ebCTC

environmental bioinformatics
Computational Toxicology Center

Computational Tools for the Source to Outcome Paradigm

Presented June 14, 2006
at USEPA's Bioinformatics Teleconference
by
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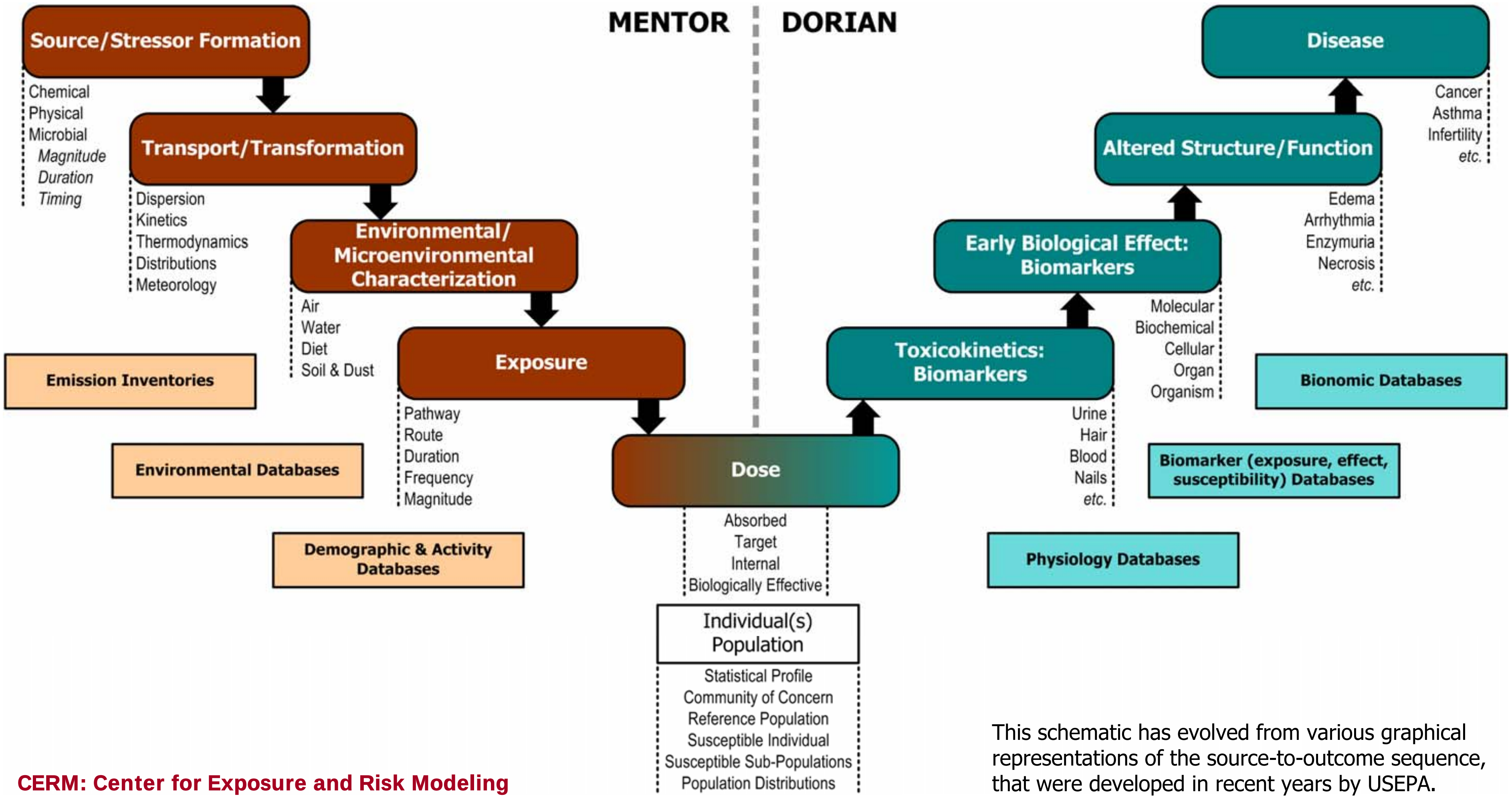
A mechanistically consistent infrastructure for exposure assessment and health impact analysis:

(CERM / MENTOR and ebCTC / DORIAN address the source-to-outcome continuum)

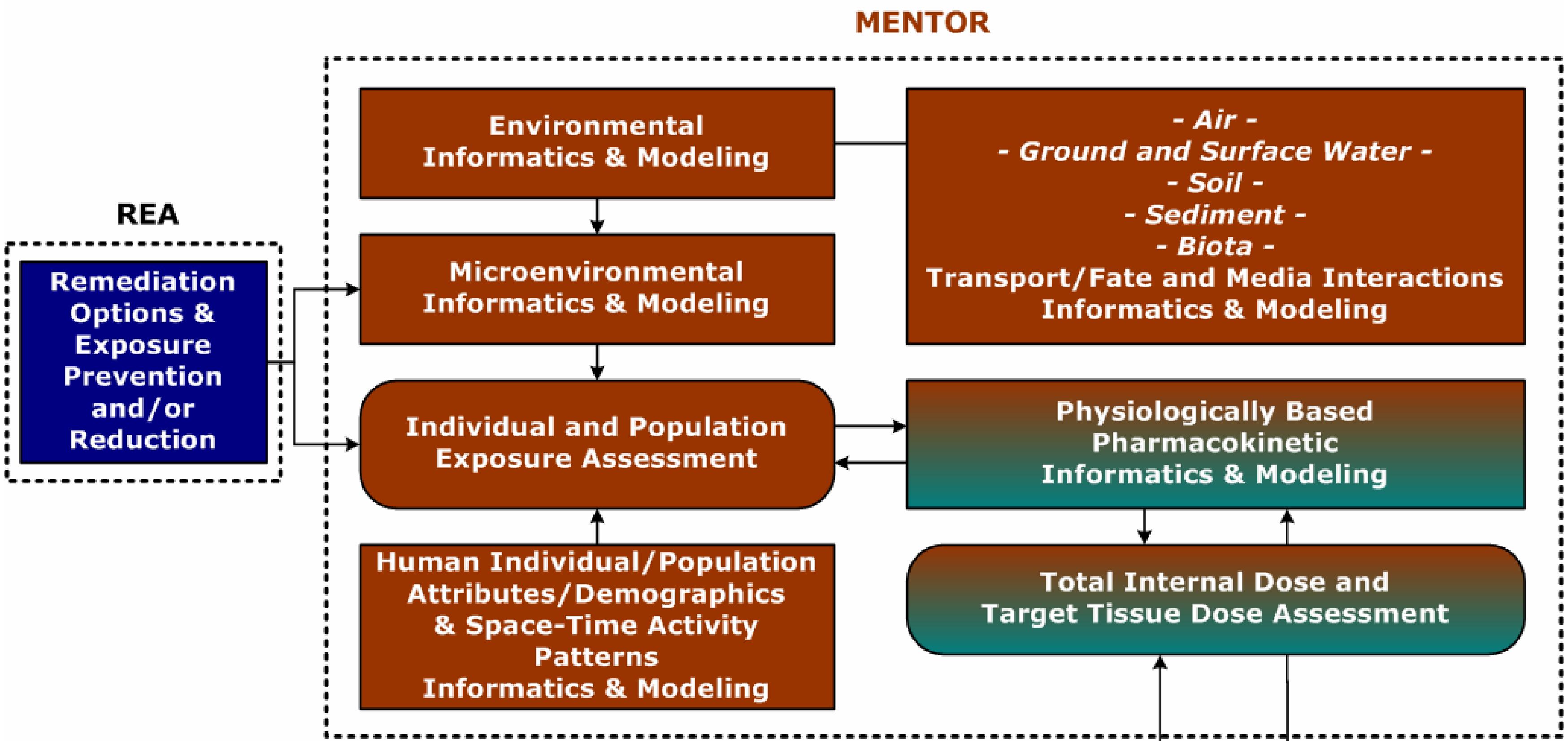


This schematic has evolved from various graphical representations of the source-to-outcome sequence, that were developed in recent years by USEPA.

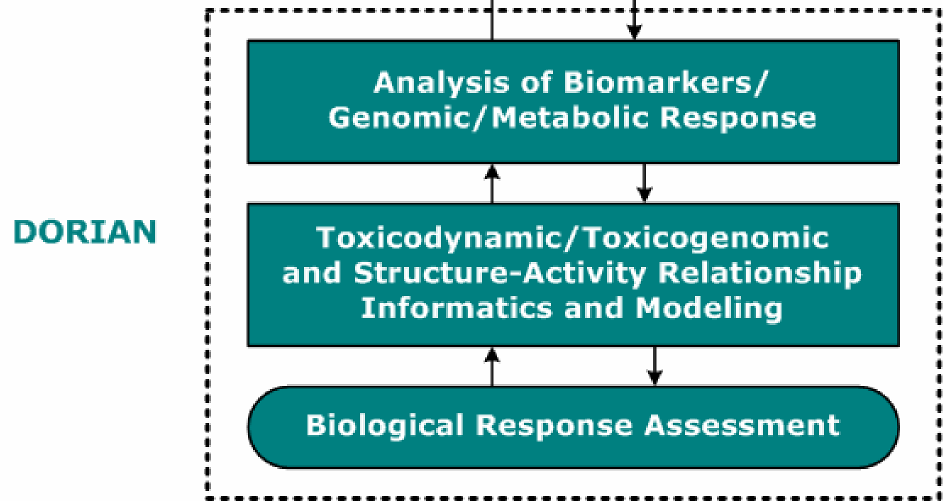
CERM: Center for Exposure and Risk Modeling
MENTOR: Modeling ENvironment for TOtal Risk studies
ebCTC: environmental bioinformatics and Computational Toxicology Center
DORIAN: DOse-Response Information Analysis system

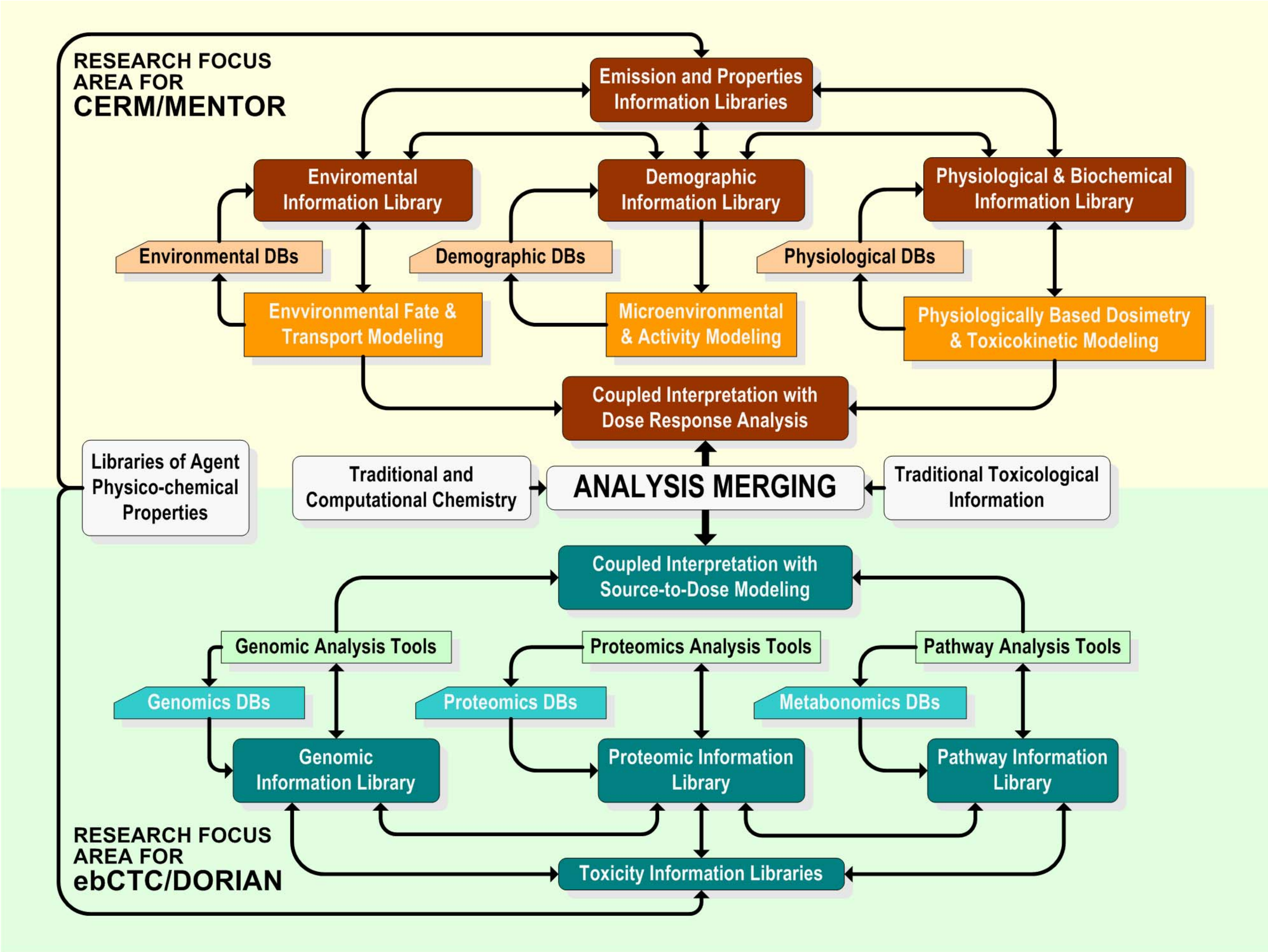
MENTOR & DORIAN

- MENTOR & DORIAN are evolving "open" computational toolboxes intended to support analyses of processes and data across the source-to-outcome sequence
  - Pre-development of MENTOR initiated with ATSDR funding in mid-90s ("EDMAS"); currently in 7th year of USEPA-ORD funding
  - Development of DORIAN is part of ebCTC research effort
  - Both employ cluster technology (Linux/Beowulf) and multiplatform software development environments
- Current MENTOR development focus is on "four plus one" application areas – the MENTOR-Π implementation set:
  - 1A (one atmosphere)
  - 4M (multipollutant, multiroute, multipathway, multimedia)
  - 2E (emergency event)
  - 3P (physiological population pharmacokinetics)
  - • (DOT) (diagnostic and optimization tools)



MENTOR provides a consistent anthropocentric or "**Person-Oriented Modeling (POM)" framework** of analysis, driven by PBPK modeling, for either Individual-Based or Population-Based studies;
the parameterizations of the PBPK modules must (a) cover the variability of the population spectrum, including attributes of susceptible individuals and populations and (b) address simultaneous exposures to multiple chemicals




RESEARCH FOCUS
AREA FOR
CERM/MENTOR
Emission and Properties
Information Libraries
Enviromental
Information Library
Demographic
Information Library
Physiological & Biochemical
Information Library
Environmental DBs
Demographic DBs
Physiological DBs
Envvironmental Fate &
Transport Modeling
Microenvironmental
& Activity Modeling
Physiologically Based Dosimetry
& Toxicokinetic Modeling
Coupled Interpretation with
Dose Response Analysis
Libraries of Agent
Physico-chemical
Properties
Traditional and
Computational Chemistry
ANALYSIS MERGING
Traditional Toxicological
Information
Coupled Interpretation with
Source-to-Dose Modeling
Genomic Analysis Tools
Proteomics Analysis Tools
Pathway Analysis Tools
Genomics DBs
Proteomics DBs
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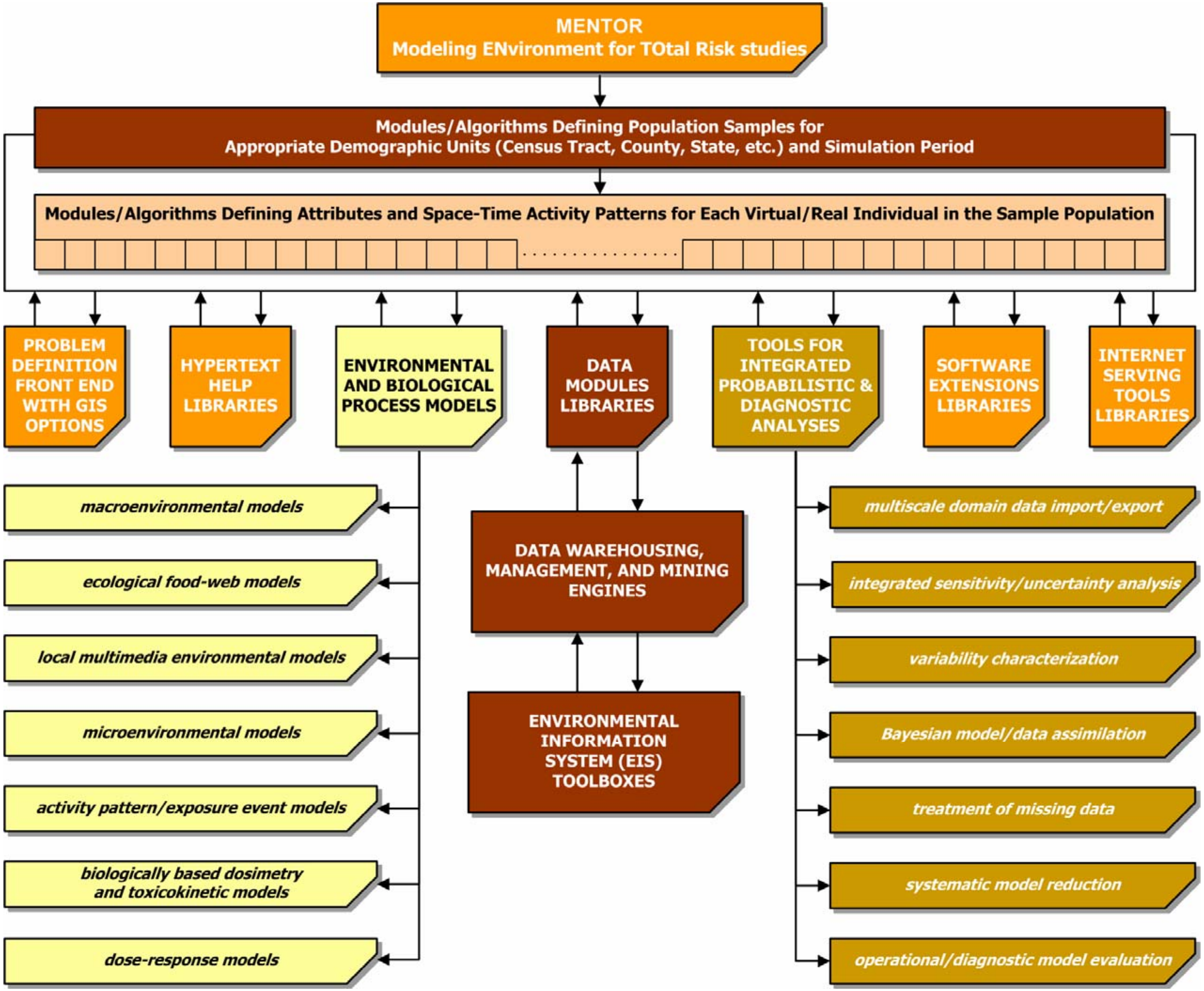
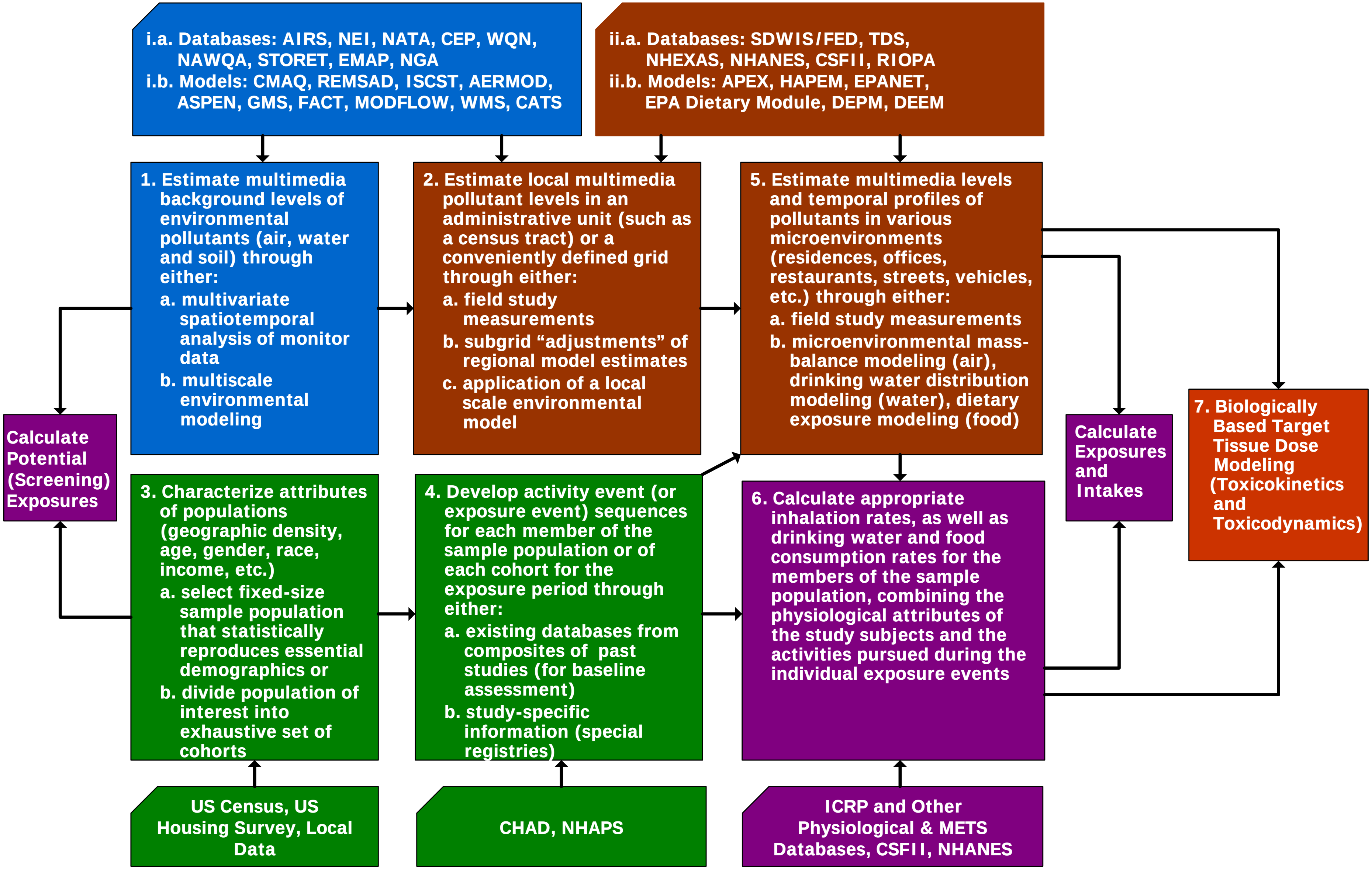
RESEARCH FOCUS
AREA FOR
ebCTC/DORIAN
Toxicity Information Libraries



MENTOR
Modeling ENvironment for TOtal Risk studies
Modules/Algorithms Defining Population Samples for
Appropriate Demographic Units (Census Tract, County, State, etc.) and Simulation Period
Modules/Algorithms Defining Attributes and Space-Time Activity Patterns for Each Virtual/Real Individual in the Sample Population
PROBLEM DEFINITION FRONT END WITH GIS OPTIONS
HYPERTEXT HELP LIBRARIES
ENVIRONMENTAL AND BIOLOGICAL PROCESS MODELS
DATA MODULES LIBRARIES
TOOLS FOR INTEGRATED PROBABILISTIC & DIAGNOSTIC ANALYSES
SOFTWARE EXTENSIONS LIBRARIES
INTERNET SERVING TOOLS LIBRARIES
macroenvironmental models
ecological food-web models
local multimedia environmental models
microenvironmental models
activity pattern/exposure event models
biologically based dosimetry and toxicokinetic models
dose-response models
DATA WAREHOUSING, MANAGEMENT, AND MINING ENGINES
ENVIRONMENTAL INFORMATION SYSTEM (EIS) TOOLBOXES
multiscale domain data import/export
integrated sensitivity/uncertainty analysis
variability characterization
Bayesian model/data assimilation
treatment of missing data
systematic model reduction
operational/diagnostic model evaluation

The MENTOR modular framework for assessing cumulative/aggregate exposures and doses for multiple multimedia contaminants



Examples of databases used in MENTOR applications for the U.S. (#1)

Database Name	Developer	Website Reference
ENVIRONMENTAL RELEASES		
HazDat - Hazardous Substance Release and Health Effects Database	ATSDR	http://www.atsdr.cdc.gov/hazdat.html
NEI - National Emission Inventory (air emissions)	USEPA	http://www.epa.gov/ttn/chief/net/
TRI - Toxics Release Inventory (multimedia releases)	USEPA	http://www.epa.gov/tri/
USGS Pesticide Use Database	USGS	http://ca.water.usgs.gov/pnsp/index.html (Notice: link will be active in late June)
NCFAP Pesticide Use Database	NCFAP	http://www.ncfap.org/pesticidedb.htm
NPIRS National Pesticide Information Retrieval System	USDA/PPIS Purdue Uni.	http://aboutnpirs.ceris.purdue.edu/
GEOGRAPHY/TOPOGRAPHY/LAND USE/VEGETATION		
Digital Elevation Data	NRCS	http://www.ncgc.nrcs.usda.gov/products/datasets/elevation/index.html
NED - National Elevation Dataset	USGS	http://ned.usgs.gov/
LandScan USA (High Resolution Population Distribution Project)	USEPA-ORNL	http://www.ornl.gov/sci/gist/landscan/landscanUSA/index.html
LULC - Land Use and Land Cover	USGS	http://edc.usgs.gov/products/landcover/lulc.html
NLCD - National Land Cover Dataset	USGS	http://landcover.usgs.gov/natllandcover.asp
MODIS Satellite Land, Ocean, Atmosphere Products	NASA	http://modis.gsfc.nasa.gov/data/dataprod/index.php
METEOROLOGY/HYDROLOGY		
ARS - Agricultural Research Service Water Database (precipitation and streamflow data)	USDA	http://hydrolab.arsusda.gov/wdc/arswater.html
ASOS/AWOS - Automated Surface & Weather Observing Systems	FAA	http://www.faa.gov/asos/
NCDC - National Climatic Data Center	NOAA	http://www.ncdc.noaa.gov/oa/ncdc.html
NWS - National Weather Service	NOAA	http://www.nws.noaa.gov/

Examples of databases used in MENTOR applications for the U.S. (#2)

Database Name	Developer	Website Reference
ENVIRONMENTAL/ MICROENVIRONMENTAL CONTAMINANT LEVELS		
AQS - Air Quality System (measurements of outdoor concentrations for criteria and toxic air pollutants)	USEPA	http://www.epa.gov/ttn/airs/airsaqs/
CEP -Cumulative Exposure Project (modeled estimates of outdoor and exposure concentrations for air toxics in census tract levels)	USEPA	http://www.epa.gov/sab/pdf/ihea9604.pdf
EMAP - Environmental Monitoring and Assessment Program (ecological monitoring data)	USEPA	http://www.epa.gov/emap/
Mercury in Fish Monitoring Program 1990-2004 (measurements of mercury concentrations in fish)	USFDA	http://www.cfsan.fda.gov/~frf/seamehg2.html
NADP - National Atmospheric Deposition Program (data for the chemistry of precipitation for monitoring of geographical and temporal long-term trends)	Multiple Agencies	http://nadp.sws.uiuc.edu/
NATA - National Air Toxics Assessment 1996 and 1999 (modeled estimates of outdoor and exposure concentrations for air toxics in census tract levels)	USEPA	http://www.epa.gov/ttn/atw/nata1999/ http://www.epa.gov/ttn/atw/nata/
NAWQA - National Water Quality Assessment Data Warehouse (measurements of chemical, biological, and physical water quality data collected from major river basins and aquifers)	USGS	http://water.usgs.gov/nawqa/
NCOD - National Contaminant Occurrence Database (measurements of samples data for both regulated and unregulated contaminants in public water systems)	USEPA	http://www.epa.gov/safewater/data/ncod/
NGA - National Geochemical Atlas (stream sediment and solid sample media)	USGS	http://tin.er.usgs.gov/metadata/ofr-98-622.faq.html
NHEXAS - National Human Exposure Assessment Survey (Measurements of multimedia (air, drinking water, food) concentrations for toxic metals and VOCs)	USEPA	http://www.epa.gov/nerl/research/nhexas/nhexas.htm http://oaspub.epa.gov/heds/study_list_frame
NWIS - National Water Information System	USGS	http://waterdata.usgs.gov/nwis
ORCA - Ocean Resources Conservation and Assessment	NOAA	http://www.nwqmc.org/98proceedings/Papers/06-CANT.html
RIOPA – Relationship of Indoor, Outdoor, and Personal Air	HEI, NUATRC	http://www.healtheffects.org/Pubs/st130.htm
SDWIS/FED - Safe Drinking Water Information System/Federal Version	USEPA	http://www.epa.gov/safewater/sdwisfed/sfed2.html
STORET - Storage and Retrieval (water quality monitoring data)	USEPA	http://www.epa.gov/storet/
TDS - Total Diet Study (contaminant measurements of U.S. food items)	USFDA	http://www.cfsan.fda.gov/~comm/tds-hist.html
TEACH - Toxicity and Exposure Assessment for Children's Health (literature summaries - 16 chemicals of concern)	USEPA	http://www.epa.gov/teach/teachdatabase.html
WQN - Water Quality Network (stream & watershed)	USGS	http://pubs.usgs.gov/fs/FS-013-97/

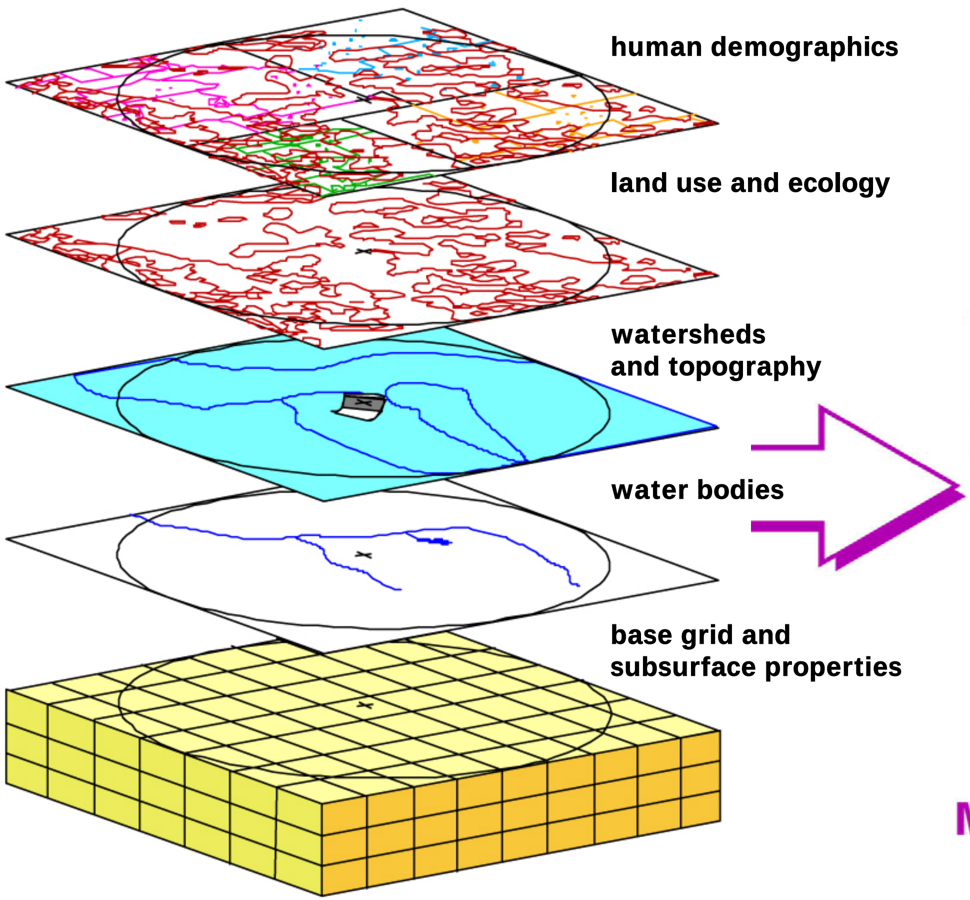
Examples of databases used in MENTOR applications for the U.S. (#3)

Database Name	Developer	Website Reference
DEMOGRAPHICS, ACTIVITY & FOOD CONSUMPTION		
AHS - American Housing Survey	USCB	http://www.census.gov/hhes/www/housing/ahs/ahs.html
CHAD - Consolidated Human Activity Database	USEPA	http://www.epa.gov/chadnet1/index.html
CSFII - Continuing Survey of Food Intakes by Individuals	USDA	http://www.barc.usda.gov/bhnrc/foodsurvey/Products9496.html
NHAPS - he National Human Activity Pattern Survey	USEPA	http://www.epa.gov/heasd/edrb/hap.htm
NMFS - National Marine Fisheries Service (estimates of recreational anglers' catch in the U.S.)	NOAA	http://www.st.nmfs.gov/st1/recreational/overview/overview.html
US Census Population Database	USCB	http://www.census.gov/population/www/
TIGER - Topologically Integrated Geographic Encoding and Referencing system	USCB	http://www.census.gov/geo/www/tiger/index.html
FOOD CONSUMPTION PATTERNS		
CSFII - Continuing Survey of Food Intakes by Individuals	USDA	http://www.barc.usda.gov/bhnrc/foodsurvey/Products9496.html
NHANES - National Health and Nutrition Examination Survey	CDC	http://www.cdc.gov/nchs/nhanes.htm
PHYSIOLOGY		
ICRP - International Commission on Radiological Protection	ICRP	http://www.icrp.org/
P^3M - Physiological Parameters for PBPK Modeling	LifeLine Group	http://www.thelifelinegroup.org/P3M/
NHANES - National Health and Nutrition Examination Survey	CDC	http://www.cdc.gov/nchs/nhanes.htm
BIOMARKERS		
NHANES - National Health and Nutrition Examination Survey	CDC	http://www.cdc.gov/nchs/nhanes.htm
NHEXAS - National Human Exposure Assessment Survey	USEPA	http://www.epa.gov/nerl/research/nhexas/nhexas.htm
NCEA Biomarkers Database	USEPA - NCEA	http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=85844

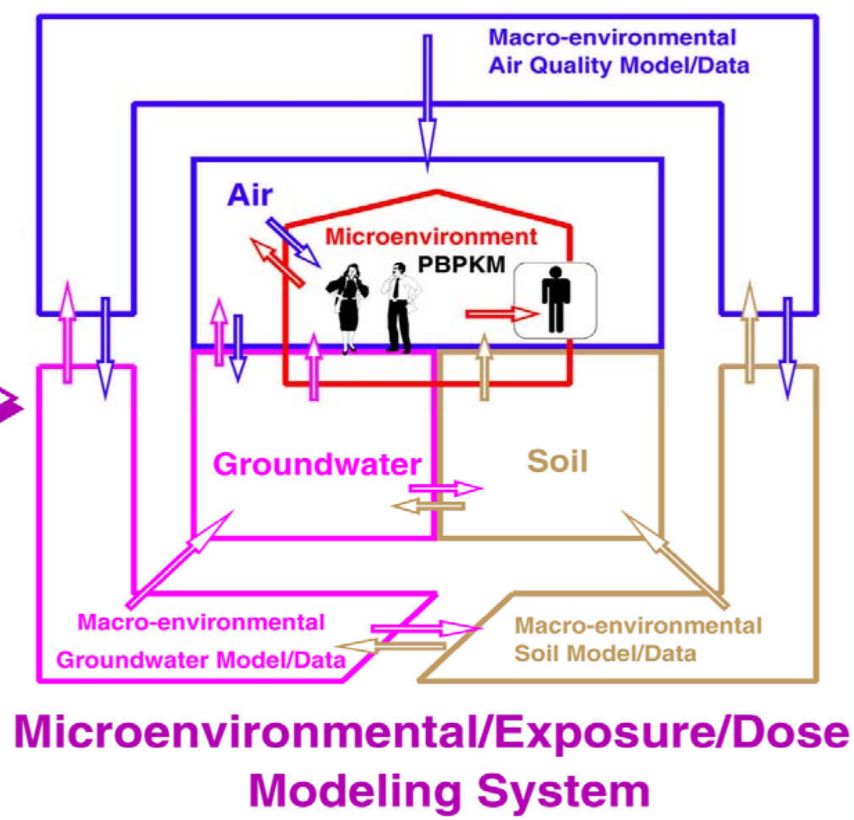
Examples of "external" environmental and exposure models linked with MENTOR for source-to-dose applications

Model Name	Developer	Website Reference
Atmospheric Models (Multiscale Emissions & Dispersion)		
CMAQ - Community Multiscale Air Quality Model	USEPA -NERL	http://www.epa.gov/asmdnerl/CMAQ/
REMSAD - Regional Modeling System for Aerosols and Deposition	ICF Consulting/ SAI	http://remsad.com/
ISCST - Industrial Source Complex Short Term Dispersion Model	USEPA	http://www.weblakes.com/lakeepa1.html#ISCST3
AERMOD - AMS/EPA Regulatory Model Improvement Committee Model	USEPA	http://www.epa.gov/scram001/dispersion_prefrec.htm#aermod
CALPUFF - California Puff Dispersion Model	USEPA/EarthTech	http://www.src.com/calpuff/calpuff1.htm
RAMS/HYPACT - Regional Atmospheric Modeling System/Hybrid Particle And Concentration Transport model	Colorado State University	http://bridge.atmet.org/users/software.php
HPAC – Hazard Prediction and Assessment Capability	DTRA	http://www.dtra.mil/
FLUENT, CFX, PHOENICS Computational Fluid Dynamics Based Models	CCL	http://www.ccl.rutgers.edu/
Groundwater and Surface Water Models		
GMS - Groundwater Modeling System	EMS Inc.	http://www.ems-i.com/GMS/GMS_Overview/gms_overview.html
MODFLOW - MODular 3D finite-difference ground-water FLOW model	USGS	http://water.usgs.gov/nrp/gwsoftware/modflow2000/modflow2000.html
SMS – Surface water Modeling System	EMS Inc.	http://www.ems-i.com/SMS/SMS_Overview/sms_overview.html
WMS - Watershed Modeling System	EMS Inc.	http://www.ems-i.com/WMS/WMS_Overview/wms_overview.html
FACT - Flow And Contaminant Transport model	USDOE	http://sti.srs.gov/fulltext/tr9900282/tr9900282.pdf
Municipal Water Network Models		
EPANET	USEPA	http://www.epa.gov/nrmrl/wswrd/epanet.html
Human Exposure Models (Air)		
APEX - Air Pollution Exposure Model	USEPA/ManTech	http://www.epa.gov/ttn/fera/human_apex.html
HAPEM - Hazardous Air Pollutant Exposure Model	USEPA	http://www.epa.gov/ttn/fera/human_hapem.html
Exposure Models (Dietary)		
DEPM - Dietary Exposure Potential Model	USEPA	http://www.epa.gov/nerlcwww/depm.htm
DEEM - Dietary Exposure Evaluation Model	USEPA	http://www.epa.gov/scipoly/sap/atozindex/deem.htm

A major issue in implementing consistent source-to-dose modeling is sequentially going to "local / neighborhood / personal resolution": MENTOR provides tools that link macroenvironmental and local information with microenvironmental conditions and human activities



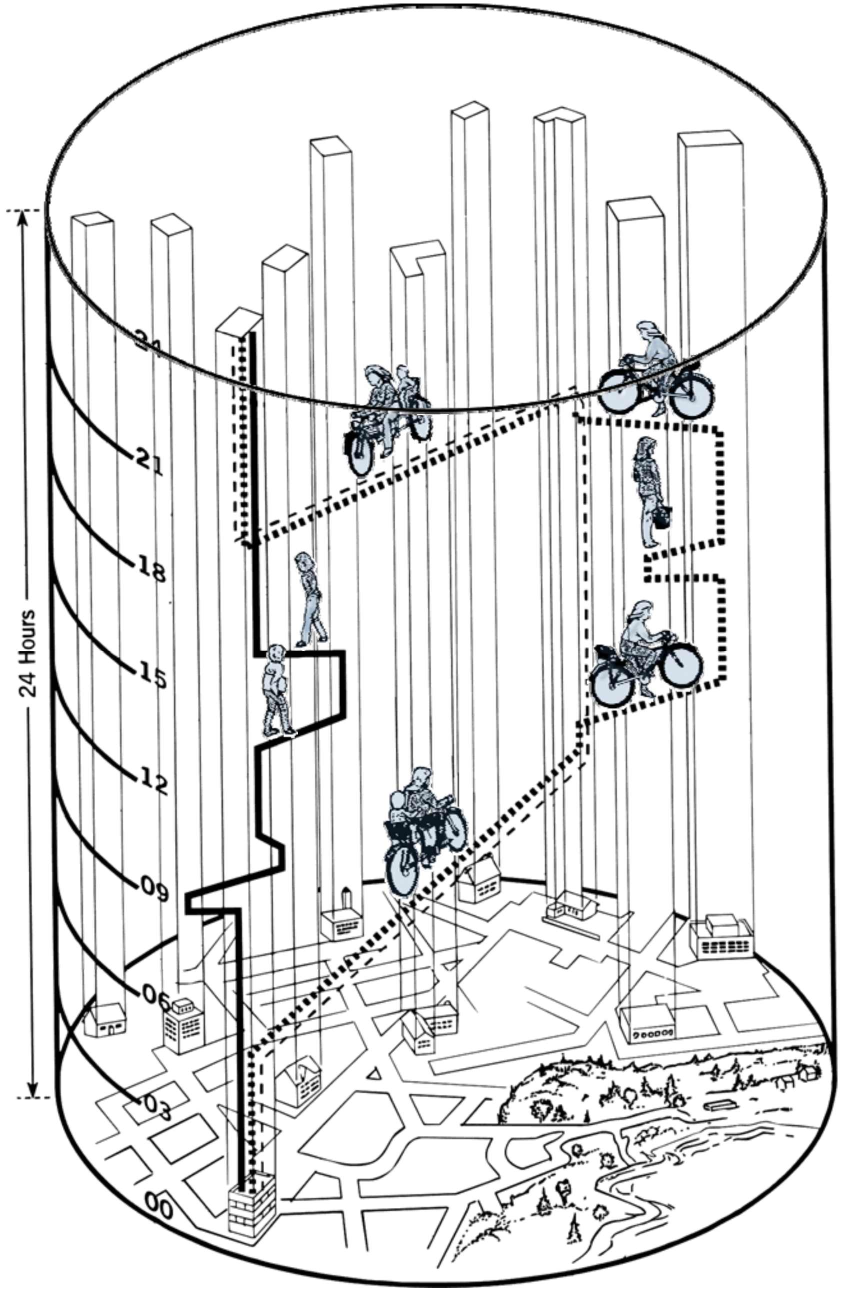
Source: 3MRA User Guide 2002



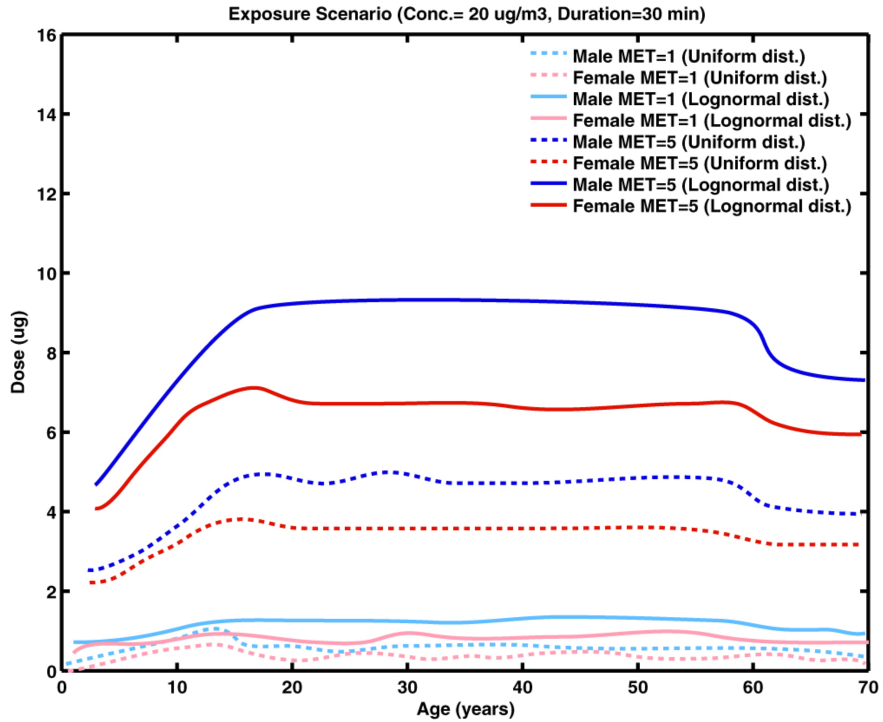
Source: Georgopoulos et al., ES&T, 1997, 31(1)

Fact: **In addition to time and geographic location, factors such as: dynamic microenvironmental attributes, demographic and physiological characteristics, activity patterns, 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)

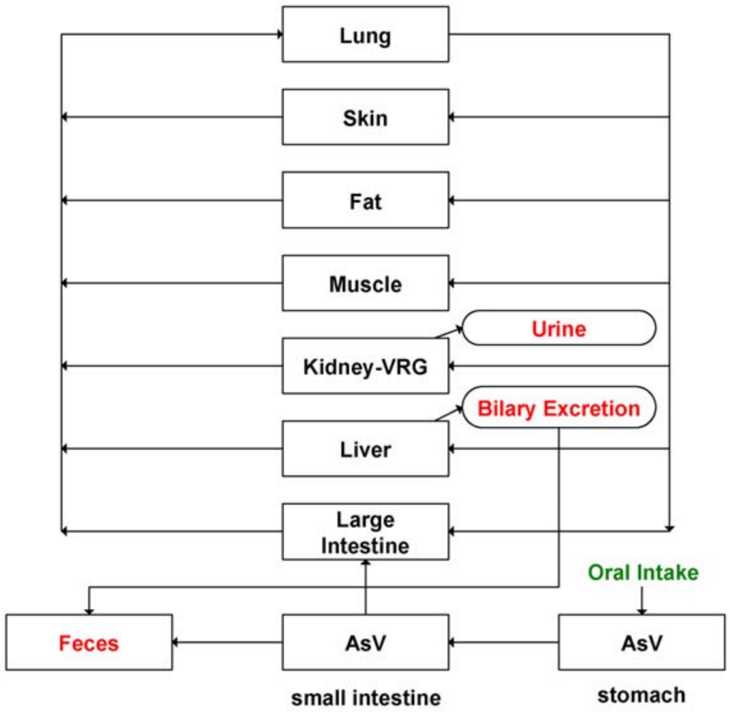


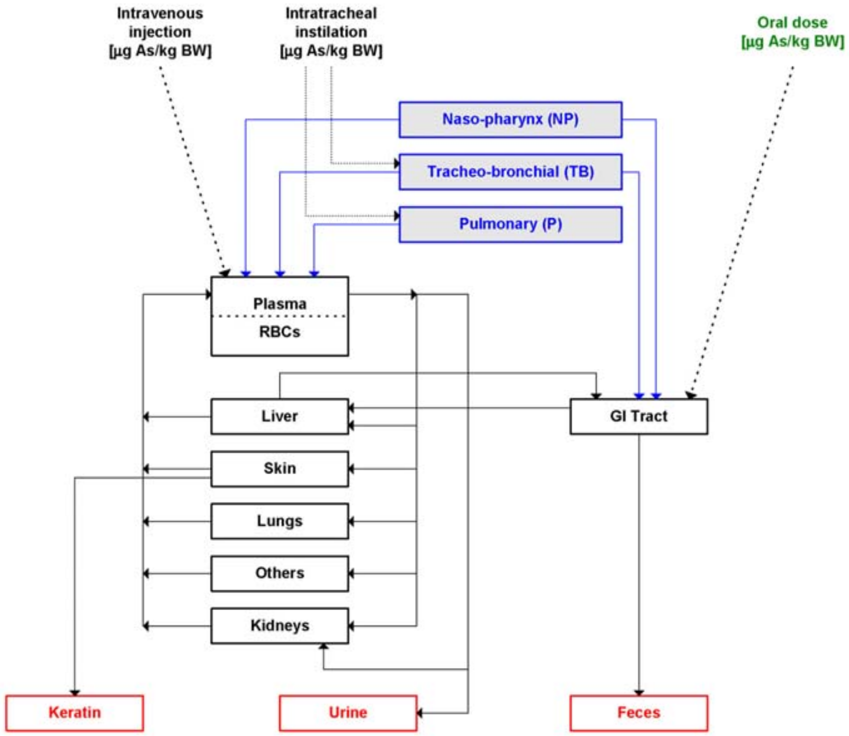
People/Time/Space: Adapted from Parkes & Thrift (1980)



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

PBPK structure (and parameterizations) traditionally depend on chemical properties
Special example: alternative human PBPK models for arsenic

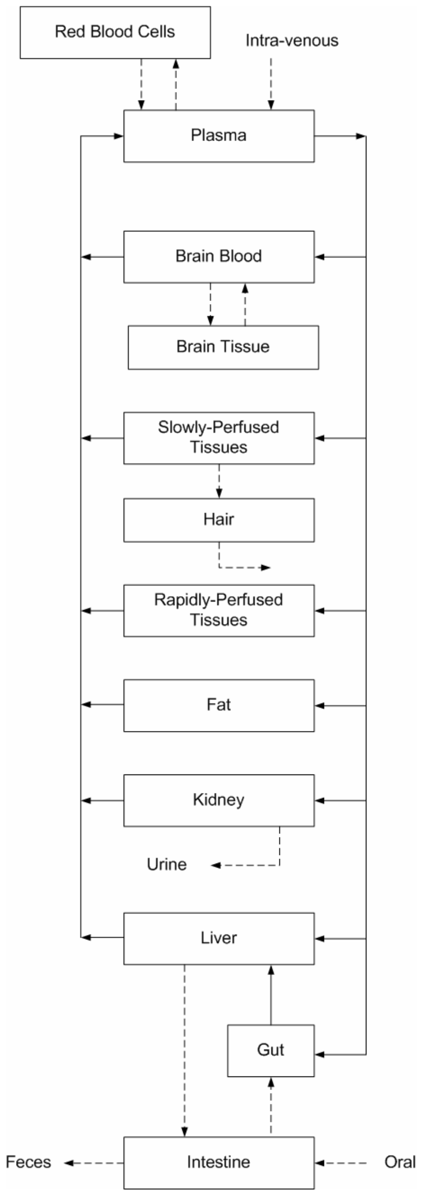




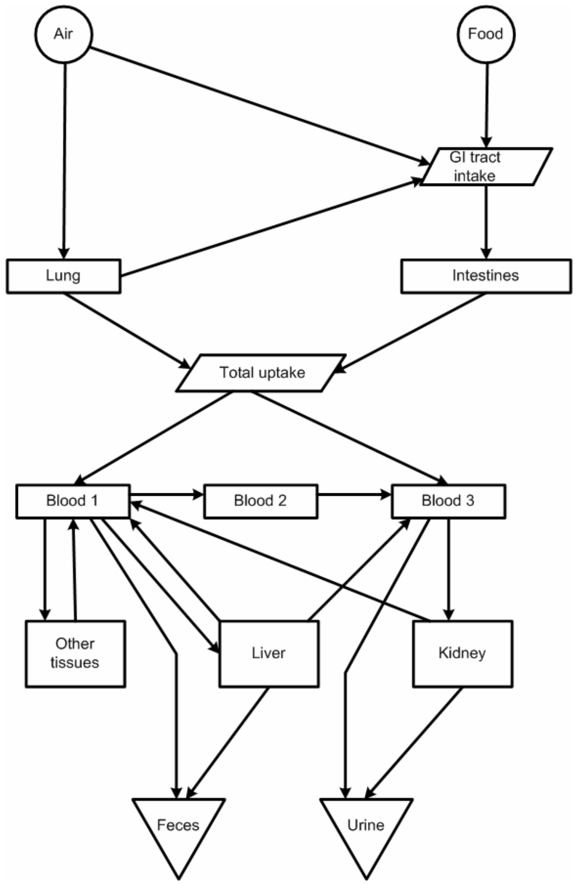
COMPARISON TABLE:

	Yu's model	Mann's model
Model structure	8 tissue compartments	5 tissue compartments
Exposure route	Oral only	Oral and inhalation
Distribution	Flow-limited	Diffusion-limited
Metabolism	Reduction reaction of inorganic arsenic in all compartments, and biotransformation in liver and kidney.	Reduction/oxidation of inorganic arsenic in plasma and kidney, and bio-transformation in liver.
Excretion	Renal and Fecal excretion	Renal, Fecal and Dermal excretion.

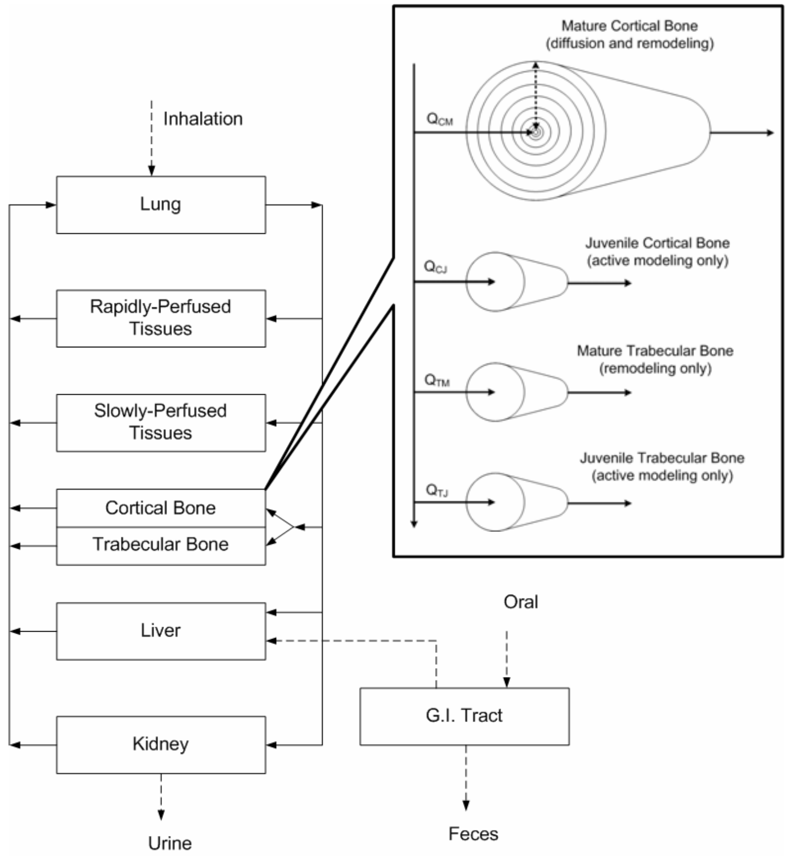
The need exists for mechanistic consistency in PBTK models for metals



Methylmercury (Shipp et al. 2000)



Cadmium (Nordberg/Kjellstrom 1979)

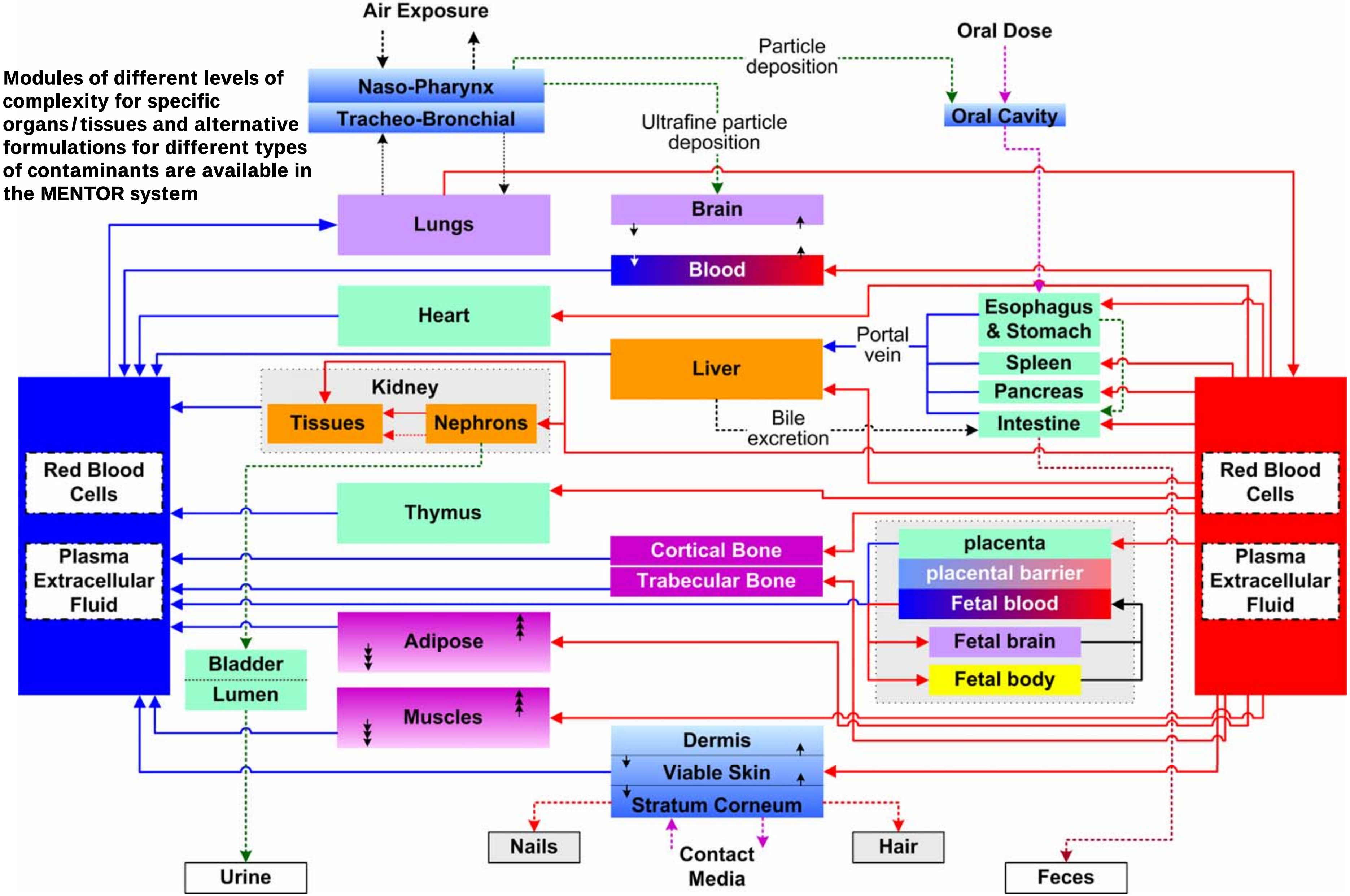


Lead (O'Flaherty 1993)

PBTK models of metals have vastly different mechanistic structures due differences in dominating transport processes. However, the multi-component nature of toxic metal exposures and potential metal-metal interactions highlight the need for simultaneous and consistent toxicokinetic modeling of these chemicals.

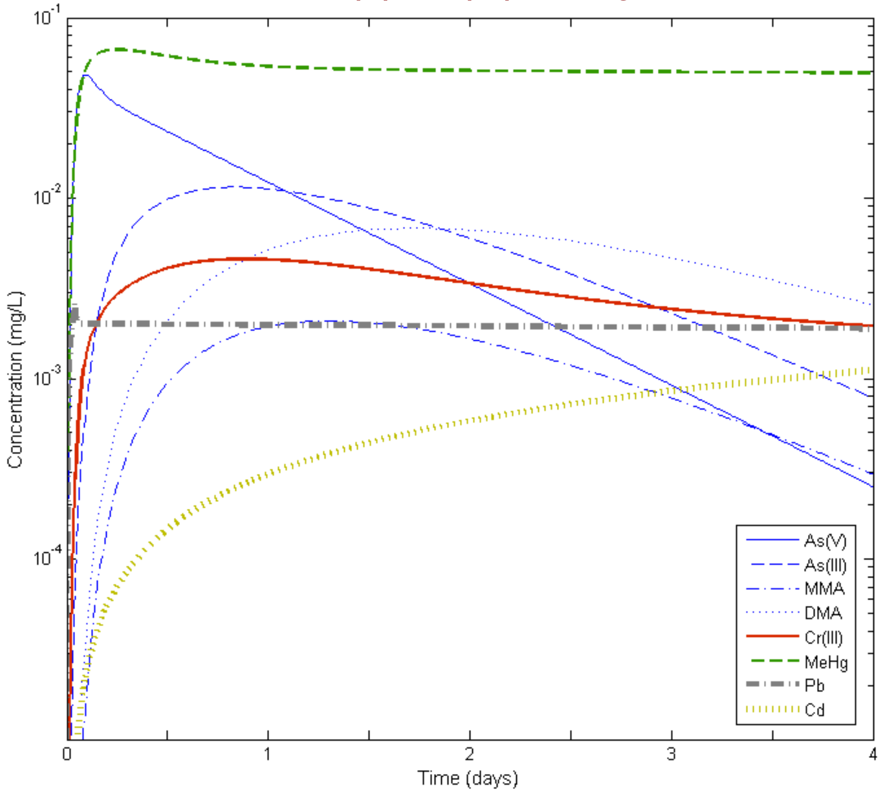
The physiologically based toxicokinetic modules of MENTOR-3P aim to characterize cumulative & aggregate exposure, uptake and target tissue dose for multiple chemicals

Modules of different levels of complexity for specific organs/tissues and alternative formulations for different types of contaminants are available in the MENTOR system



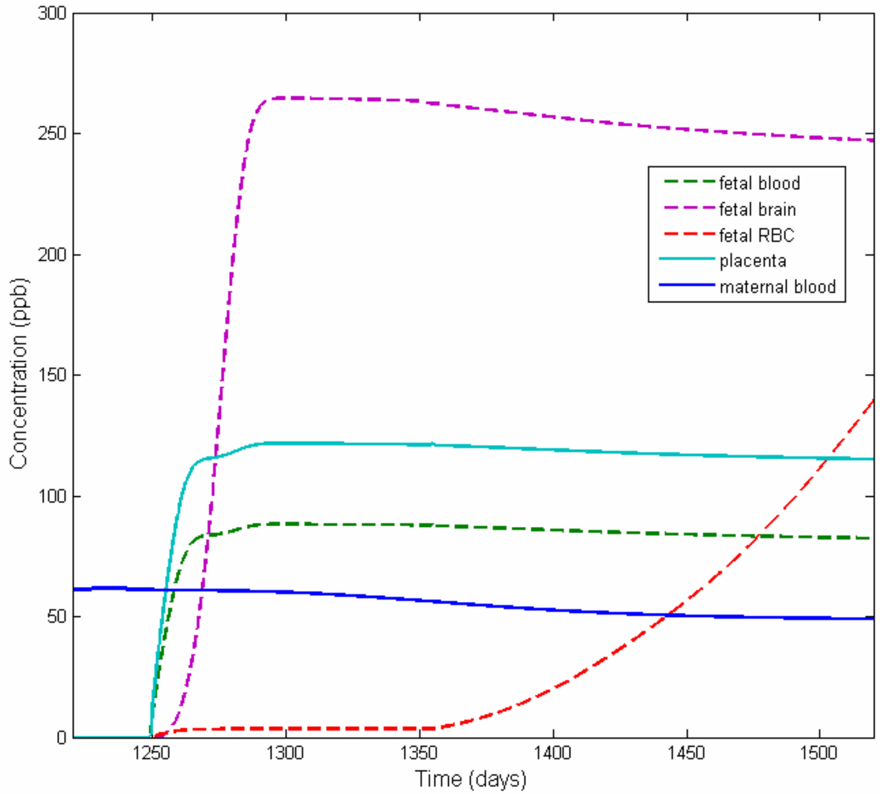
Example demonstration: Individual-based modeling

Standard 70 kg male consuming a 1 mg oral dose each of As(V), Cr(VI), MeHg, Pb, and Cd.



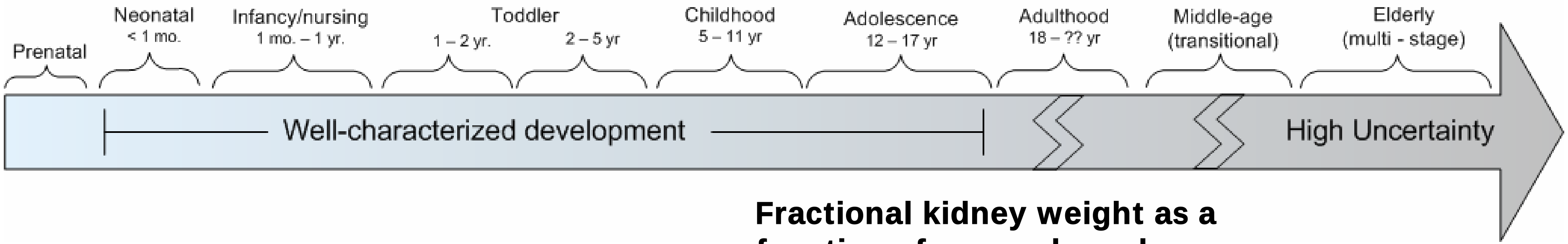
Simulated concentration profile of chemicals and metabolites in the liver of a standard reference male ingesting a mixture of metals.

Standard 65 kg female consuming 65 μg methylmercury per day (gestation at day 1250)



Simulated concentration profile of methylmercury for a pregnant woman and fetus. The physiological parameters of both the maternal and fetal systems are changing over time.

Modeling considerations for aging and toxicokinetics



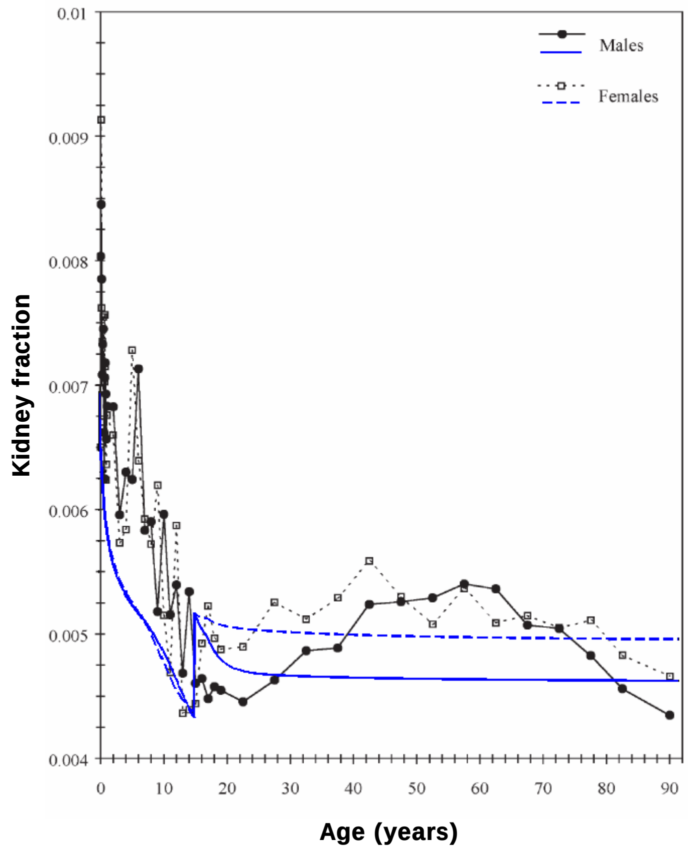
Estimates exist for physiological values over entire spectrum of aging

- P3M database provides "mean" values based on NHANES III measurements
- Literature models (such as HUMTRN) provide parameterized functions of physiological parameters (dependent on age) of age for lifetime exposure studies (including prenatal)
- However, high uncertainty and variability still exist in the aging population

Physiochemical/biochemical changes with age are not as well defined

- Databases relating age, enzyme levels, and toxicokinetic parameters for specific compounds in humans are needed
- Sensitivity analysis of these parameters on a case-by-case basis is needed

Fractional kidney weight as a function of age and gender



Blue: P3M function (Reference human)

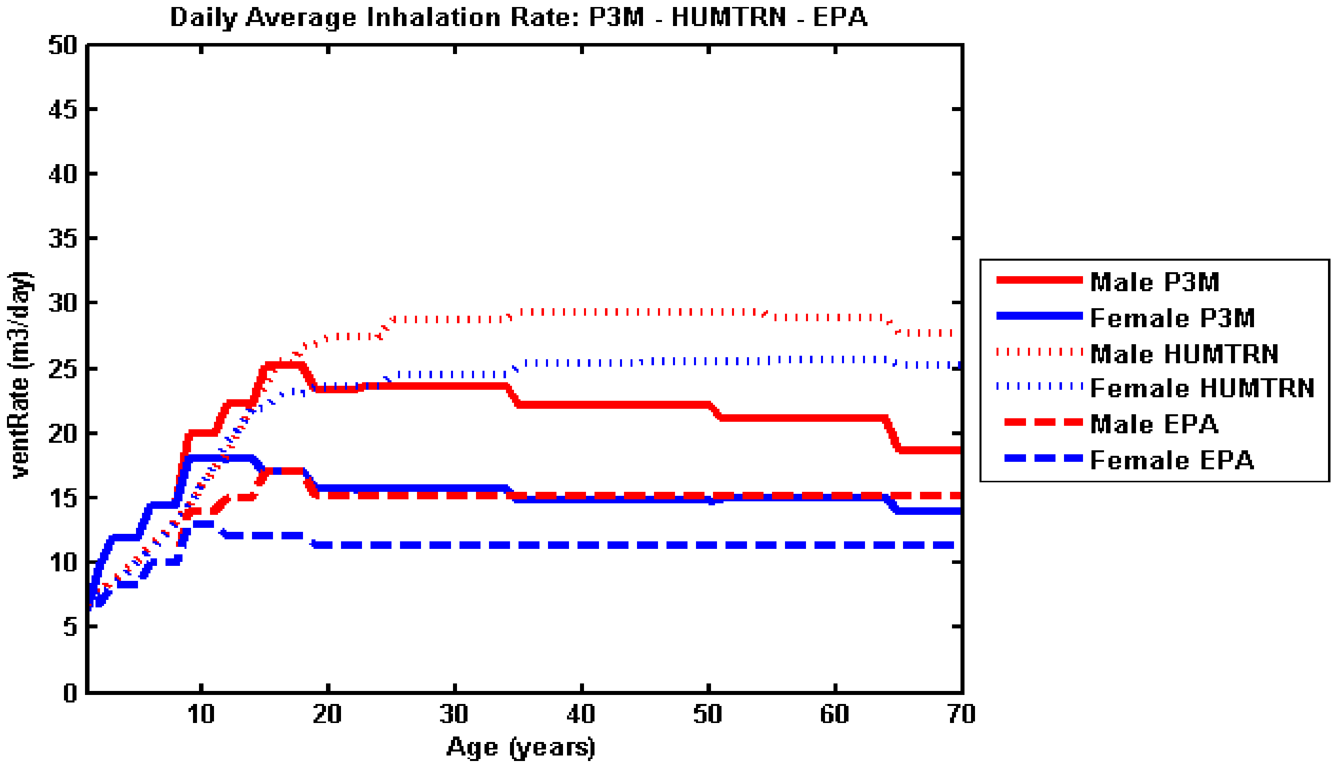
Black: Data (Japanese population)

Clewell, et al. 2002. *Crit Rev Toxicol* 32 (5):329-89.

The effects of aging: respiratory system

Parameter	Definition	Aging Effects	Cause
RV	Residual Volume	Air trapping increases ~50% from 20-70 yrs	Chest wall stiffens with diminished elastic recoil
CV	Closing Volume	Increases linearly with age from 10% of TLC at 20 yrs of age to 30% of TLC at 70 yrs	Loss of lung elasticity means that by the mid-40s, airway closure occurs, while supine, at the end of a normal tidal volume, and by the mid-60s, closure occurs while erect (i.e. at FRC)
VC	Vital Capacity	Decreases to 75% of best values; 21-34mL/yr male, 19-29mL/yr female	Chest wall stiffens with diminished elastic recoil
FRC	Functional Residual Capacity	Increases with age	Increased elastic recoil of chest wall + diminished elastic recoil of lung parenchyma
TLC	Total Lung Capacity	Constant	Diminished elastic recoil of lungs balanced by increased elastic load from chest wall
FVC	Forced Vital Capacity	Increases up to 20 years of age in females and 27 years of age in males, then diminishes with advancing age	Change in chest wall stiffness/compliance of lungs
FEV_1	Forced Expiratory Volume (1 sec)	Increases up to 20 years of age in females and 27 years of age in males, then diminishes with advancing age; annual decrease of 20mL in 25-39yrs and 38mL in ≥ 65yrs	Change in chest wall stiffness/compliance of lungs
CV	Closing Volume	May reach 55-60% of TLC and equal FRC	Premature closing of terminal airways due to loss of supporting tissues around the airways
Alveolar Gas Exchange	O_2 exchange	Declines at rate of 0.5% per year	Decline correlates to decrease in internal surface area of lung with age; 15% decrease in functional alveolar surface area by age 70
Peak Flow Rates	Maximum Flow	Decrease with age	No changes for inspiratory flow curves, only change in maximum inspiratory flow
R_{aw}	Airway Resistance	Constant	No age effects when adjusted for lung volume
V_T	Tidal Volume	Decreases with age	Multifactorial cause including altered receptor function; since respiratory rates are unchanged, elderly will have diminished response to hypoxia and hypercapnia

Effects of aging on the respiratory system
(There are significant differences among existing models)



Daily average ventilation rate (m^3/day) increases during the development and maturation of the lung and reaches a plateau. Later in adulthood, a slow decline begins in this parameter.

These values for daily average ventilation rate were calculated using the P^3M and HUMTRN models. The recommended values from EPA's *Exposure Factors Handbook* (1997) are included for reference.

Table summarizing age-related changes in humans over 65 and their consideration in MENTOR-3P

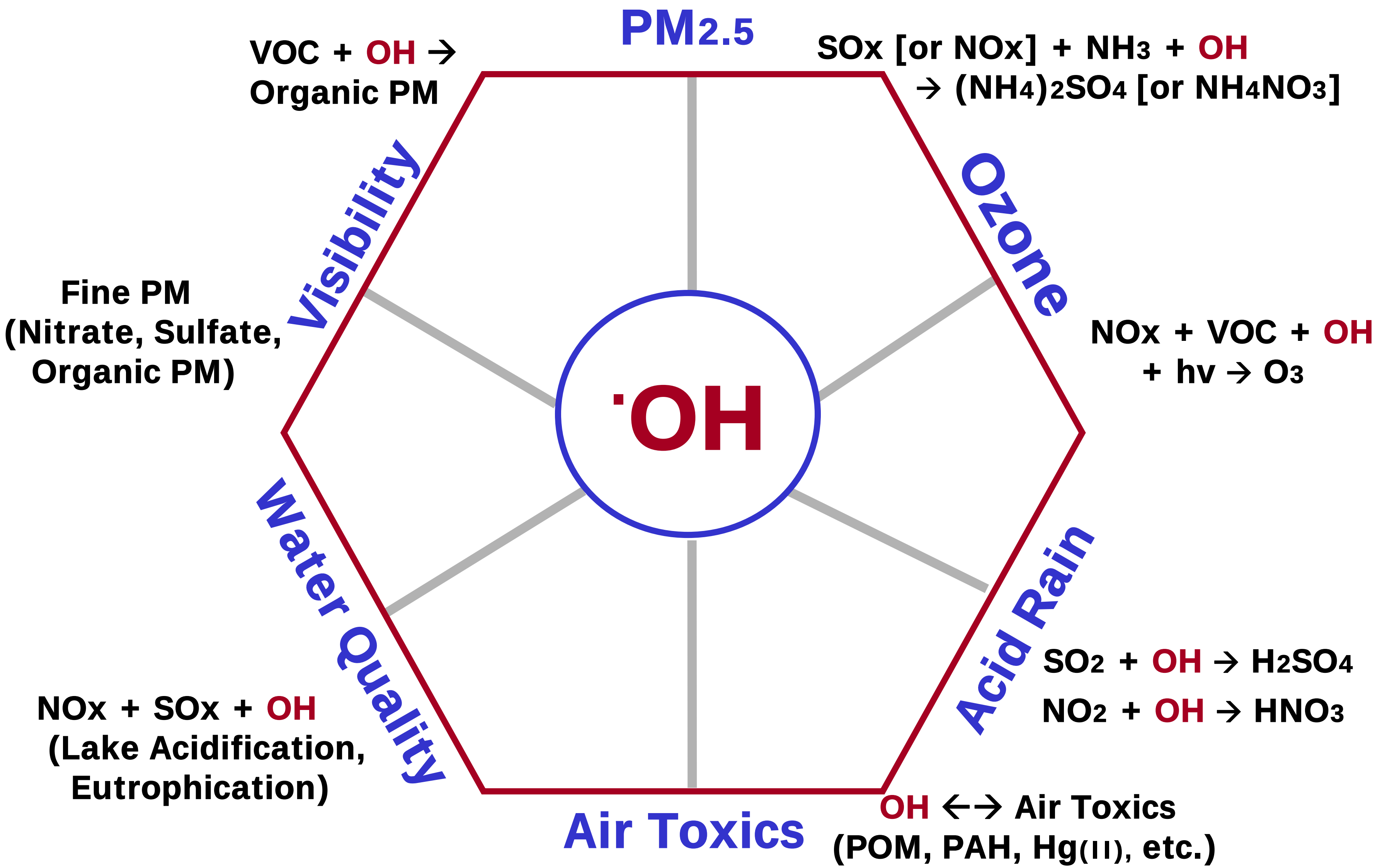
System or feature	Subcomponent	Effect of aging	Considered in MENTOR-3P
Body composition	Body fat	↑	x x
	Lean body mass	↓	x x
	Total body water	↓	-
	Plasma albumen	↓	-
Hepatic / digestive	Size of liver	↓	x x
	Hepatic blood flow	↓	x
	Enzyme concentration	↓	-
	Splanchnic blood flow	↓	x
	Gastric pH	↑	-
	G.I. tract transit time	↑	-
Renal	Glomerular filtration rate	↓	x
	Renal plasma flow	↓	x
	Renal mass	↓	x x
	Tubular secretion/reabsorption	↓	-
Cardio / pulmonary	Vital lung capacity	↓	x x
	Lung elasticity	↓	-
	Inhalation rate (scaled by BW)	↑	x x
	Cardiac output	↓	x x
Other	Bone loss	↑	x
	Immune system function	↓	-
	Protein affinity	↓	-
	Dermal absorption	↑	x x

x x full consideration; x partial consideration; - no consideration

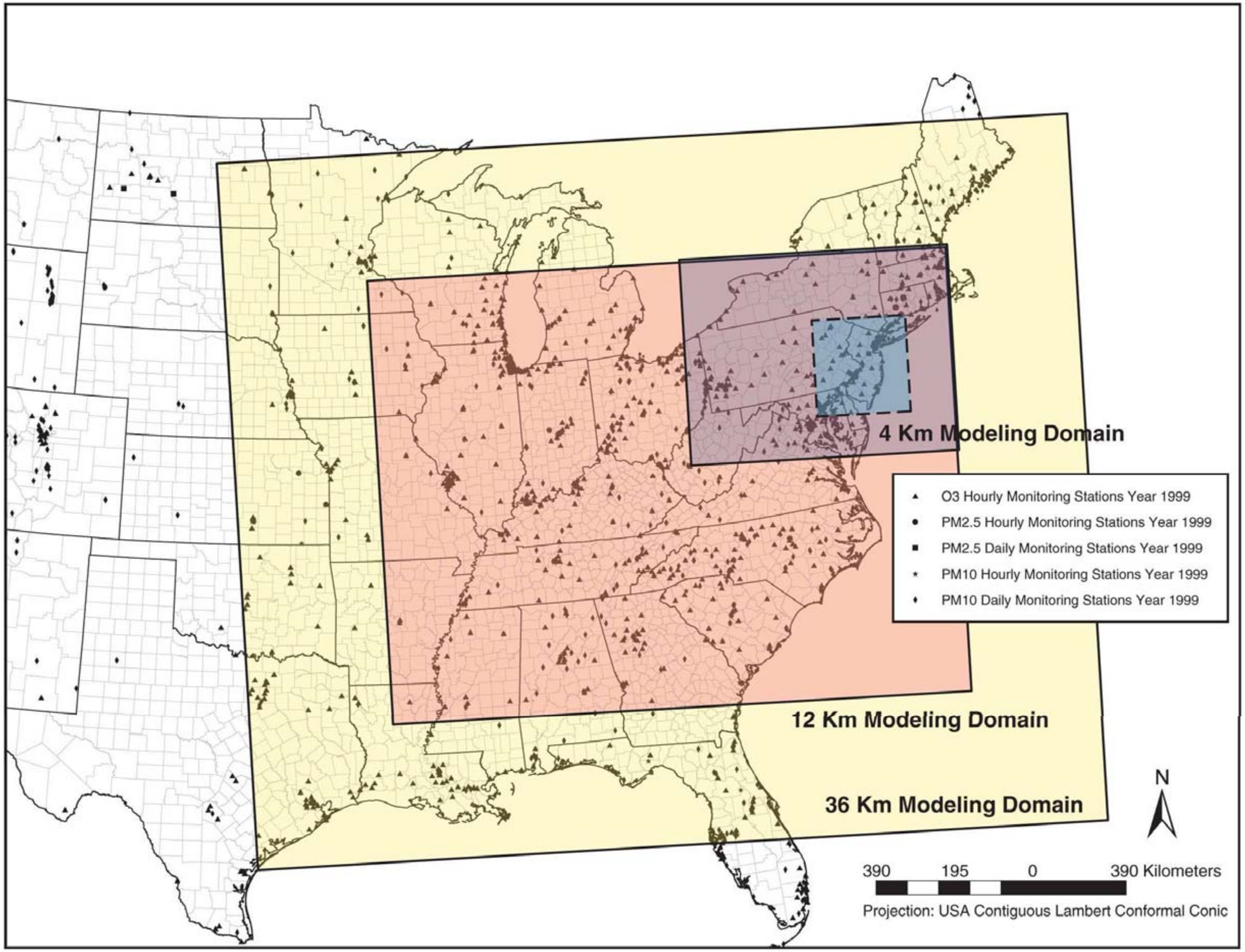
Examples of Mechanistic Source-to-Dose Studies

**1. One Atmosphere Analyses of Human Exposure
to Co-Occurring Air Pollutants
(ozone, particulate matter and inert reactive air toxics)**

MENTOR-1A employs the “One-Atmosphere” approach to account for physical/chemical transformations (e.g. involving ·OH) over multiple spatial/temporal scales that “couple” the dynamics of multiple gaseous and particulate air pollutants



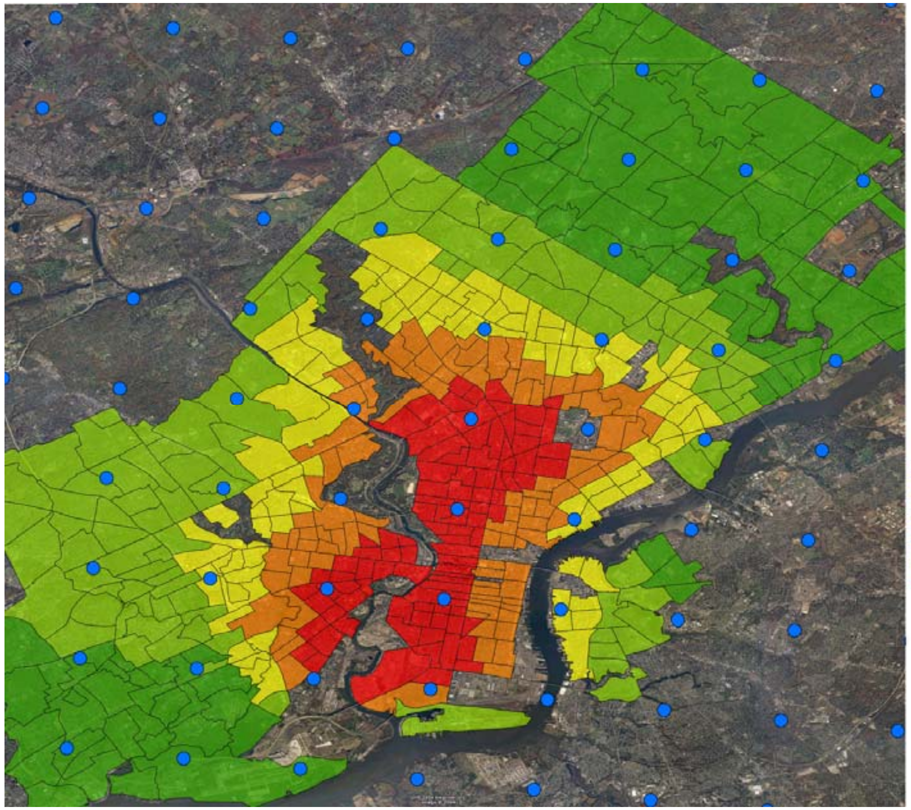
Example domains for multiscale regional to local air quality and exposure modeling applications



Map of Models-3/CMAQ air quality modeling domain with 36 km, 12 km, and 4 km horizontal grid resolutions employed in the MENTOR applications

Philadelphia and Camden modeling area census tracts and photochemical air quality model nodes

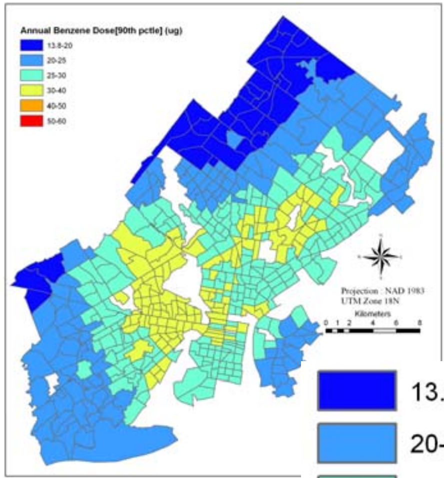
Example of local scale results from "episodic" MENTOR-1A application employing CMAQ: comparison of PM 2.5 outdoor concentrations with the 95th percentiles of 24-hour aggregated PM 2.5 total dose for 7/19/1999

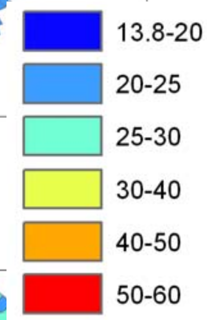


This application of MENTOR-1A incorporates an extension of USEPA's SHEDS (Stochastic Human Exposure and Dose Simulation) methodology

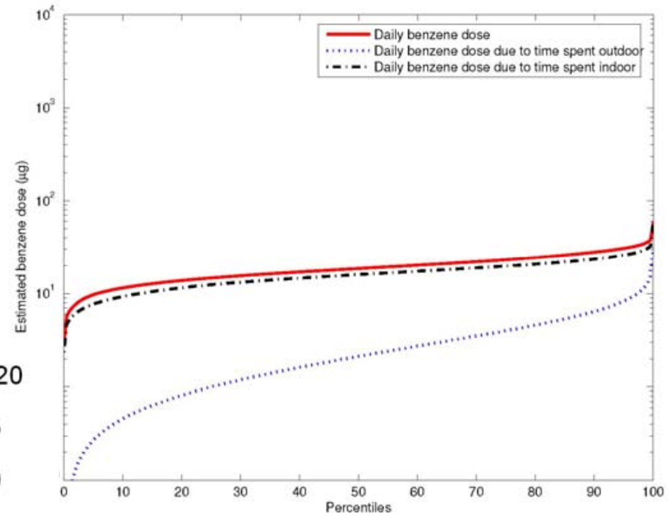
MENTOR-1A estimates of the 90th percentile of annual/seasonal averages of daily personal benzene intake ("dose") (μg) due to outdoor air for 2001

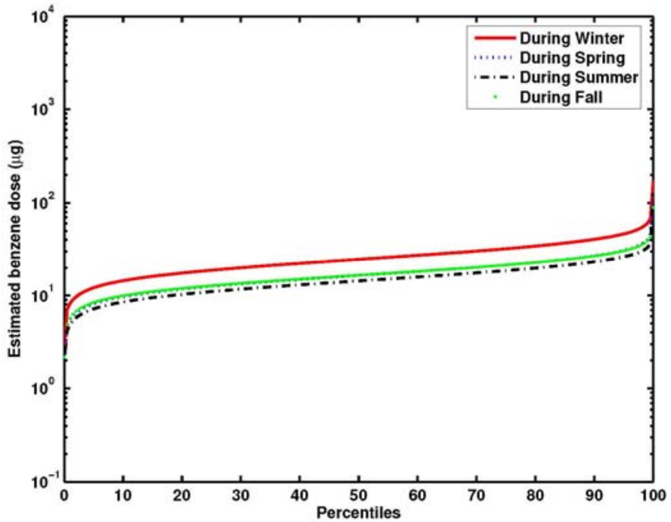
This application of MENTOR-1A incorporates an extension of USEPA's SHEDS (Stochastic Human Exposure and Dose Simulation) methodology

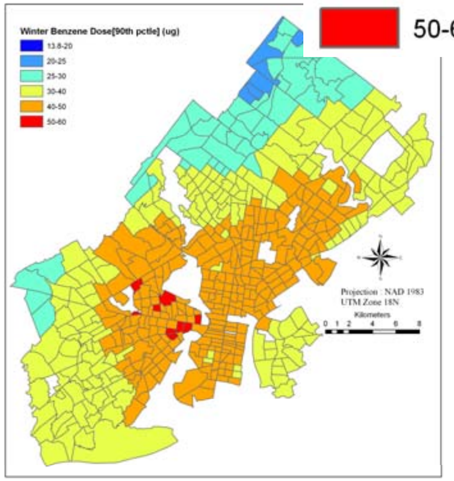




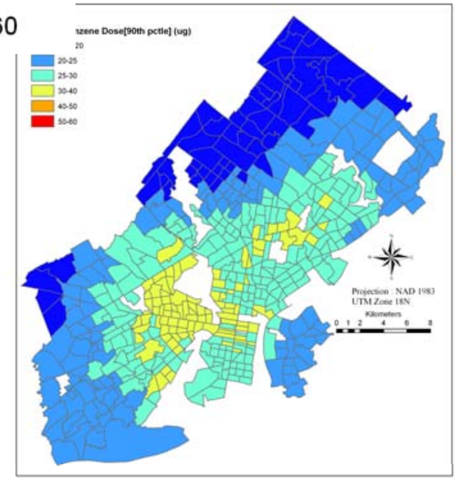
Annual



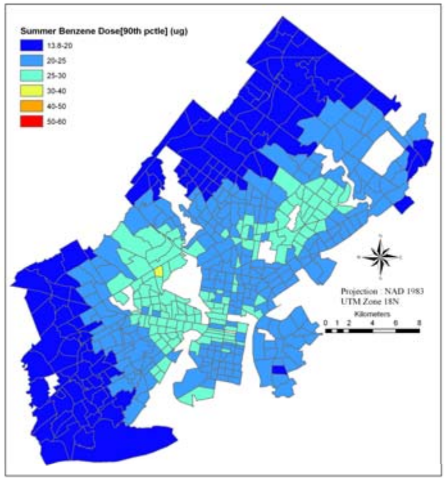




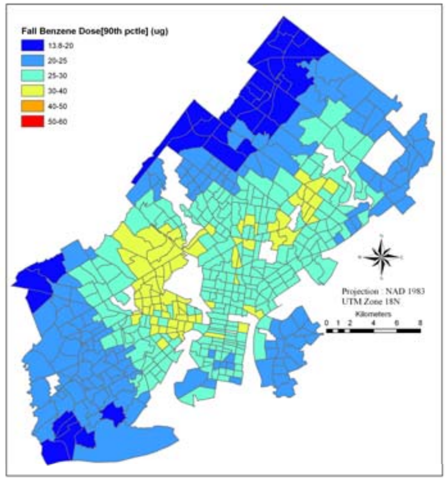
Winter



Spring

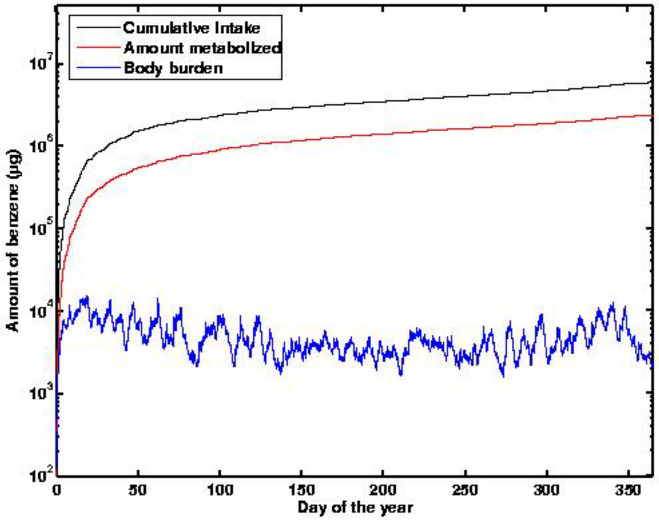


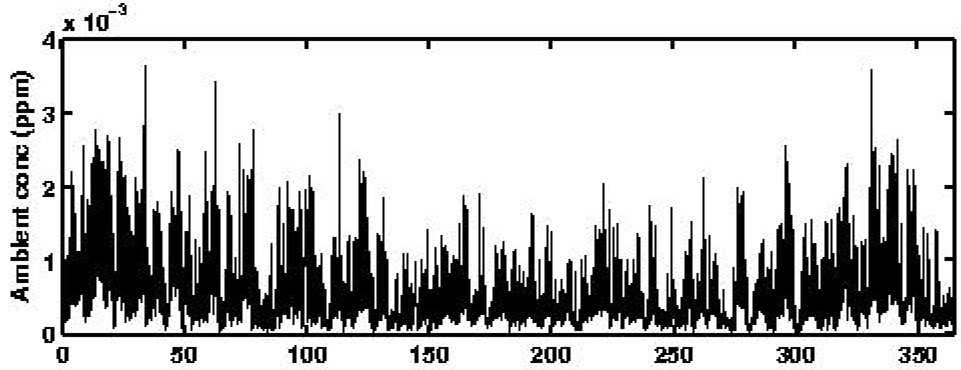
Summer

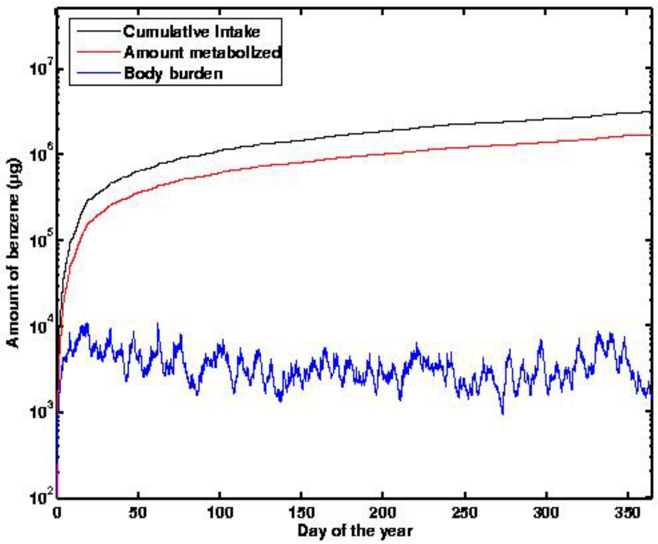


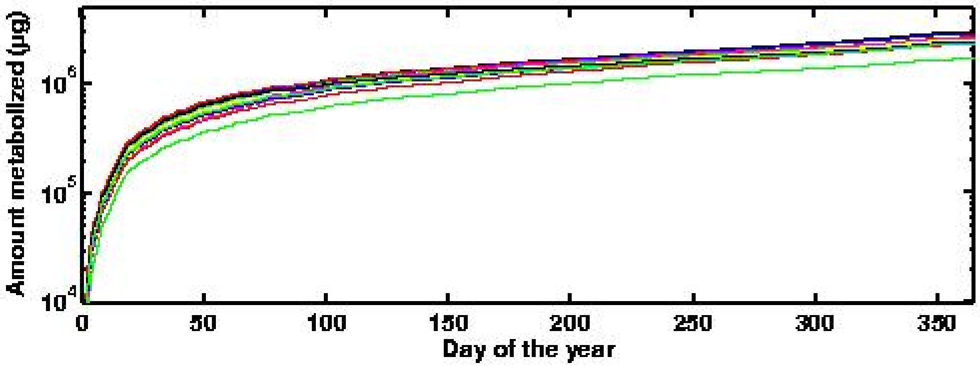
Fall

Application of the PBTK modules of MENTOR-1A: 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)





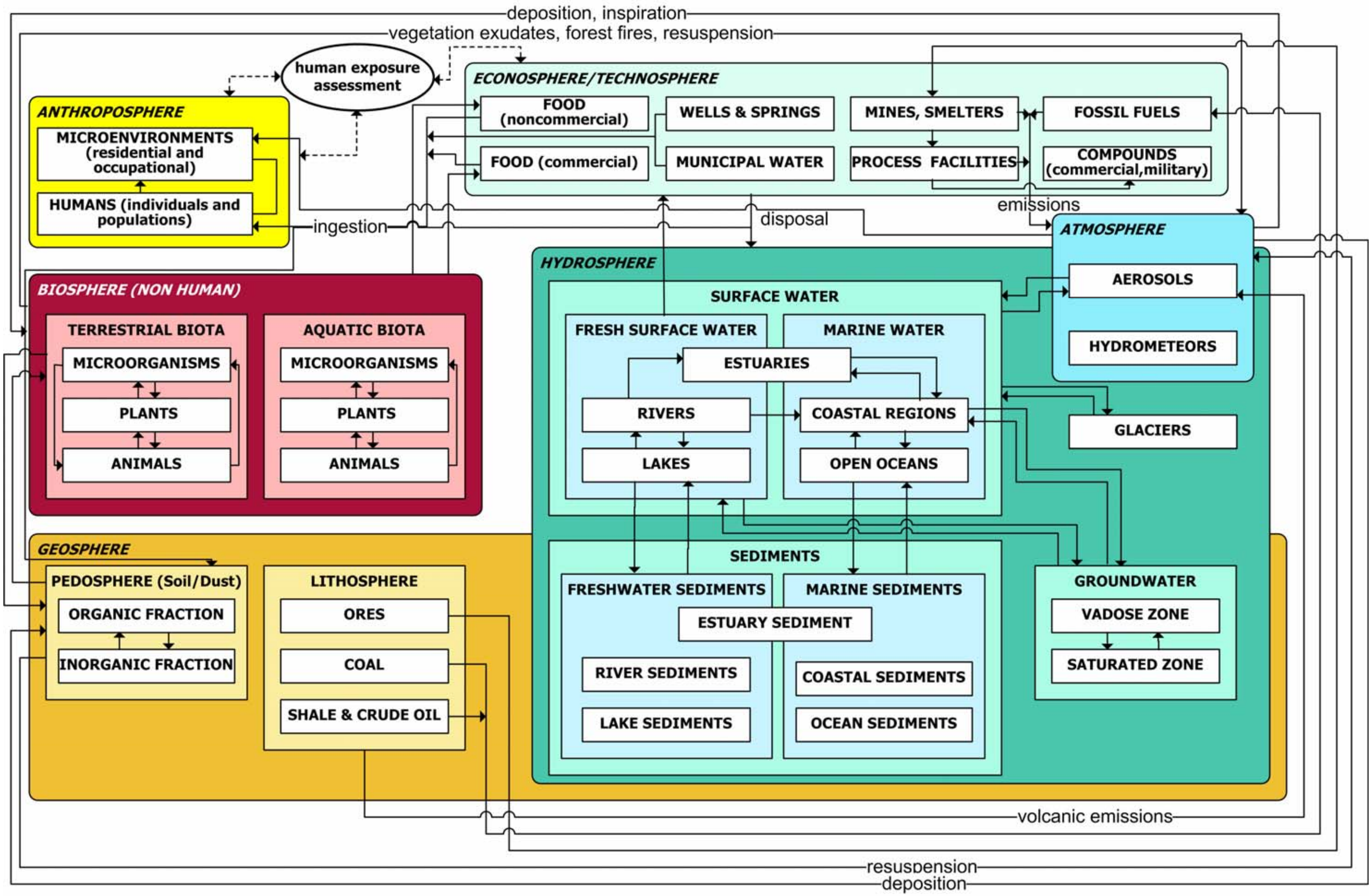




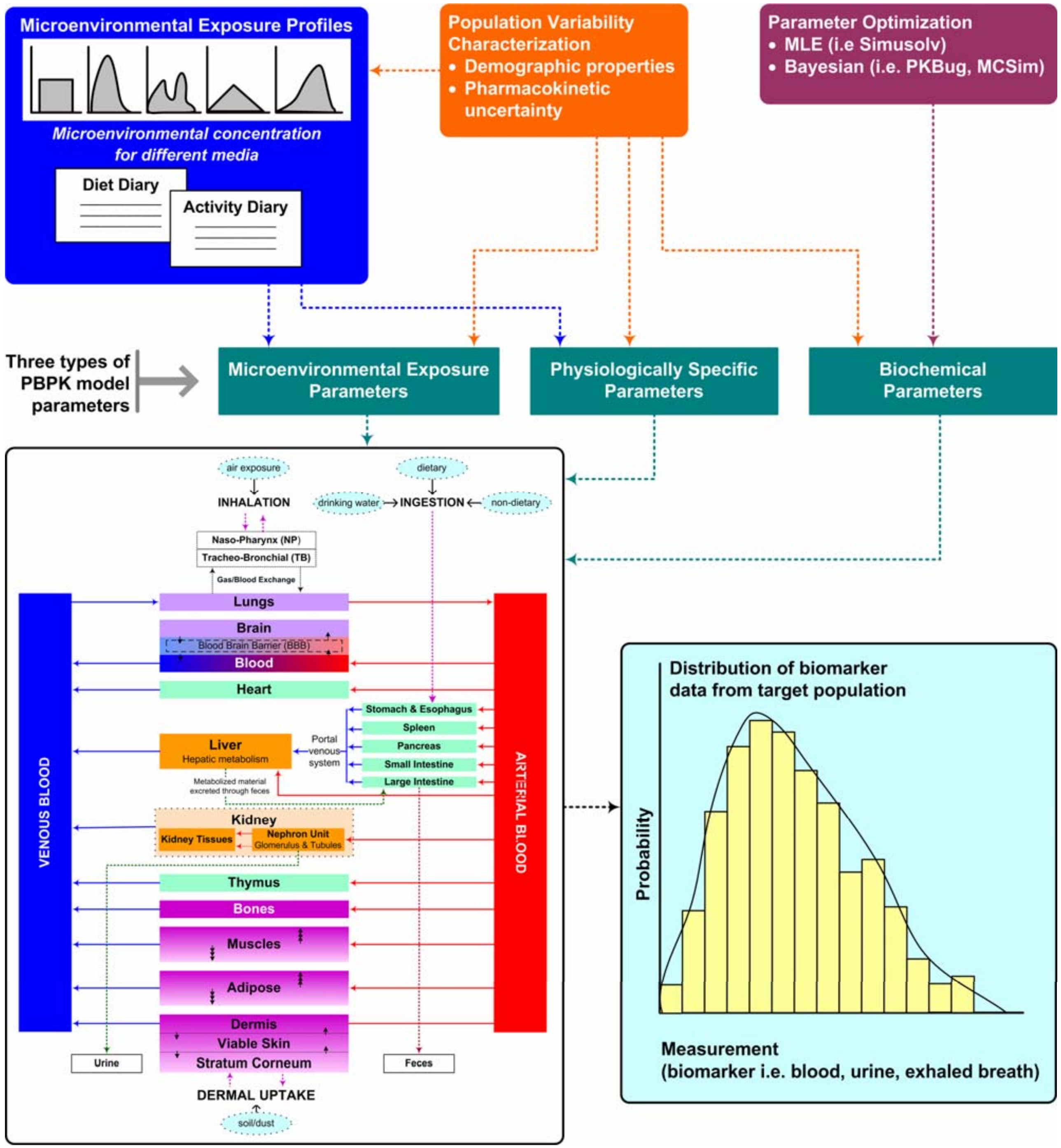
Examples of Mechanistic Source-to-Dose Studies

2. Multiroute / Multipathway Analyses of Human Exposure to Multimedia Pollutants (Case studies: As and TCE, Hg / MeHg)

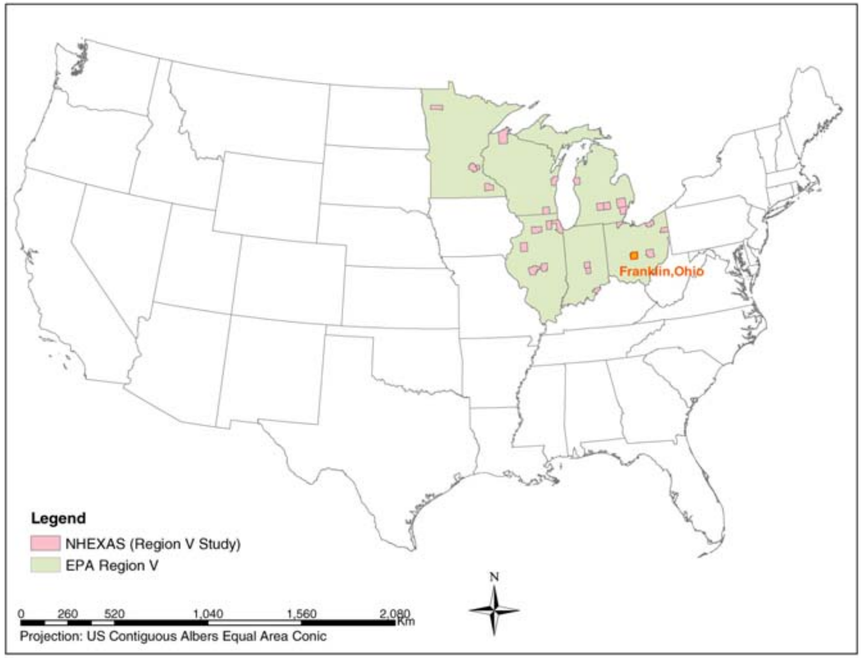
MENTOR-4M provides a unified multimedia/multiscale modeling approach to support aggregate/cumulative exposure assessments



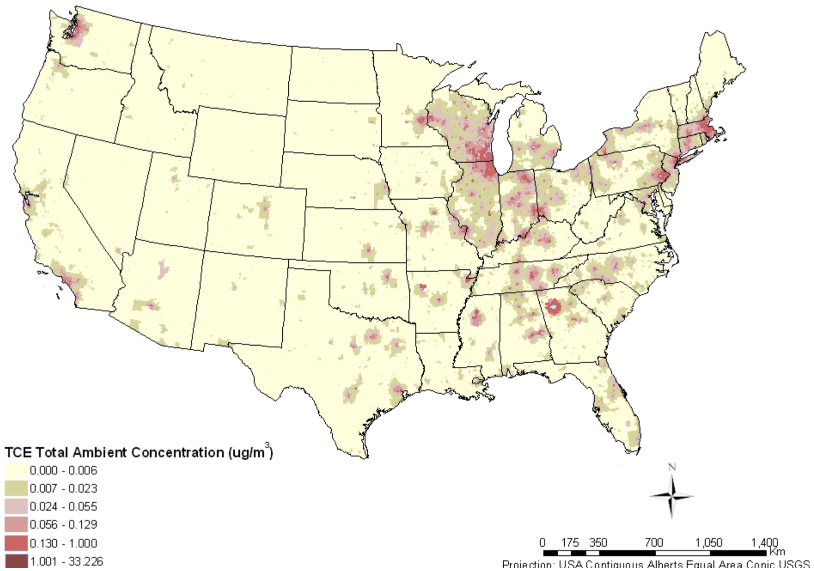
In the present case studies PBPK modeling was used in conjunction with demographic, environmental and microenvironmental data and modeling to predict distributions of biomarker levels in populations of NHEXAS-V and of NHANES



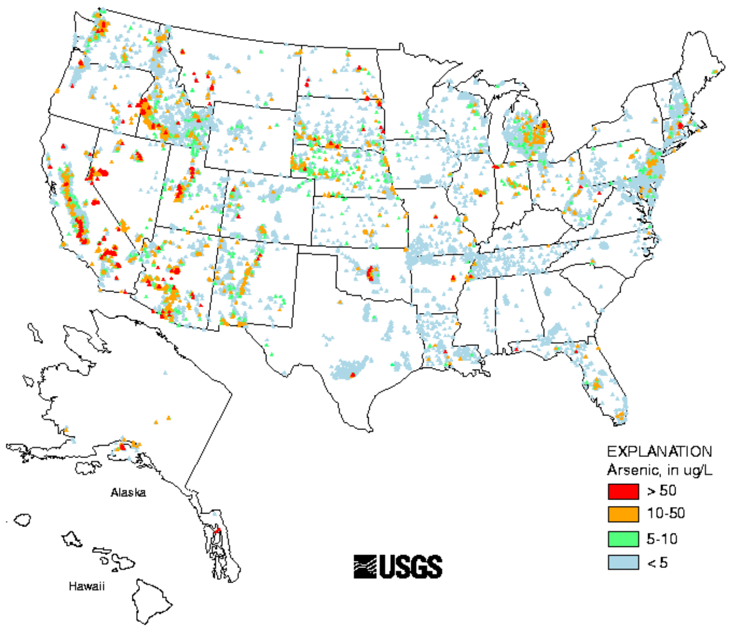
MENTOR-4M evaluation case study: a source-to-dose assessment exposures to multiple co-occurring contaminants in multiple media for the general population sampled in the NHEXAS Region-V survey



Modeled annual average estimates of ambient air TCE concentrations for 1996 from NATA (source: USEPA 2002)



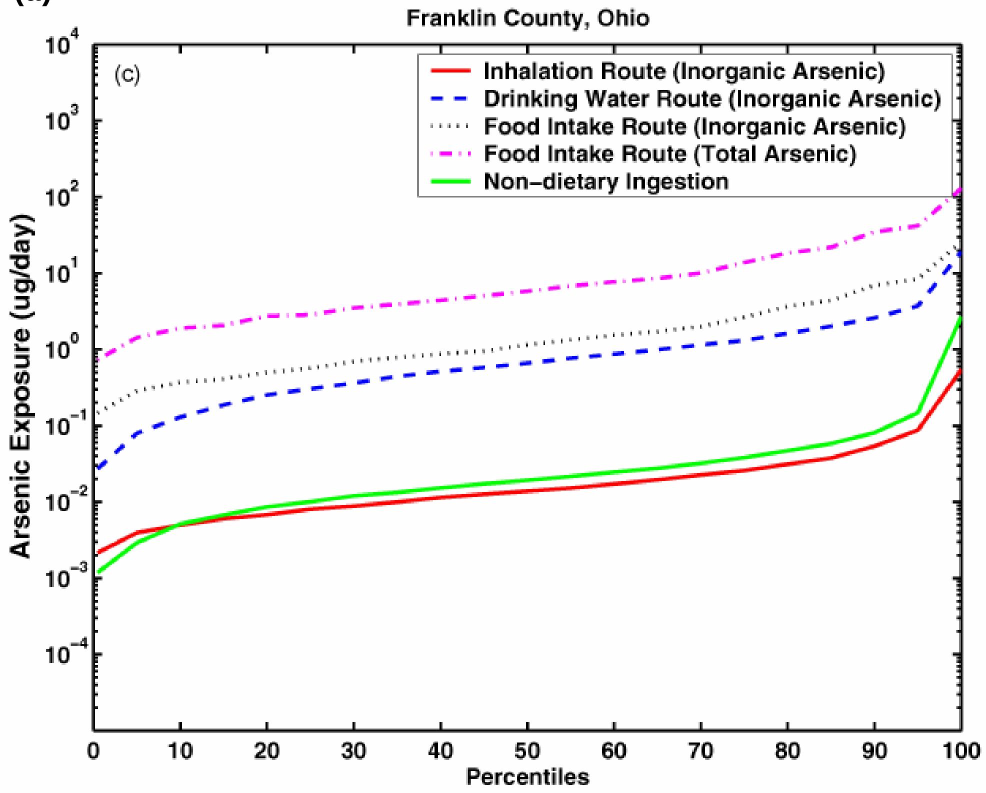
Arsenic Groundwater Observations 1973-97 in USGS Database



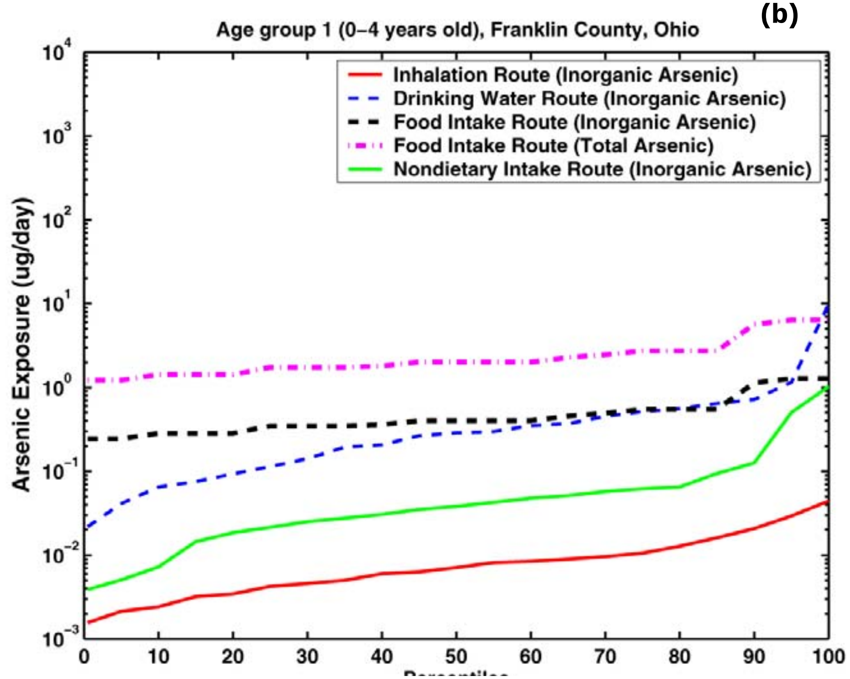
Multiroute/multipathway population exposure to arsenic(total and inorganic) for NHEXAS Region V modeled with MENTOR-4M: Comparison of exposure route contributions

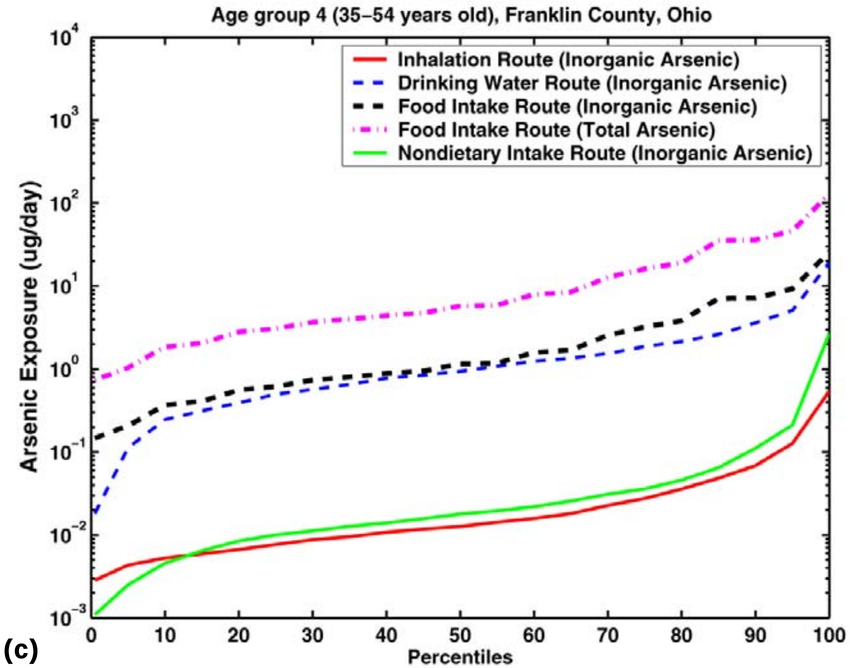
This application of MENTOR-4M incorporates an extension of USEPA's SHEDS (Stochastic Human Exposure and Dose Simulation) methodology

(a)



(b)



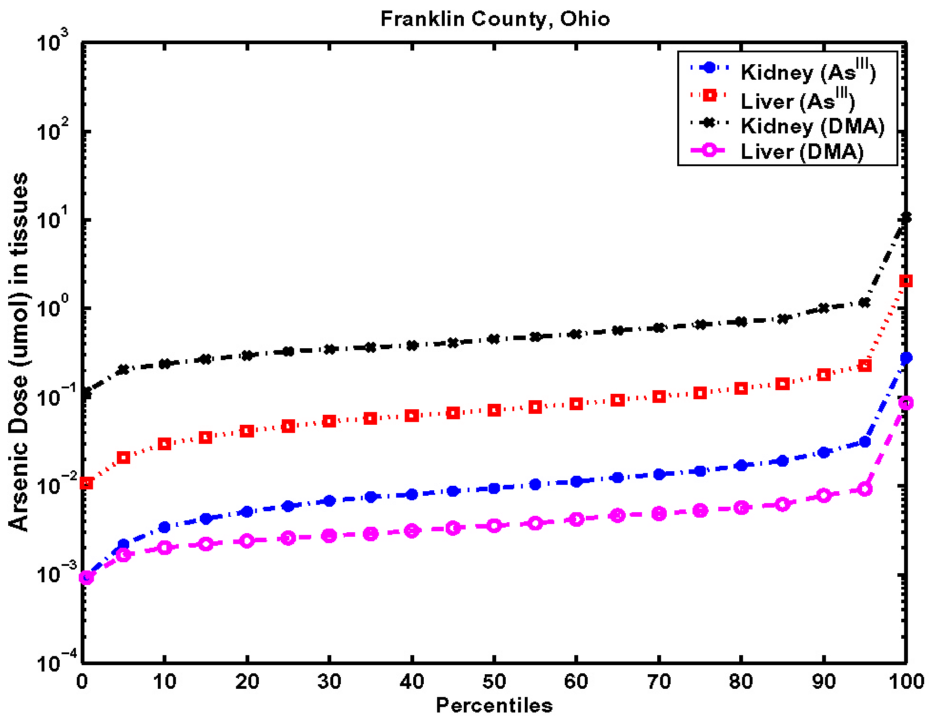


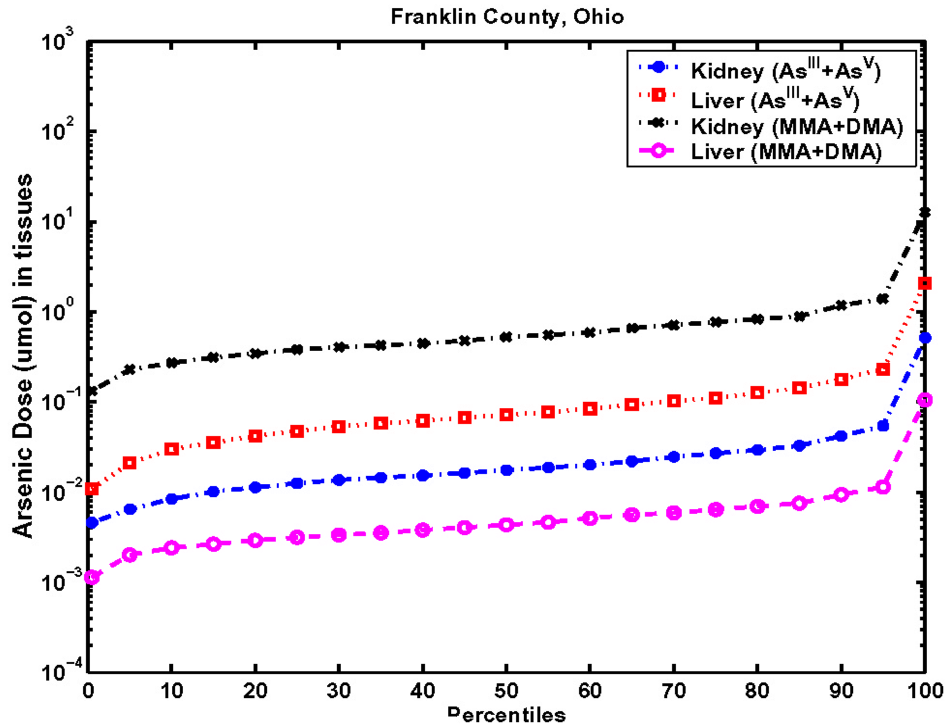
(c)

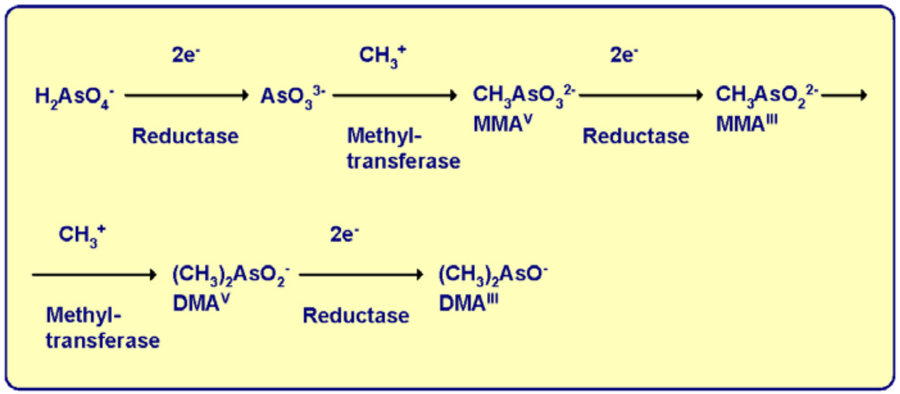
Cumulative arsenic exposure distributions from inhalation, food intake, and drinking water consumption routes for (a) the 1st age group (0-4 years old) and (b) the 4th age group (35-54 years old) of Franklin County, Ohio

Population distributions of target tissue doses for arsenic species and metabolites predicted using MENTOR-4M

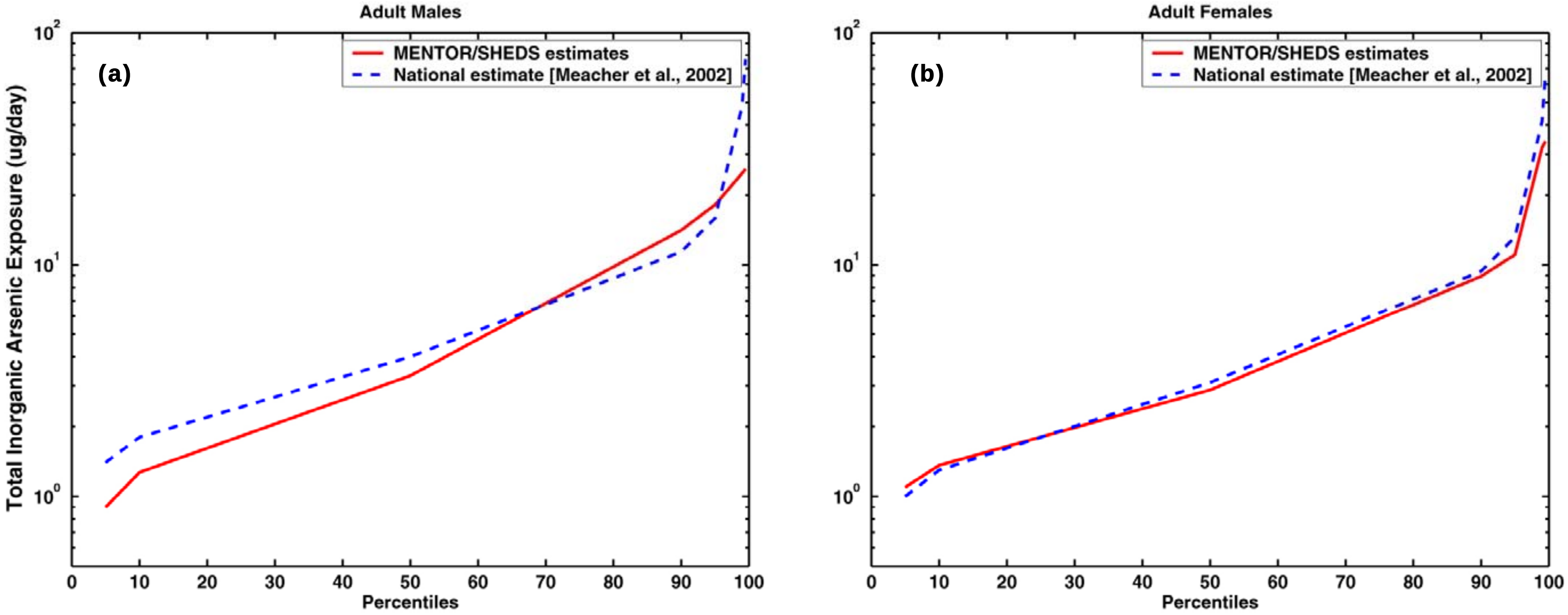
(for Franklin County, OH from NHEXAS Region V)





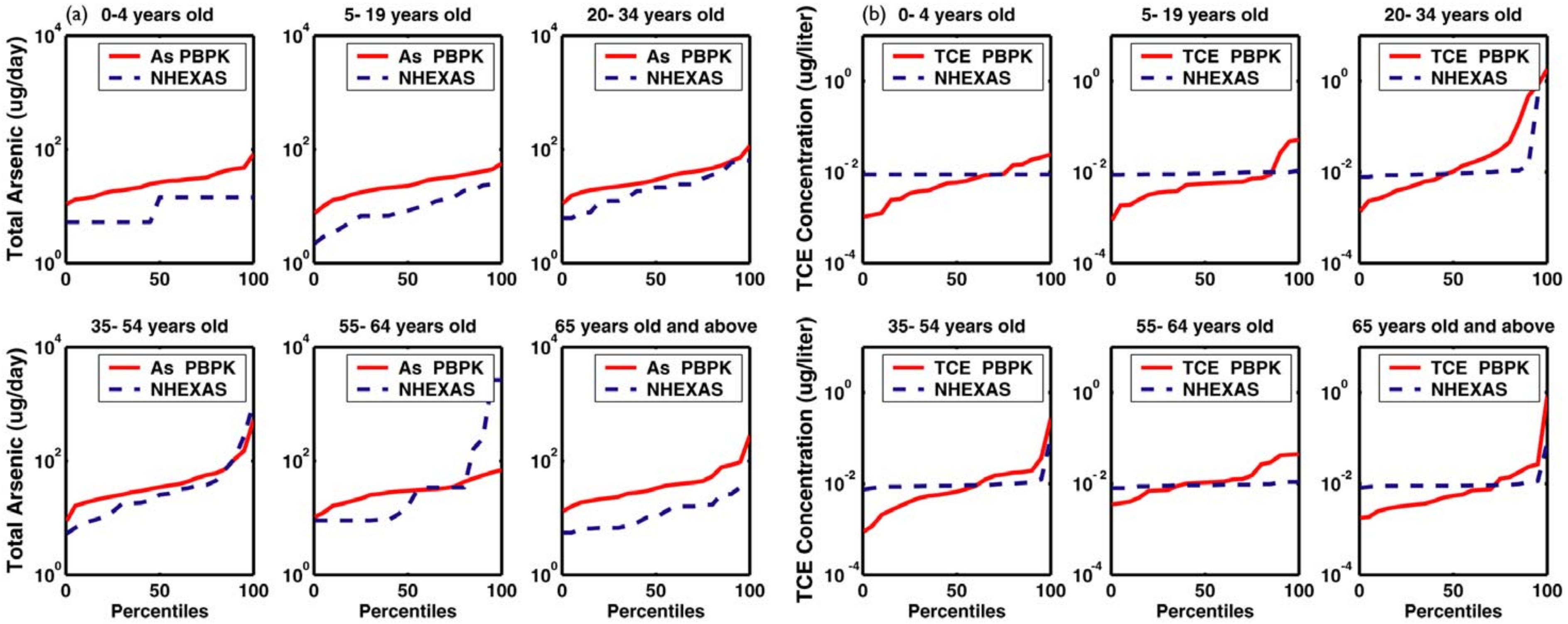


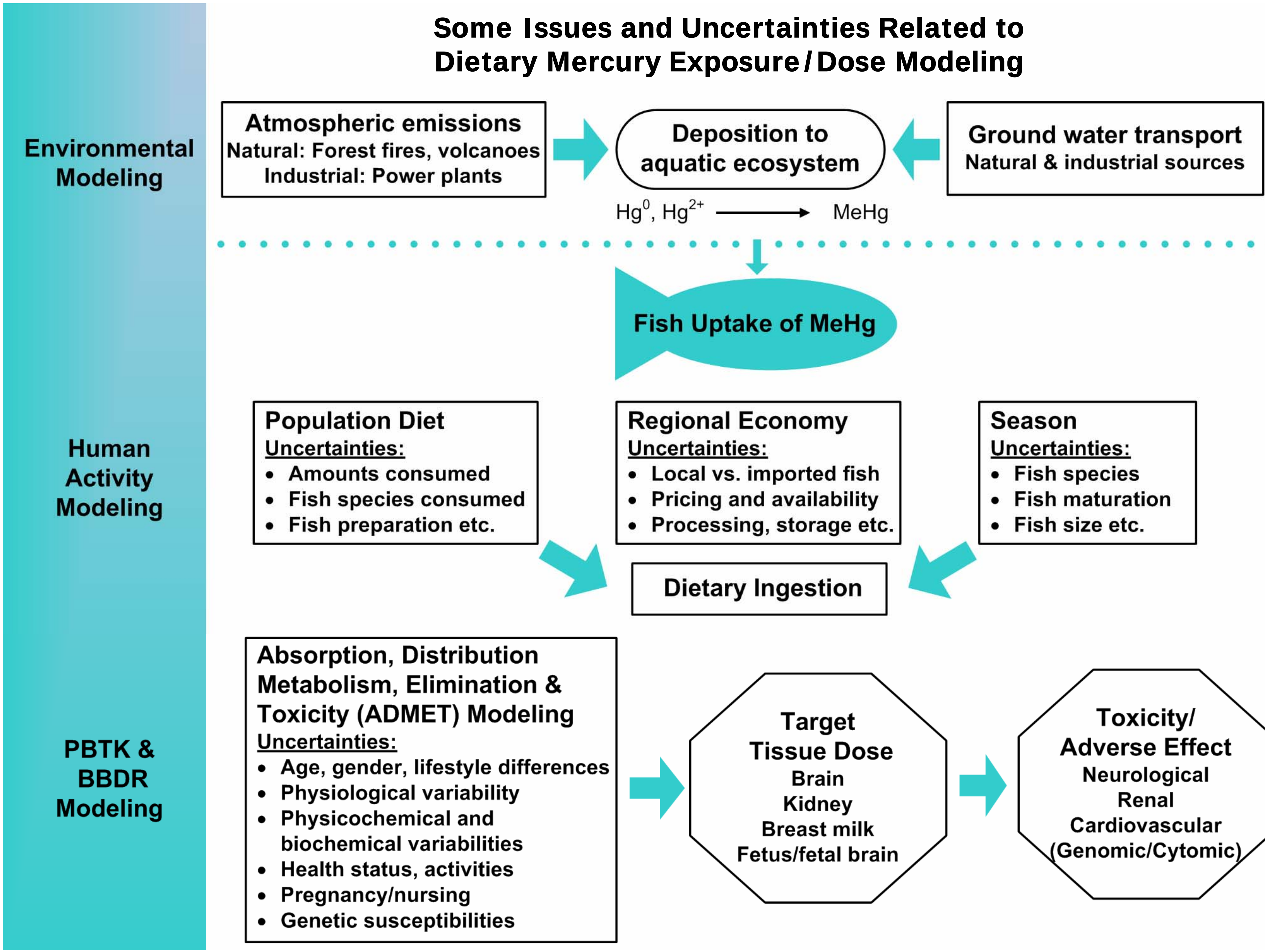
Comparison of NHEXAS case predictions with national level estimates



Comparison of the cumulative distributions of total inorganic arsenic intakes between the MENTOR-4M study (Franklin County, Ohio) and the study of Meacher et al. (2002) for (a) adult males and (b) adult females

Representative MENTOR-4M example study results: comparison of observed and predicted cumulative distributions of (a) total arsenic amount in urine, (b) TCE blood concentration from MENTOR-4M calculations and NHEXAS-Region V measurements for six age groups in Franklin County, Ohio



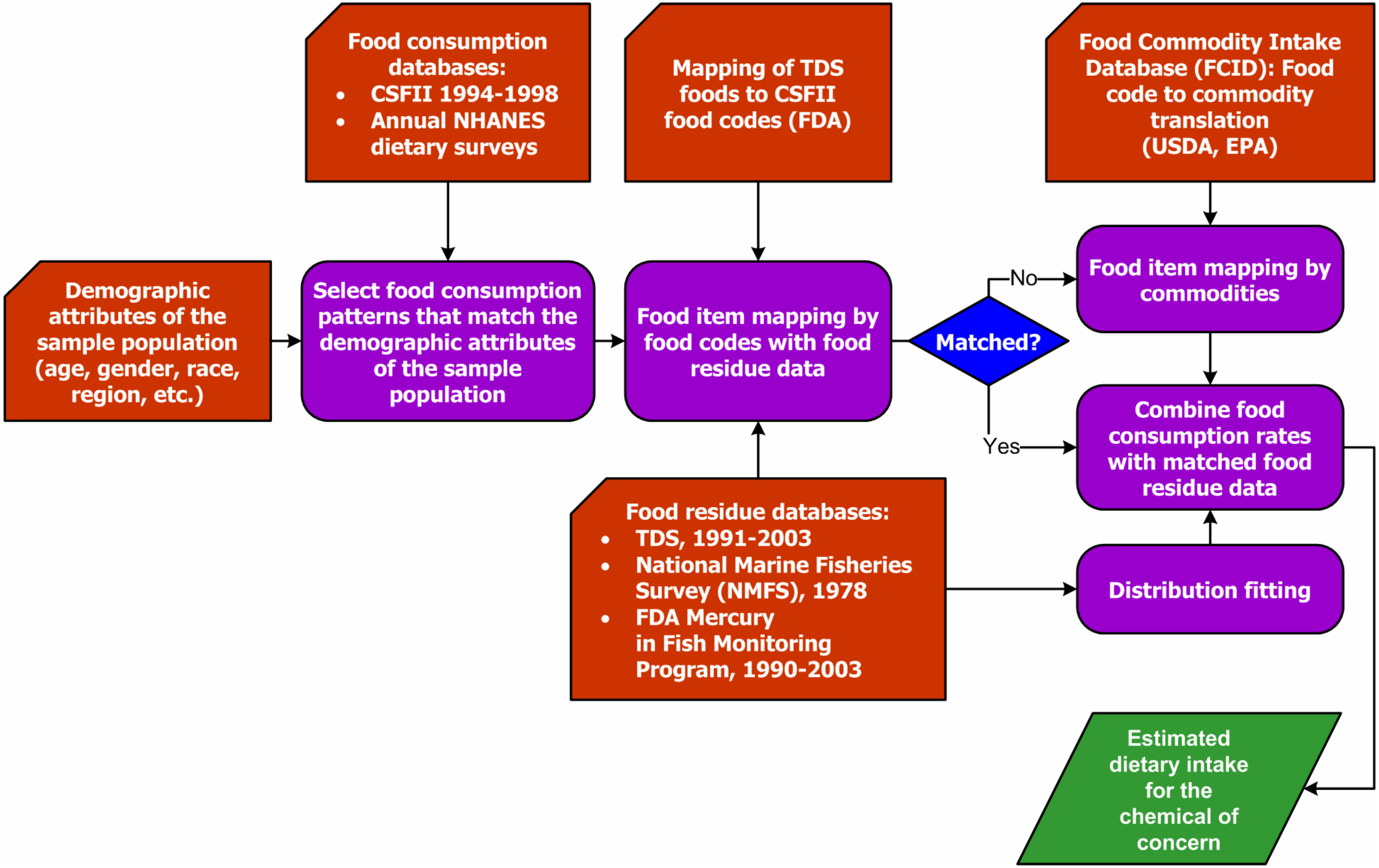


Some Issues and Uncertainties Related to Dietary Mercury Exposure / Dose Modeling
Environmental Modeling
Atmospheric emissions
Natural: Forest fires, volcanoes
Industrial: Power plants
Deposition to aquatic ecosystem
Ground water transport
Natural & industrial sources
Hg^0, Hg^{2+} → MeHg
Fish Uptake of MeHg
Human Activity Modeling
Population Diet
Uncertainties:
• Amounts consumed
• Fish species consumed
• Fish preparation etc.
Regional Economy
Uncertainties:
• Local vs. imported fish
• Pricing and availability
• Processing, storage etc.
Season
Uncertainties:
• Fish species
• Fish maturation
• Fish size etc.
Dietary Ingestion
PBTK & BBDR Modeling
Absorption, Distribution Metabolism, Elimination & Toxicity (ADMET) Modeling
Uncertainties:
• Age, gender, lifestyle differences
• Physiological variability
• Physicochemical and biochemical variabilities
• Health status, activities
• Pregnancy/nursing
• Genetic susceptibilities
Target Tissue Dose
Brain
Kidney
Breast milk
Fetus/fetal brain
Toxicity/ Adverse Effect
Neurological
Renal
Cardiovascular
(Genomic/Cytomic)

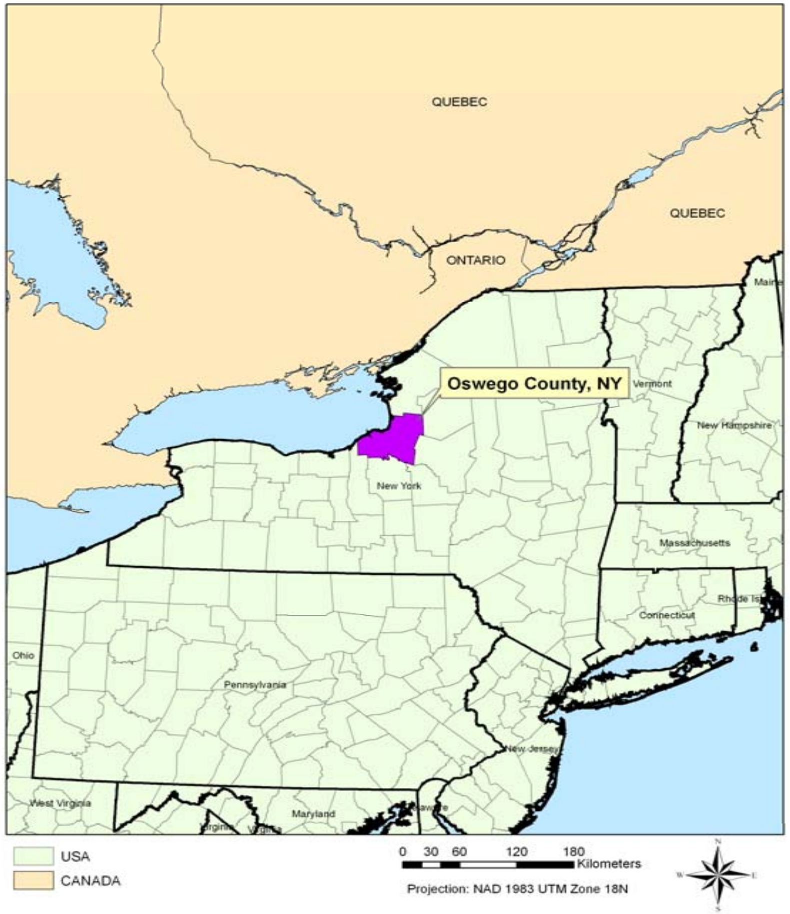
Data Sources Used for Dietary Exposure Modeling

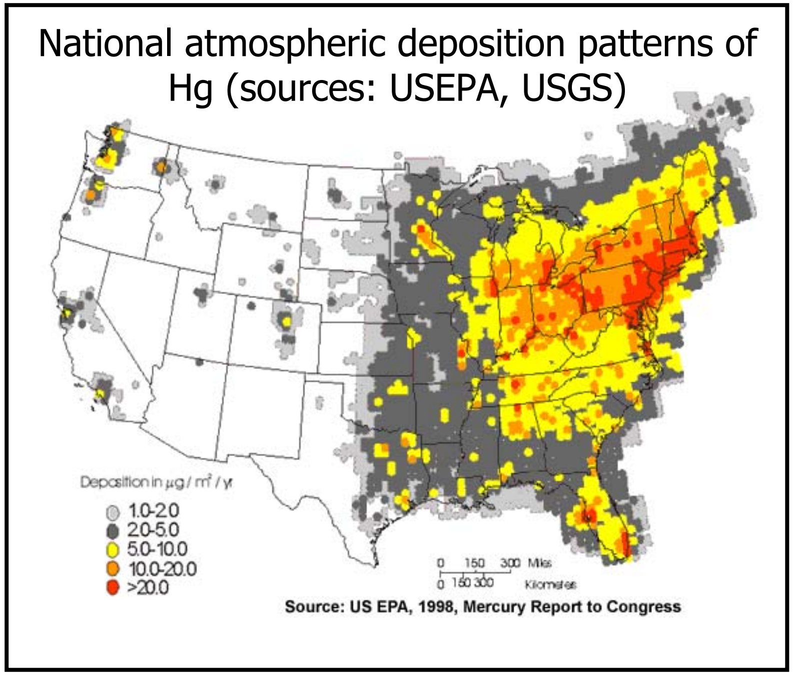
Type of Data	Database	Source
Food Consumption Patterns	Continuing Survey of Food Intakes by Individuals (CSFII) 1994-98	USDA
	National Health & Nutrition Examination Survey (NHANES) Annual Data	CDC
Food Residue	Total Diet Study (TDS) 1991-2003	USFDA
	National Marine Fisheries Survey (NMFS) 1978	NOAA
	Mercury in Fish Monitoring Program 1990-2003	USFDA
	National Listing of Fish Advisories	USEPA
	Great Lakes Fish Consumption Advisories	GLIN (Great Lakes Information Network)
Mapping of Food Consumption to Food Residue	Food Commodity Intake Database (FCID)	USDA, USEPA
	Mapping Profile of TDS Foods to CSFII Food Codes	USFDA

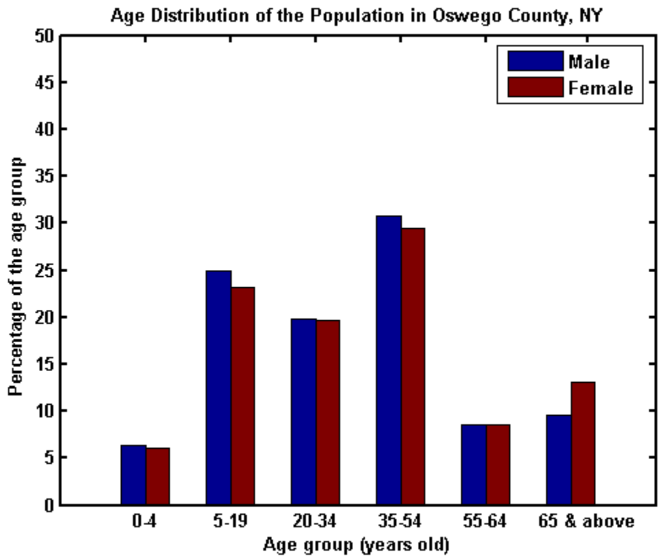
Structure of the Probabilistic USEPA-NERL Dietary Module



MENTOR-4M demonstration case study: human exposure to Hg and MeHg through the dietary pathway for the general population in Oswego County, NY

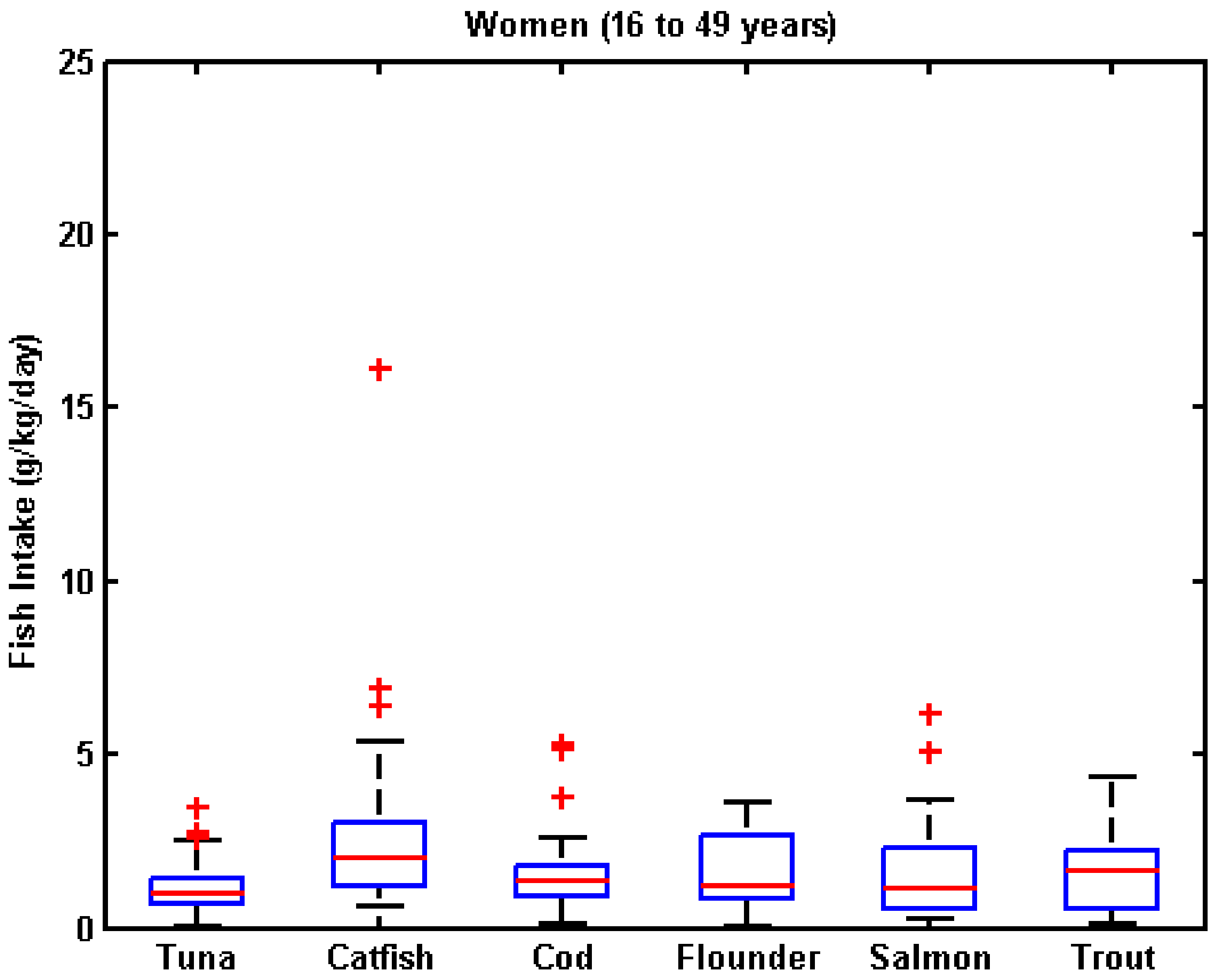






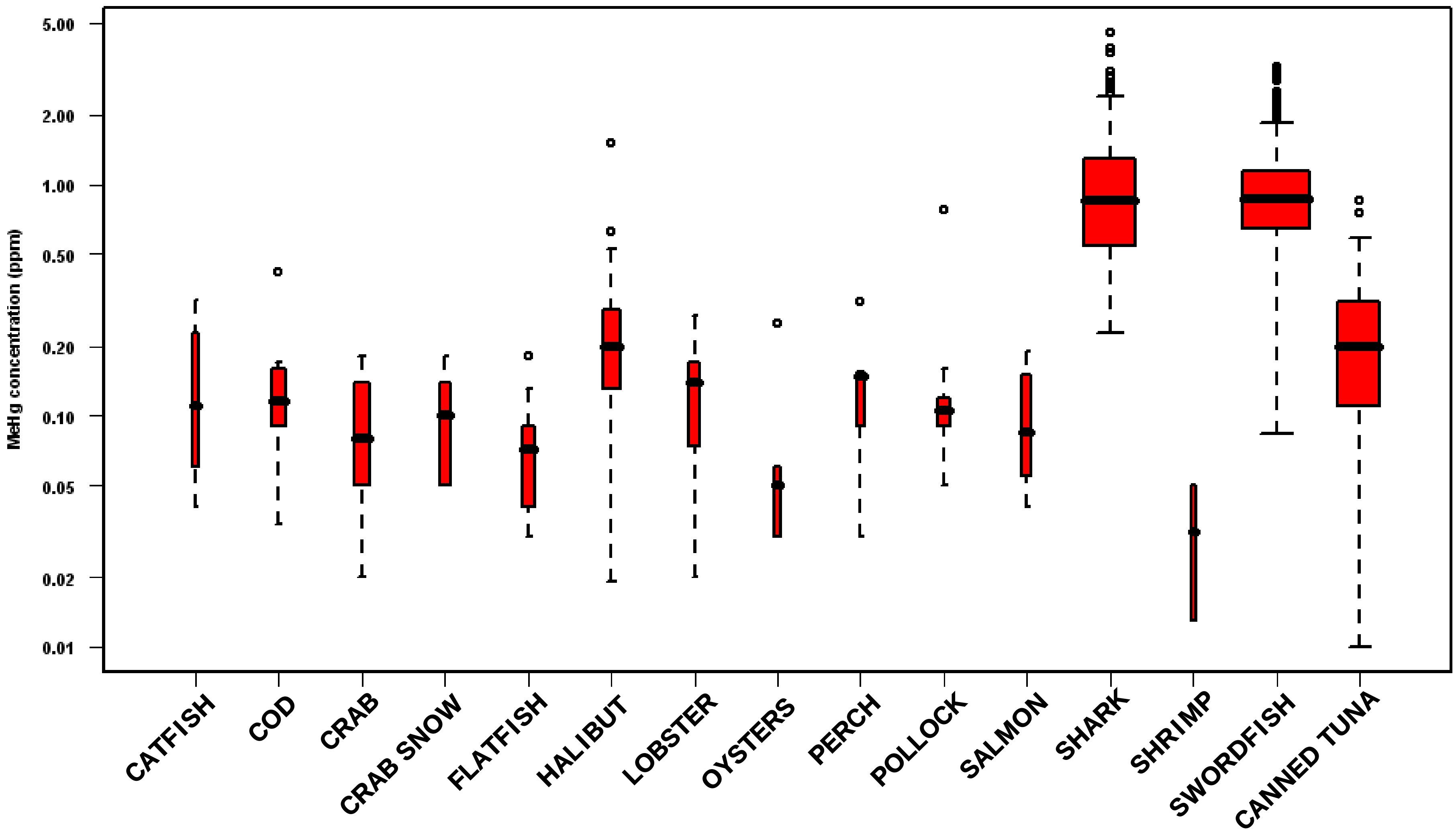
10,000 "virtual individuals" were generated to match the demographic characteristics of Oswego County, NY. (Data source: US Census Survey 2000)

Fish intake distributions for selected fish species for U.S. women 16-49 yrs of age (CSFII, 1994-1996, 1998)

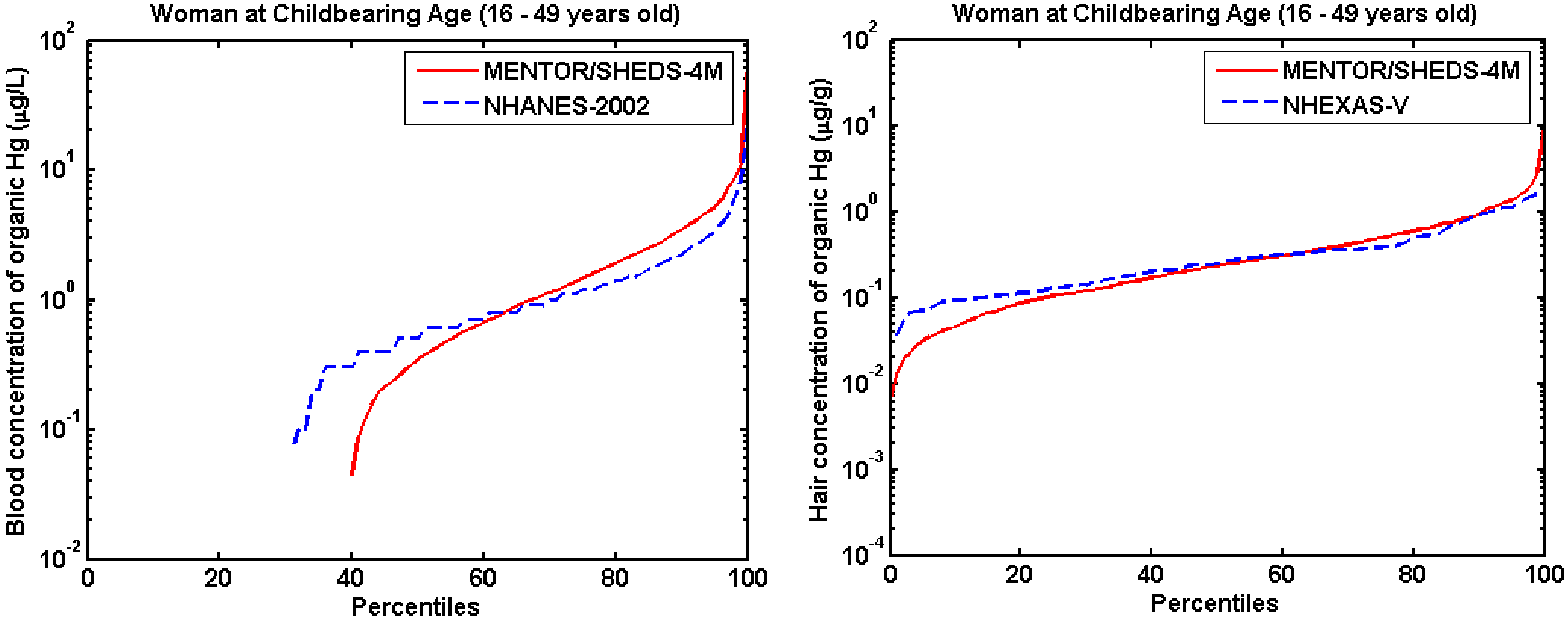


MeHg Concentrations for Selected Species of Fish Most Commonly Consumed in the U.S. Commercial Seafood Market

Data Source: USFDA's Mercury in Fish Monitoring Program (1991-2003)



Comparison of biomarker results predicted by the MeHg PBTK model with biomarker measurements from NHEXAS-V and NHANES-2002



The MENTOR-4M simulations use inputs from various databases (CSFII 1994-96, 1998, TDS 1991-2003, NHANES 2001-2002) to estimate MeHg dietary exposures for the sub-population of women at childbearing age (16 to 49 years) in Oswego county, NY. These estimates were used as inputs to the PBTK modules of MENTOR-3P to develop distributions of MeHg blood and hair concentrations for this sub-population.

The NHEXAS-V distribution of MeHg hair concentrations is based on the samples collected from the NHEXAS-V female participants at childbearing age during July 1995 to May 1997.

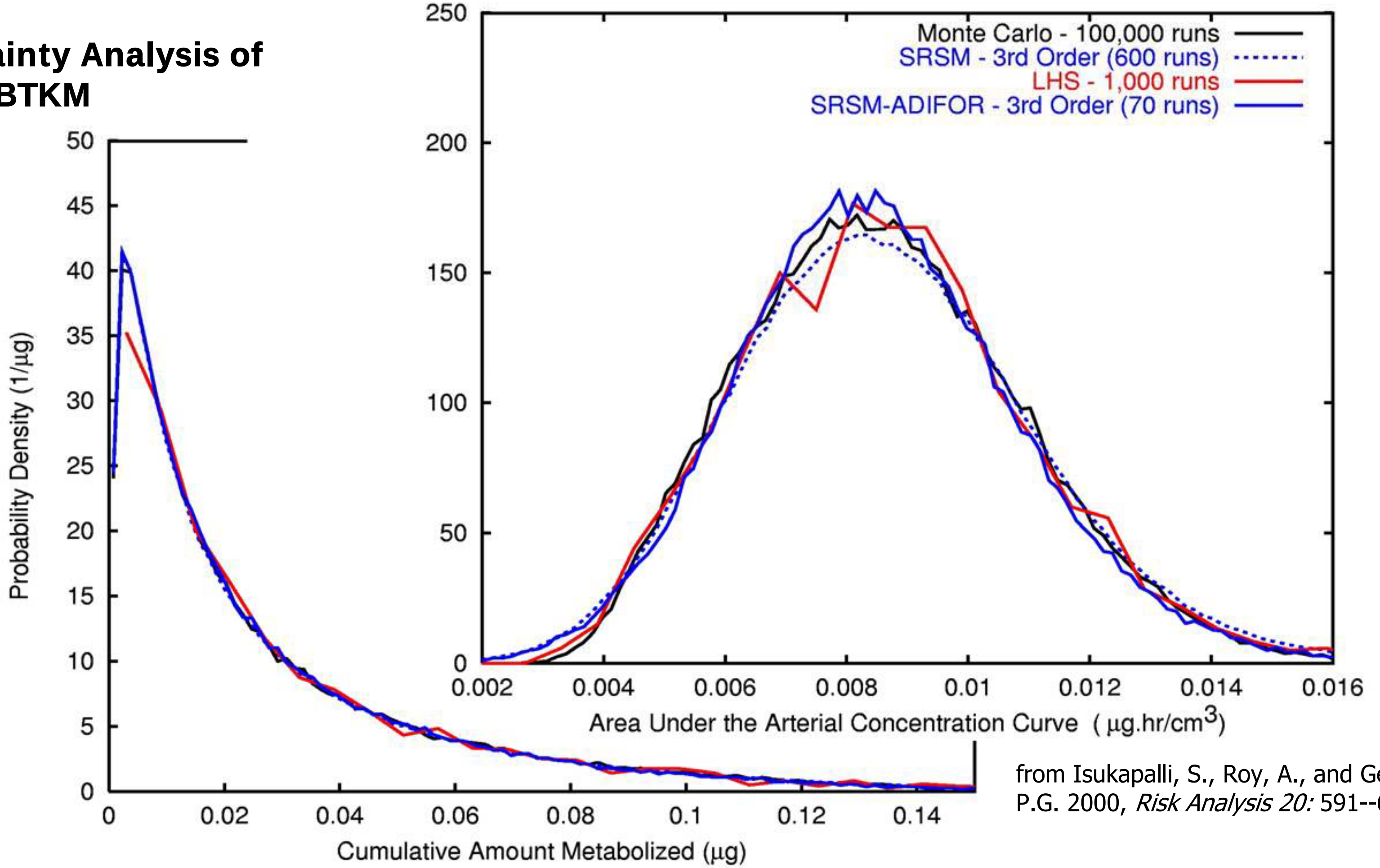
The NHANES-2002 distribution of MeHg blood concentrations is based on the samples collected from the NHANES female participants at childbearing age during 2002.

ADDENDUM
Examples of Novel Diagnostic and Optimization Tools Available in the MENTOR and DORIAN Toolboxes

MENTOR/DORIAN include novel tools for the efficient uncertainty analysis of complex models using stochastic surface response method (SRSM) and automated differentiation (ADIC/ADIFOR)

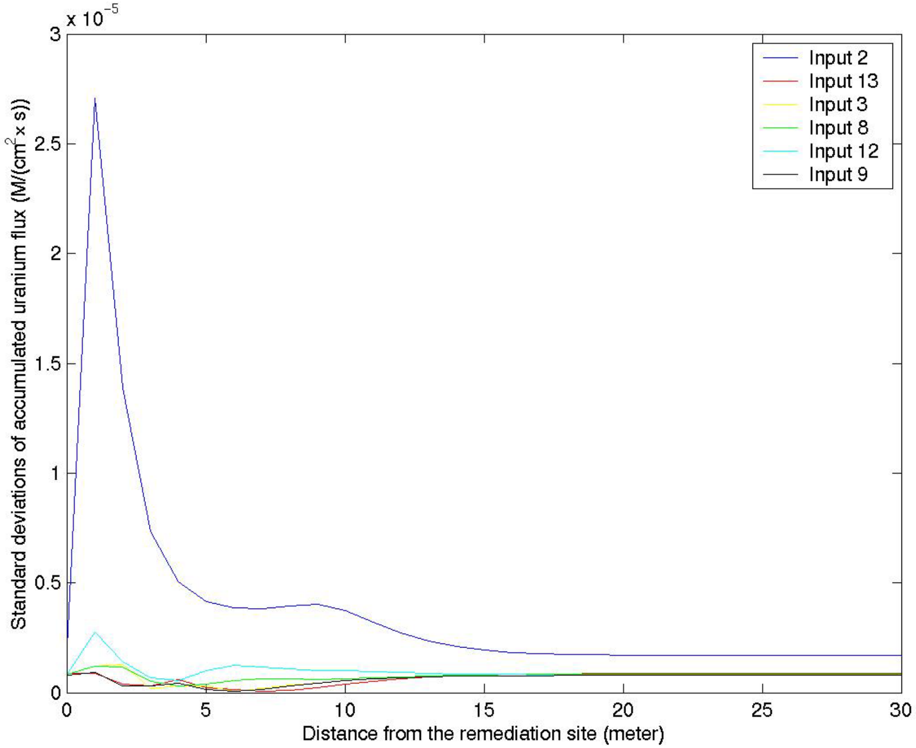
Probability densities of dose surrogates, estimated by Standard Monte Carlo, Latin Hypercube Sampling (LHS), SRSM, and the SRSM-ADIFOR

Uncertainty Analysis of PERC PBTKM



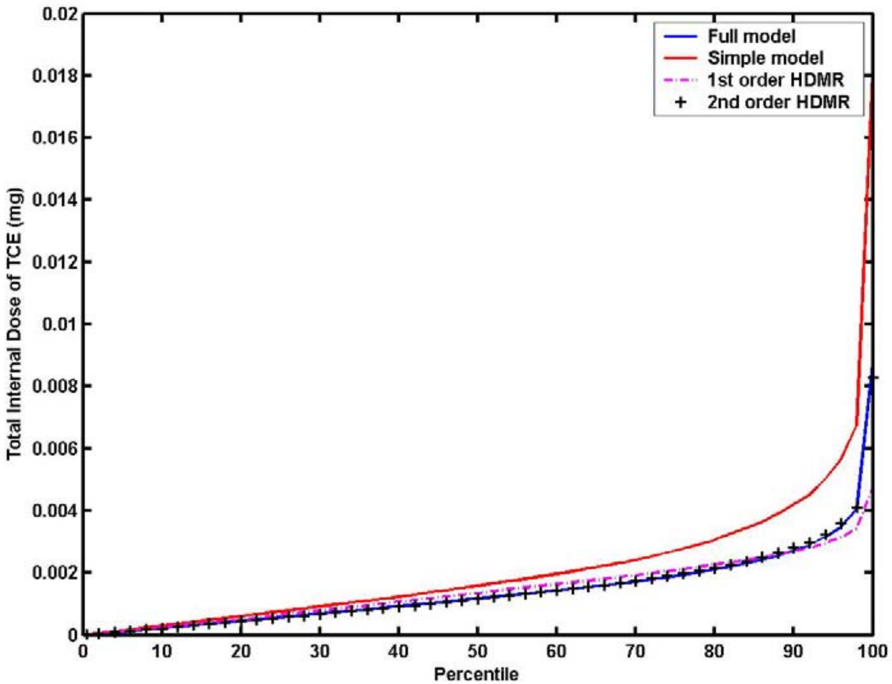
from Isukapalli, S., Roy, A., and Georgopoulos, P.G. 2000, *Risk Analysis 20:* 591--602.

MENTOR/DORIAN provide the High Dimensional Model Representation (HDMR) method for sensitivity analysis and for the systematic simplification of complex models to produce fast equivalent operational models (FEOMs)



Sensitivity analysis of the Princeton Groundwater Model using HDMR

(2: U reduction rate; 13: 2nd order Mn redox rate; 3: NH_3 oxidation rate; 8: FE(III) oxidation rate; 12: 2nd order Fe(II) redox rate; 9: sulfate/OC oxidation rate)

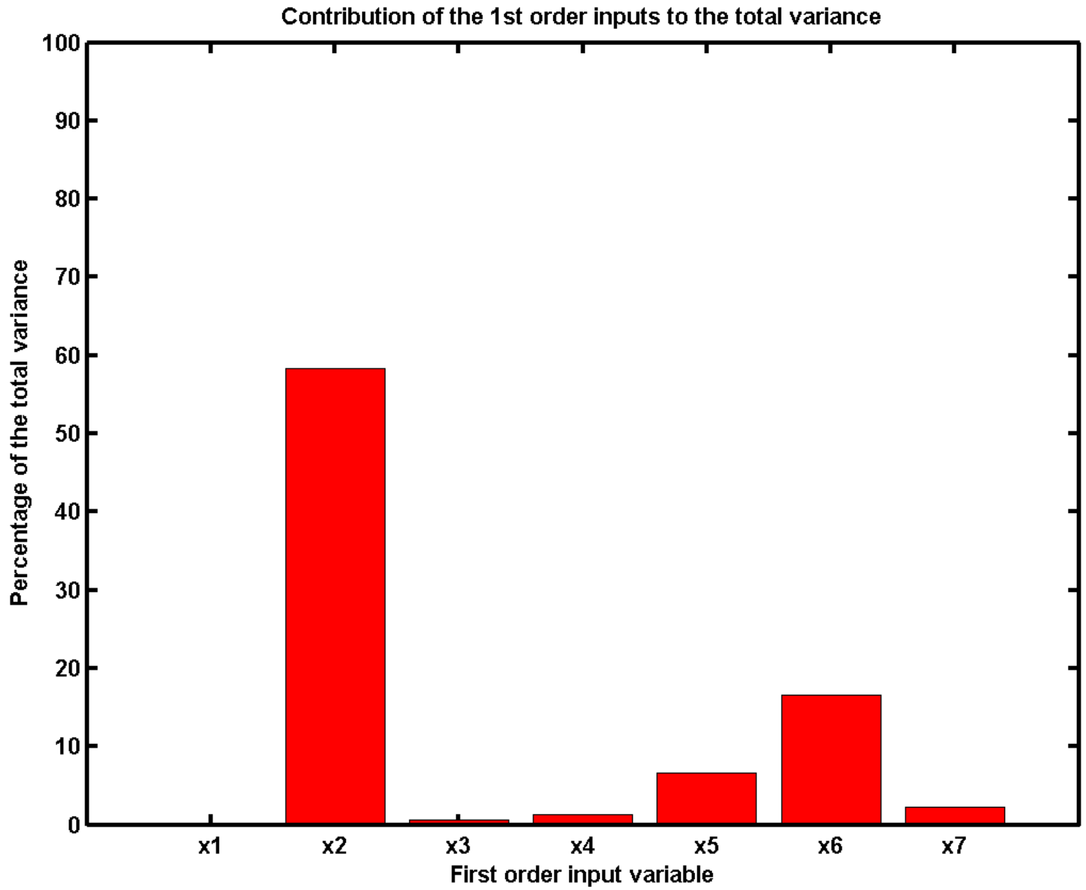


Comparison of cumulative distributions of internal doses calculated by the full integrated microenvironmental/pharmacokinetic model for TCE; the simplified model; and 1st and 2nd order HDMR expansions.

Note: the 1st and 2nd order HDMR expansions are used as the FEOM approximations of the full model, while the simplified model is the steady-state approximation of the full model.

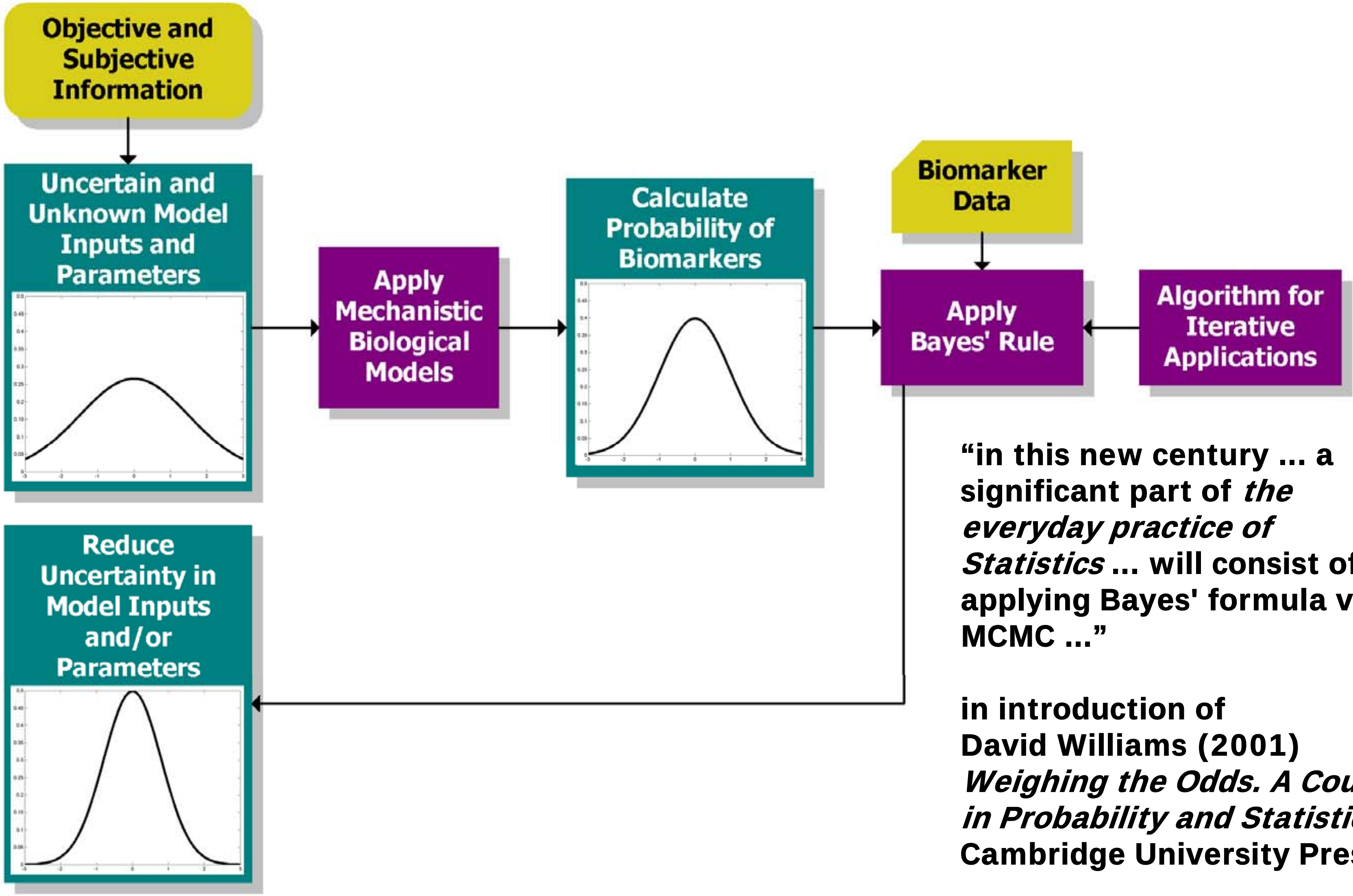
from Wang et al., 2003, *Journal of Physical Chemistry (107: 4707-16)* and Li et al. 2004, *International Journal of Risk Assessment and Management (accepted for publication)*

Application of the RS-HDMR (global uncertainty/sensitivity analysis)



Quantitative estimates of the 7 input variables to the total variance of outputs (the TCE concentration in tap water (x2) is the most important factor, followed by shower time (x6) and shower flow rate (x5) etc., for determining the internal doses of TCE)

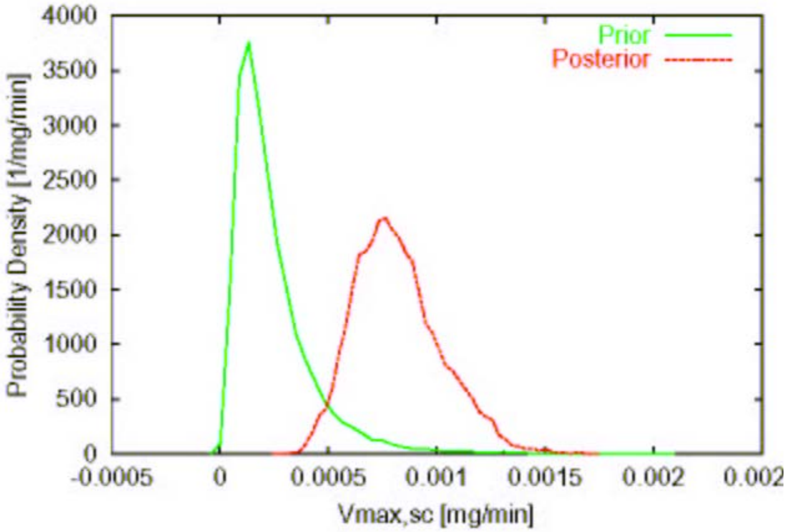
MENTOR & DORIAN include modules for Bayesian "model/data fusion"

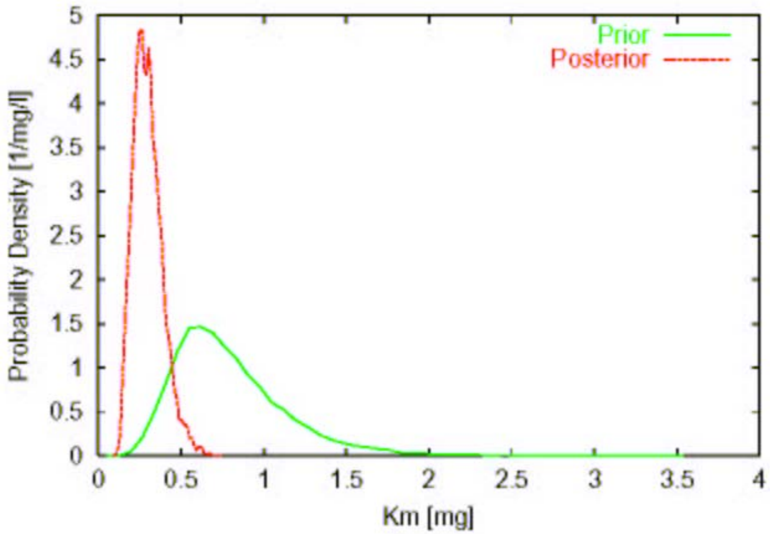


"in this new century ... a significant part of *the everyday practice of Statistics* ... will consist of applying Bayes' formula via MCMC ..."

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

Bayesian MCMC Application to PBTKM for tetrachloroethylene (intraindividual variability and uncertainty)

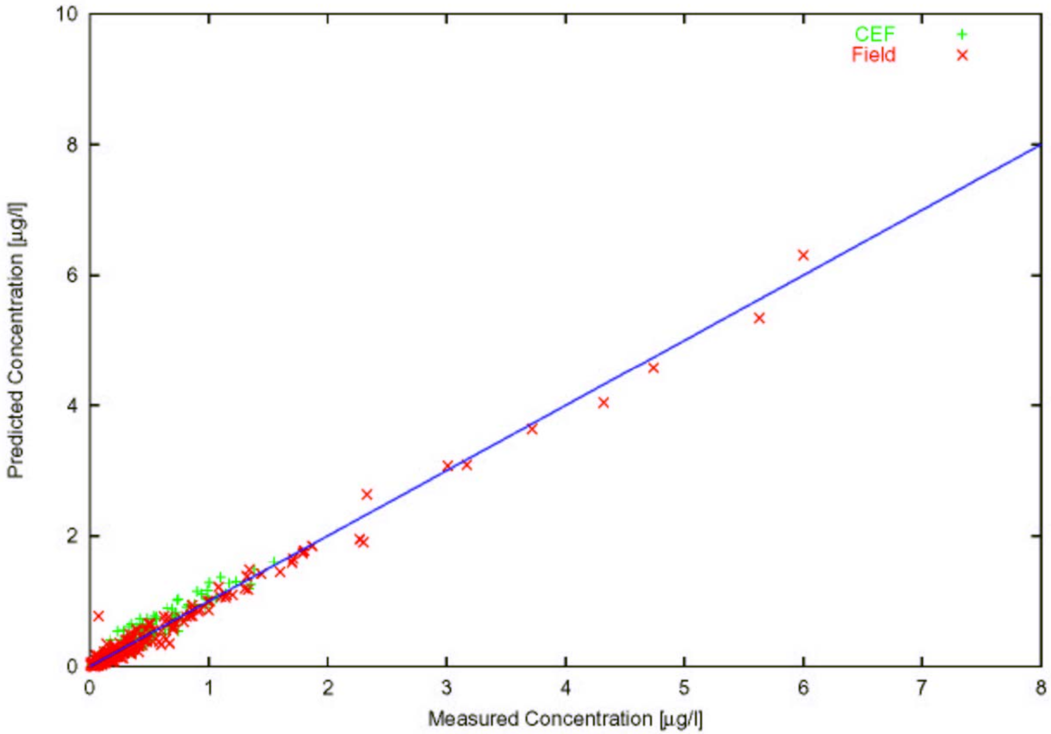




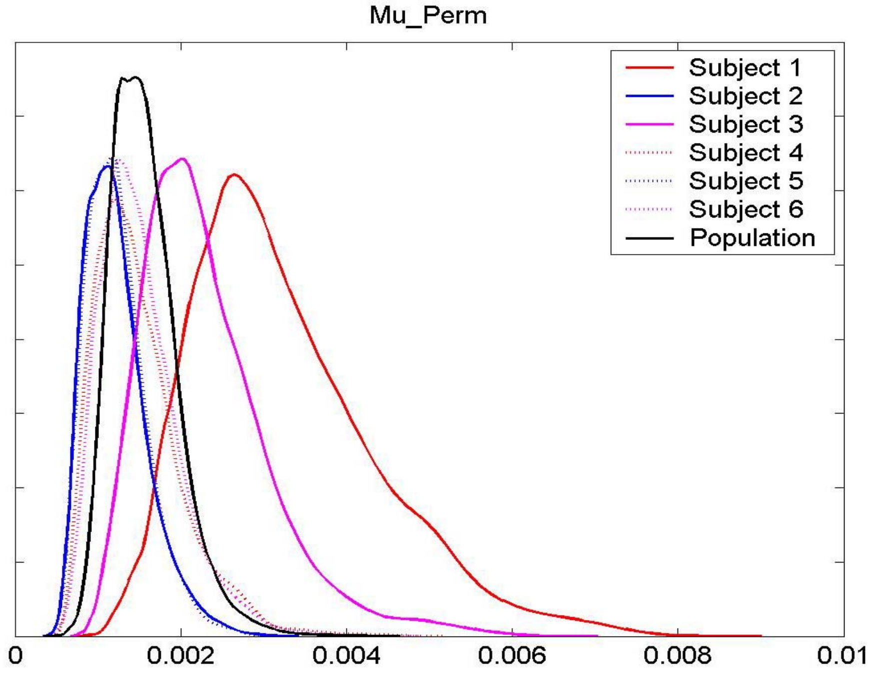
Single subject - multiple experiments

0.5 to 3 ppm PERC for 30 to 90 min; 12 CEF experiments; 22 field (dry cleaner)

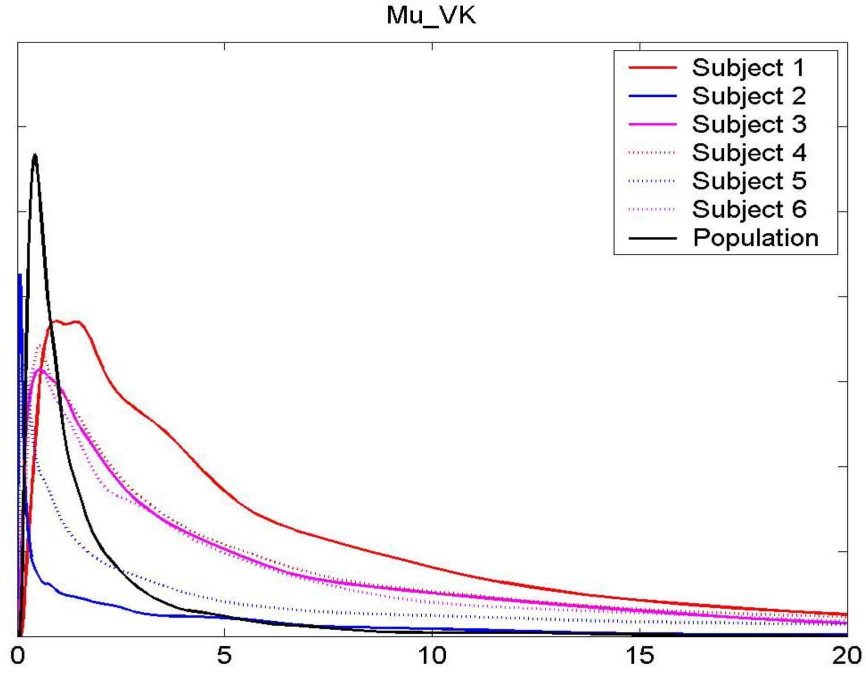
Observed response: exhaled breath concentration



Case Study - PBTK modeling of inhalation and dermal exposures to chloroform: Bayesian characterization of interindividual variability (using laboratory data from 3 male and 3 female subjects)



Posterior Distributions of Skin Permeability



Posterior Distributions of Vmax/Km Ratio

Conclusions

- The MENTOR source-to-dose approach has been successfully demonstrated in case studies involving exposures of populations to air and to multimedia contaminants
  - *Case studies have included source-to-dose analyses of co-occurring air pollutants and multimedia As/TCE and Hg/MeHg exposures*
- PBTK modeling "links" the MENTOR and DORIAN frameworks of analysis
  - *New, computationally efficient techniques are used to perform PBTKM calculations for populations and to characterize inter- and intra-individual variability and uncertainty*
- Bayesian techniques are employed for model-data fusion in MENTOR and DORIAN applications
- Integration of deterministic/stochastic variability (for age, gender, as well as physiology and biochemistry - linked to genetics and lifestyle - is currently a major focus of the MENTOR and DORIAN development efforts in the area of computational toxicology

Acknowledgements (a partial list…)

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- Tom Pierce
- Jim Xue
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