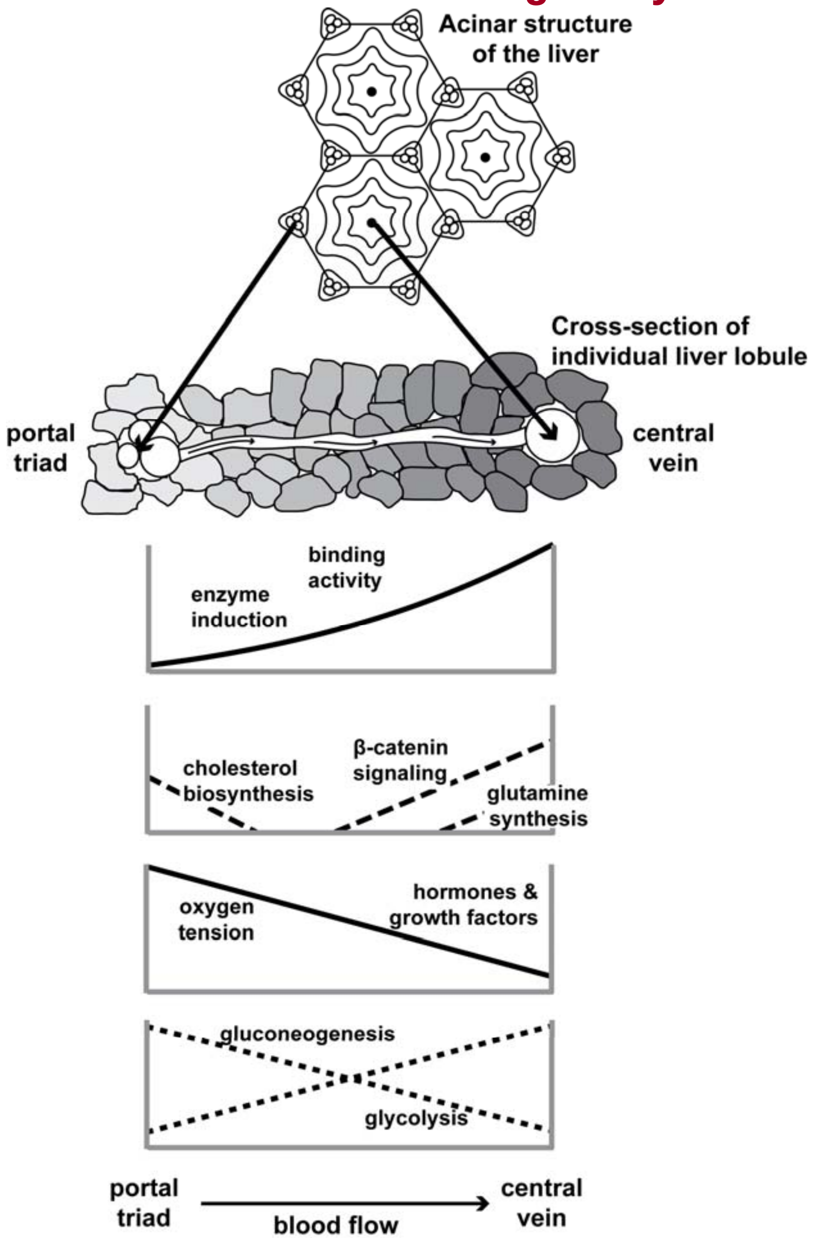
From Georgopoulos (2008) *Water Air Soil Poll: Focus 8* (1): 3-21



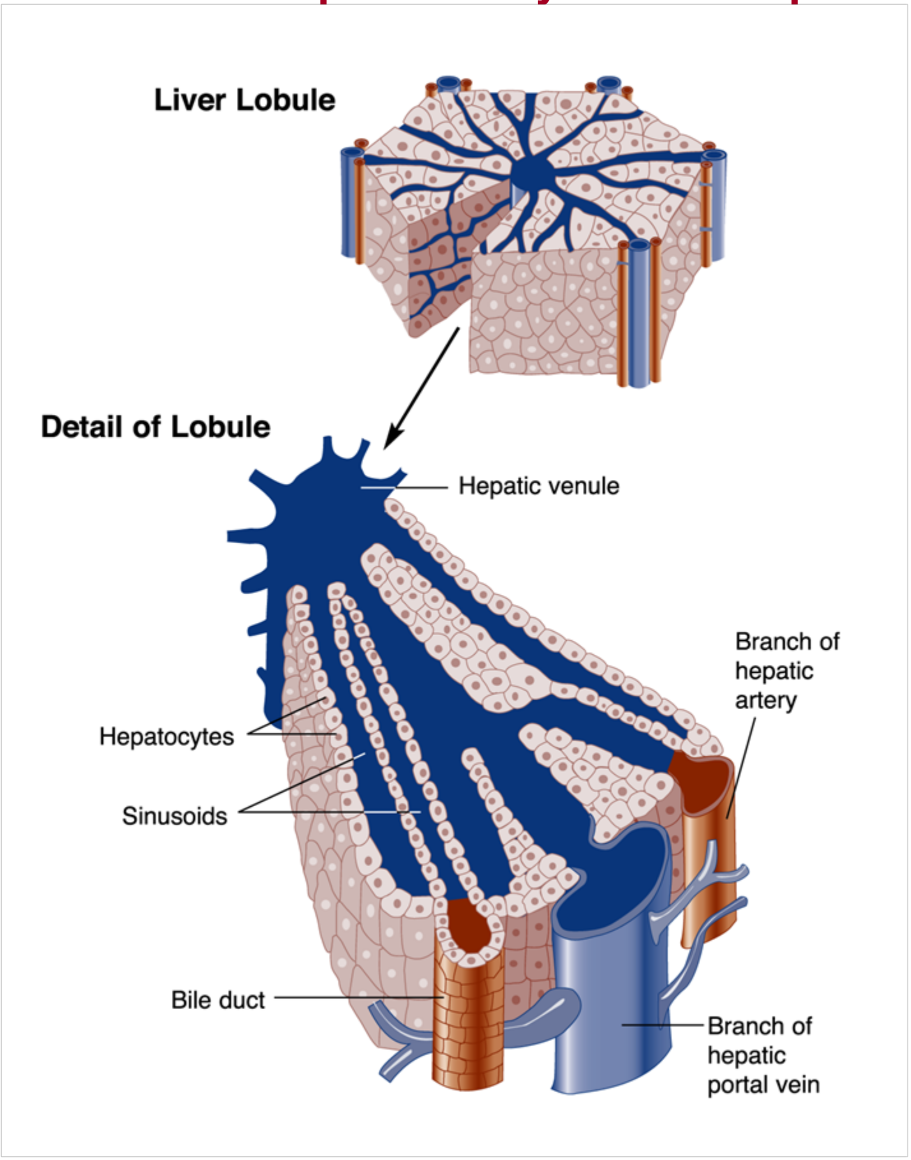
(Graphics from Physiome Project)

Lung and skin models are critical for assessing exposure and intake / uptake; liver is critical for biotransformation and elimination of xenobiotics: recent / current liver modeling efforts in MENTOR-3P development focus primarily on computationally efficient representations of the effects of heterogeneity

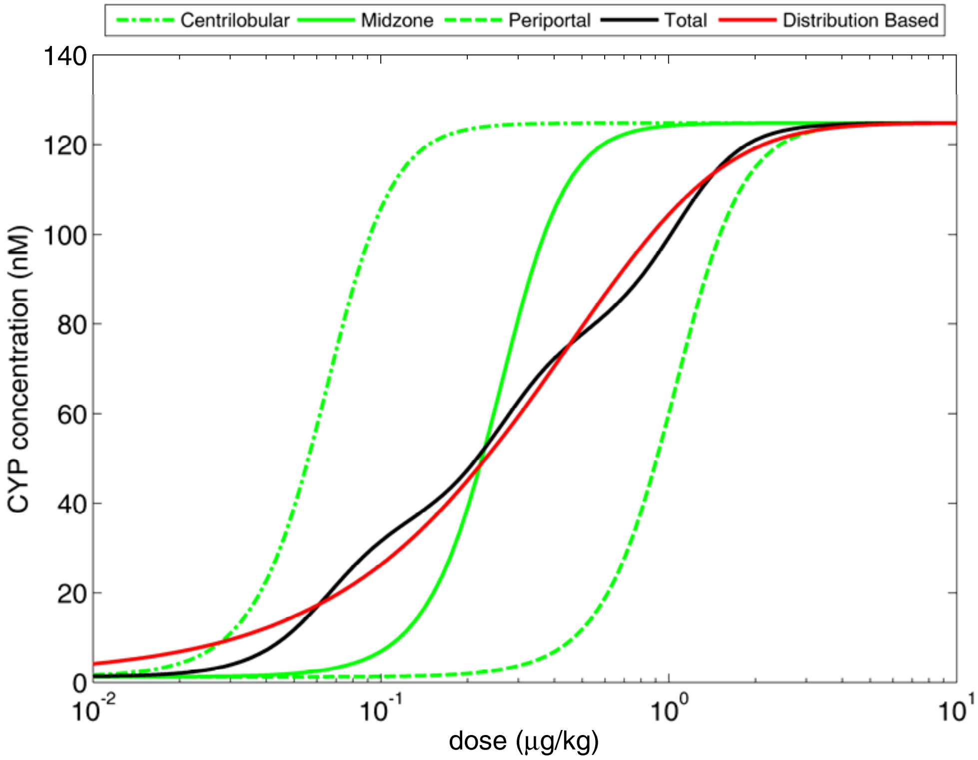




Lung and skin models are critical for assessing exposure and intake/uptake; liver is critical for biotransformation and elimination of xenobiotics: recent/current liver modeling efforts in MENTOR-3P development focus primarily on computationally efficient representations of the effects of heterogeneity

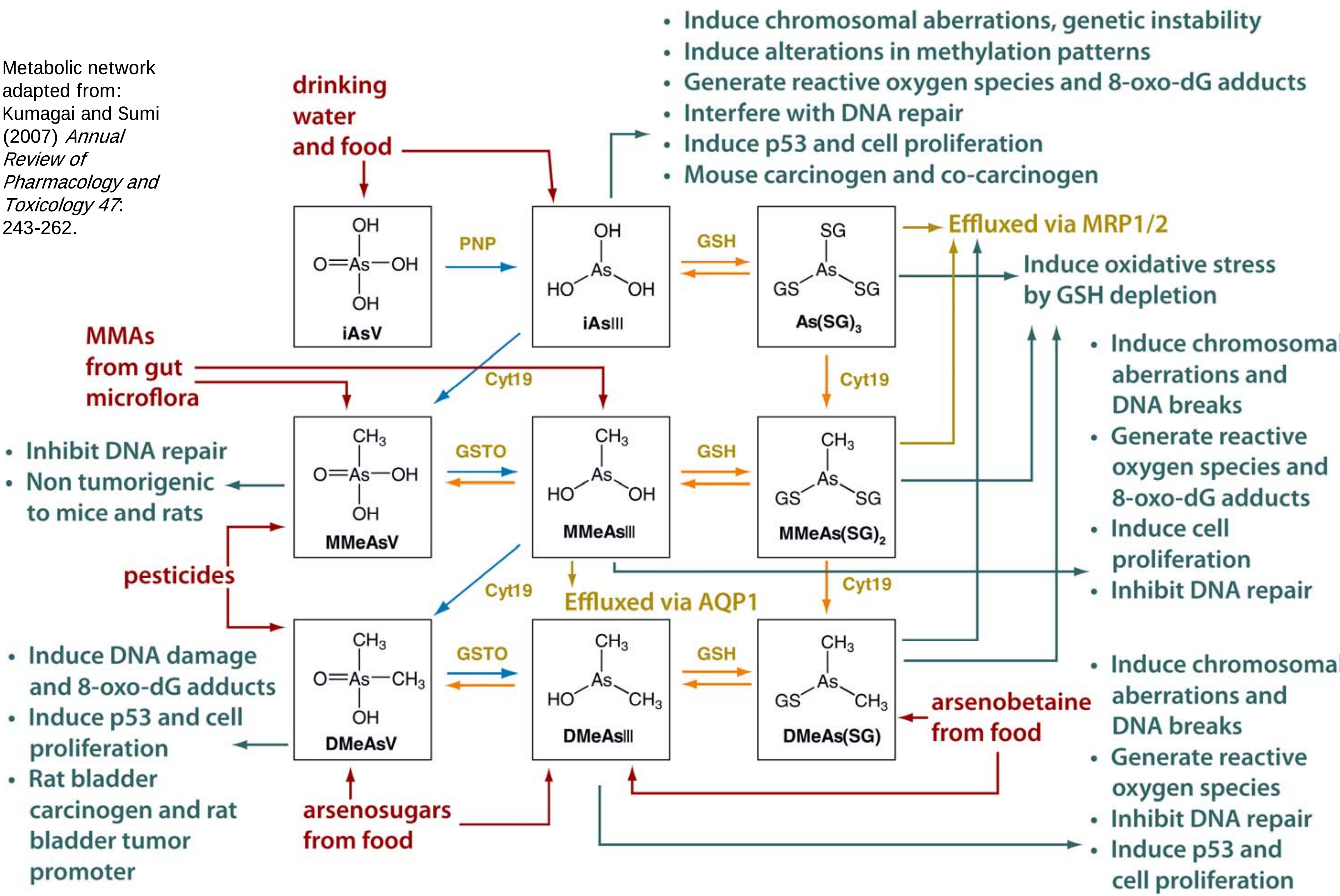


Currently available liver modules within MENTOR-3P can account efficiently for biochemical heterogeneity through the use of either multi-compartment or distribution-based approaches



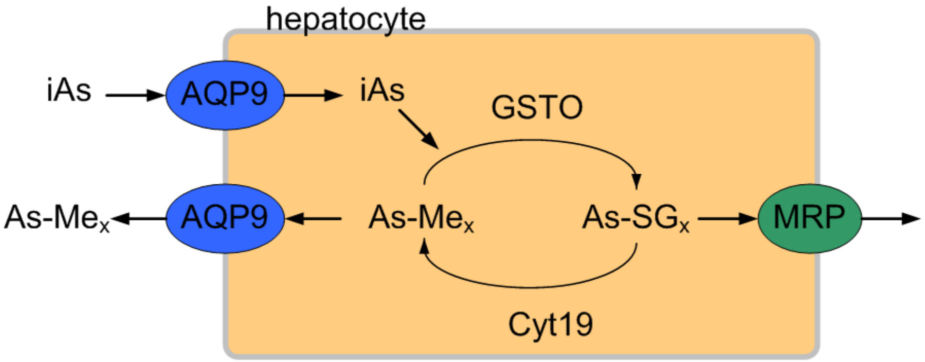
Example of on-going research: Modeling sources, transport, biotransformations, and effects of As species in the human body

Metabolic network adapted from: Kumagai and Sumi (2007) *Annual Review of Pharmacology and Toxicology 47*: 243-262.

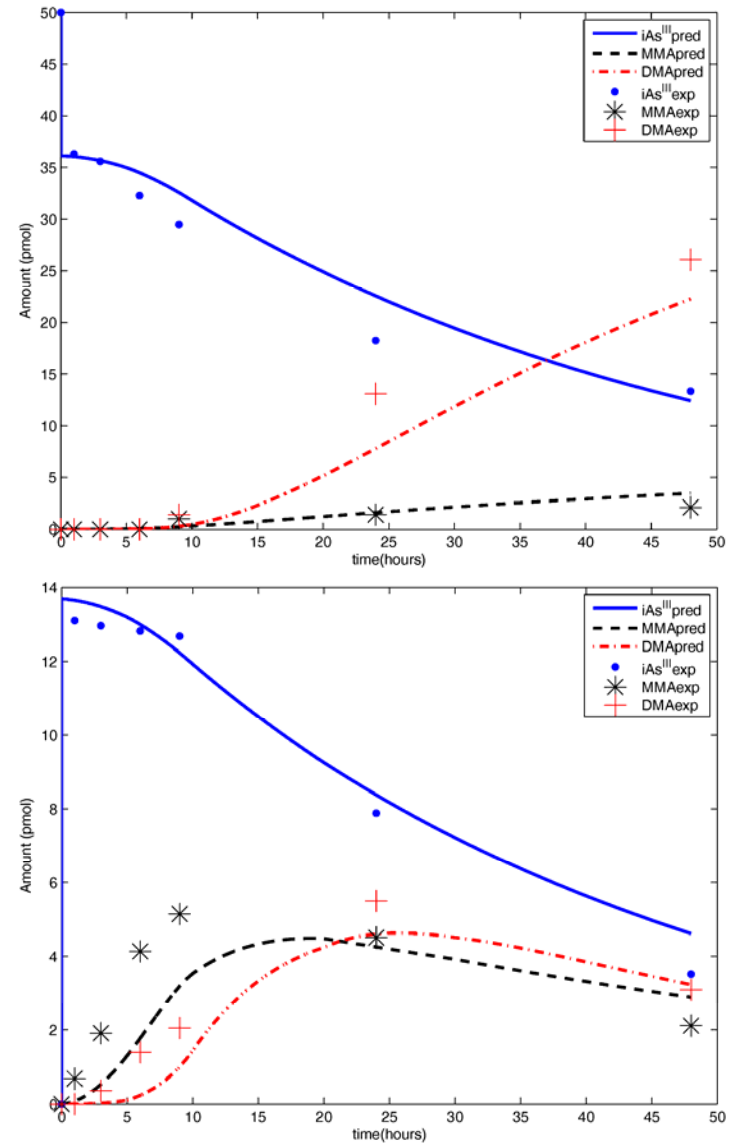


Research in-progress: "reconciliation" of biotransformation and transport of As modeled at both the individual hepatocyte and the whole organ level

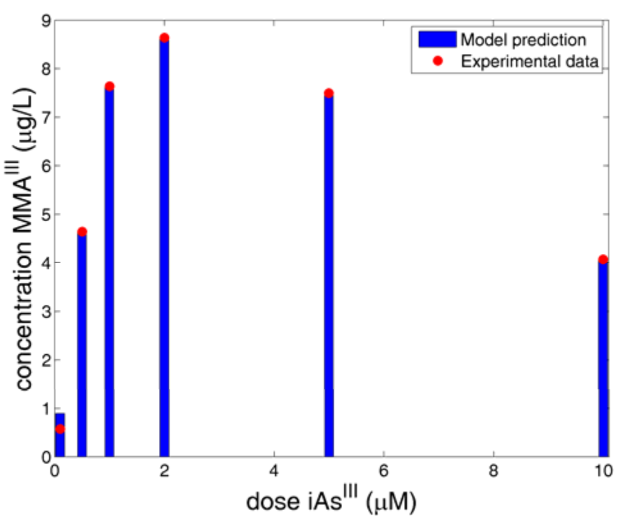
Arsenic uptake and metabolism



Time course prediction of As methylation in human hepatocytes vs data from Styblo et al. 1999



Dose-response predictions of As methylation in mice hepatocytes vs data from Kedderis et al. 2000

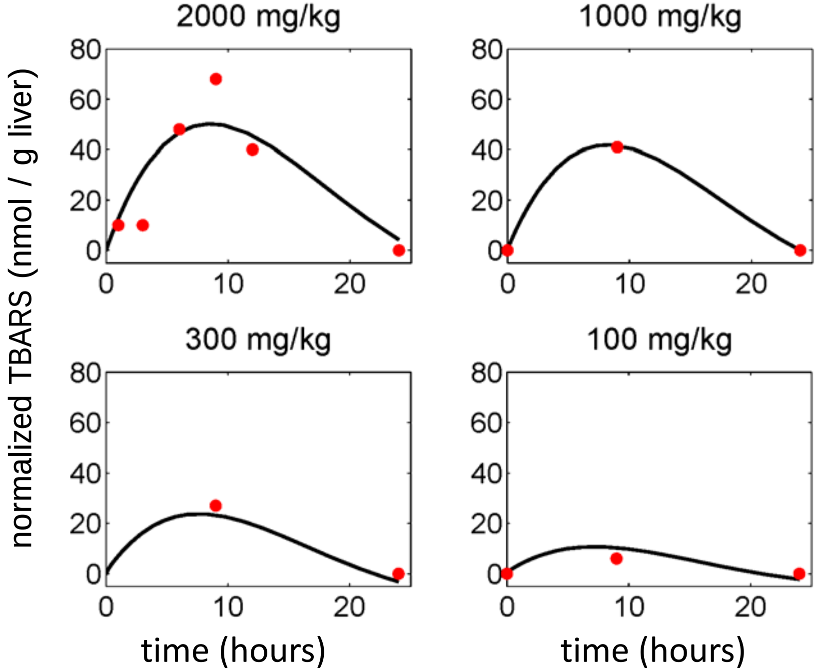


A parallel example of on-going research: Modeling quantitative metrics of oxidative stress from exposure to TCE

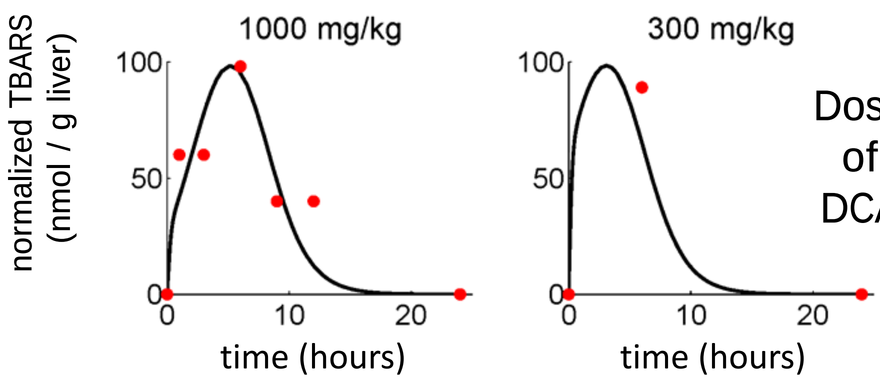
Toxicokinetic model

“evolved” from Abbas & *Fisher, Toxicol Appl Pharmacol (1997) 147:* 15-30

TCE $\xrightarrow{\text{P450}}$ TCA → DCA



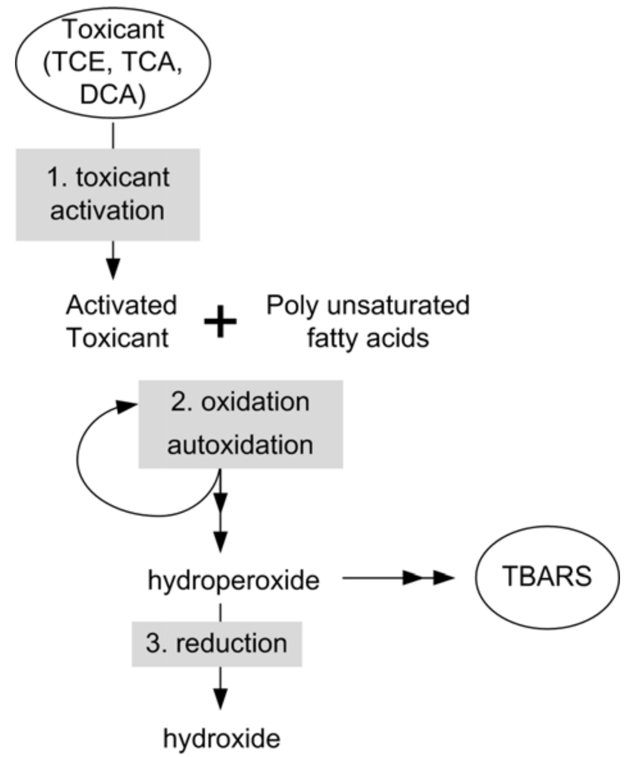
Dose of TCA



Dose of DCA

Experimental data of Larson & Bull, *Toxicol Appl Pharmacol (1992) 115:* 268-277

Toxicodynamic model



TBARS = thiobarbituric acid-reactive substances

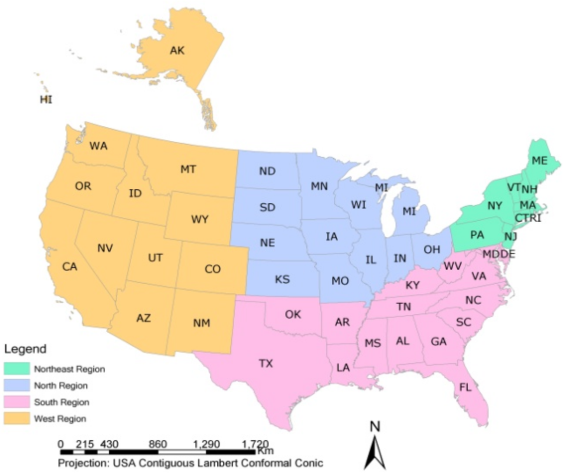
Toxicodynamic equation

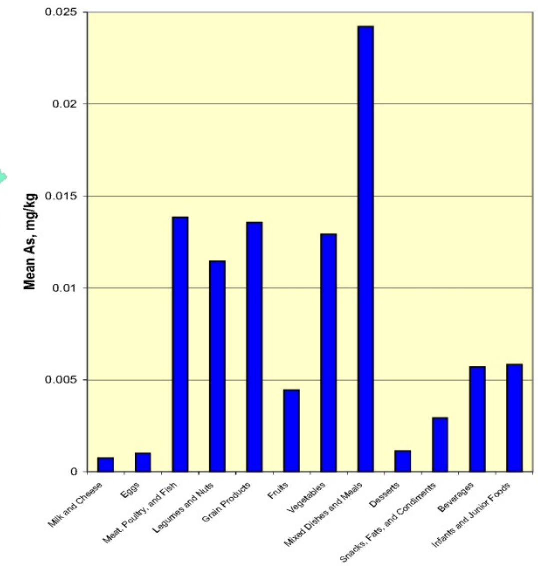
$$\frac{d[TBARS]}{dt} = \frac{V_{max}[Toxicant]}{K_m + [Toxicant]} - \left(k_1[TBARS] + k_2 * TBARS_{AUC}\right)$$

A prototype source-to-dose MENTOR-4M / 3P evaluation for As

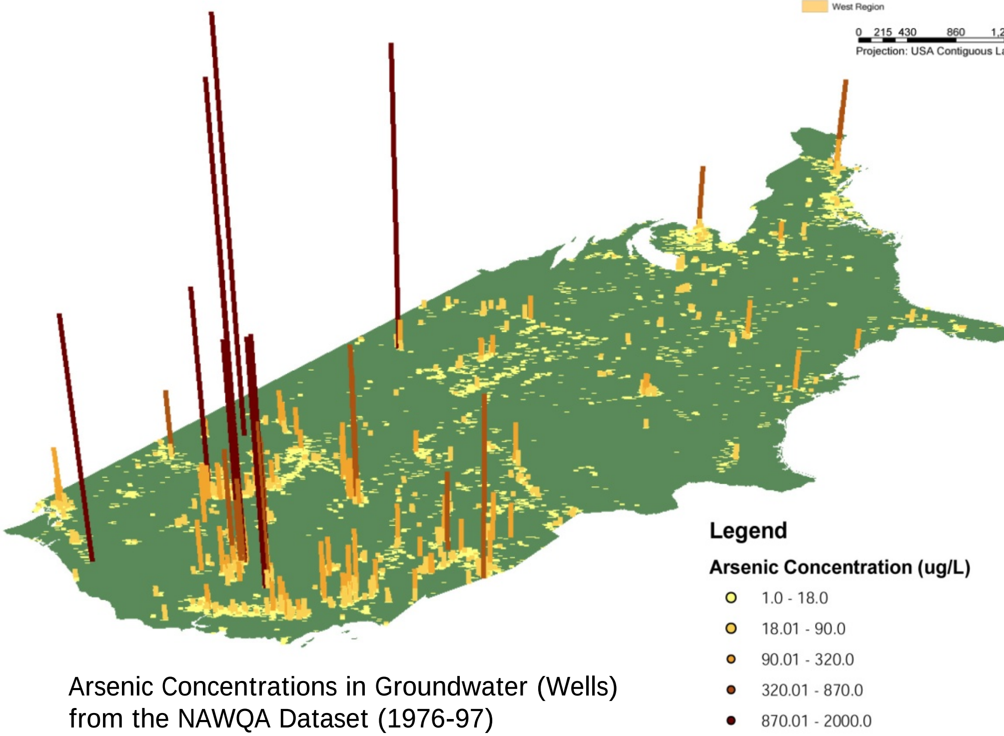
Source-to-dose assessments of exposures to multiple co-occurring contaminants from multiple media for

- the general population of three counties with different demographics (OH, NJ, AZ)
- the NHEXAS Region-V population
- the NHANES 2003 population

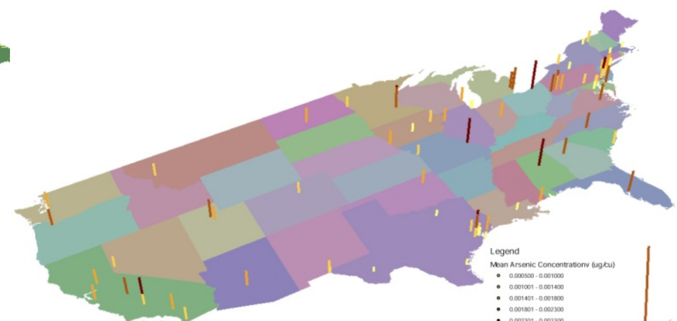




Total arsenic (mg/kg) measured in 12 major food groups generated from a total 267 food items (from USFDA Total Dietary Study)

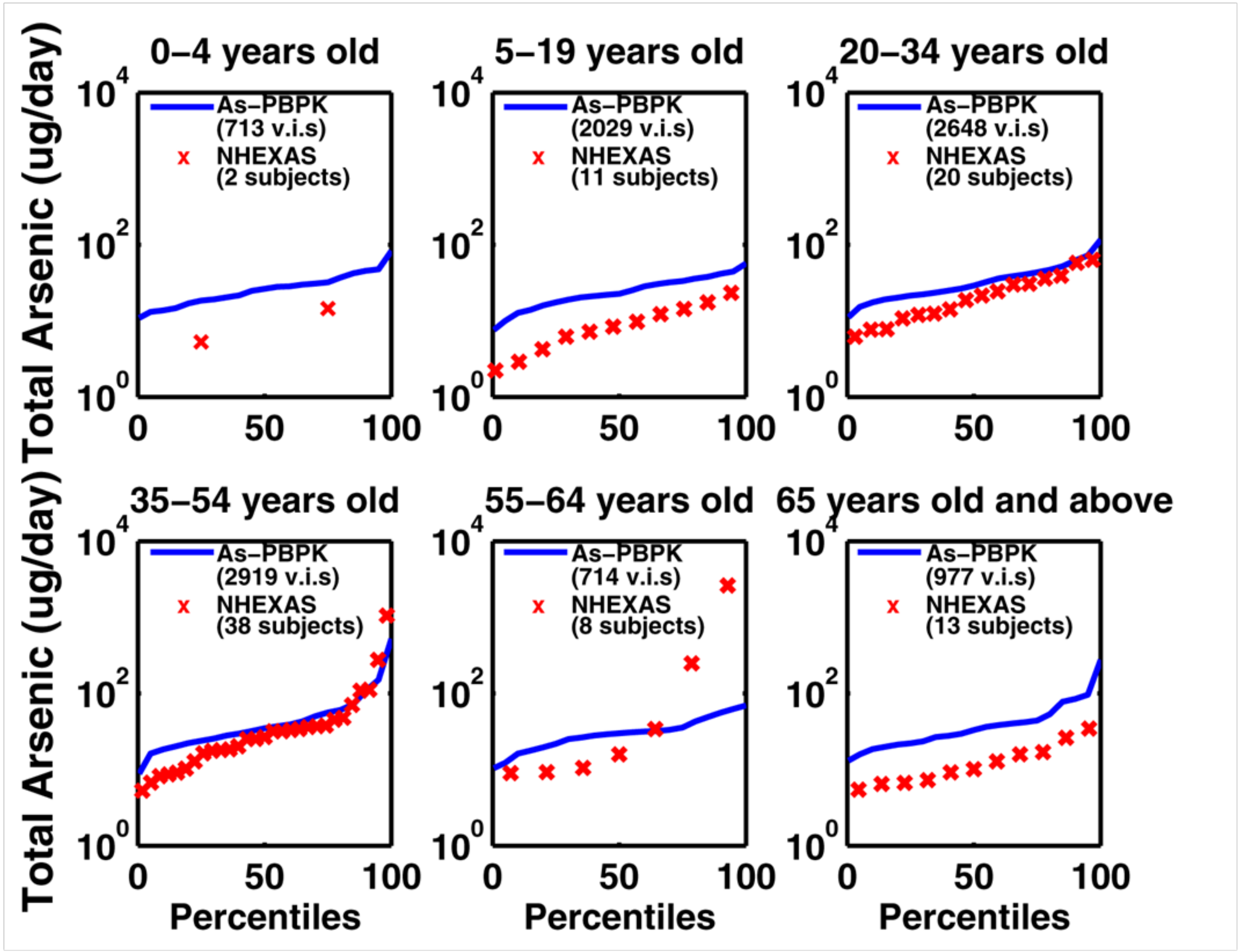


Arsenic Concentrations in Groundwater (Wells) from the NAWQA Dataset (1976-97)



Average and maximum arsenic concentations measured in PM2.5 at AIRS monitoring stations during 2001

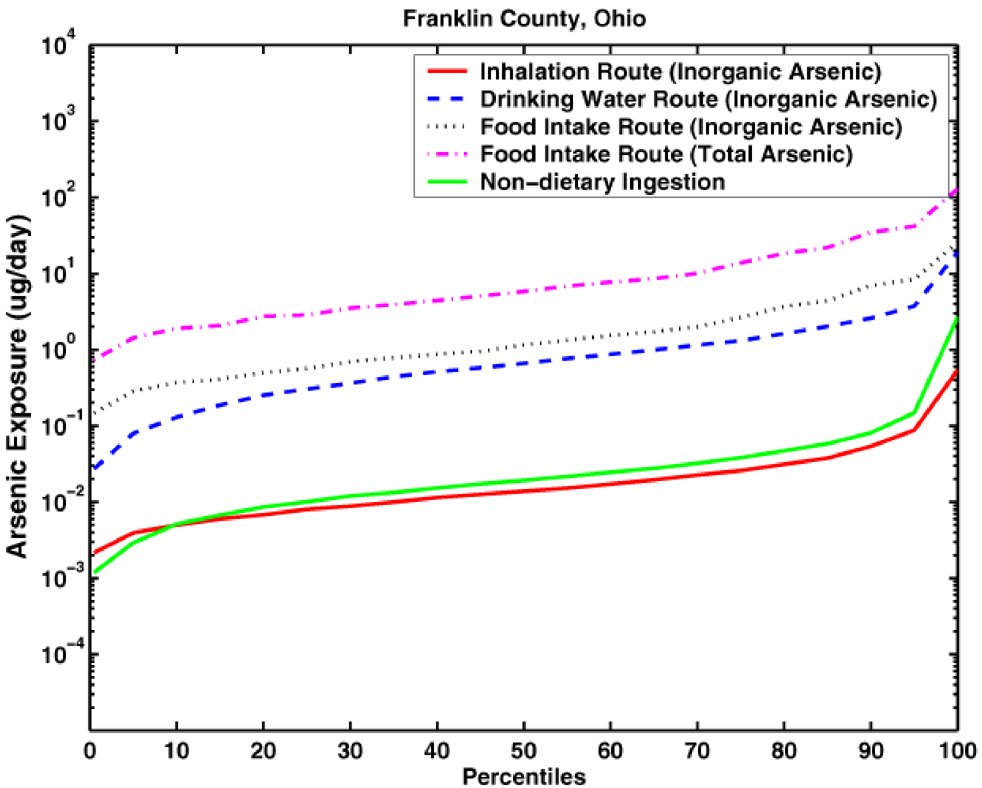
Cumulative distributions of total arsenic amount in urine from MENTOR predictions for Franklin County, OH and from individual NHEXAS-V measurements (corresponding percentiles) for different age groups



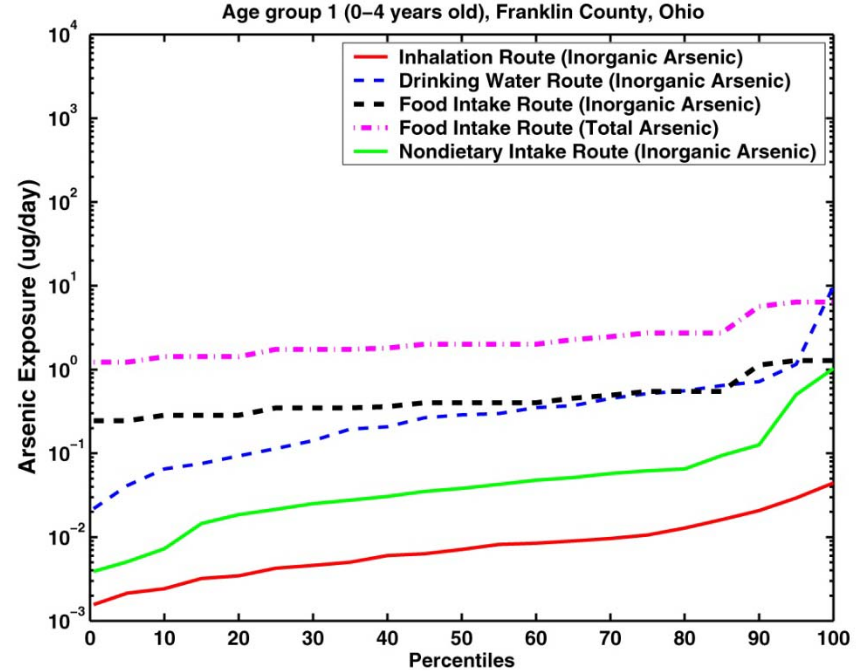
v.i.s. = virtual individuals

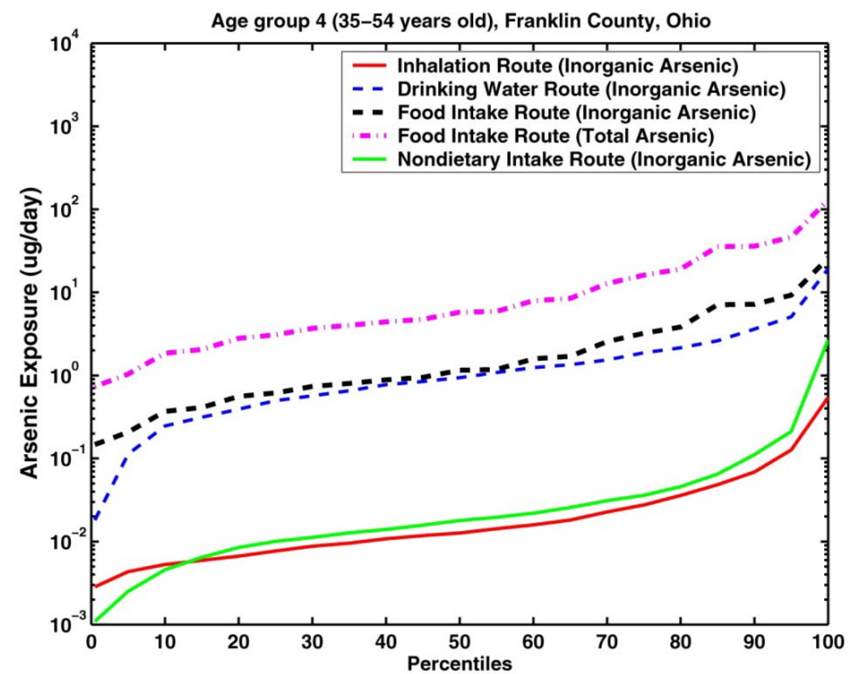
From: Georgopoulos, et al. (2008) *J Expo Sci Environ Epidemiol 18 (5): 462-476.*

Multiroute/multipathway population exposure to arsenic (total and inorganic) for NHEXAS Region V modeled with MENTOR-4M: Comparison of exposure route contributions



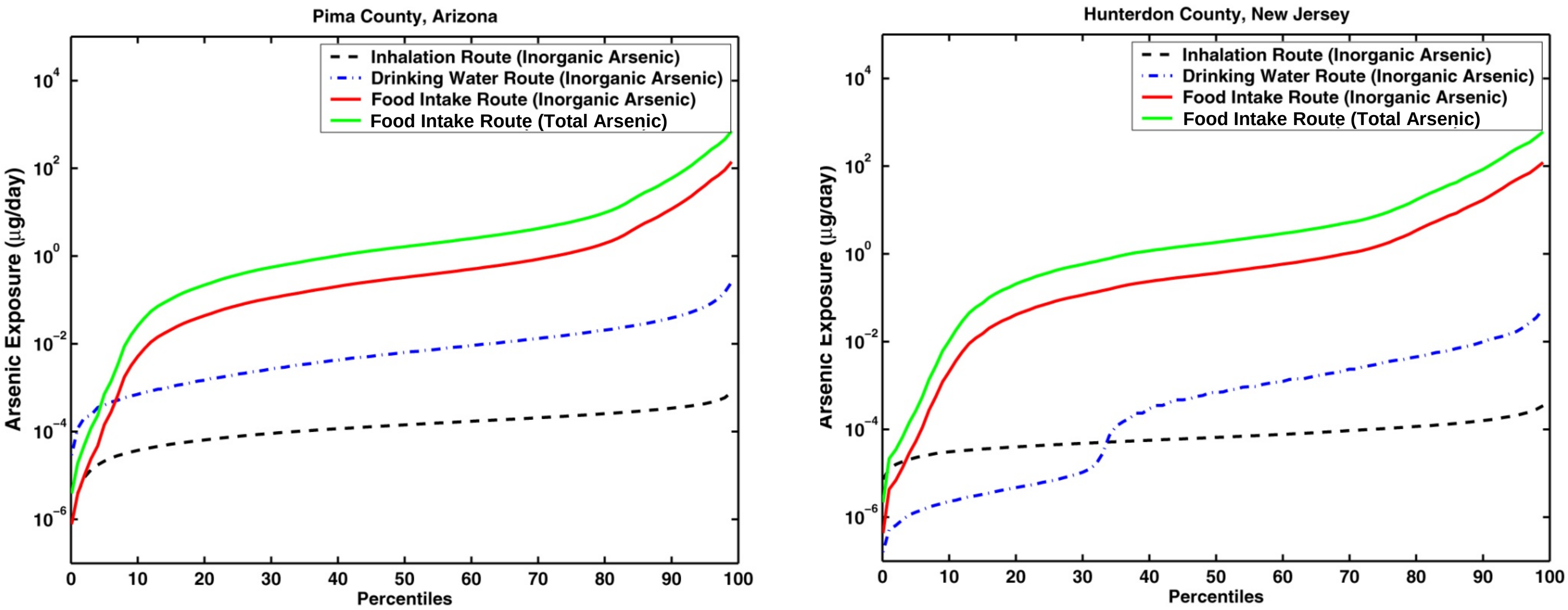
Cumulative arsenic exposure distributions from inhalation, food intake, non-dietary ingestion, and drinking water consumption routes for Franklin County, Ohio





From: Georgopoulos, et al. (2008) *J Expos Sci Environ Epidemiol 18 (5): 462-476.*

Predicted cumulative distributions of arsenic (inorganic and total) intake (ingestion and inhalation) from the populations of Pima, AZ and Hunterdon, NJ

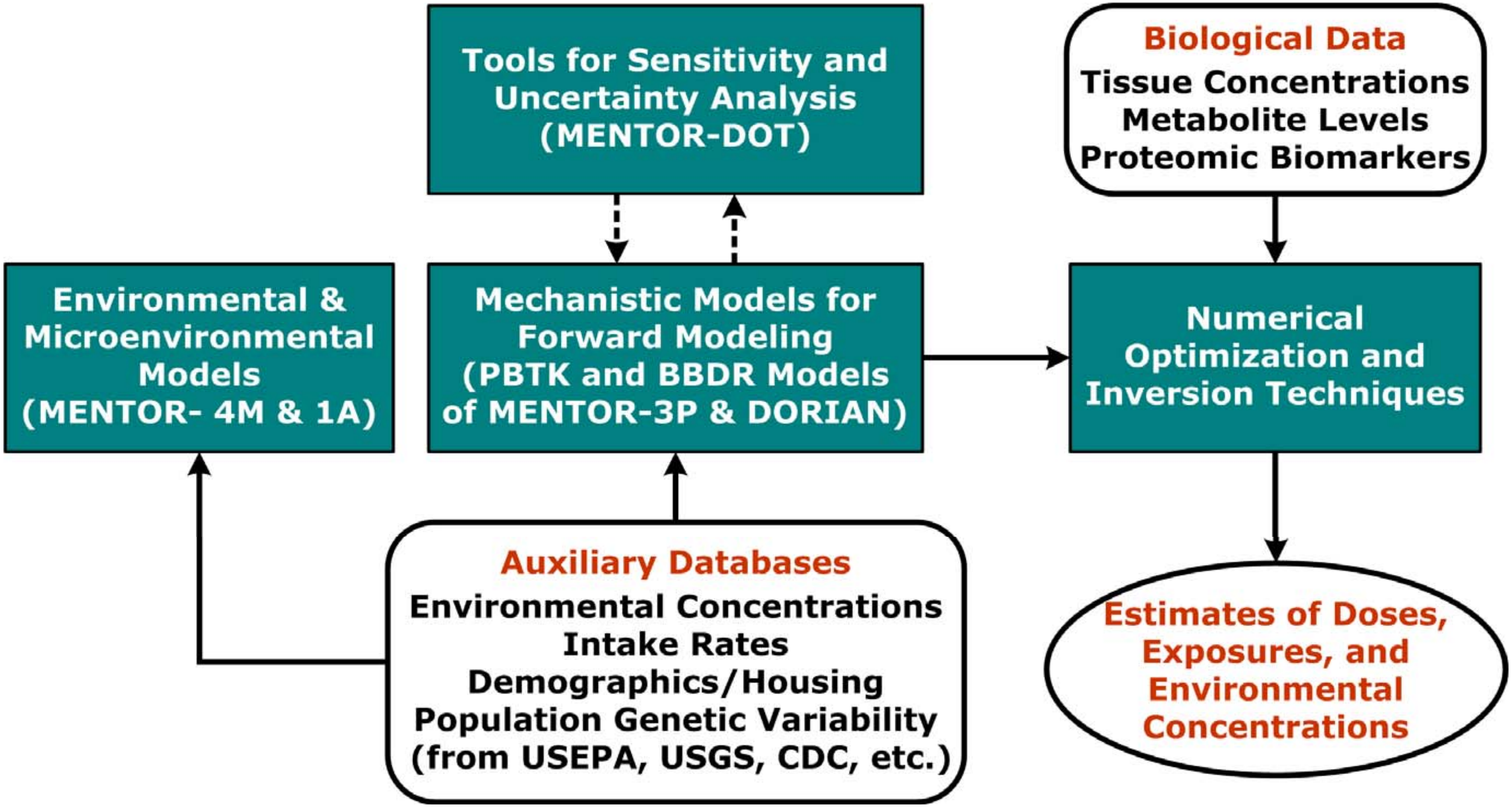


Inhalation dose from arsenic component in outdoor PM estimated using the MENTOR-3P gender/age/activity specific population inhalation dosimetry module (outdoor concentrations calculated using EPA's NATA)

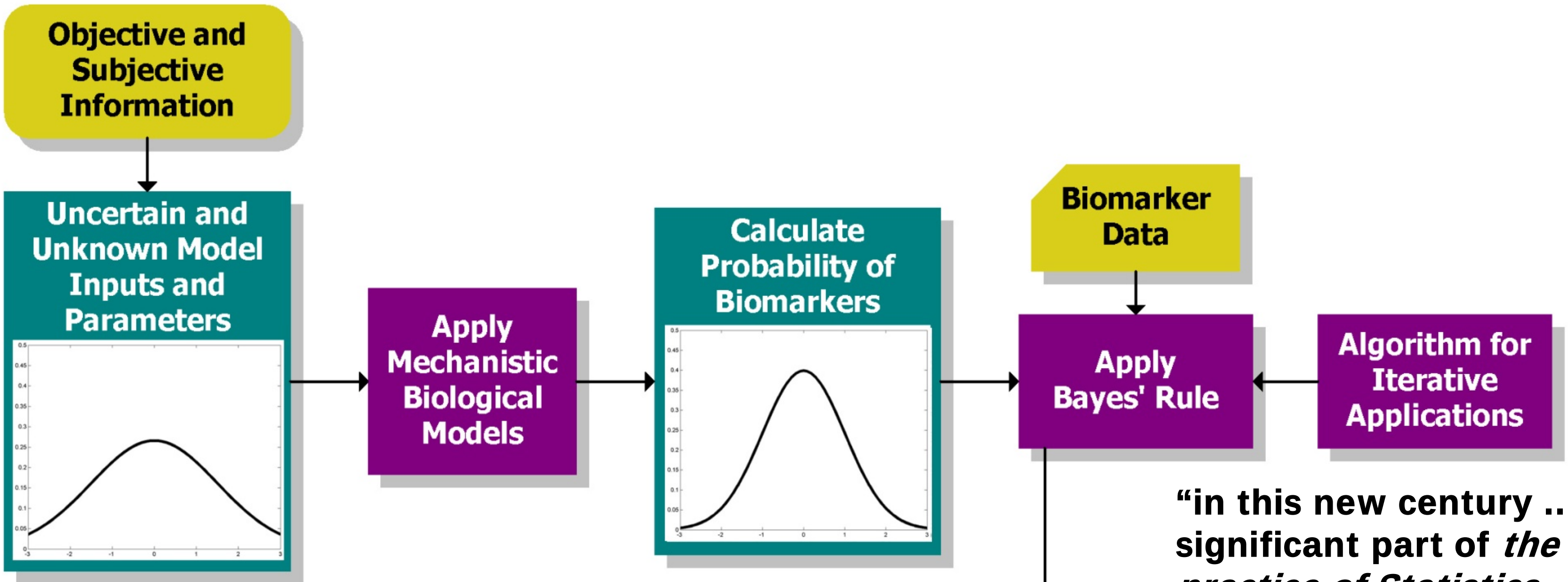
Drinking water concentration distributions from Pima, AZ and Hunterdon, NJ were derived respectively from the Arsenic Occurrence and Exposure Database and from NJDEP's Water Quality Database. The bimodal distribution in NJ reflects the different source quality (municipality system vs. private wells – the latter are arsenic contaminated).

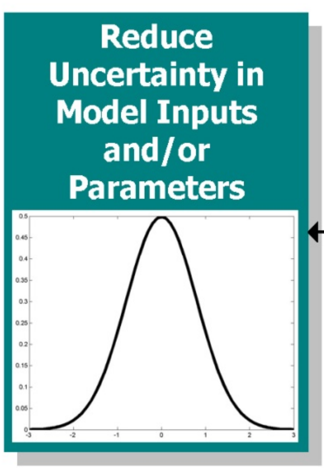
From: Georgopoulos, et al. (2008) *J Expos Sci Environ Epidemiol 18 (5): 462-476.*

MENTOR-DOT in conjunction with MENTOR-1A / 4M / 3P provide a general framework for systematic exposure reconstruction from biomarker data



The Bayesian approach offers a powerful framework for the analysis of "uncertain" environmental and biological information in conjunction with process ("mechanistic") models and optimization algorithms



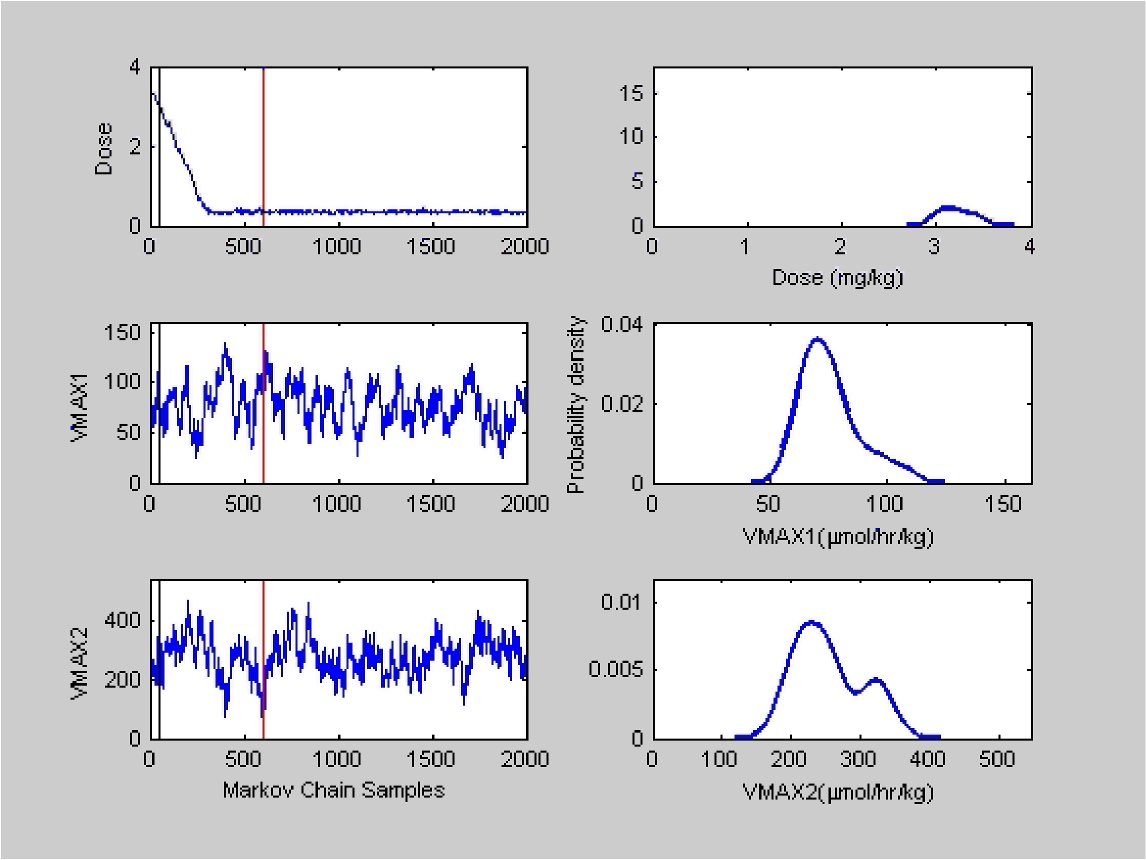


"in this new century ... a significant part of *the everyday practice of Statistics* ... will consist of applying Bayes' formula via MCMC ..."

in introduction of
David Williams (2001) *Weighing the Odds. A Course in Probability and Statistics.*
Cambridge University Press

- Assimilates prior information and information contained in data
  - prior information on parameters are specified by probability distribution functions Convenient for mechanistic, biological and environmental process models
  - <u>However – it presents serious challenges for the non-expert</u>
- Parameters characterized by probability *pdf* s
  - in contrast to classical parameter estimation, no single "true" value

Markov Chain convergence (left) and probability density (right) of chlorpyrifos dose and metabolic parameters



<- Please click to animate

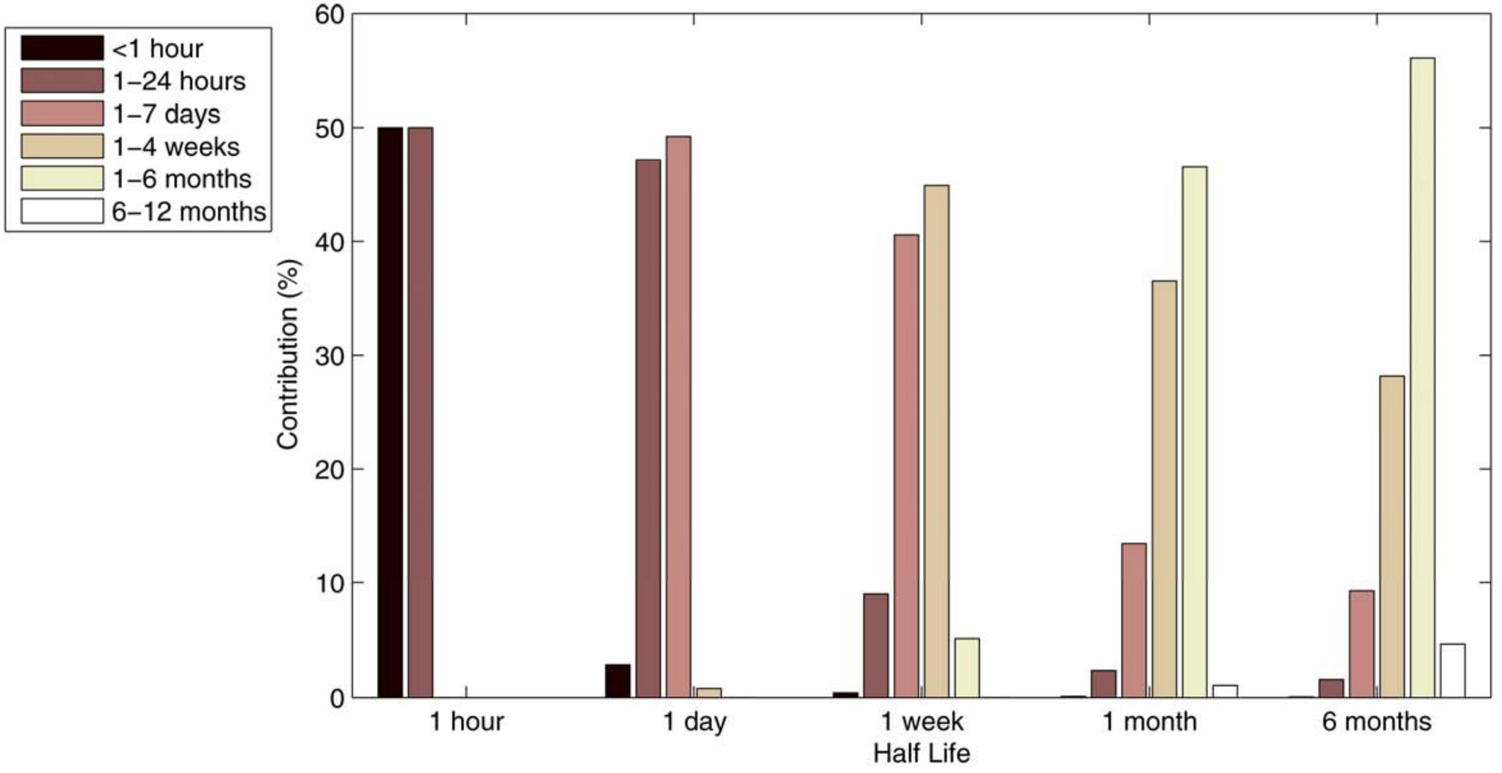
The red bar indicates the "burn-in"; the black lines indicate a span of samples; the green bars indicate accepted samples after convergence

Examples of available population biomarker databases

	OP			VOCs					Metals					
Program/Study	Chlorpyrifos	Diazinon	Malathion	Benzene	Toluene	Ethylbenzene	m,p-Xylene	o-Xylene	As	Cd	Cr	Hg/MeHg	Pb	Location; Number of Subjects
CHAMACOS (1999-2000) [Castorina et al., 2003]	bd	bd	bd											CA; 600 pregnant women
CTEPP (2000-01) [Wilson et al., 2004] (*)	ac	ac												NC, OH; 257 children (1.5-5 yrs)
MNCPES (1997) [Quackenboss et al., 2000] (*)	ac	ac	ac											MN; 102 children (3-12 yrs)
NHANES-III (1988-94) [Hill et al., 1995] (*)	c			c	c	c	c	c		c			bc	US; 1000 adults (20-59 yrs)
NHANES (1999-2000) [CDC, 2005b] (*)	cd	cd	cd	bc	bc	bc	bc	bc		c		c	bc	US; 9,282 subjects (all ages)
NHANES 2001-02 [CDC, 2005b] (*)	cd	cd	cd							c		c	bc	US; 10,477 subjects (all ages)
NHANES 2003-04 (*)	cd	cd	cd						c	c		c	bc	US; 9,643 subjects (all ages)
NHEXAS-AZ (1995-97) [Robertson et al., 1999]	ac	ac	ac	ac	ac				ac	ac	ac		ac	AZ; 179 subjects (all ages)
NHEXAS-MD (1995-96)	ac		ac						ac	ac	ac		ac	MD; 80 subjects (above 10 yrs)
NHEXAS-V (1995-97) [Whitmore et al., 1999] (*)				ac	ac	bc	ac	ac	ac	ac	ac	c	ac	EPA Region V; 251 subj. (all ages)

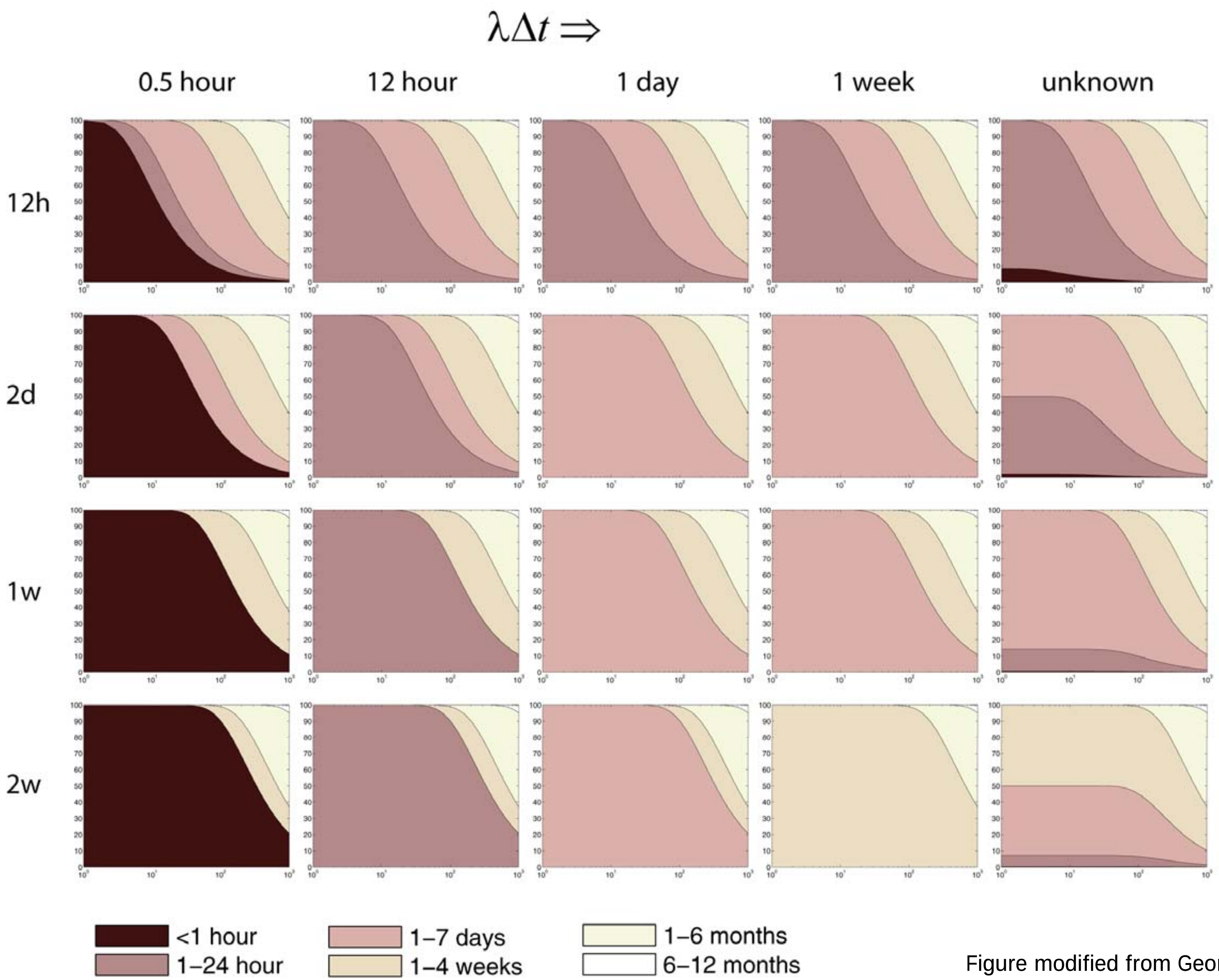
Key: a: Measurements of multimedia concentrations (indoor, outdoor, and personal air; drinking water; duplicate diet; dust; and soil). b: Partial measurements of environmental concentrations (e.g. outdoor air concentrations; pesticide use; etc.). c: Specific metabolites. d: Non-specific metabolites. OP: Organophosphates

Contribution of prior exposures to observed biomarker levels as a function of biochemical properties: Case of idealized linear single-compartment biokinetics



- Pyrethroids (6-12 h)
- Organophosphates/BTEX (~1 d)
- As (2-3 d)
- MeHg (2-3 mo)
- Cd (2-3 mo in blood; 10-40 y in body)

Contribution of prior exposures to observed biomarker levels as a function of intake frequency, sampling time, and biochemical properties: Case of idealized linear single-compartment biokinetics



The rows represent the time period of exposure (e.g. every 12 h, every 2 days, etc), the columns represent the time of sampling after the last exposure. For cases when sampling time is unknown, the mean values of the contributions are shown, assuming a uniformly random sampling time.

Figure modified from Georgopoulos, et al. (2009) *J Expos Sci Environ Epidemiol 19* (2): 149-171.

“Brute-force” approach for exposure reconstruction from inversion of biomarker data

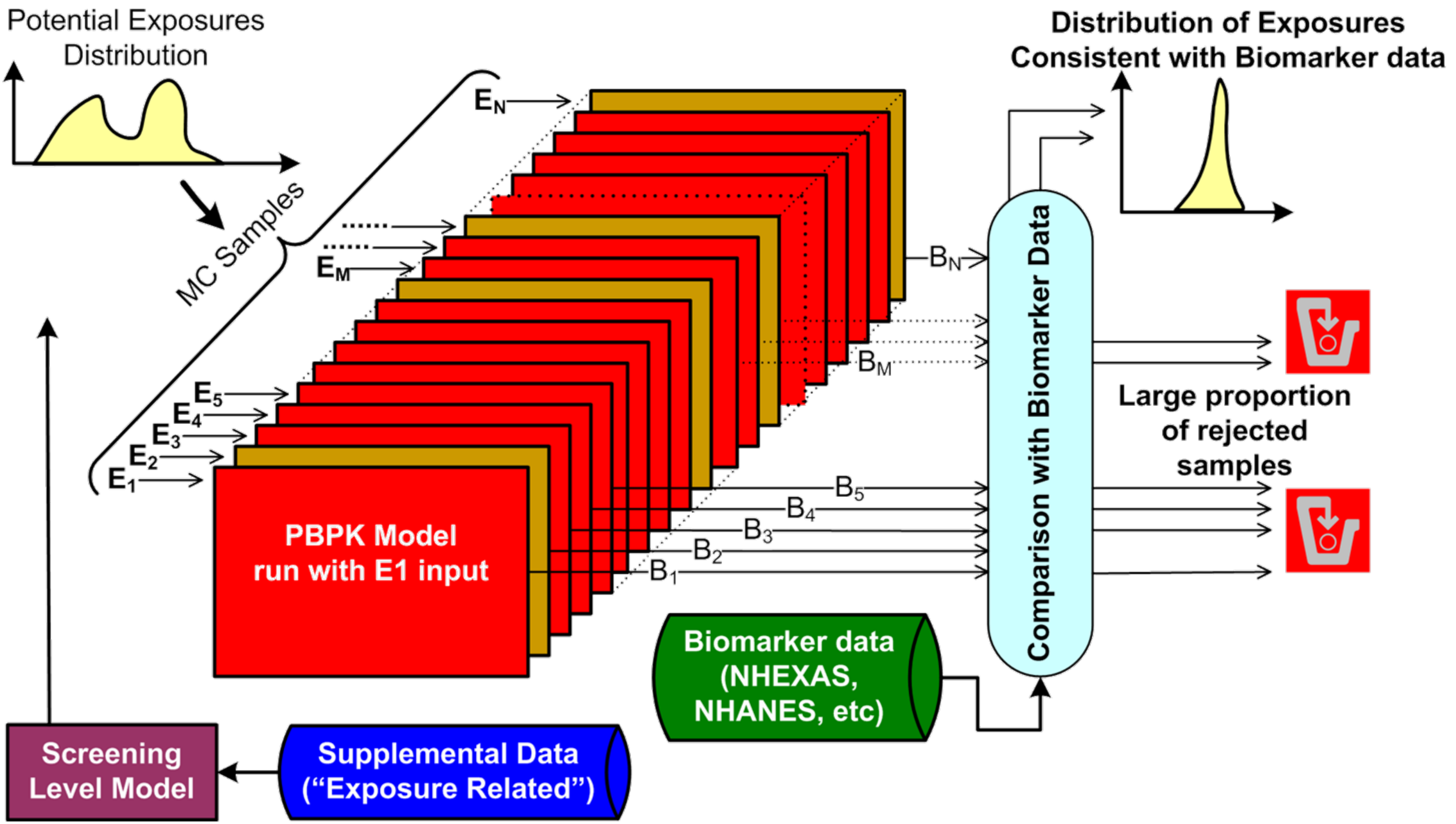


Figure modified from Georgopoulos, et al. (2009) *J Expos Sci Environ Epidemiol 19* (2): 149-171.

In progress: Optimization-aided Bayesian approach for exposure reconstruction from inversion of biomarker data

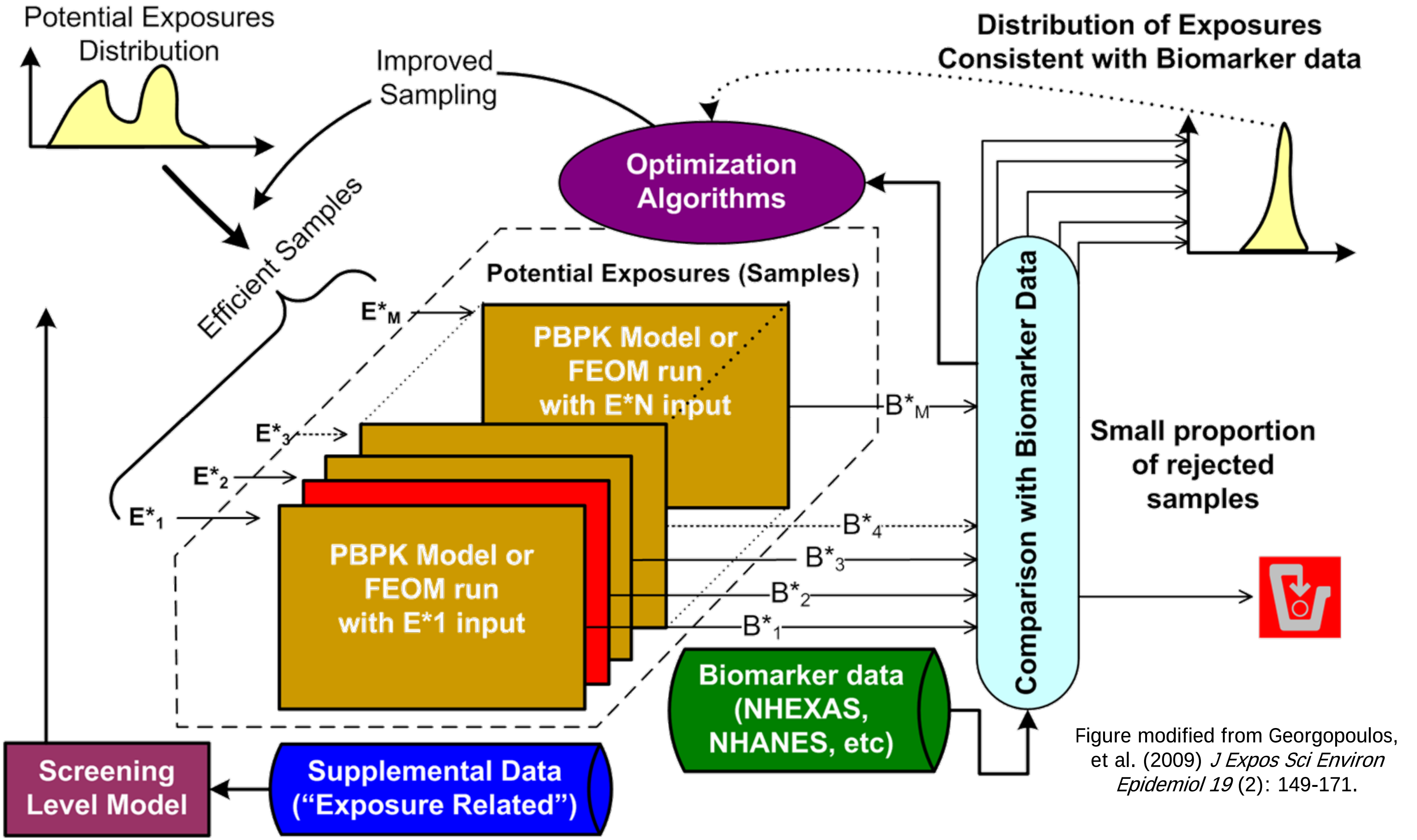
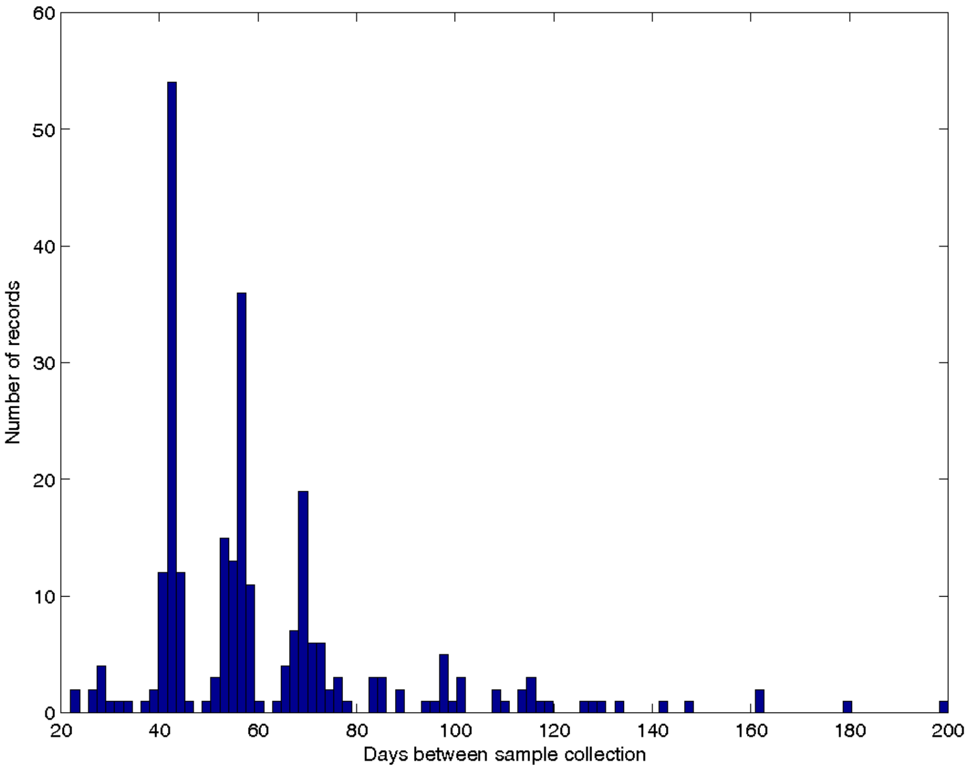


Figure modified from Georgopoulos, et al. (2009) *J Expos Sci Environ Epidemiol 19* (2): 149-171.

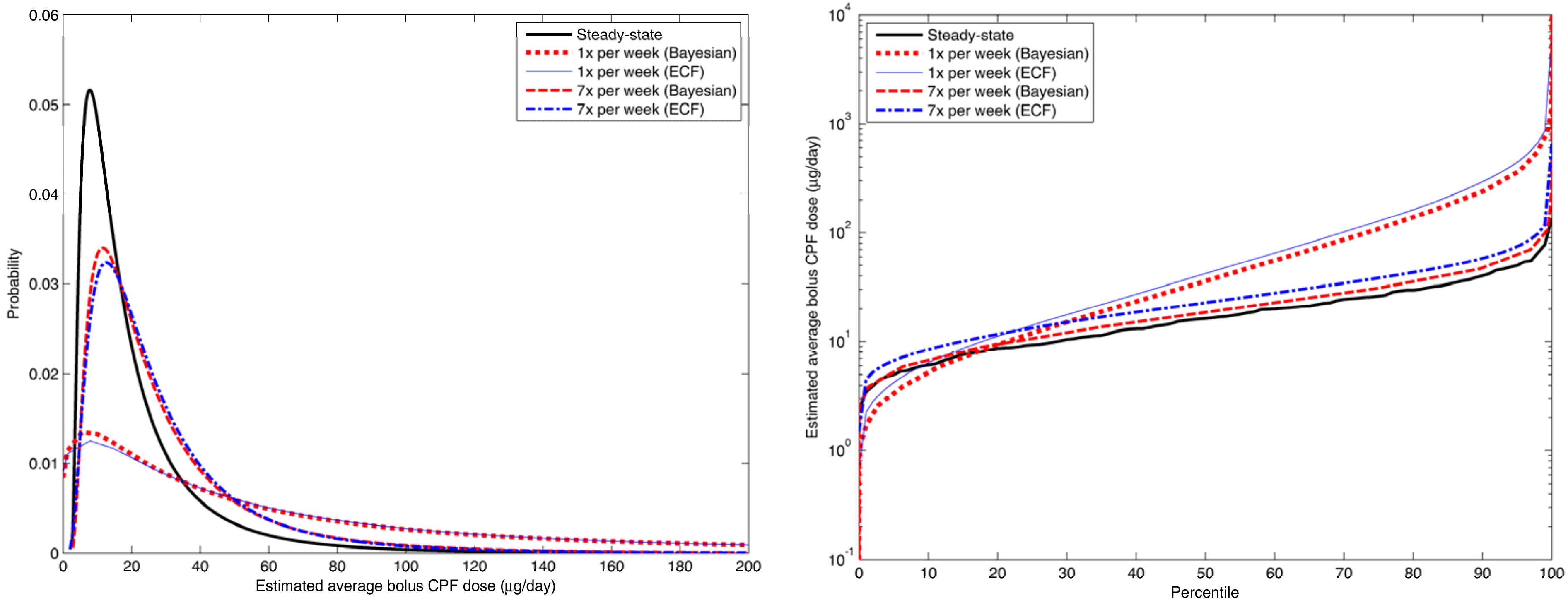
Novel methods have been developed that allow the systematic construction of Fast Equivalent Operational Models (FEOMs); these include the Stochastic Response Surface Method (SRSM) and the High Dimensional Model Representation (HDMR)

NHEXAS Maryland (NHEXAS-MD) data for chlorpyrifos (CPF)

- Longitudinal; multiple biomarkers
- Environmental measurements at homes
- CPF data
  - urinary TCPy measurements
  - first void of the day
- Concentrations of CPF chlorpyrifos in food, air (at home), dust, etc.,
- Corresponding TCPy concentrations in food, however, were <u>not measured</u>
- Food intake through 4-day duplicate plate
  - actual amount not available easily
- Also <u>not available</u>
  - Urinary void volume
  - Time of earlier urination
  - Last food intake time

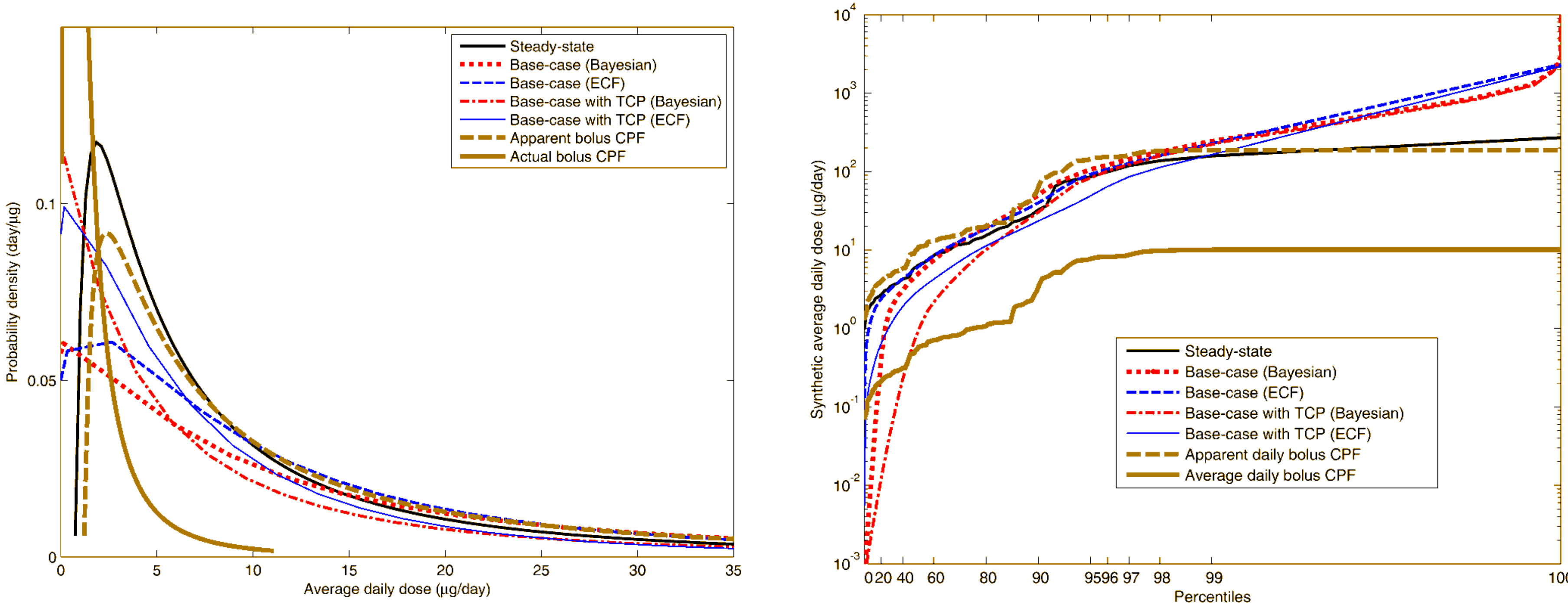


Assumptions regarding unknown exposure factors (e.g. frequency of exposures) affect substantially the outcomes of reconstruction ("inversion"): Demonstration case study with with NHEXAS-MD data



From Georgopoulos, et al. (2009) *J Expos Sci Environ Epidemiol 19* (2): 149-171.

Comparison of different methods for exposure reconstruction ("inversion") and Bayesian "caveats:" Demonstration of a "computational" case study with synthetic data consistent with the National Human Exposure Assessment Survey-Maryland (NHEXAS-MD) data (incorporating lower but reasonable levels of uncertainty)



CPF exposures were estimated from the urinary TCPy data (metabolite of CPF). However, direct exposures to TCPy are possible, and are often an order of magnitude higher than CPF exposures. Therefore, if direct exposure to TCPy is not considered in the reconstruction process, the "apparent" CPF dose will be significantly higher than the true exposures.

Some concluding thoughts:

Integrative exposure-dosimetry-toxicity frameworks for environmental health risk assessment provide several examples of situations that can benefit from incorporating more detailed biology in mechanistic, person-oriented, population analyses

PAST: Single Pathway Analysis of Risk	PRESENT: Multiple Pathway Analysis of Risk	FUTURE: Integrated "Person-Oriented" Systems Analysis of Risk
Single Contaminant	Multiple Contaminants	Mixtures of Contaminants with Environmental and Biological Interactions
Multiple Contaminant Sources	Multiple Contaminant Sources	Multiple Co-occurring Chemical and Nonchemical Stressors Affecting an Individual
Single Medium Environmental Fate & Transport	Linked Fate & Transport in Different Environmental Media	Dynamically Integrated Multimedia Fate & Transport in the Environmental and Biological systems
Single Exposure Route	Multiple Exposure Routes	Aggregate/Cumulative Exposure and Dose Analysis
Phenotype-based Toxicity	Phenotype-based Toxicity with Susceptibility Considerations	Mechanistic Linkage of Phenotype with Genotype
Primary Human Health Criteria for Individual Contaminants	Chemical and Exposure-Route Specific Risk for "Standard Individuals"	Aggregated Risk for Diverse Human Populations (with Susceptible Subpopulations)
Qualitative Uncertainty	Quantitative Uncertainty	Quantitative Uncertainty and Variability Resolved for Specific Environmental and Biological Processes

"Exposure Biology" provides valuable tools for the systematic development of "quasi-personalized" risk assessments that will improve accountability with more and better options for prevention and intervention

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