Assessing Multimedia/Multipathway Exposures to Arsenic in a Source-to-Dose Framework: Demonstration Studies Using MENTOR

Peer-Review of US EPA - National Exposure Research Laboratory's
Human Exposure and Dose Simulation University Partnership (HEADSUP) Program
Washington, DC - July 9-10, 2002

An EOHSI – EPA NERL Collaborative Effort

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Project and Presentation Overview

- "Test of Concept" Case Study
  - issue of significant current concern
  - challenging multimedia aspects (a "model contaminant")
  - extensive new information bases for multiple environmental media and biomarkers
  - combines multiplicity of scientific, technical, and societal/policy issues
- Modeling tools developed to support exposure studies
  - dynamic/mechanistic framework for detailed assessment of multimedia/multipathway exposures and doses (MENTOR)
  - a prototype extension of EPA's SHEDS (incorporating dynamic linking with activity & media databases) that accounts for inhalation and ingestion (food & drinking water)
- Results presented
  - test demonstration of integrated environmental, microenvironmental, and PBPK model for assessing "source-to-dose" dynamics of exposure for individuals
  - comparison of multipathway (inhalation and drinking water ingestion) population exposure for Hunterdon (NJ) and an Pima (AZ) Counties; use of NHEXAS V data for assessing multipathway exposure and dose at Franklin County (OH)
- Work in progress
  - Exposure Information System for Arsenic; database mining; multimedia modeling

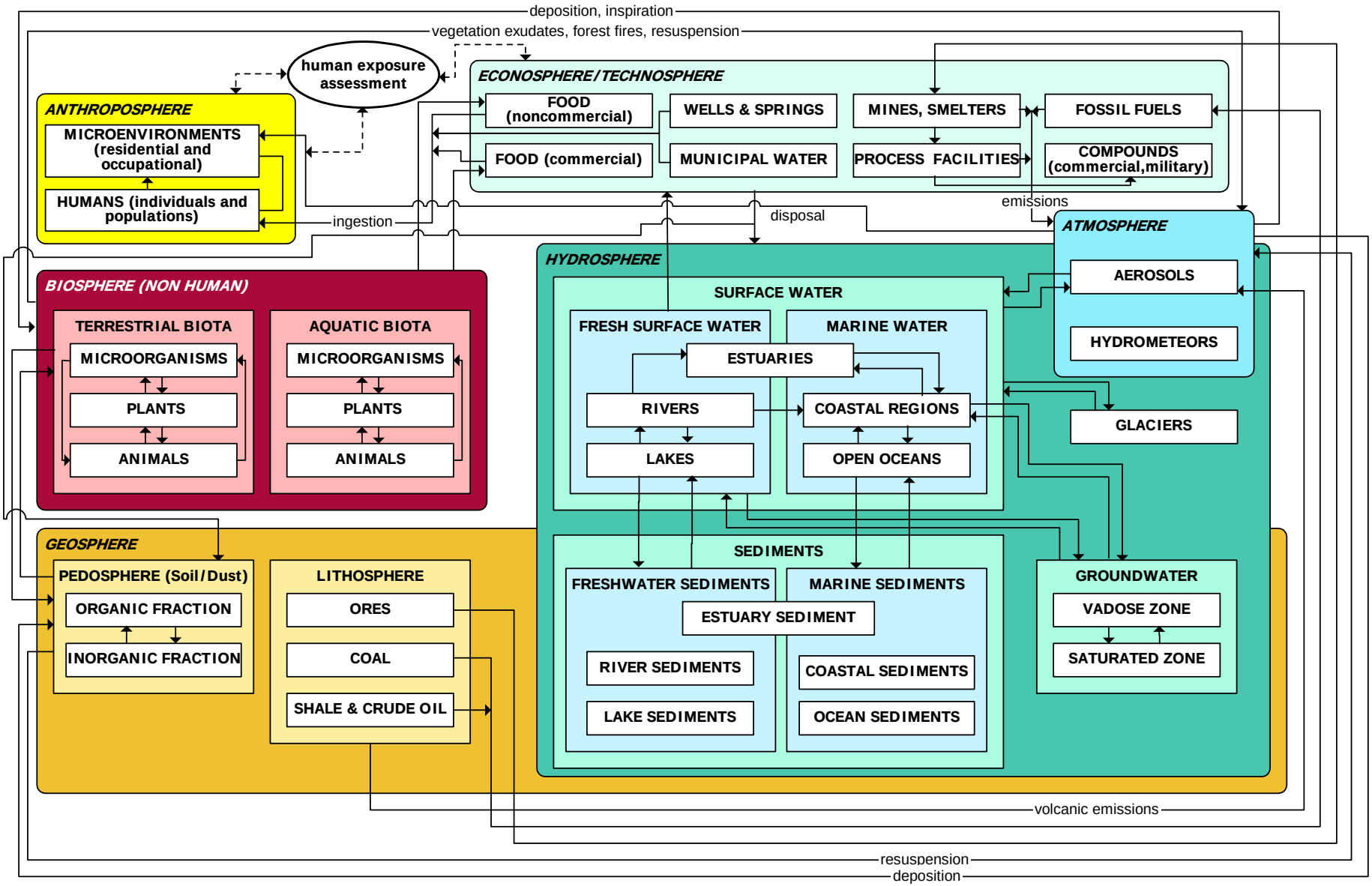
History of U.S. Standards for Arsenic in Drinking Water

1942	USPHS sets an interim drinking water standard of 50 µg As/L
1962	USPHS identifies 10 µg As/L as the goal
1975	EPA adopts the interim standard of 50 µg As/L set by the USPHS in 1942
1986	Congress directs EPA to revise the standard by 1989
1988	EPA estimates that ingestion of 50 µg As/L results in a skin cancer risk of 1 in 400
1992	Internal cancer risk estimated to be 1.3 per 100 persons at 50 µg As/L
1993	WHO recommends lowering arsenic in drinking water to 10 µg As/L
1996	Congress directs EPA to propose a new drinking water standard by January 2000
1999	NRC estimates cancer mortality risks to be about 1 in 100 at 50 µg As/L
2000	EPA proposes standard of 5 µg As/L ; requests comment on 3, 10, and 20 µg As/L
2001	(January) Clinton EPA lowers the standard to 10 µg As/L
2001	(March) Bush EPA delays lowering the standard
2001	(September) New NRC report concludes that EPA underestimated cancer risks
2001	(October) EPA announces it will adopt the standard of 10 µg/L
2002	(February) The effective date for new standard of 10 µg As/L
2006	Compliance date for the new arsenic standard

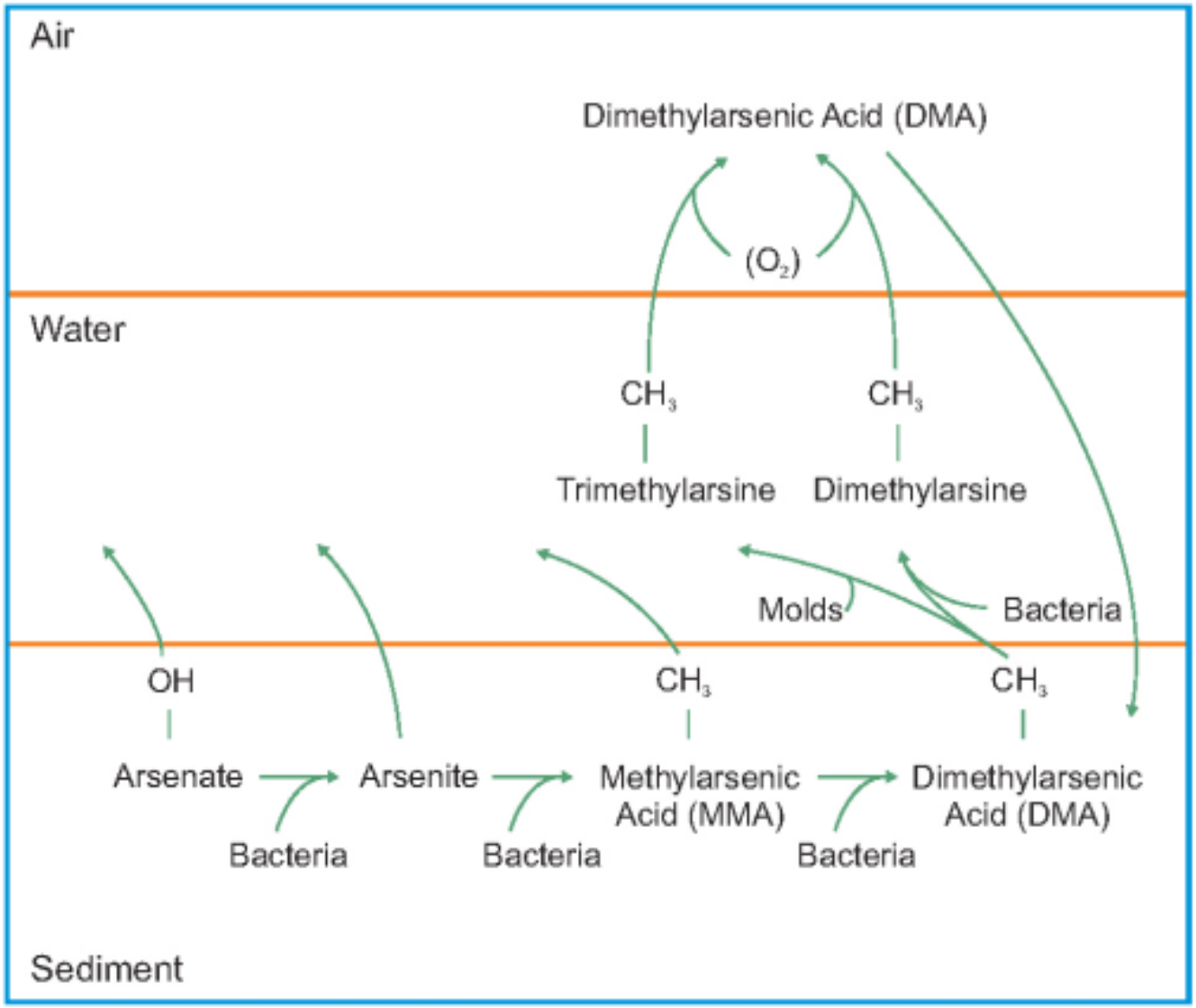
Adapted from Smith et al. 2002. *Science* 296 (5576) 2145

1992 USEPA's National Toxic Rule: Water Quality Criterion for As = 0.018 µg/L

A Unified Multimedia/Multiscale Modeling Framework to Support Human/Ecological Exposure Assessments for Arsenic

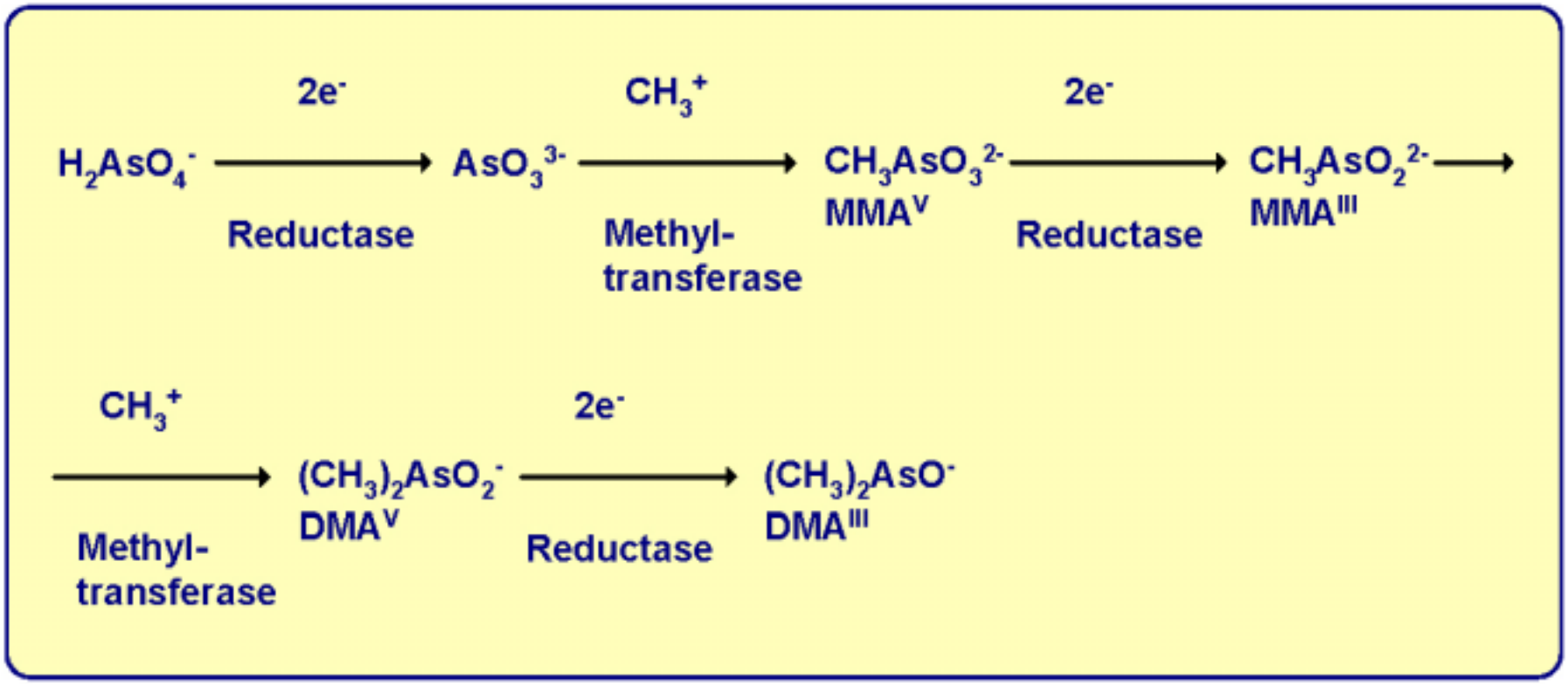


Summary of Ecological (Terrestrial) Biotransformation of Arsenic

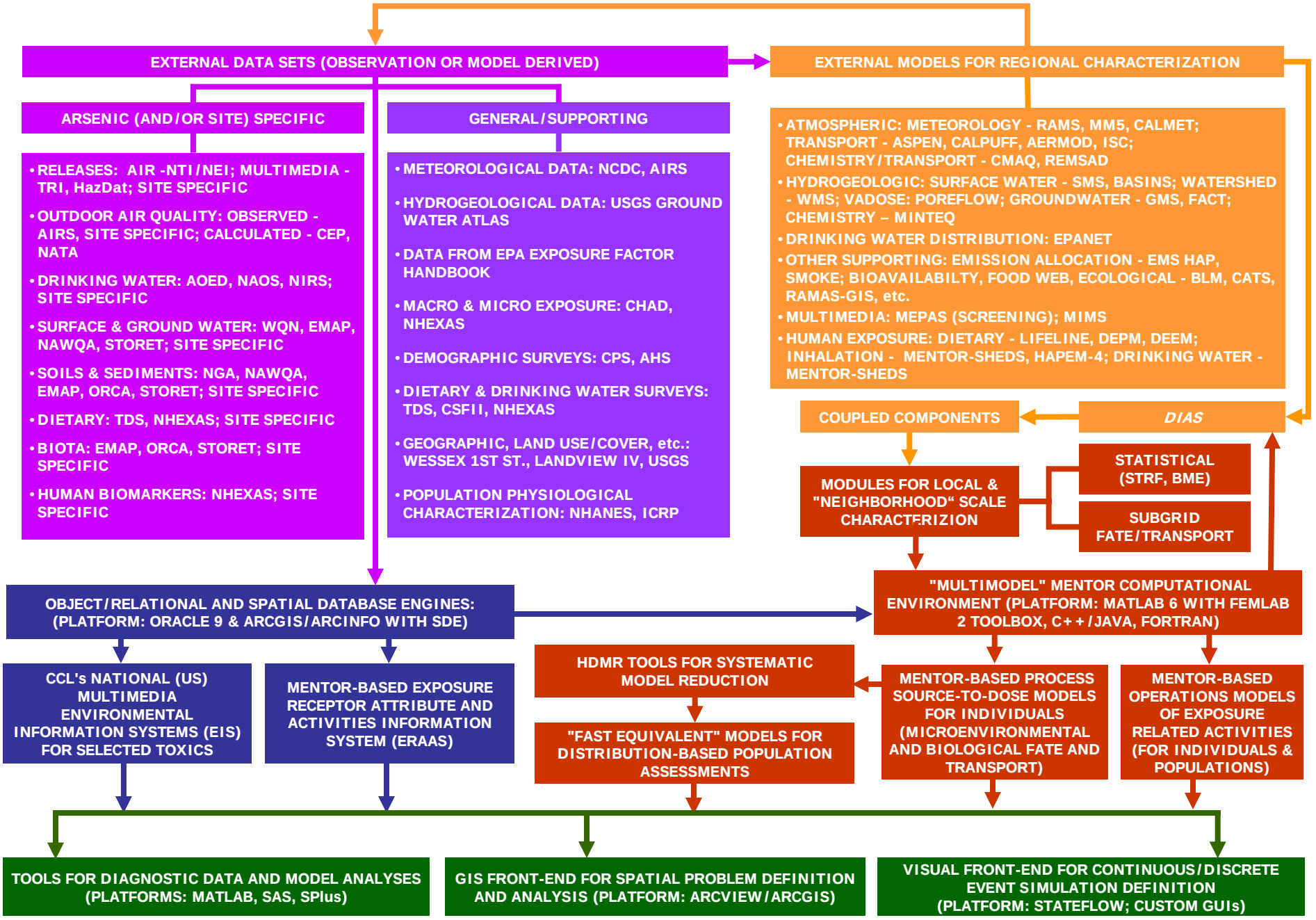


Adapted from Salamons & Forstner (1984).
Metals in the Hydrocycle. New York, NY, Springer-Verlag

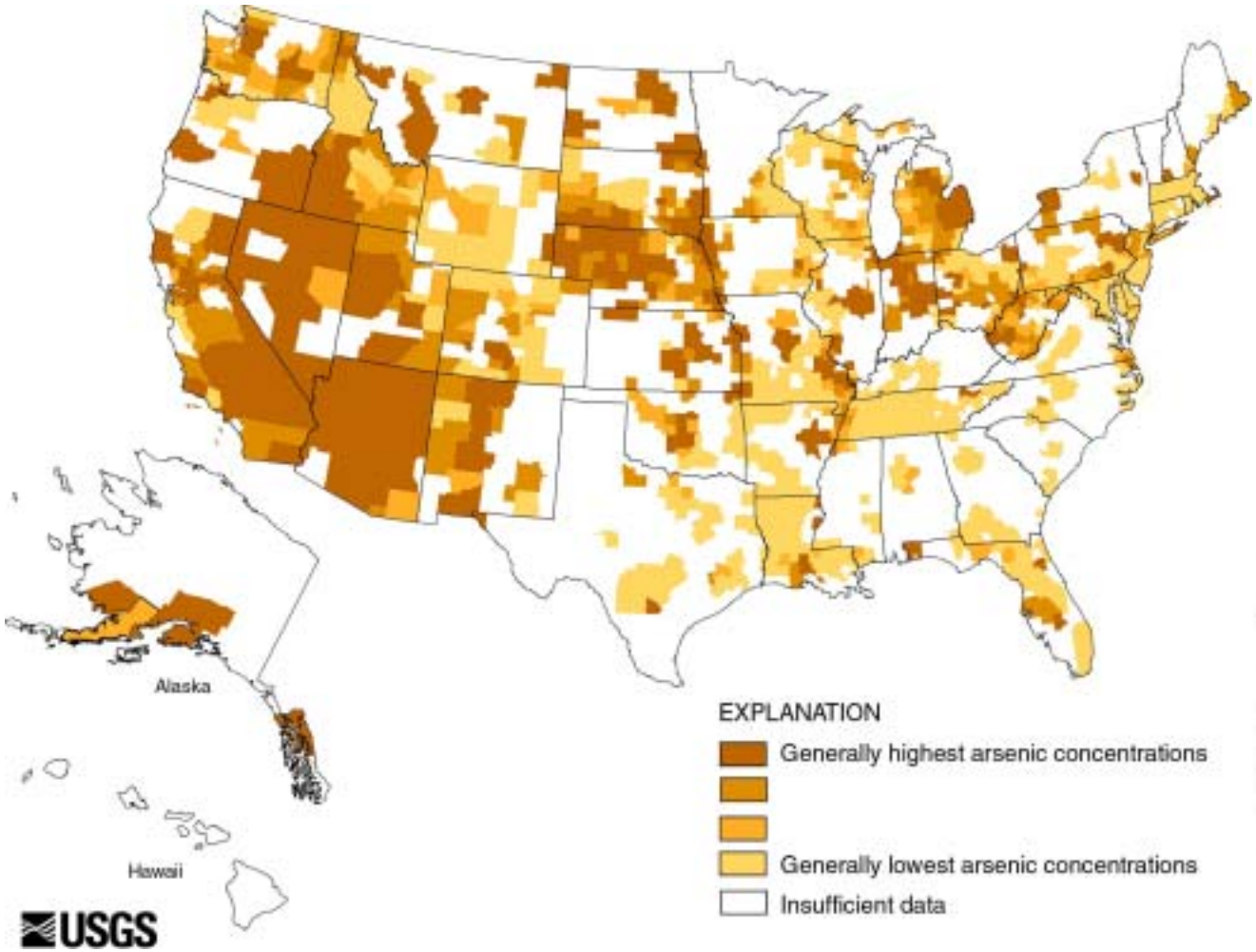
Summary of Human Biotransformation of Arsenic

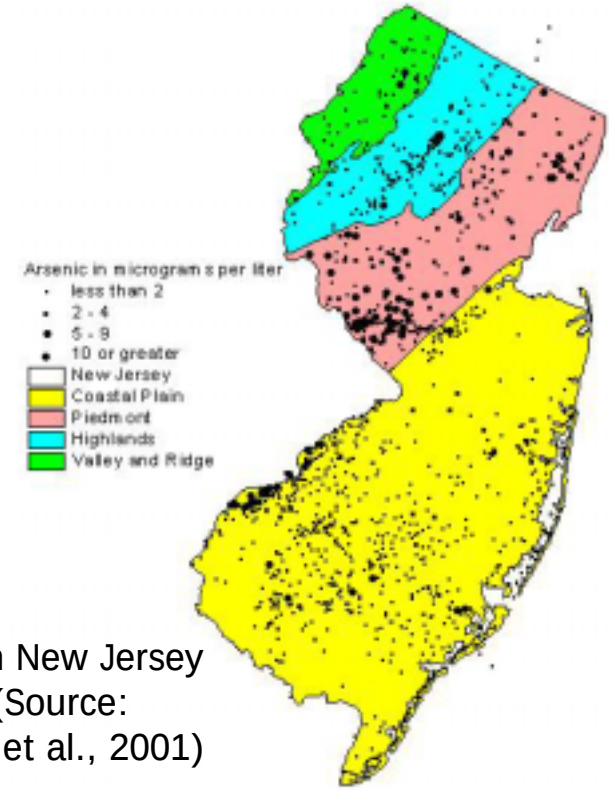


Adapted from NRC (2001)


EXTERNAL DATA SETS (OBSERVATION OR MODEL DERIVED)
EXTERNAL MODELS FOR REGIONAL CHARACTERIZATION
ARSENIC (AND/OR SITE) SPECIFIC
GENERAL/SUPPORTING
• RELEASES: AIR -NTI/NEI; MULTIMEDIA - TRI, HazDat; SITE SPECIFIC
• OUTDOOR AIR QUALITY: OBSERVED - AIRS, SITE SPECIFIC; CALCULATED - CEP, NATA
• DRINKING WATER: AOED, NAOS, NIRS; SITE SPECIFIC
• SURFACE & GROUND WATER: WQN, EMAP, NAWQA, STORET; SITE SPECIFIC
• SOILS & SEDIMENTS: NGA, NAWQA, EMAP, ORCA, STORET; SITE SPECIFIC
• DIETARY: TDS, NHEXAS; SITE SPECIFIC
• BIOTA: EMAP, ORCA, STORET; SITE SPECIFIC
• HUMAN BIOMARKERS: NHEXAS; SITE SPECIFIC
• METEOROLOGICAL DATA: NCDC, AIRS
• HYDROGEOLOGICAL DATA: USGS GROUND WATER ATLAS
• DATA FROM EPA EXPOSURE FACTOR HANDBOOK
• MACRO & MICRO EXPOSURE: CHAD, NHEXAS
• DEMOGRAPHIC SURVEYS: CPS, AHS
• DIETARY & DRINKING WATER SURVEYS: TDS, CSFII, NHEXAS
• GEOGRAPHIC, LAND USE/COVER, etc.: WESSEX 1ST ST., LANDVIEW IV, USGS
• POPULATION PHYSIOLOGICAL CHARACTERIZATION: NHANES, ICRP
• ATMOSPHERIC: METEOROLOGY - RAMS, MM5, CALMET; TRANSPORT - ASPEN, CALPUFF, AERMOD, ISC; CHEMISTRY/TRANSPORT - CMAQ, REMSAD
• HYDROGEOLOGIC: SURFACE WATER - SMS, BASINS; WATERSHED - WMS; VADOSE: POREFLOW; GROUNDWATER - GMS, FACT; CHEMISTRY – MINTEQ
• DRINKING WATER DISTRIBUTION: EPANET
• OTHER SUPPORTING: EMISSION ALLOCATION - EMS HAP, SMOKE; BIOAVAILABILTY, FOOD WEB, ECOLOGICAL - BLM, CATS, RAMAS-GIS, etc.
• MULTIMEDIA: MEPAS (SCREENING); MIMS
• HUMAN EXPOSURE: DIETARY - LIFELINE, DEPM, DEEM; INHALATION - MENTOR-SHEDS, HAPEM-4; DRINKING WATER - MENTOR-SHEDS
COUPLED COMPONENTS
DIAS
MODULES FOR LOCAL & "NEIGHBORHOOD" SCALE CHARACTERIZION
STATISTICAL (STRF, BME)
SUBGRID FATE/TRANSPORT
OBJECT/RELATIONAL AND SPATIAL DATABASE ENGINES: (PLATFORM: ORACLE 9 & ARCGIS/ARCINFO WITH SDE)
"MULTIMODEL" MENTOR COMPUTATIONAL ENVIRONMENT (PLATFORM: MATLAB 6 WITH FEMLAB 2 TOOLBOX, C++/JAVA, FORTRAN)
CCL's NATIONAL (US) MULTIMEDIA ENVIRONMENTAL INFORMATION SYSTEMS (EIS) FOR SELECTED TOXICS
MENTOR-BASED EXPOSURE RECEPTOR ATTRIBUTE AND ACTIVITIES INFORMATION SYSTEM (ERAAS)
HDMR TOOLS FOR SYSTEMATIC MODEL REDUCTION
"FAST EQUIVALENT" MODELS FOR DISTRIBUTION-BASED POPULATION ASSESSMENTS
MENTOR-BASED PROCESS SOURCE-TO-DOSE MODELS FOR INDIVIDUALS (MICROENVIRONMENTAL AND BIOLOGICAL FATE AND TRANSPORT)
MENTOR-BASED OPERATIONS MODELS OF EXPOSURE RELATED ACTIVITIES (FOR INDIVIDUALS & POPULATIONS)
TOOLS FOR DIAGNOSTIC DATA AND MODEL ANALYSES (PLATFORMS: MATLAB, SAS, SPlus)
GIS FRONT-END FOR SPATIAL PROBLEM DEFINITION AND ANALYSIS (PLATFORM: ARCVIEW/ARCGIS)
VISUAL FRONT-END FOR CONTINUOUS/DISCRETE EVENT SIMULATION DEFINITION (PLATFORM: STATEFLOW; CUSTOM GUIs)

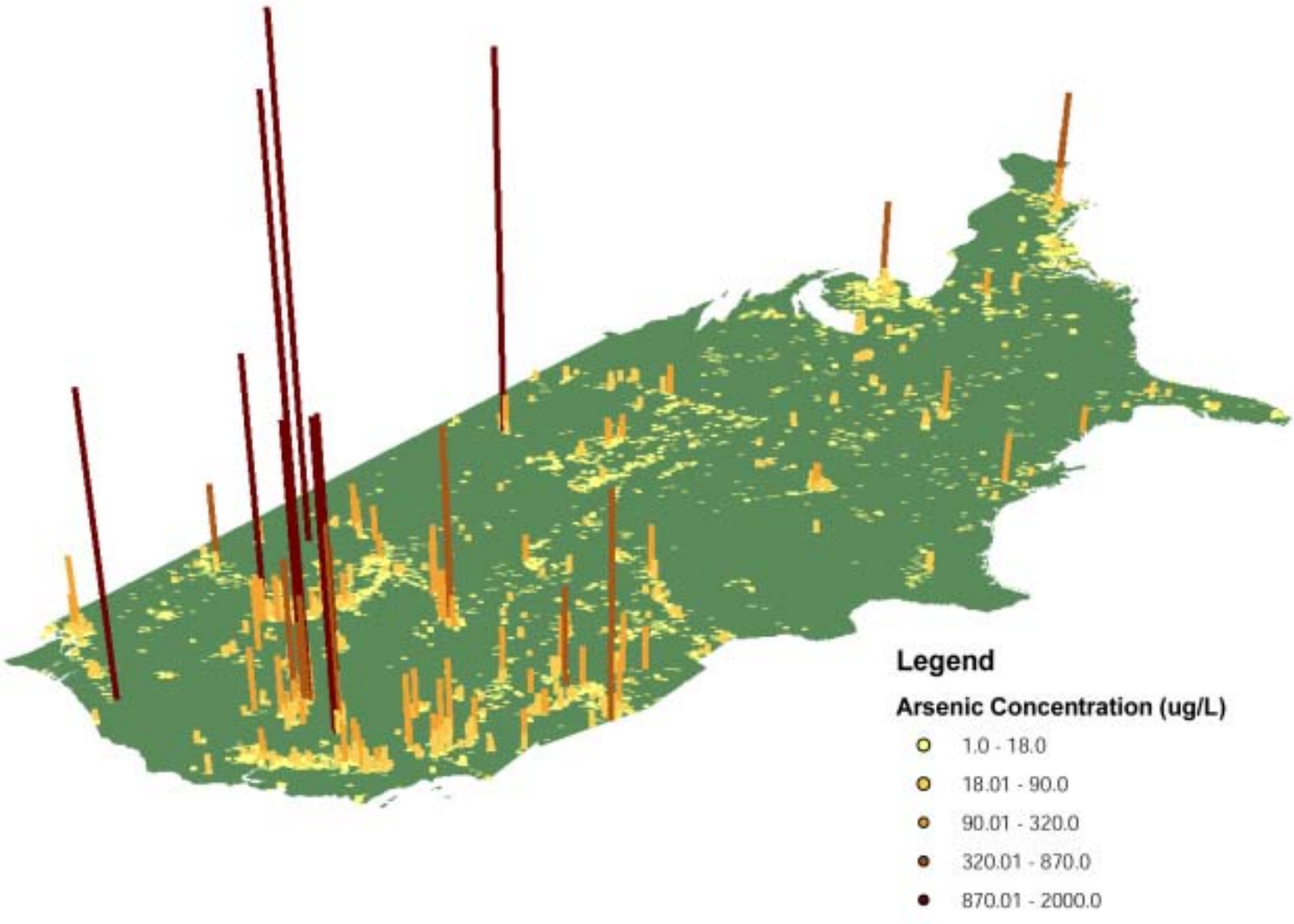
Counties in Which at Least 10% of Wells Exceed Different As Levels (10, 5, 3, and 0 μg/L; from USGS Database)



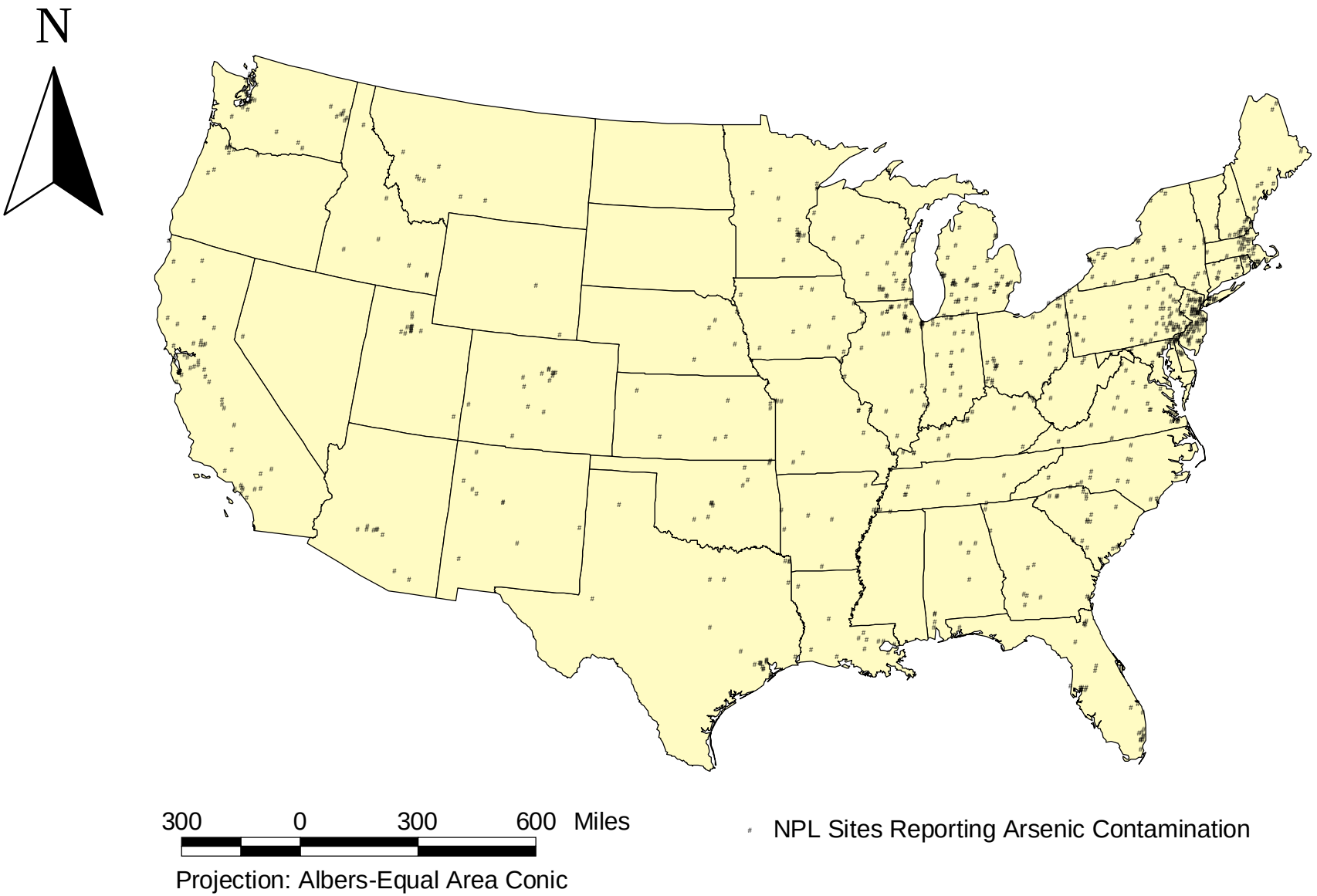


Arsenic in New Jersey Aquifers (Source: Vowinkel et al., 2001)

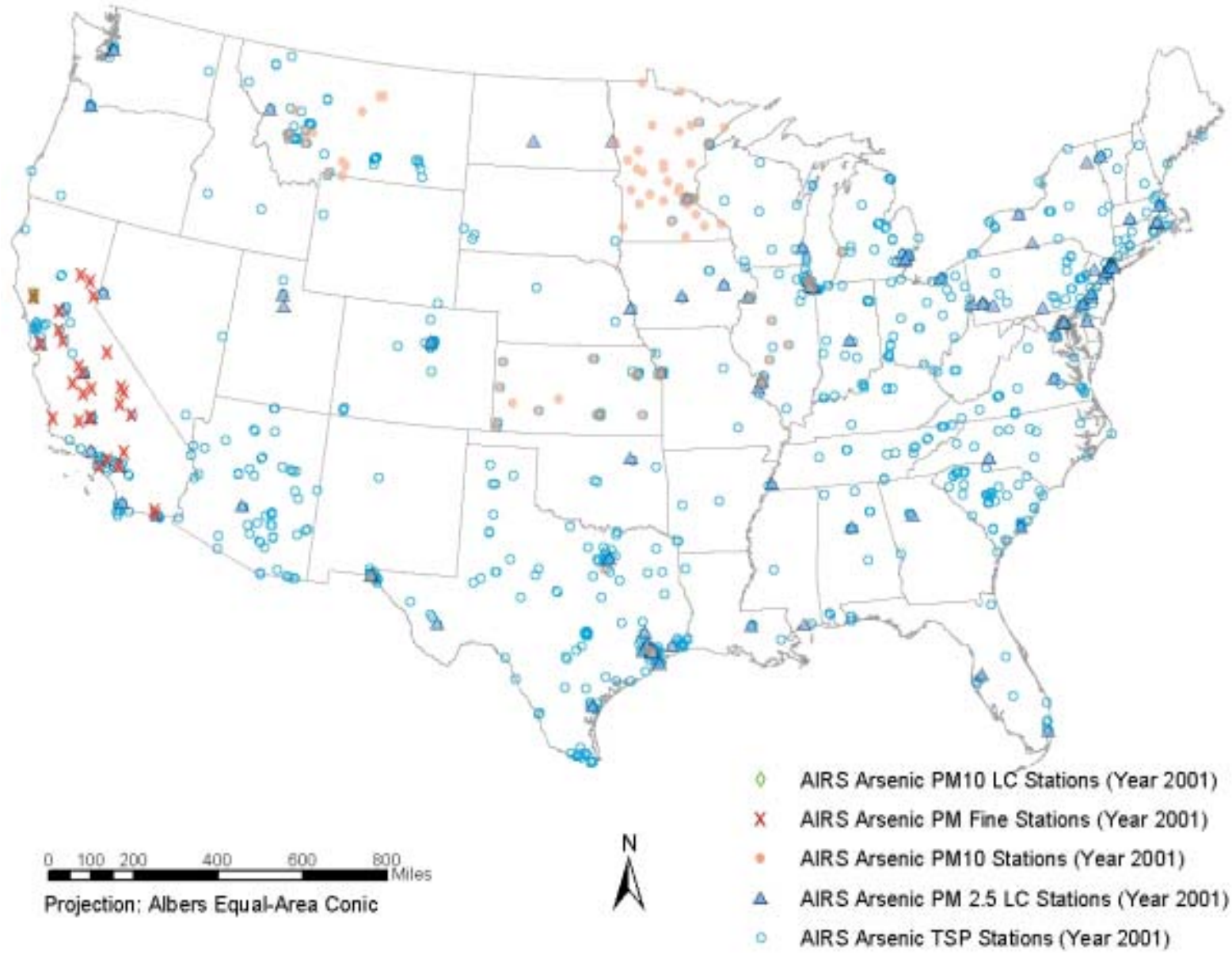
Arsenic Concentrations in Groundwater (Wells) from the NAWQA Dataset (1976-97)



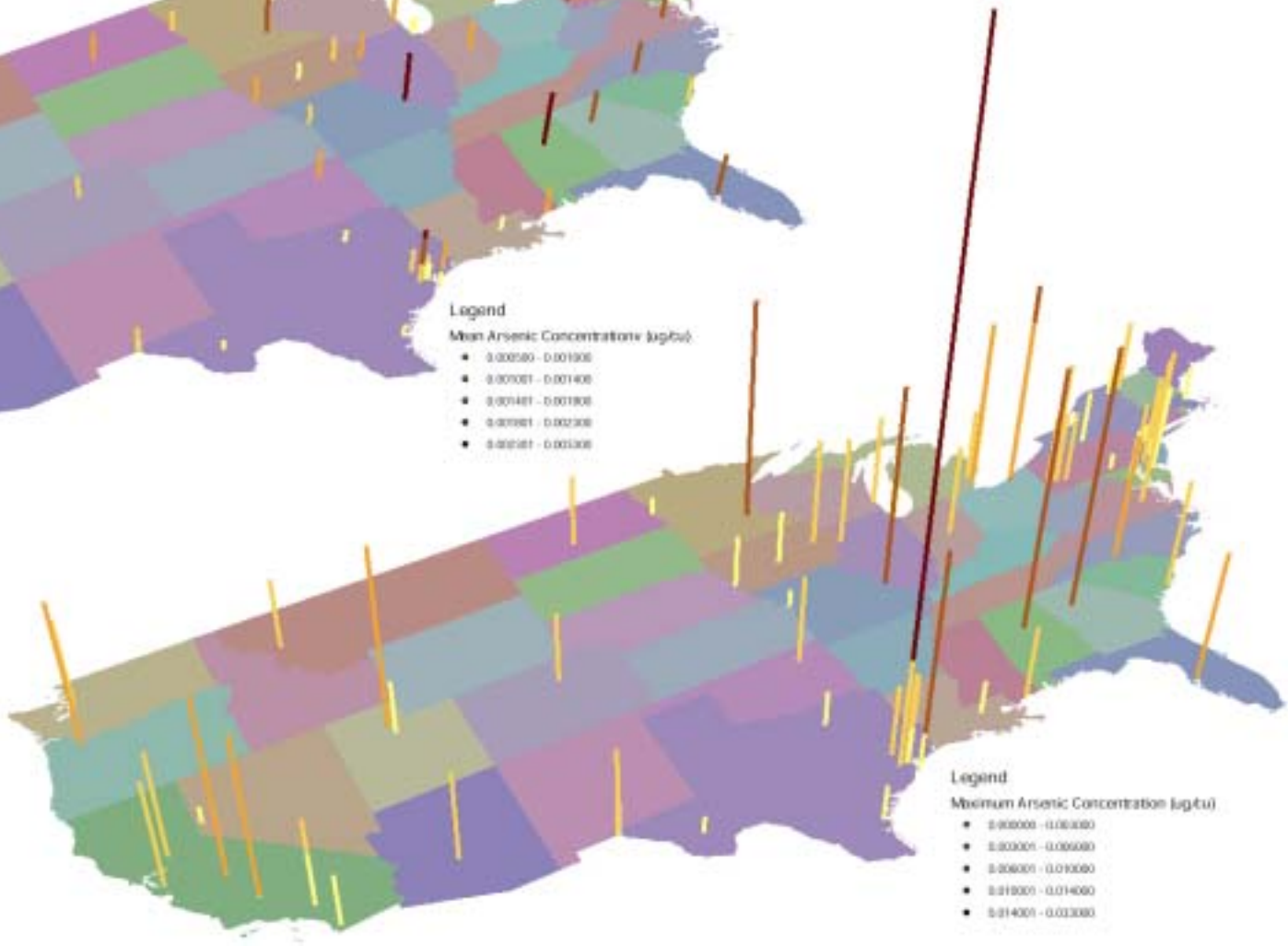
NPL Sites Reporting Arsenic Contamination



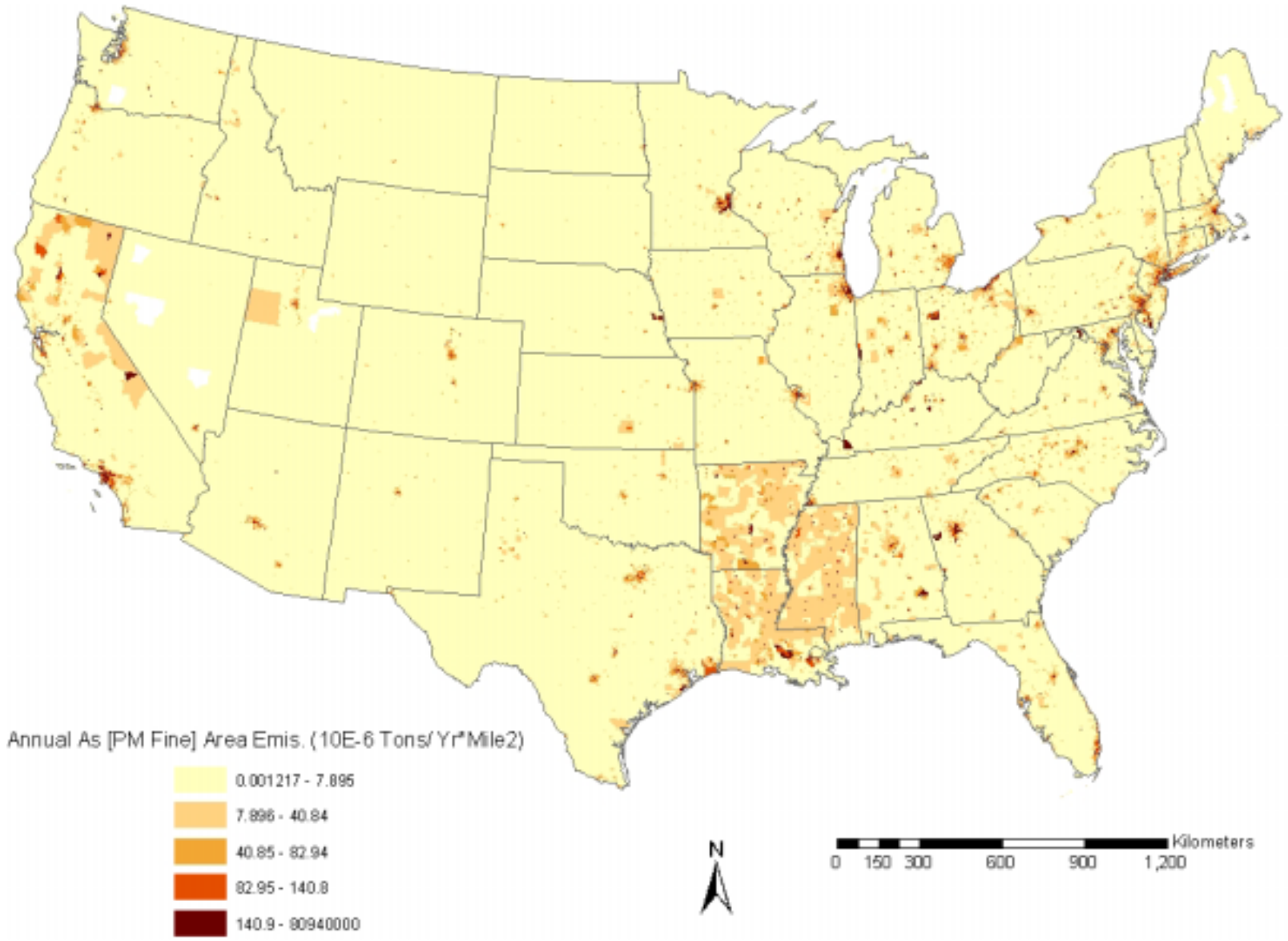
Locations of AIRS Monitoring Stations that Measured Arsenic Compounds in 2001



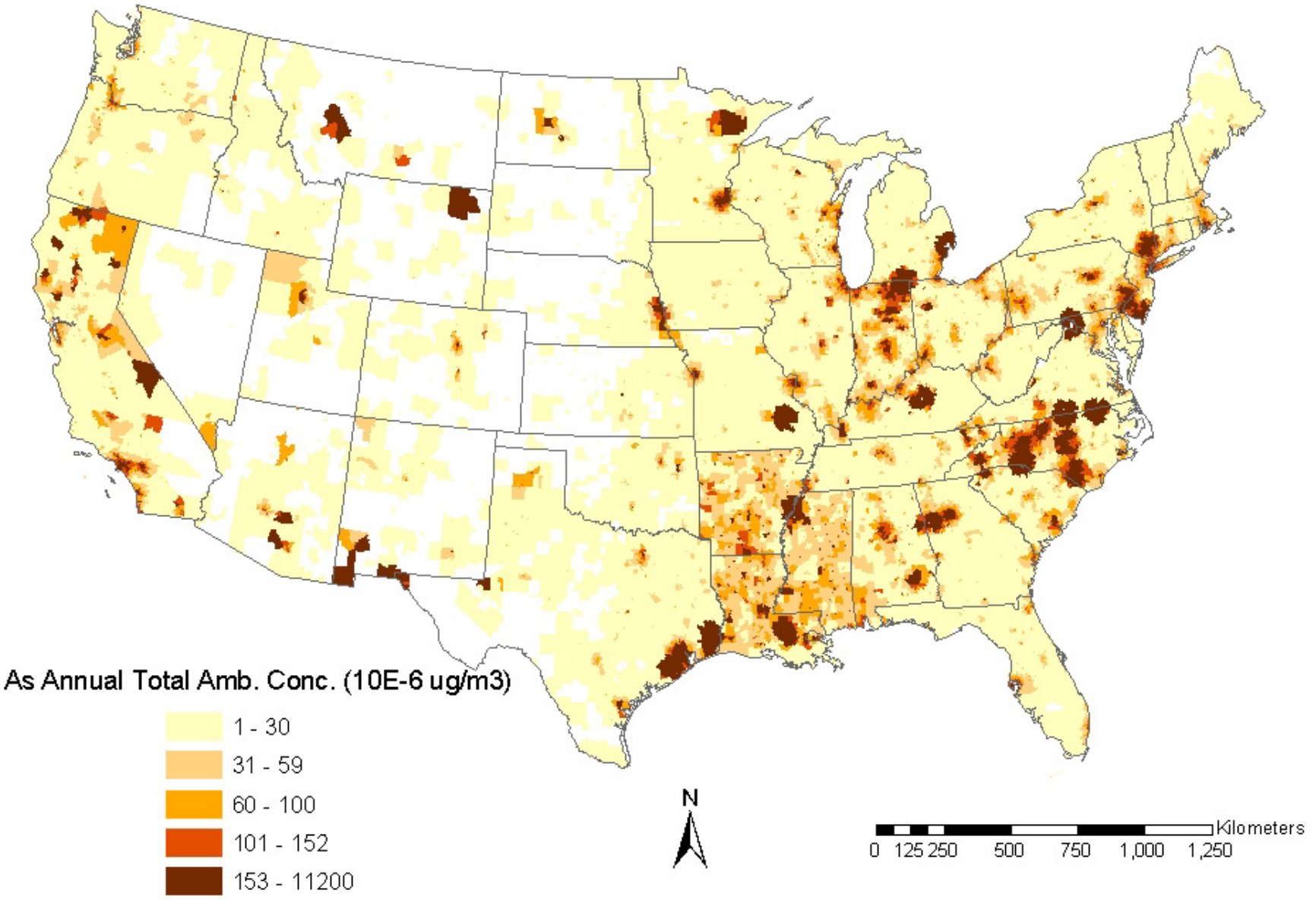
Average and Maximum Arsenic Concentations Measured in PM2.5 at AIRS Monitoring Stations During 2001



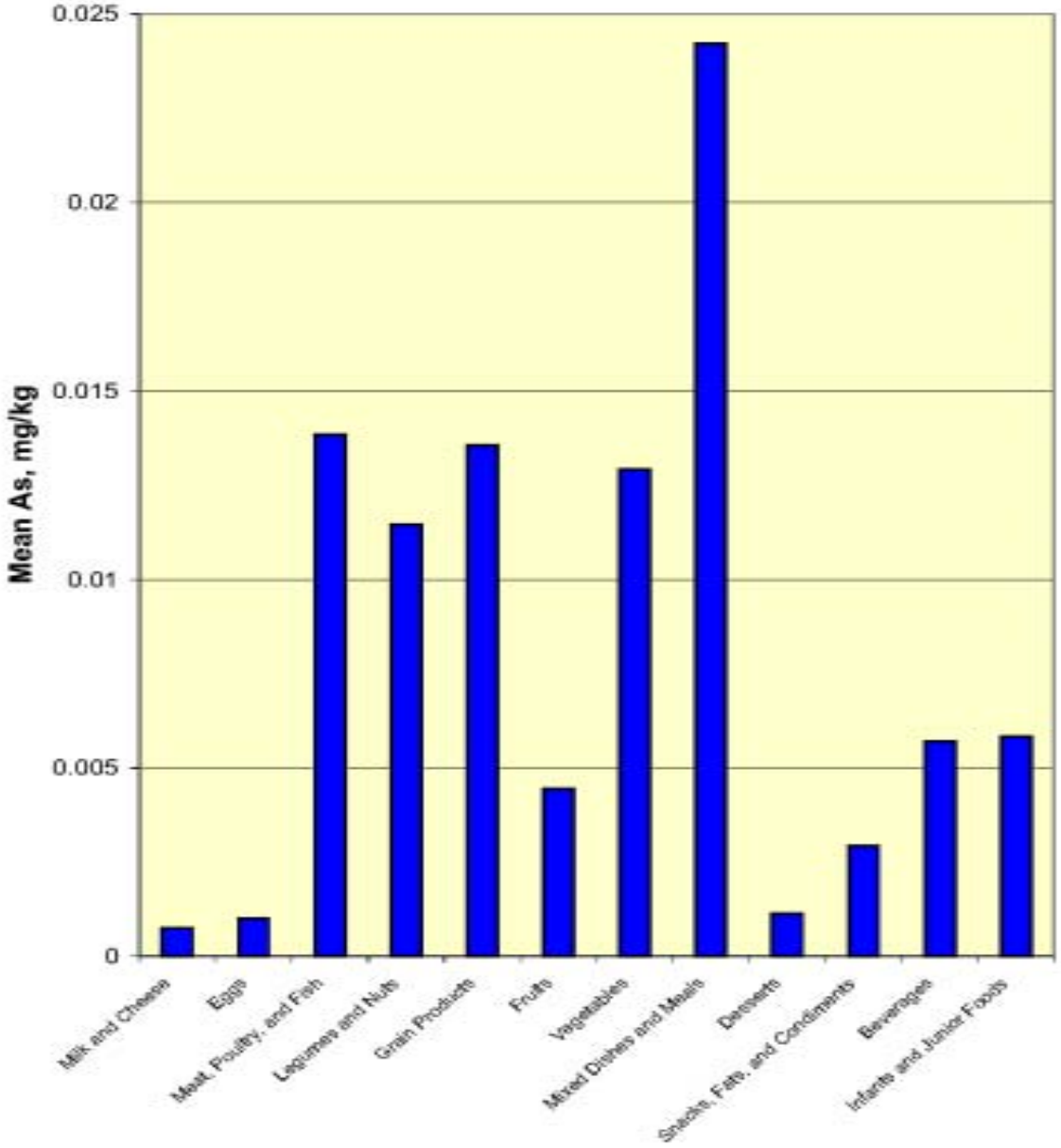
USEPA NTI (1996) Estimates of Annual Arsenic Air Emissions from Area Sources (as PM_fine; census tract allocation via EMS-HAP)

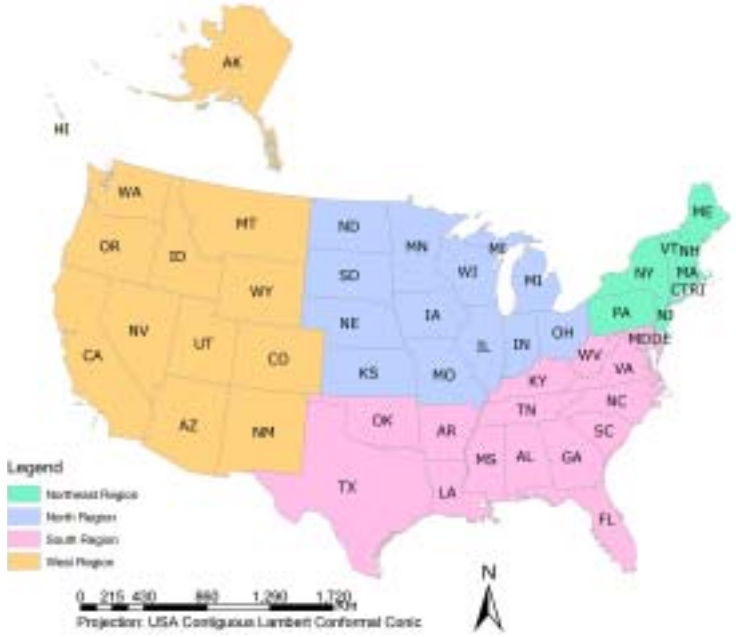


1996 NATA Estimates of Ambient Annual Average Total Arsenic Concentrations (Based on USEPA EMS-HAP/ASPEN Simulations)

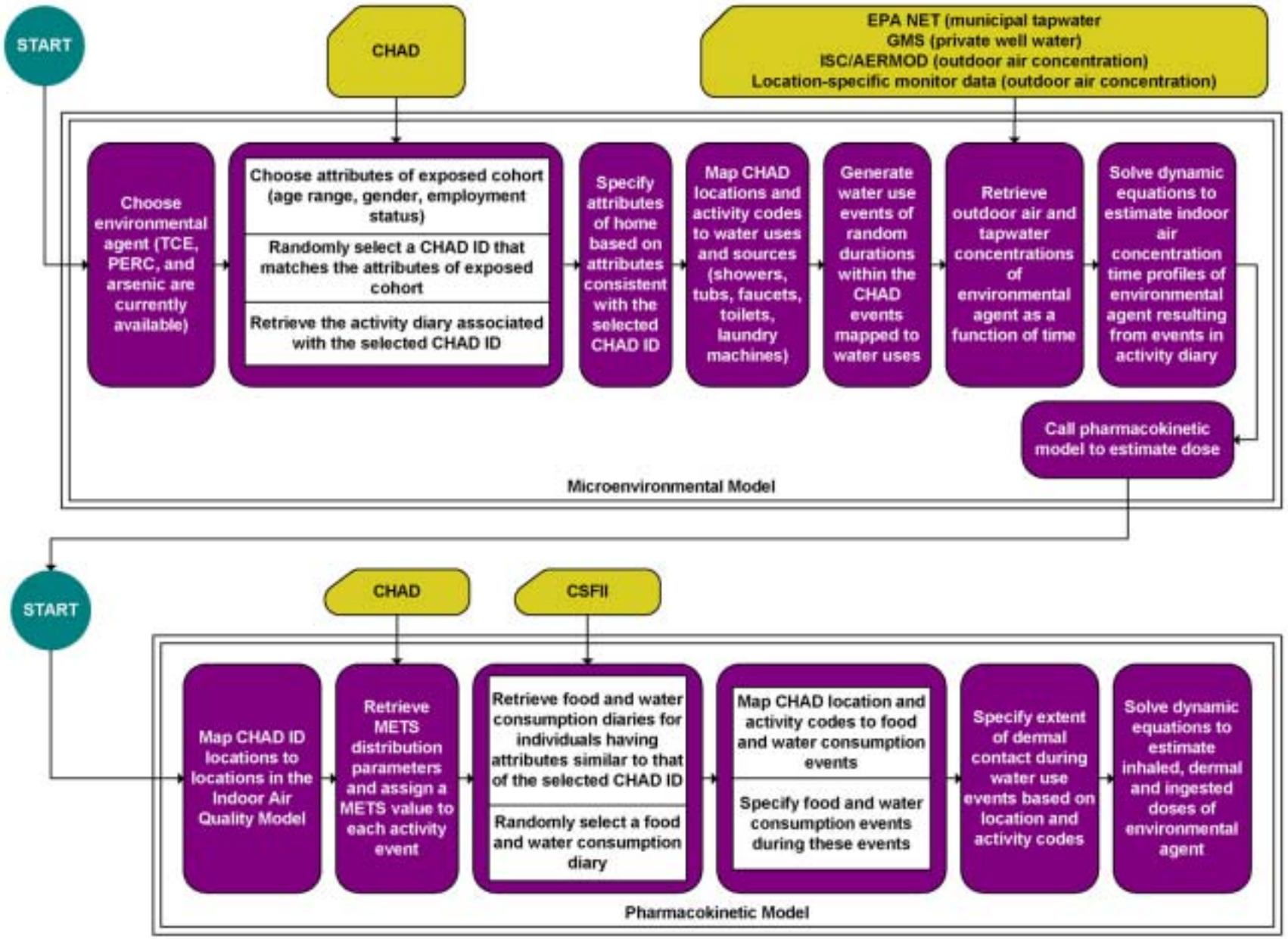


Total Arsenic (mg/kg) Measured in 12 Major Food Groups Gernerated from a Total 267 Food Items (from USFDA Total Dietary Study)

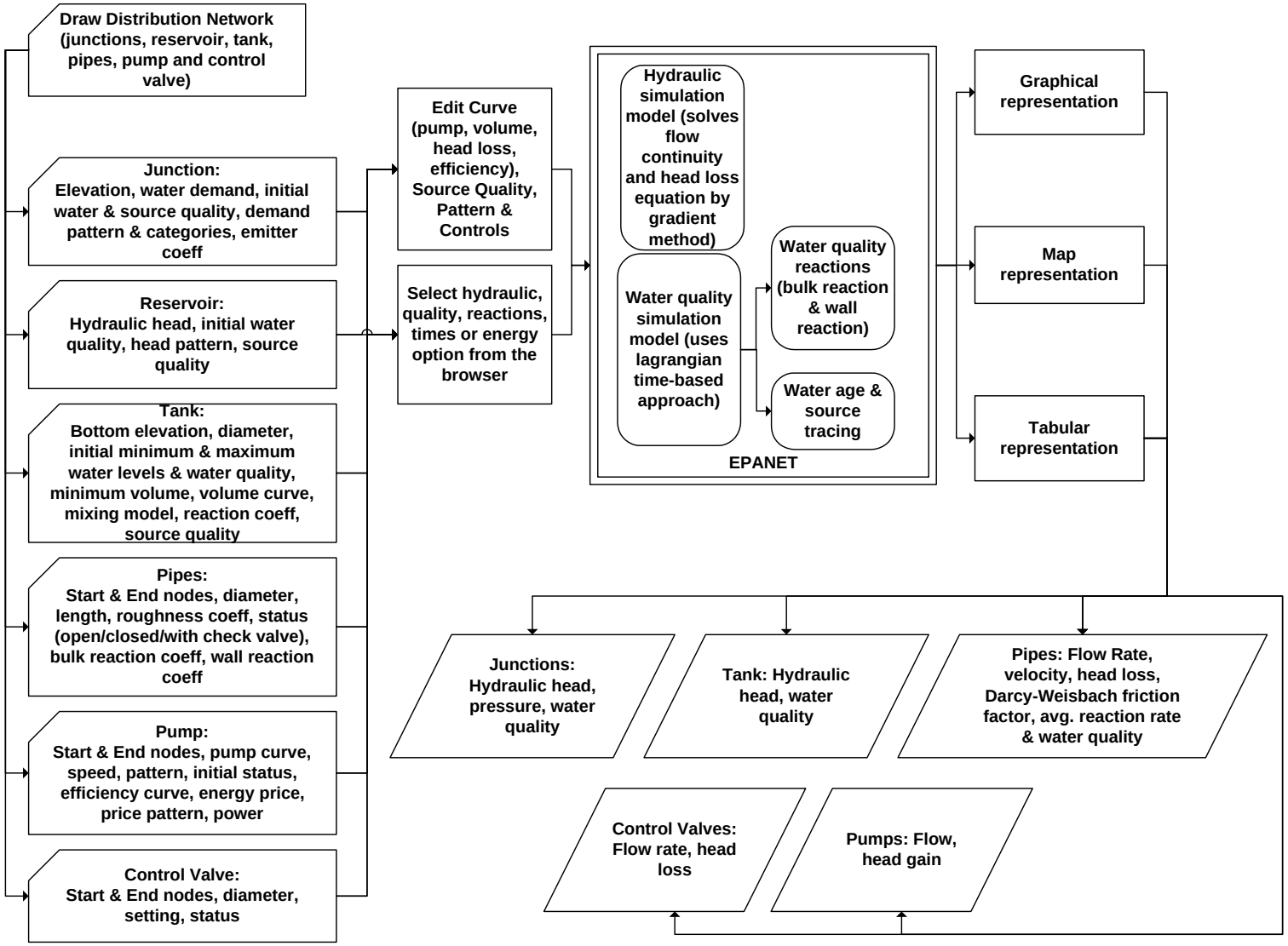




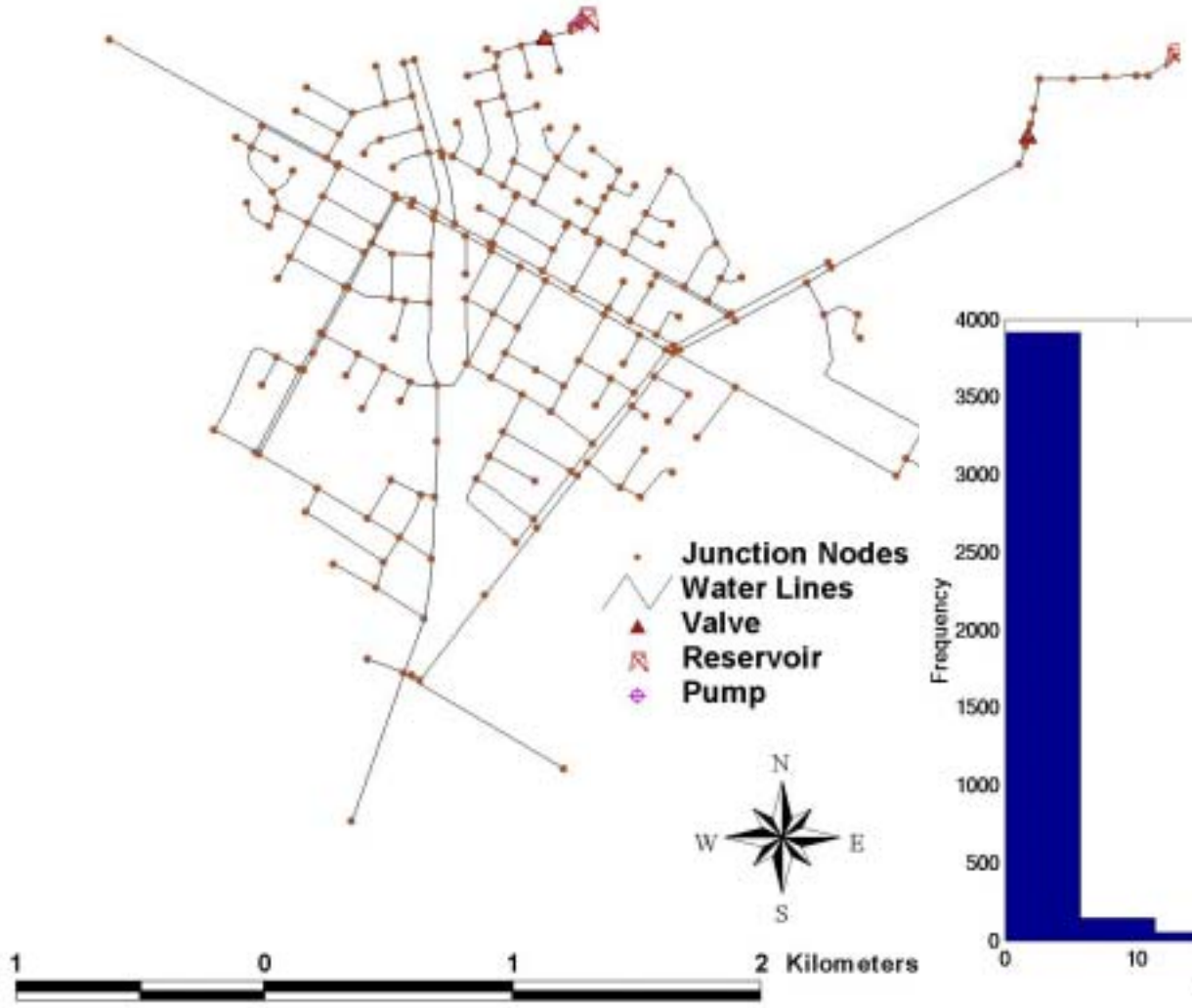
The Individual-Based Modeling Framework Links Interactively Biological (PBPK) Models with Microenvironmental Models

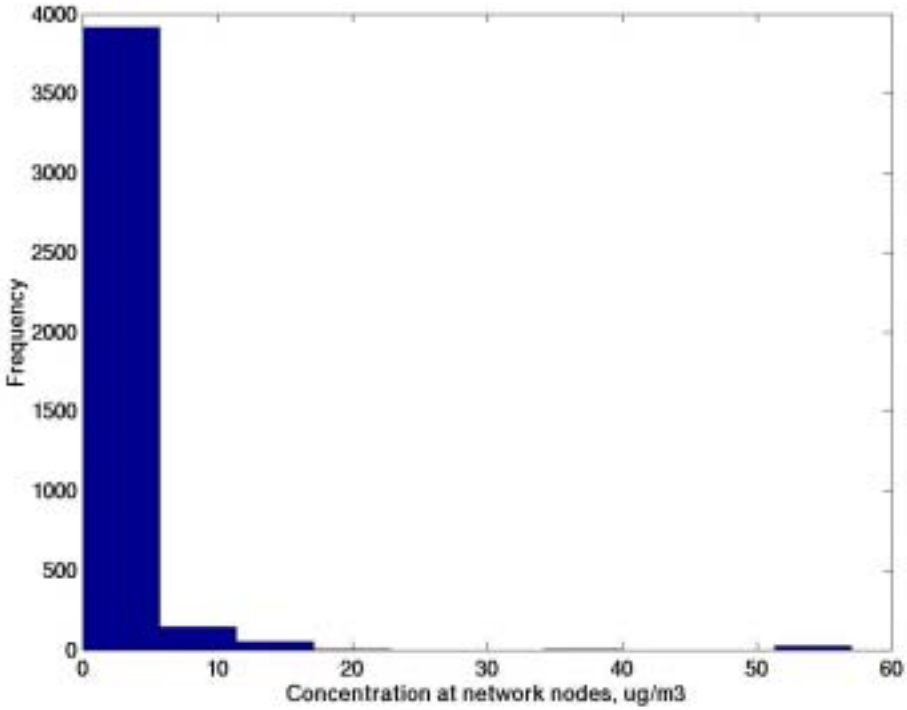


Assessing Individual and Population Exposures to Arsenic: Drinking Water Distribution Modeling with EPANET

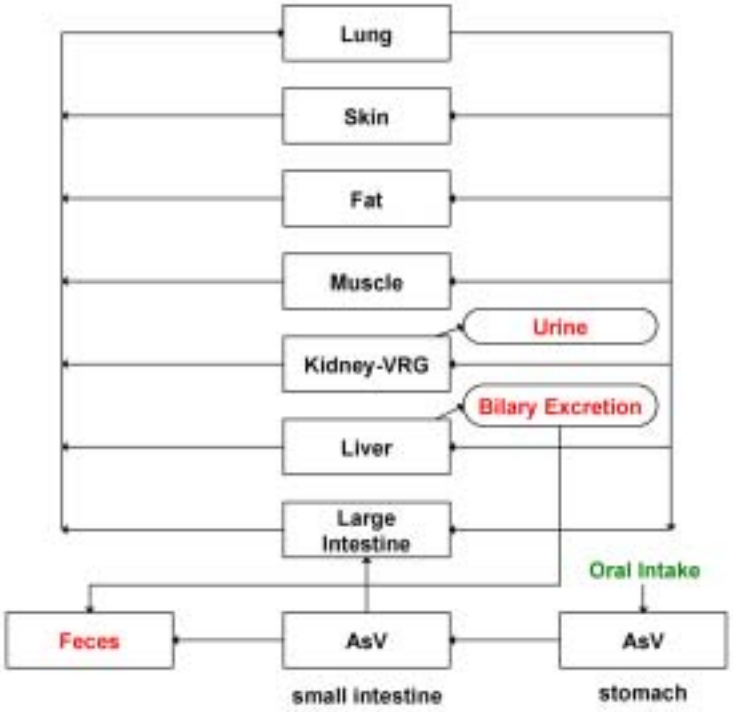


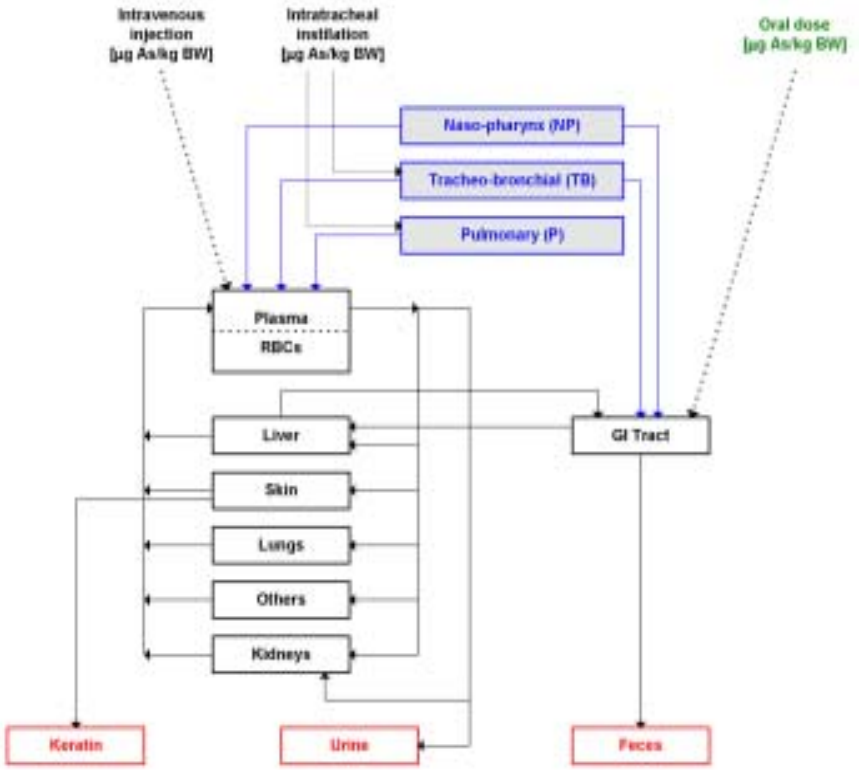
Example EPANET Application: Estimation of Arsenic Distribution in Municipal Water Network (Two Suppliers)





Modular Framework Allows Alternative Biological Descriptions
Example: Alternative Human PBPK Models for Arsenic

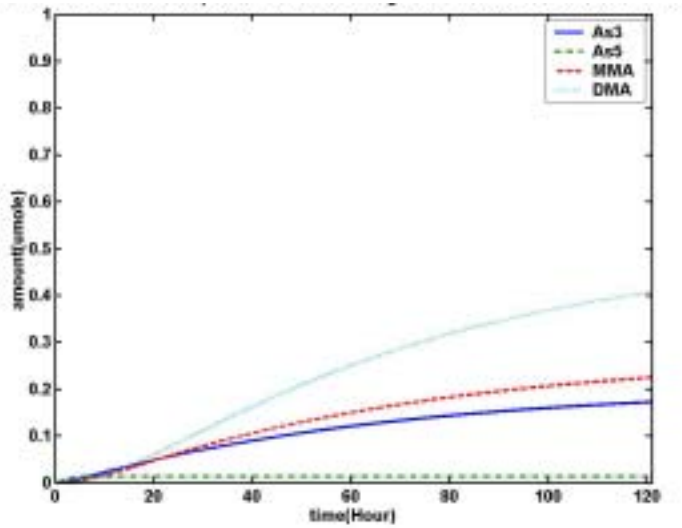




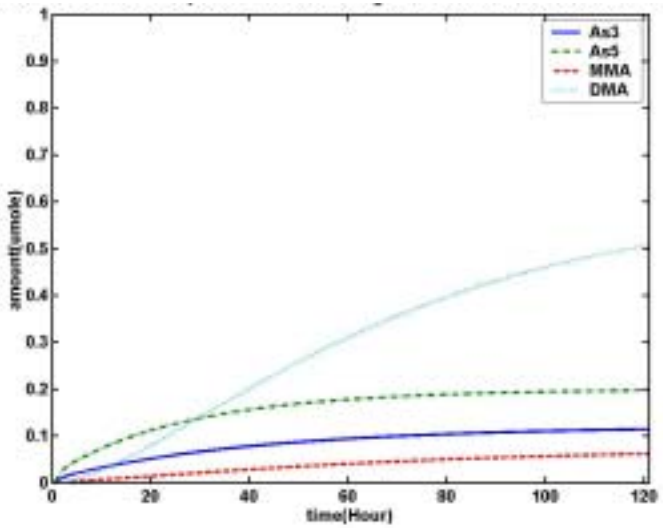
COMPARISON TABLE:

	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.

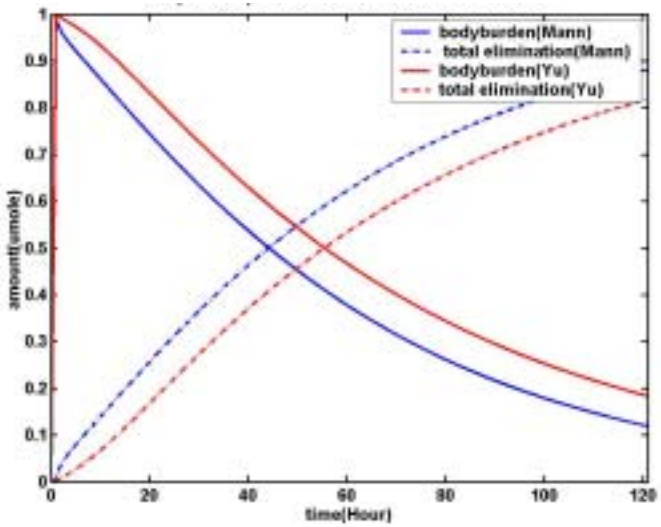
Alternative Arsenic PBPK Model Output Comparisons



Amount of four arsenic species in urine for a single 1.0 umol oral dose of AsV – Yu Model



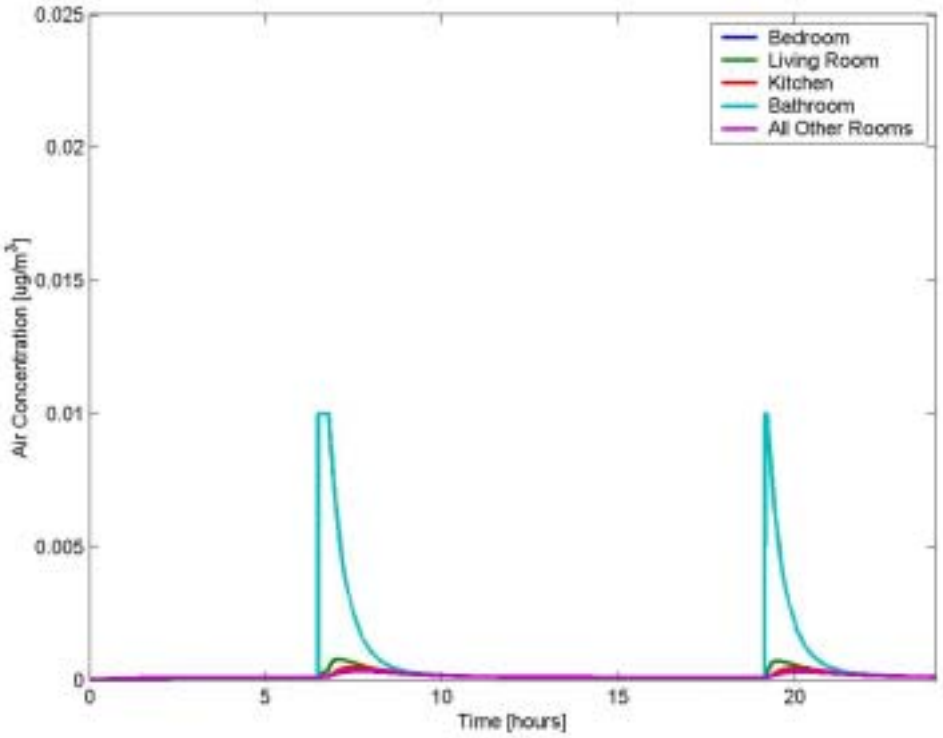
Amount of four arsenic species in urine for a single 1.0 umol oral dose of AsV – Mann Model

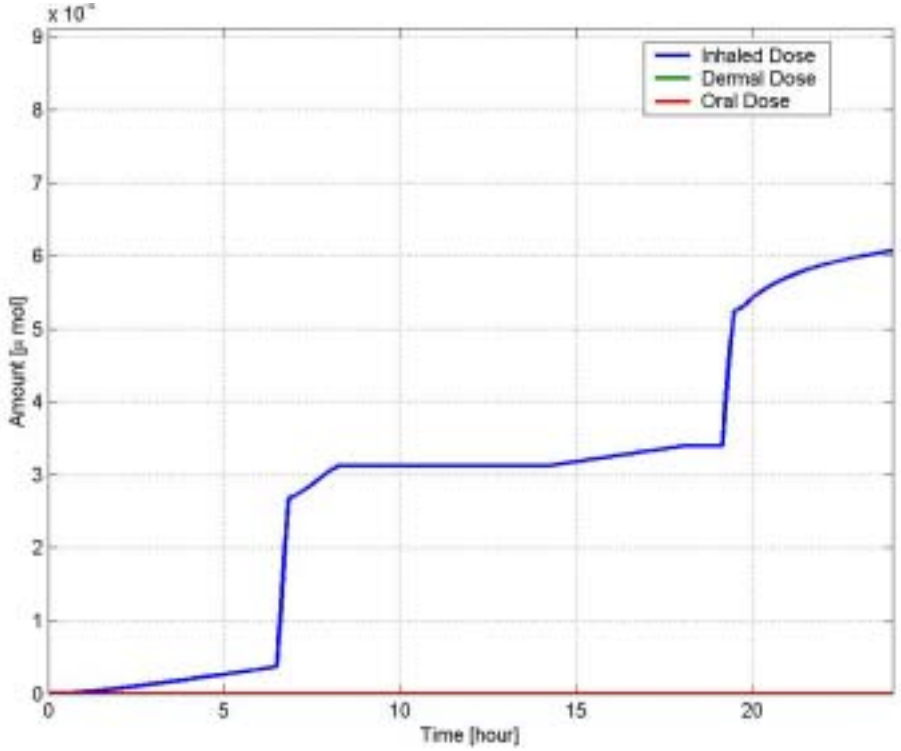


Output Comparison Between Mann and Yu Models:

- body burden (Mann)
- total elimination (Mann)
- body burden (Yu)
- total elimination (Yu)

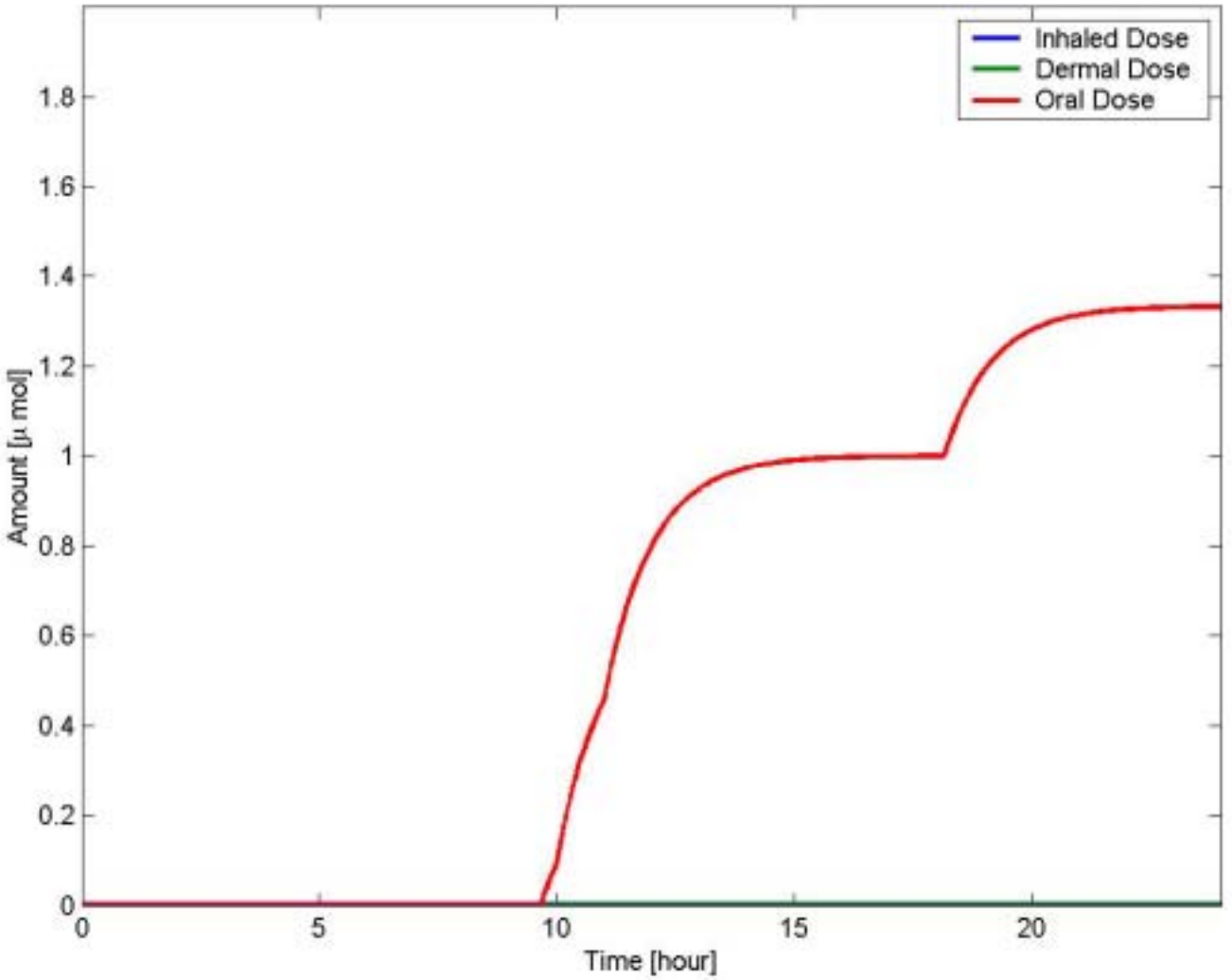
Microenvironmental – PBPK Model Test: Indoors Inhalation Exposure/Dose to Arsenic (Source: Tap Water Use, Outdoor Air)





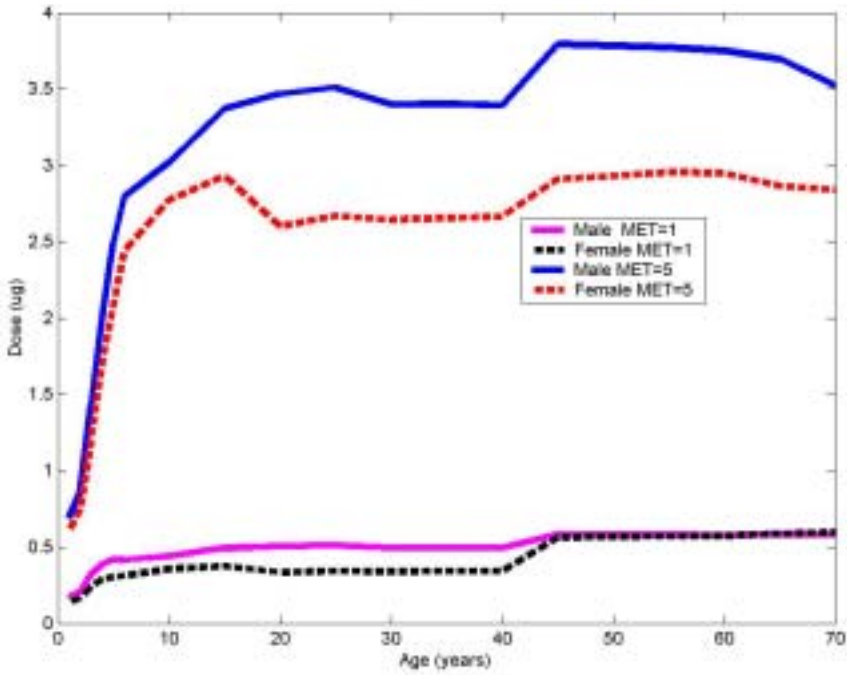
(Outdoor air: 100 pg/m3; Tap water: 50 ppb)

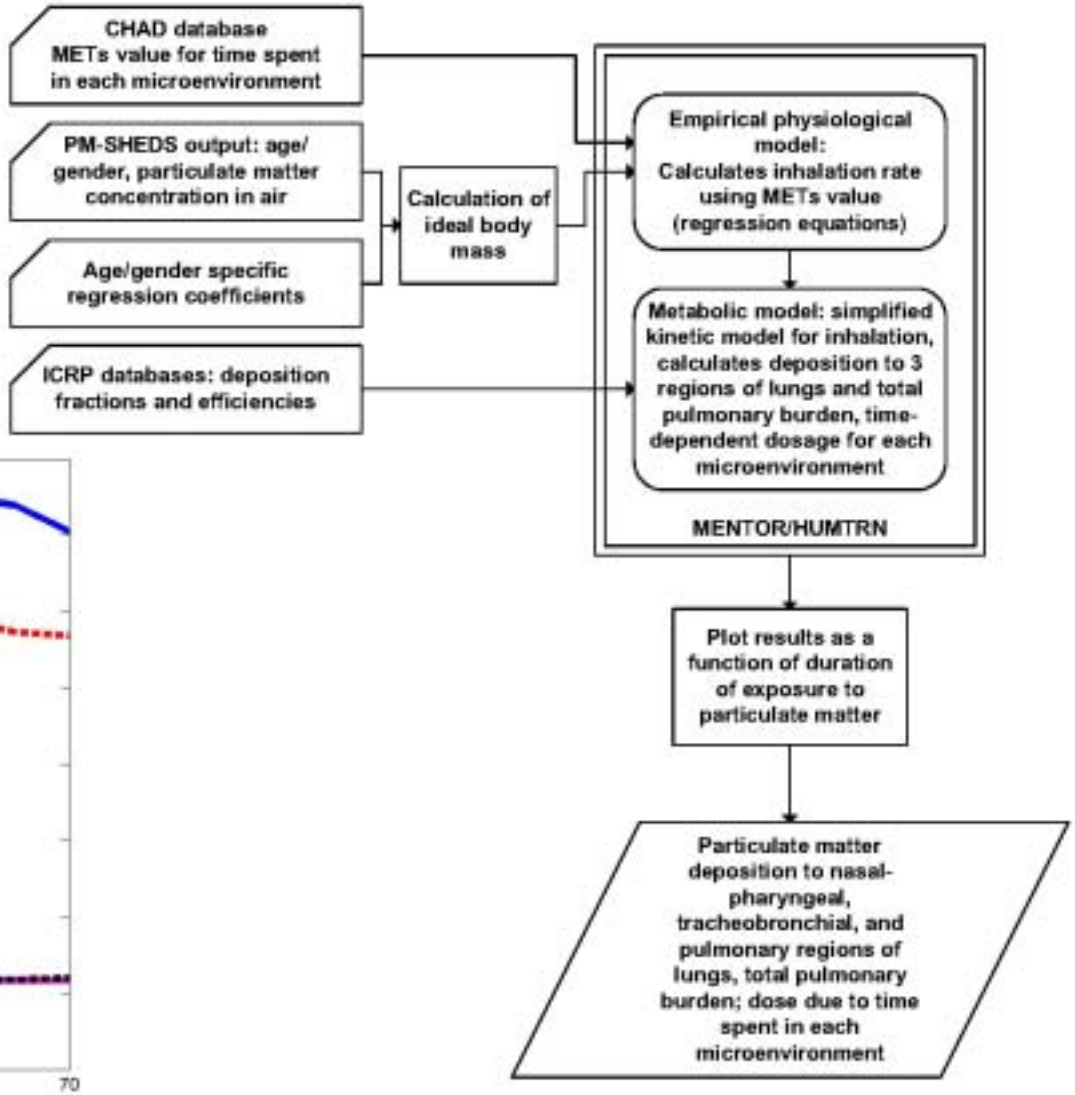
Microenvironmental – PBPK Model Test: Inhalation and Oral Exposure and Dose to Arsenic (Source: Tap Water Use, 50 ppb As)



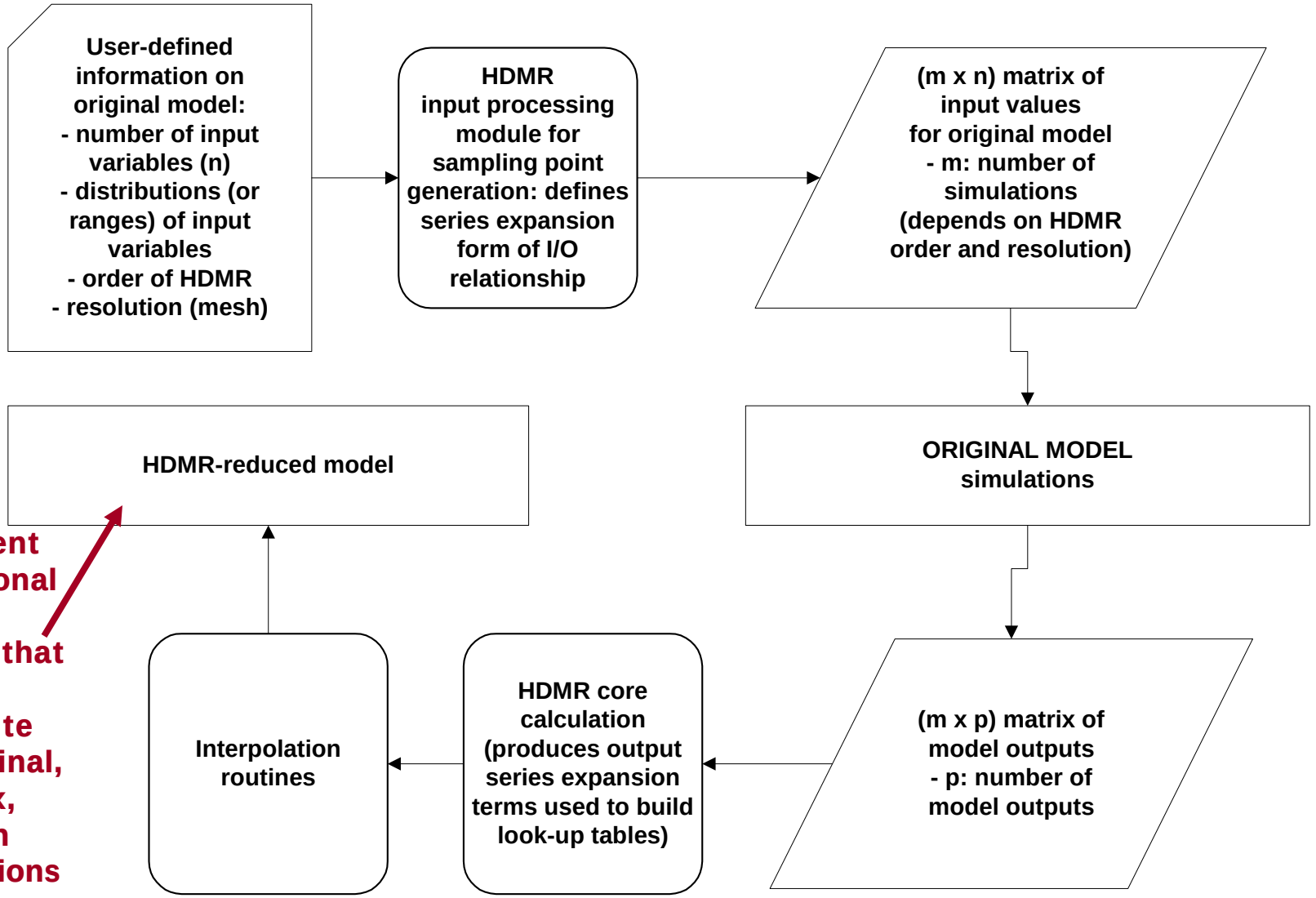
Example Calculations of Age and Gender Dependent Inhalation Dose of PM 2.5 (in µg) for Two Different Intensity Levels of Activity

"MENTOR Level C": Semiempirical (Population-Oriented) Module



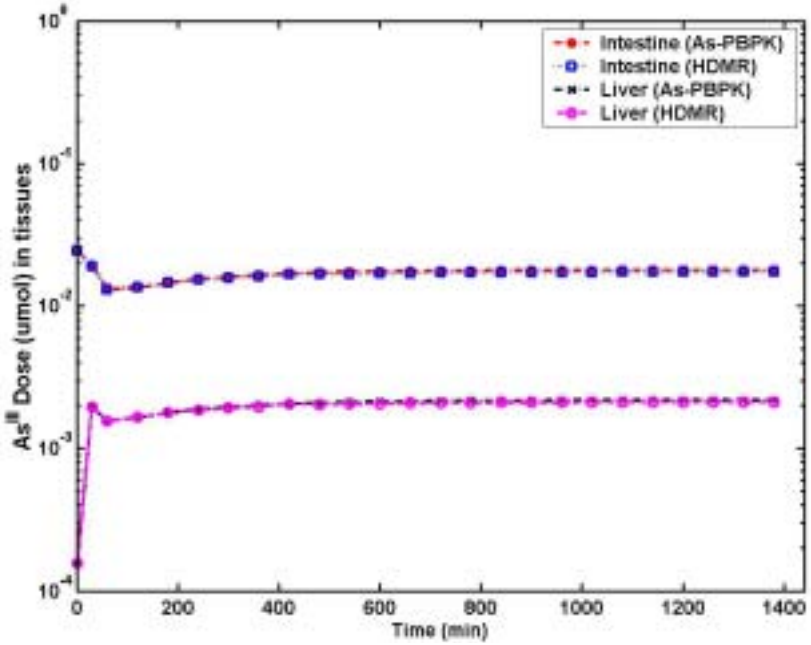


Model Reduction and Sensitivity/Uncertainty Analysis: HDMR (High Dimensional Model Representation) Based Tools



A "Fast Equivalent Operational Model" (FEOM) that can substitute the original, complex, model in calculations

FEOM Development via HDMR
Example: Arsenic PBPK Modeling for Individuals

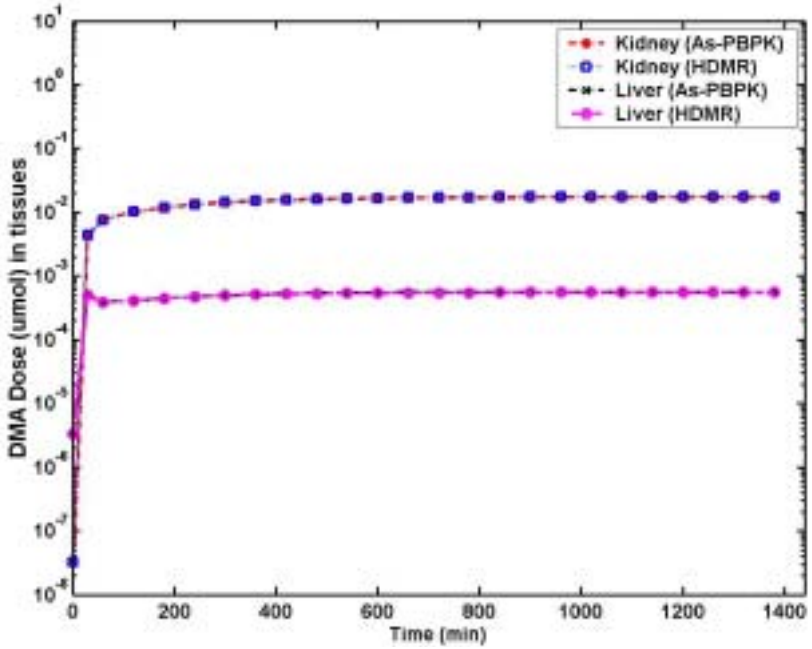


Diurnal profiles of As^{III} Dose, for an individual (female, 50 years old)

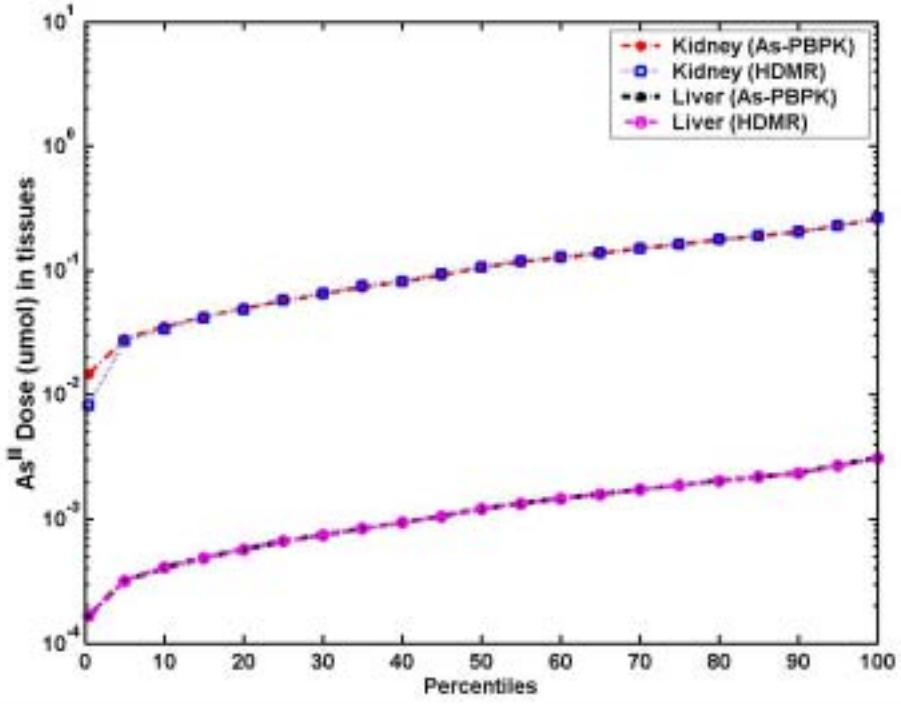
Exposure Scenario:
Air-conc. = 8×10^{-5} (μmol/L), DW-conc. = 7.8×10^{-2} (μmol/L)
Food Intake = 1.2×10^{-2} (μmol/L), DW-rate = 7×10^{-4} (L/min)

Diurnal profiles of DMA Dose, for an individual (female, 50 years old)

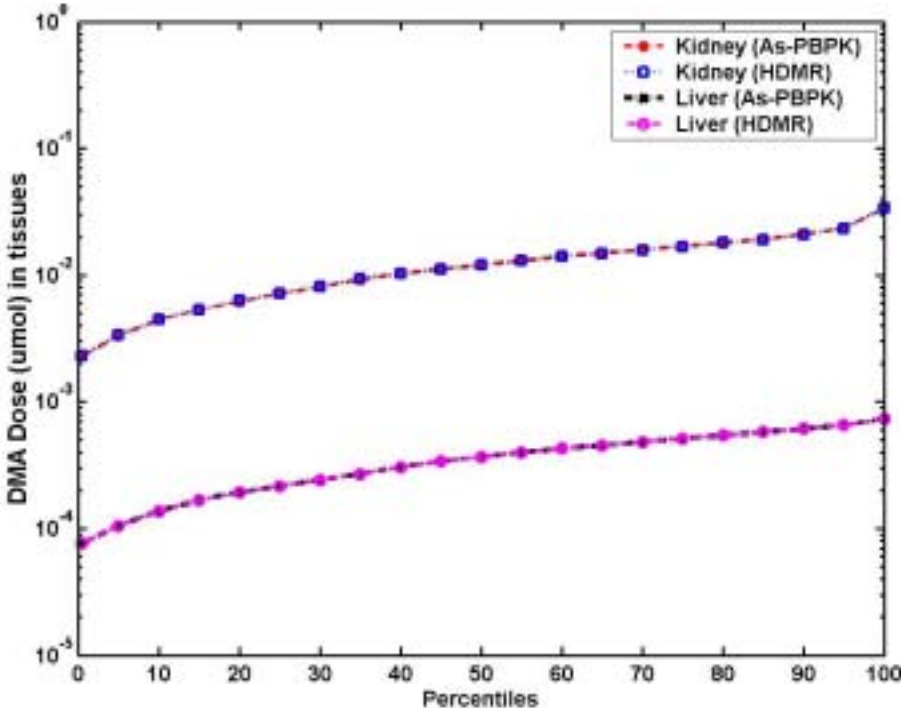
Exposure Scenario:
Air-conc. = 8×10^{-5} (μmol/L), DW-conc. = 7.8×10^{-2} (μmol/L)
Food Intake = 1.2×10^{-2} (μmol/L), DW-rate = 7×10^{-4} (L/min)



FEOM Development via HDMR
Example: Arsenic PBPK Modeling for Populations

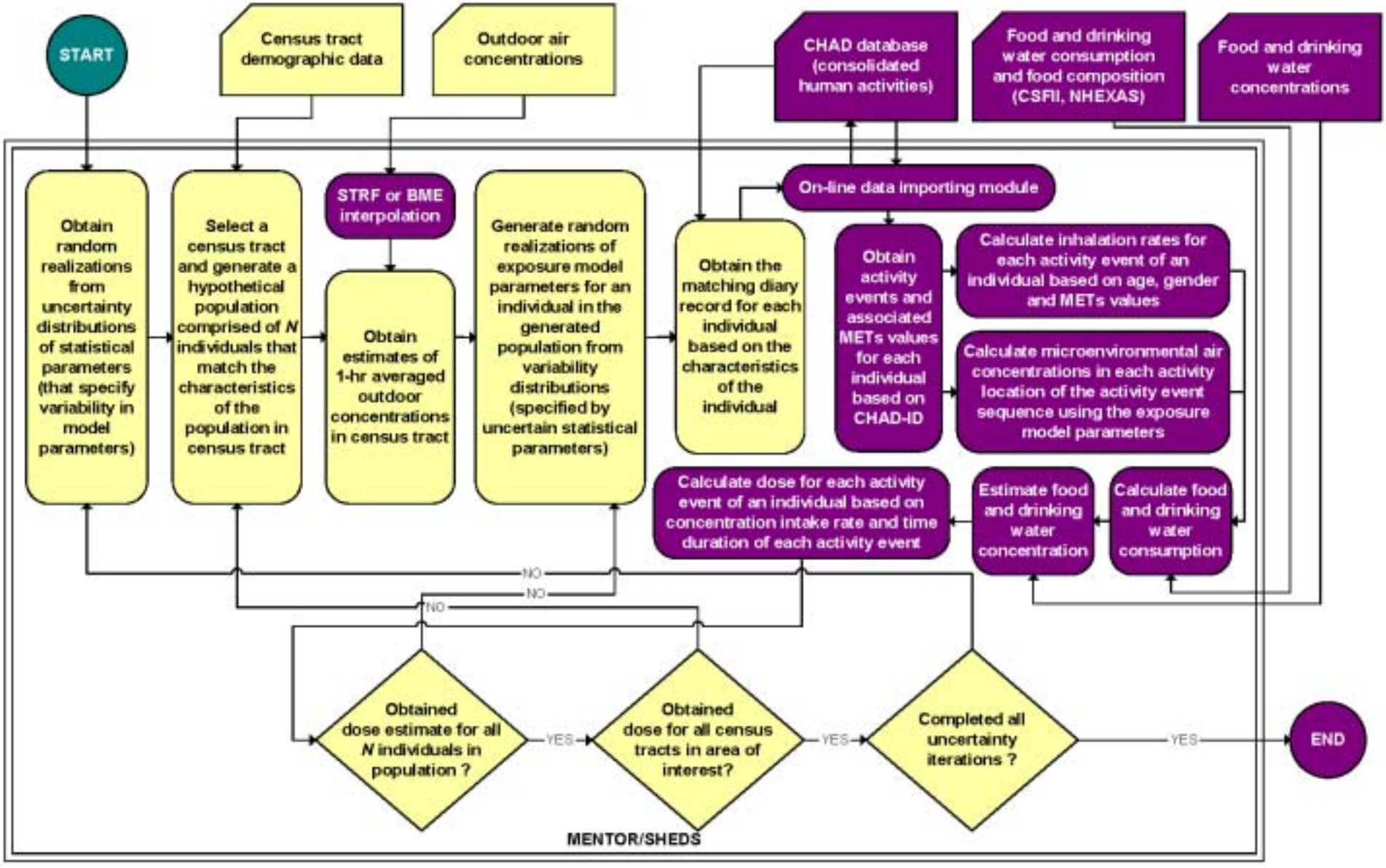


Comparison of As^{III} dose distributions by As-PBPK model and HDMR calculations for the population of 1000 people



Comparison of DMA dose distributions by As-PBPK model and HDMR calculations for the population of 1000 people

Population-Based Exposure and Dose Assessment Incorporates Biologically Based Uptake/Disposition Models

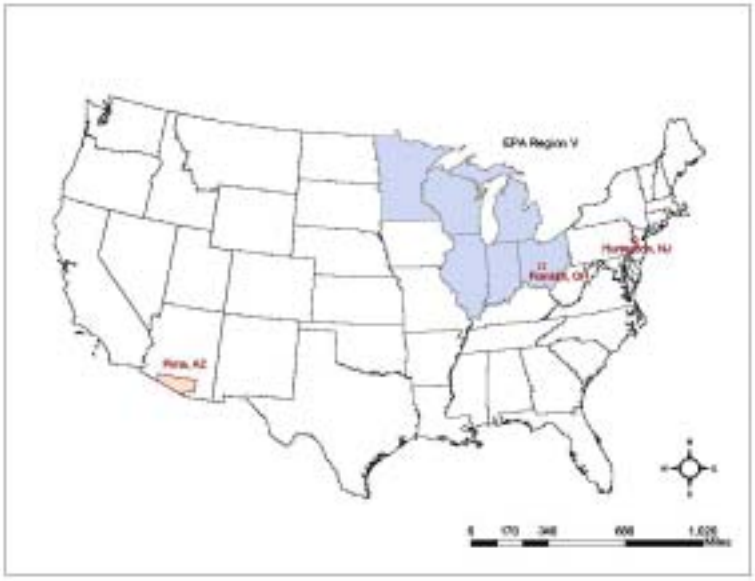


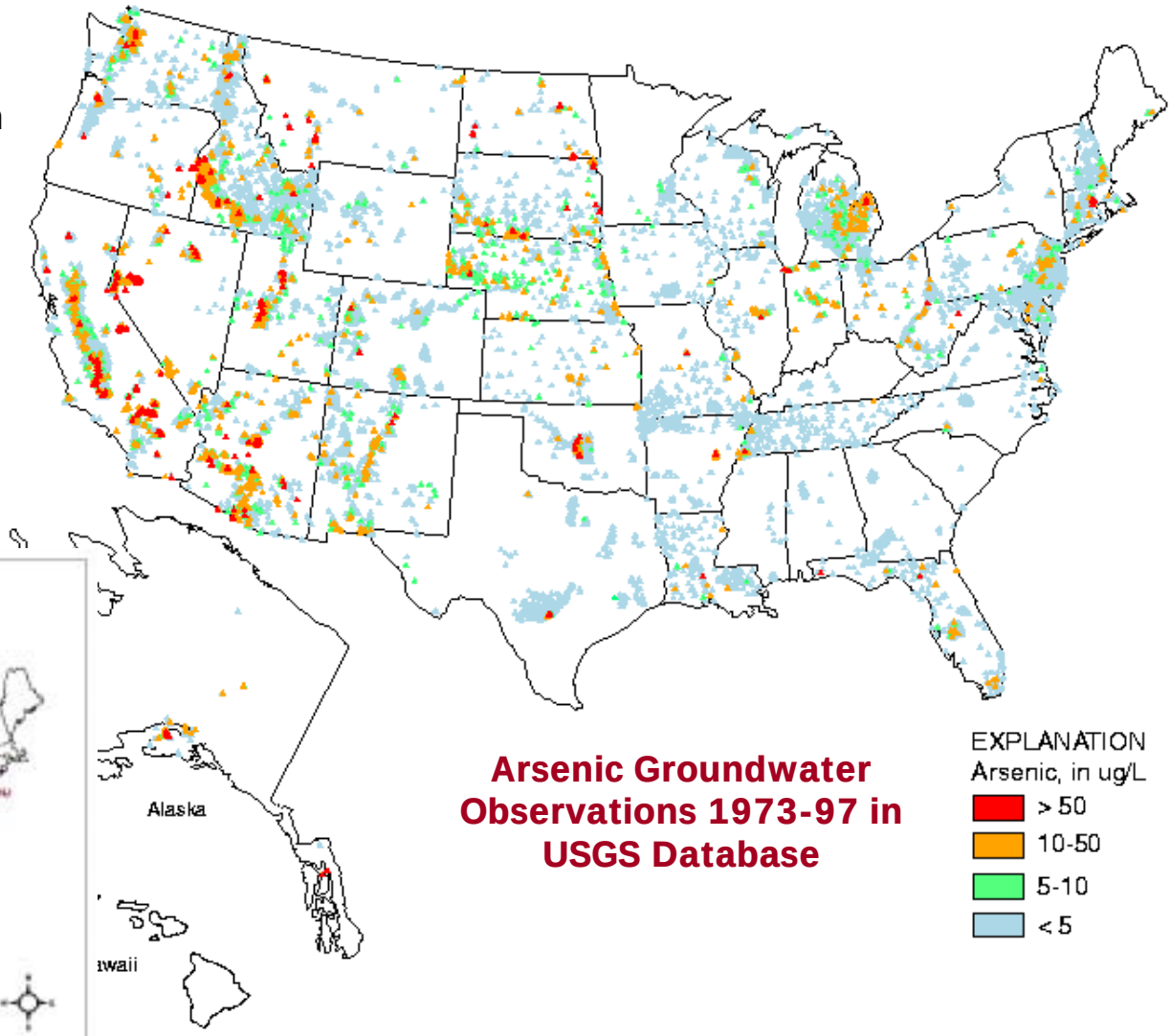
Population Exposure to Arsenic: Source-to-Dose Applications of Multimedia MENTOR/SHEDS

Test applications:

I. **Comparison of population exposures due to inhalation (from outdoor sources) and ingestion (from drinking water) in two counties with reported groundwater arsenic problems: Pima, AZ and Hunterdon, NJ**

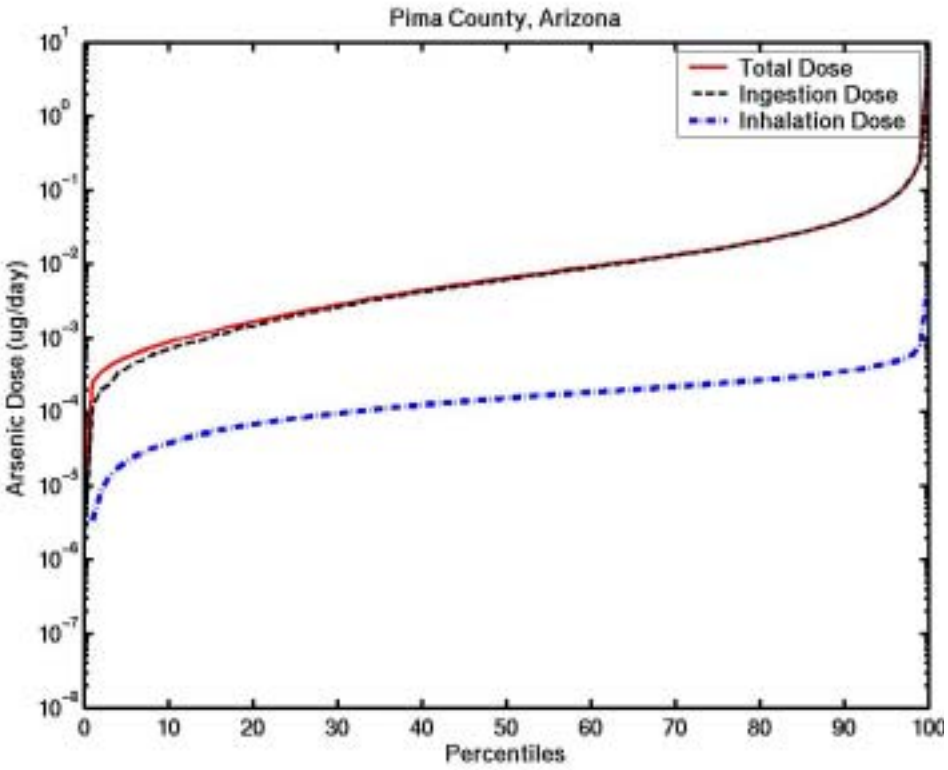
II. **Multipathway exposure/dose assessment using NHEXAS V data**

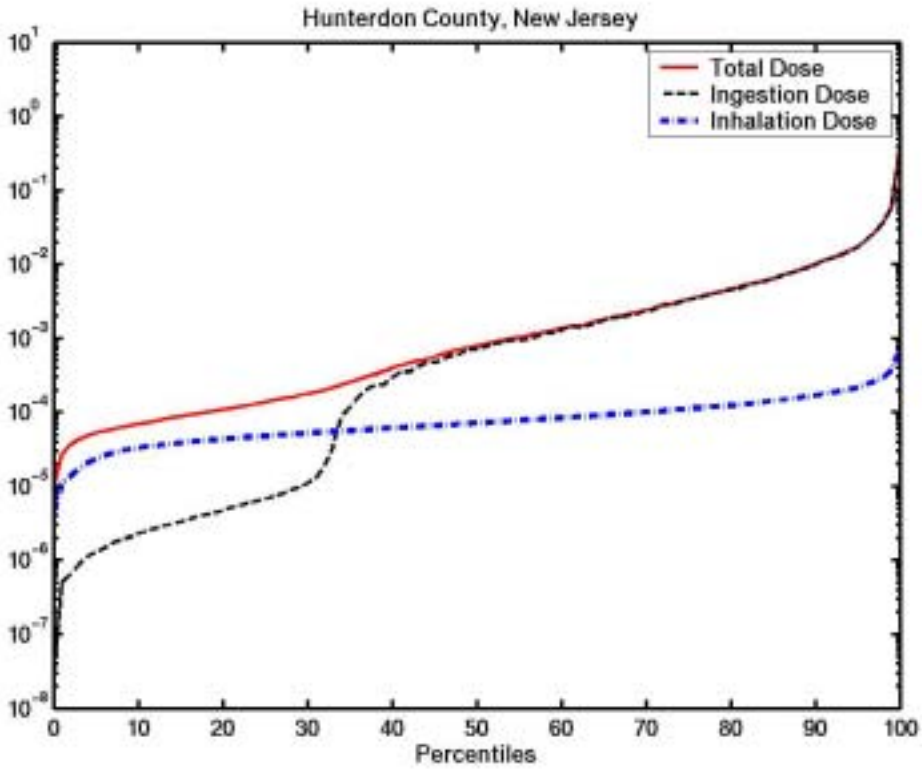




Arsenic Groundwater Observations 1973-97 in USGS Database

(I) Population Exposure to Arsenic: Source-to-Dose Application of Multimedia MENTOR/SHEDS

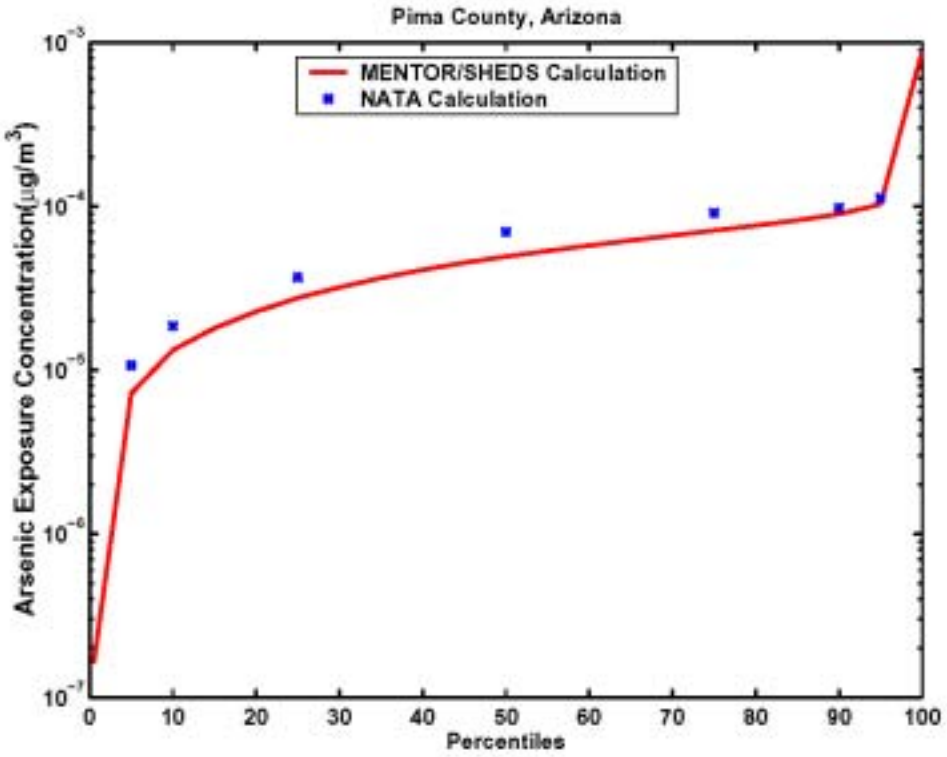




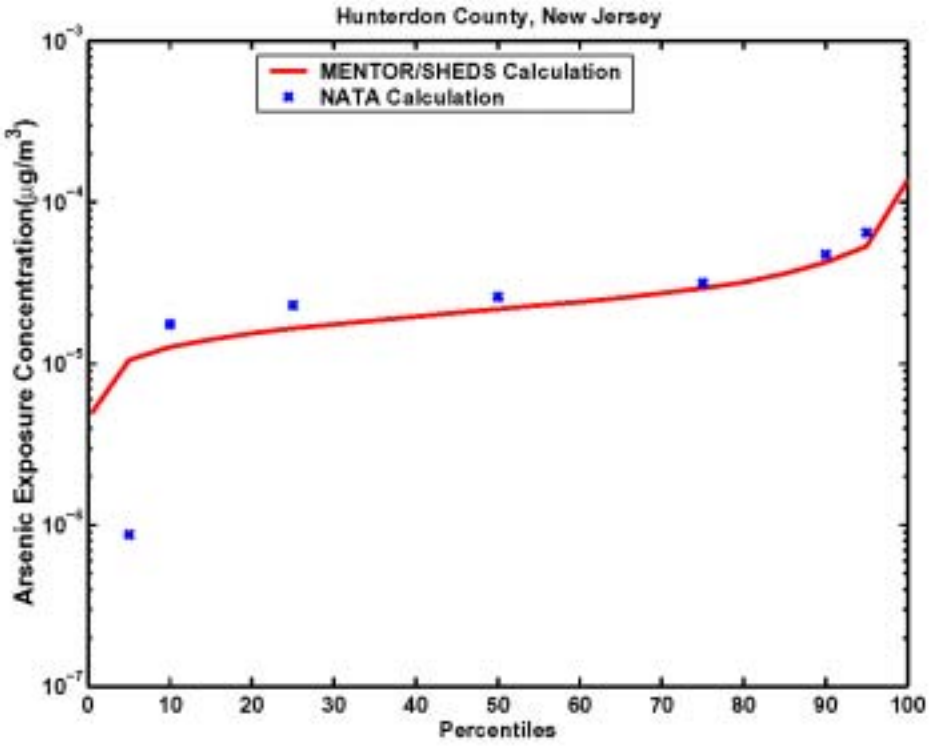
Inhalation dose in the above figures: dose from arsenic component in outdoor PM estimated using the MENTOR gender/age/activity specific population inhalation dosimetry module (outdoor concentrations calculated using EPA's 1996 NATA approach with the 1996 NTI inventory and the ASPEN model).

Ingestion dose refers only to the component due to consumption of drinking water (concentration distributions for 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).

Comparison of Cumulative Distributions of Time-Weighted Average Arsenic Exposure Concentrations in Air Calculated by MENTOR/SHEDS and NATA Studies for (A) Pima County, AZ and (B) Hunterdon County, NJ



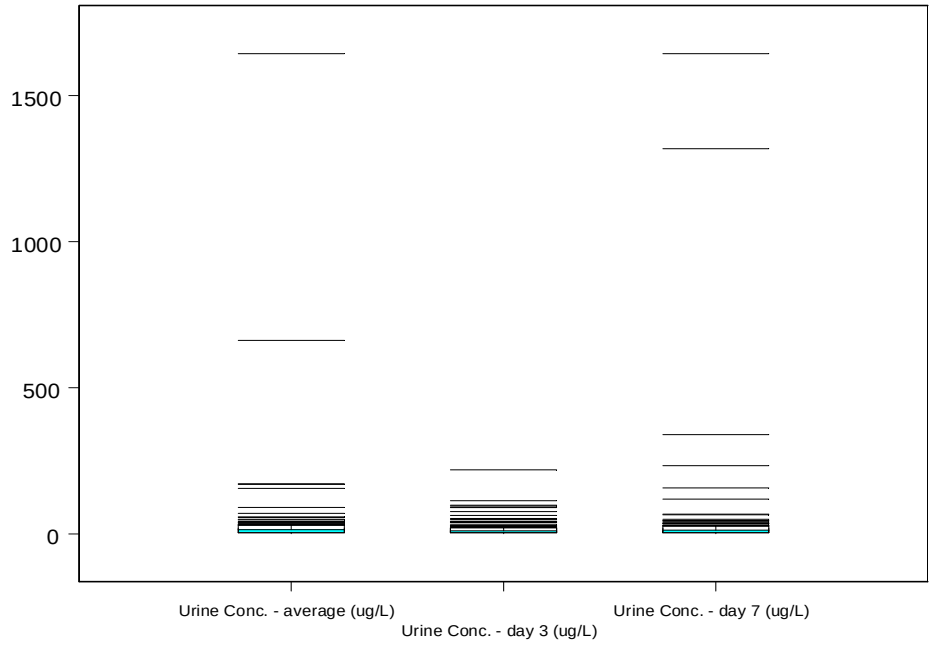
(A)



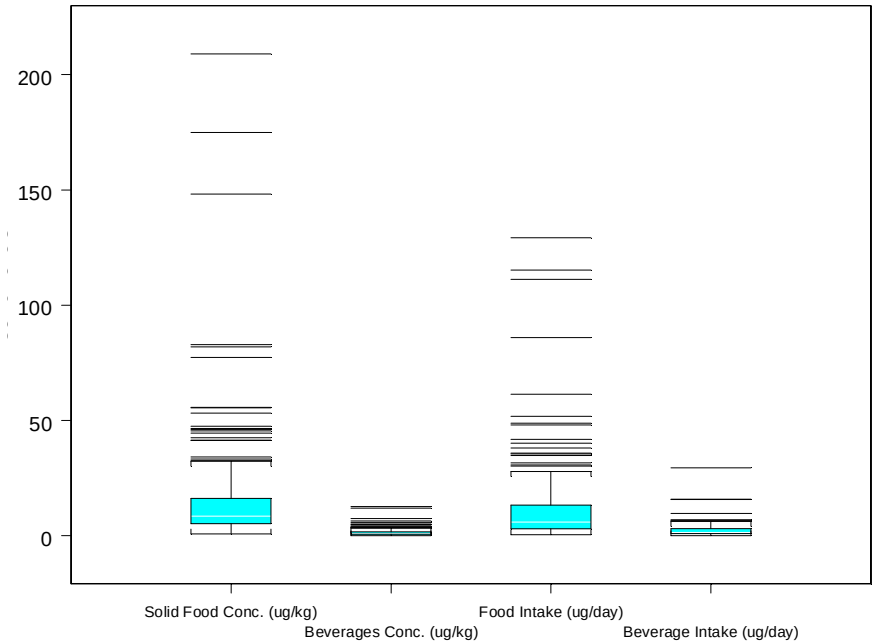
(B)

(II) Multipathway Population Exposure Assessment to Arsenic for NHEXAS Phase I Region V

Example Data Sets :
Arsenic in Media (Food and Beverages) and Biomarkers (Urine)

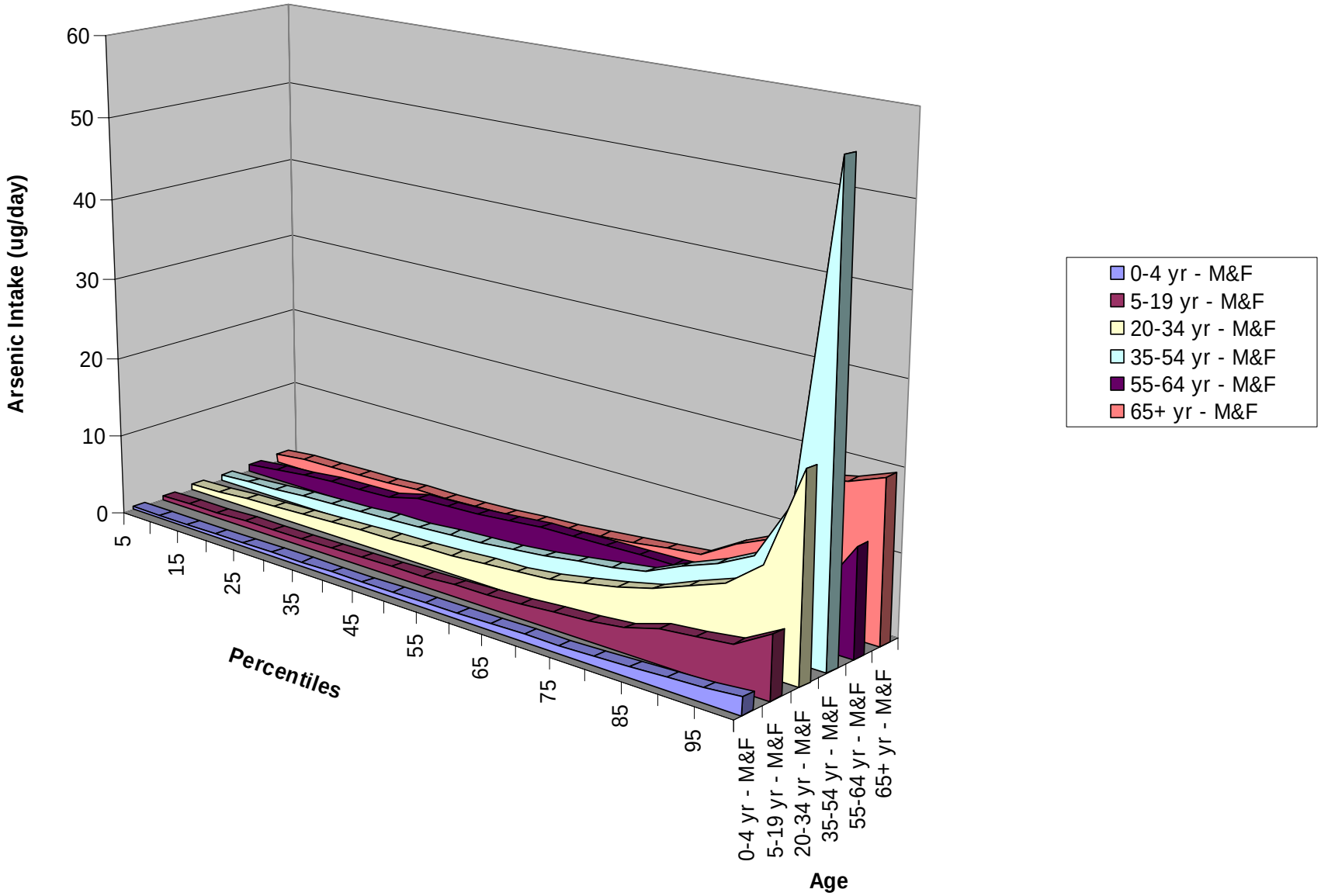


Arsenic in Urine

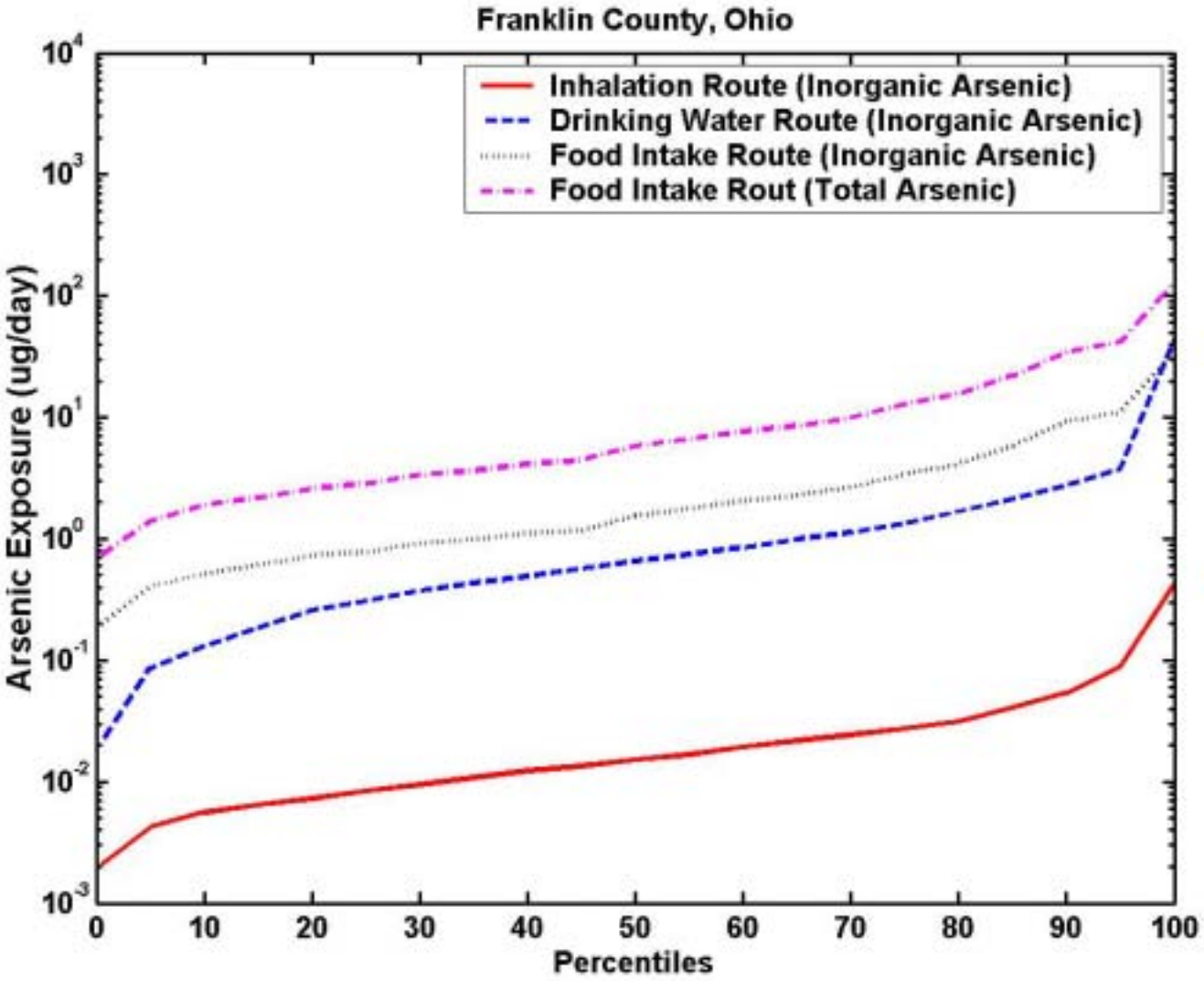


Arsenic in Food and Beverages

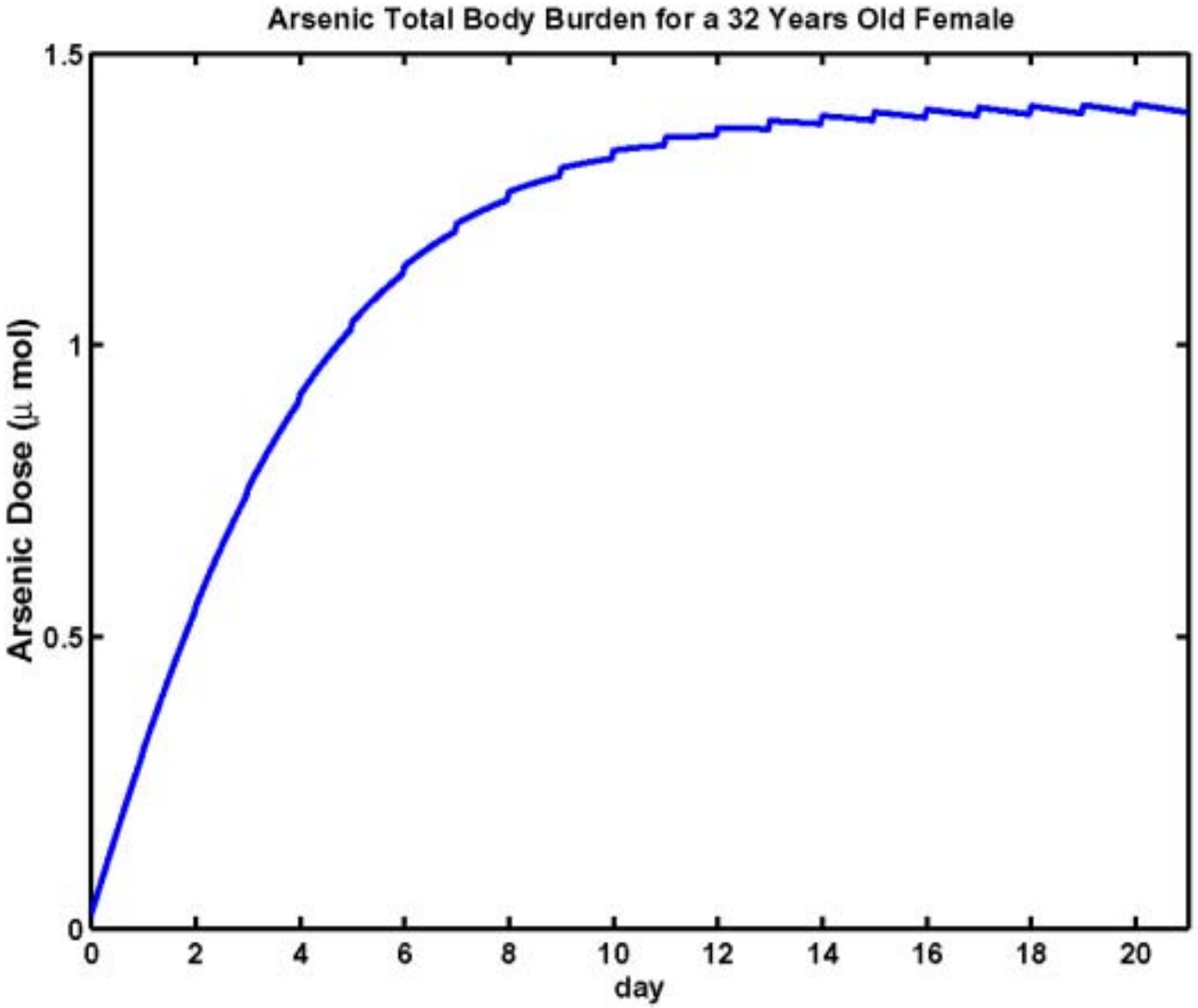
Estimated Cumulative Distributions of Total Inorganic Arsenic Intake for 6 Age Groups in Franklin County, OH Using MENTOR/SHEDS



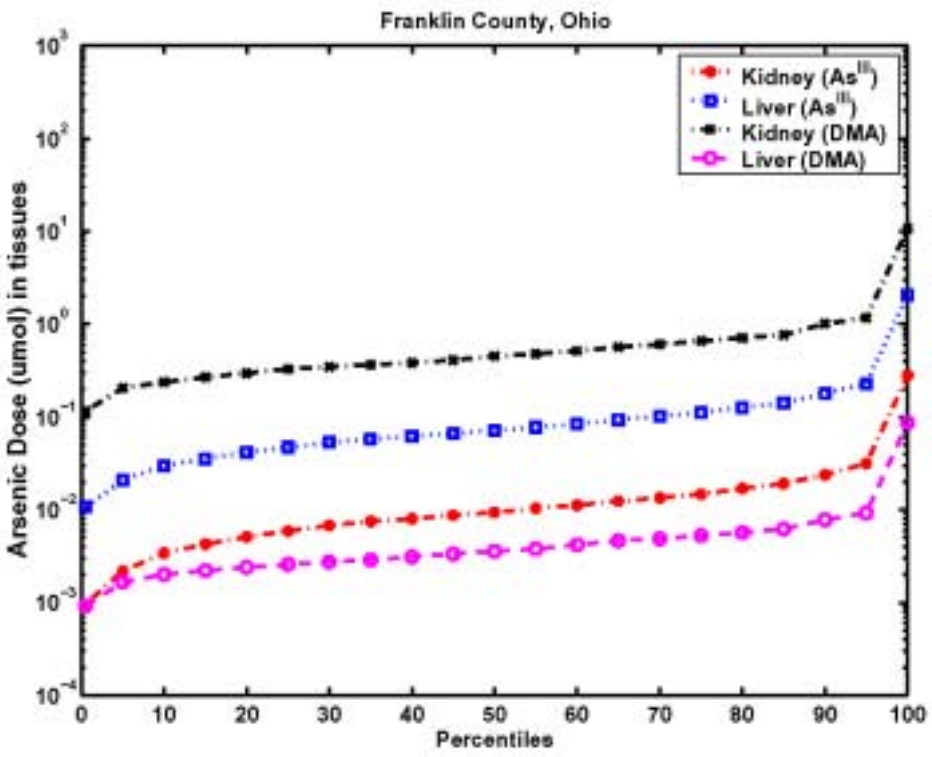
Multiroute Population Exposure to Arsenic (Total and Inorganic) – NHEXAS Region V

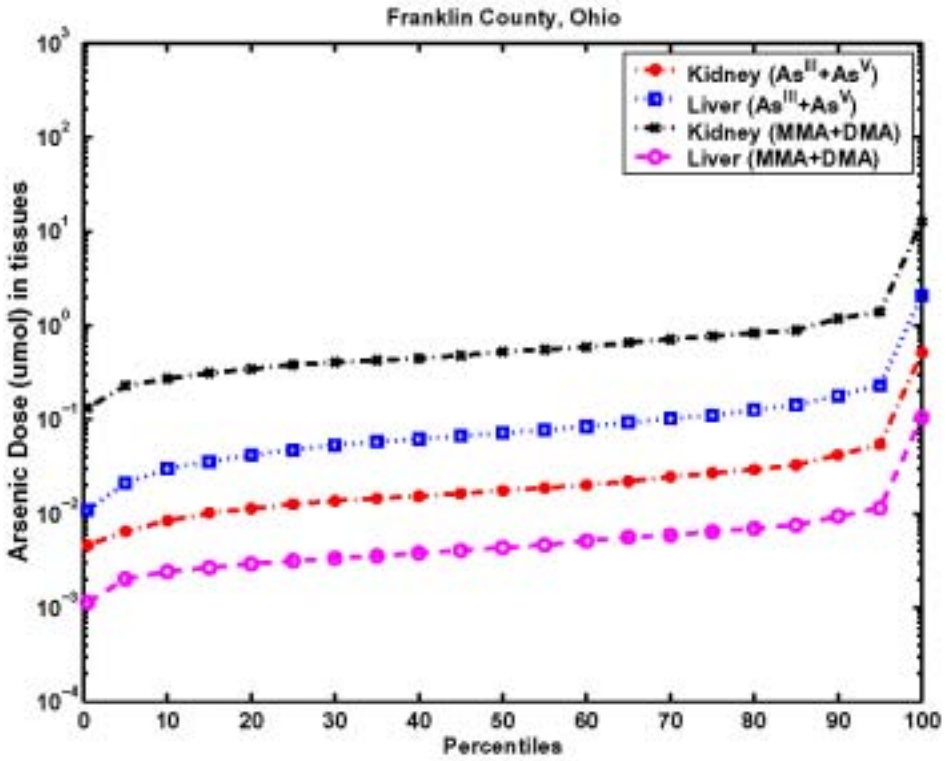


Profile of Total Body Burden of Arsenic Dose (Inorganic + Organic) During a Three-Week Continuous Exposure for a 32-year-old Female

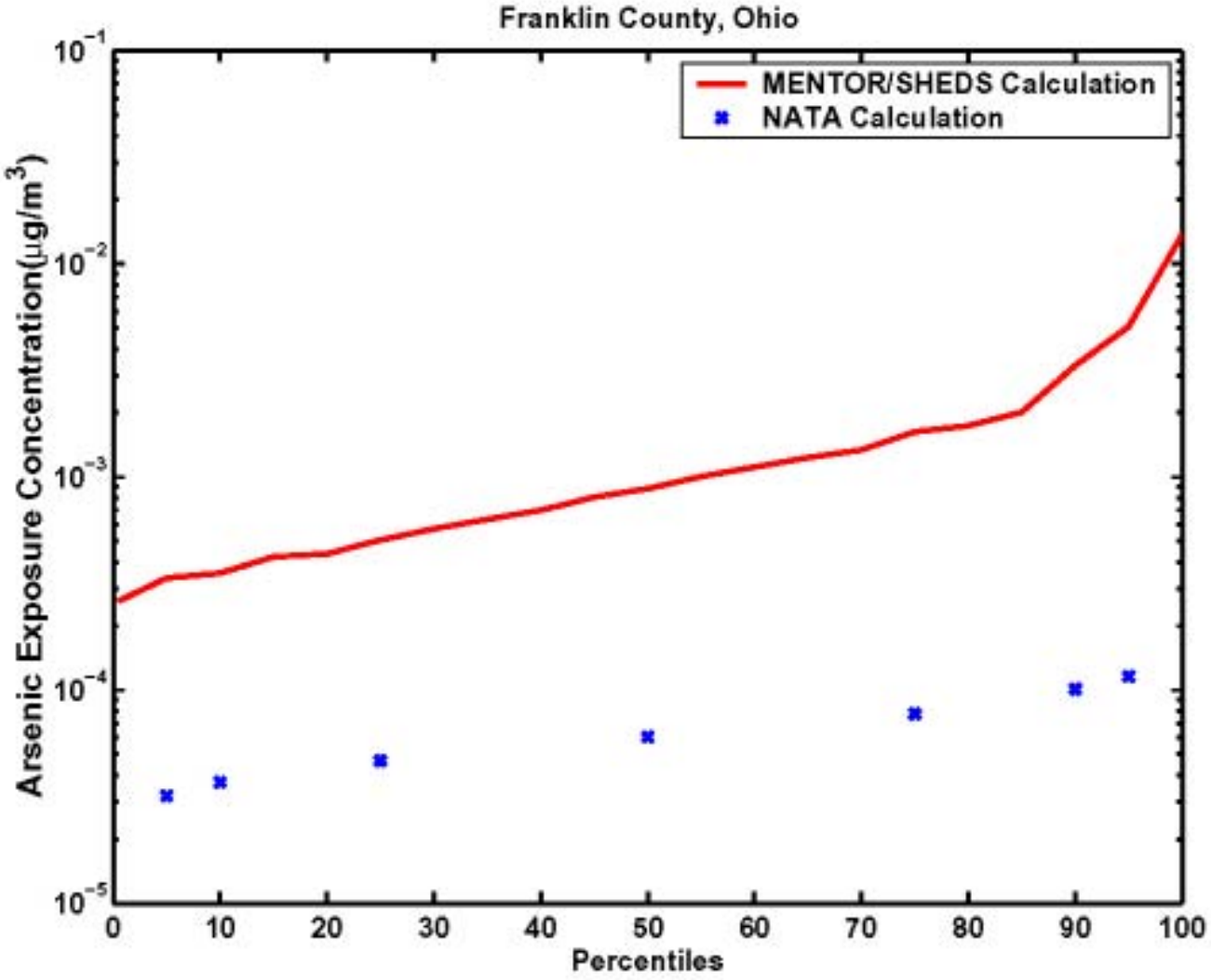


Population Dose Assessments for Arsenic Species and Metabolites (Franklin County, OH from NHEXAS Region V)

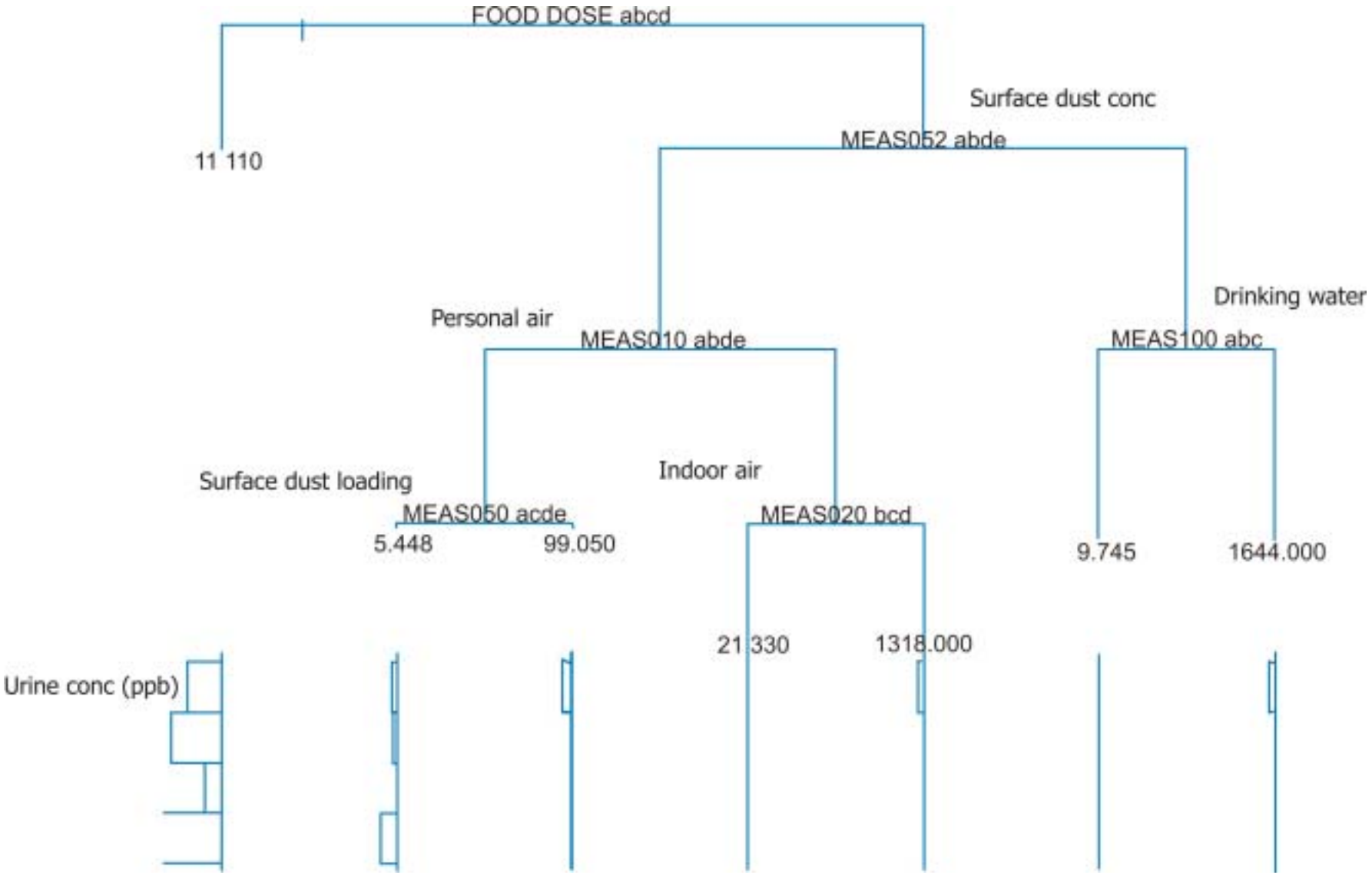




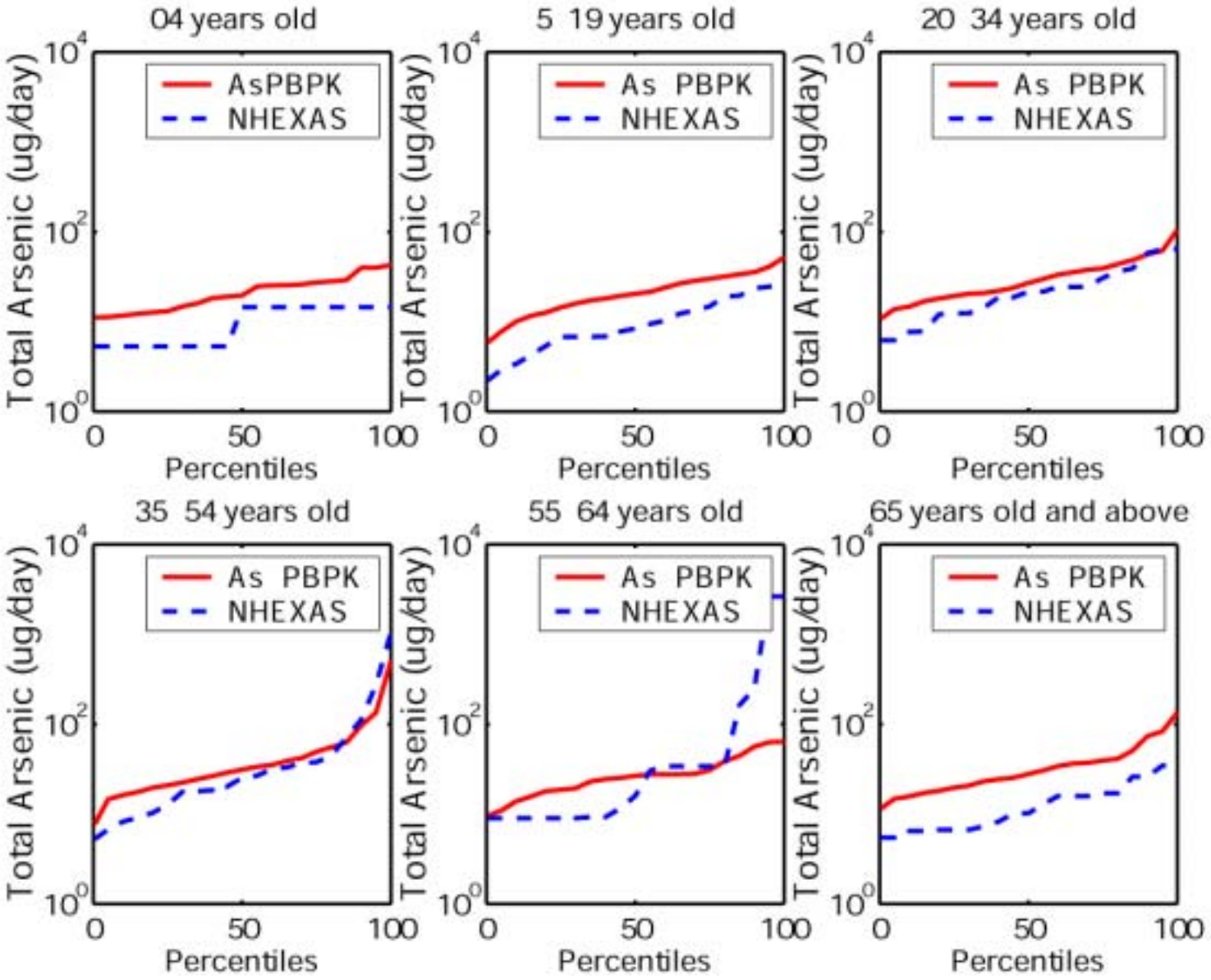
Comparison of Cumulative Distributions of Time-Weighted Average Arsenic Exposure Concentrations in Air Calculated by MENTOR/SHEDS and NATA Studies for Franklin County, OH



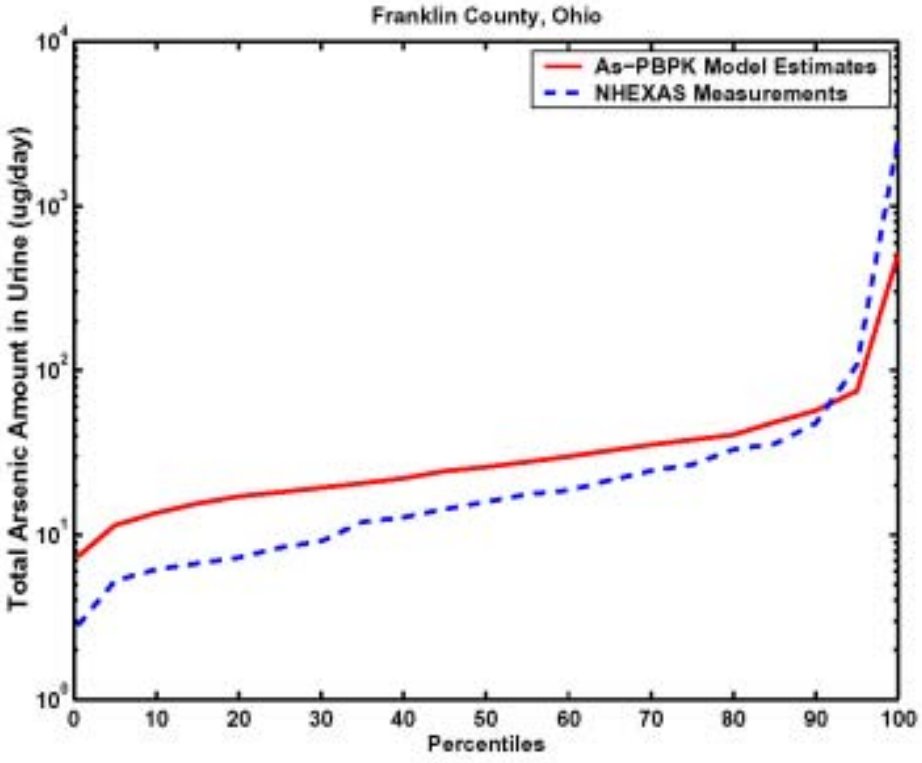
Example of "Mining" Data from the NHEXAS Region V Study via CART for Arsenic in Exposure Media (Food, Water, Air, Dust) and Biomarkers (Urine) for Corroborative Analysis of Predictive MENTOR/SHEDS Modeling



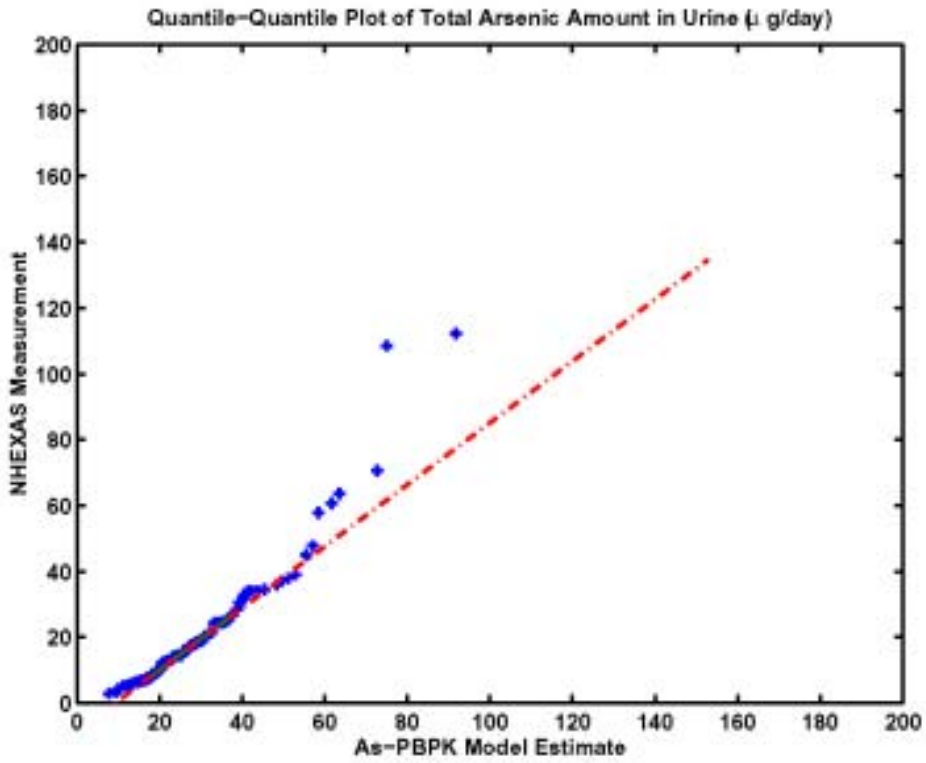
Comparison of Cumulative Distributions of Total Arsenic Amount in Urine from MENTOR/SHEDS Calculations and NHEXAS Measurments for the 6 Age Groups in Franklin County, OH



Comparison of Cumulative Distributions of Total Arsenic Amount in Urine from MENTOR/SHEDS Calculations and NHEXAS Measurements



Comparison of percentile distributions of total arsenic amount in urine calculated by MENTOR/SHEDS and estimated from NHEXAS-Region V measurements for Franklin County, OH



Quantile-quantile plot of total arsenic amount in urine for MENTOR/SHEDS calculations and estimates from NHEXAS measurements for Franklin County, OH

On-Going Work and Research Plans: Collaborative with EPA NERL, LBLNL and Other Research Groups

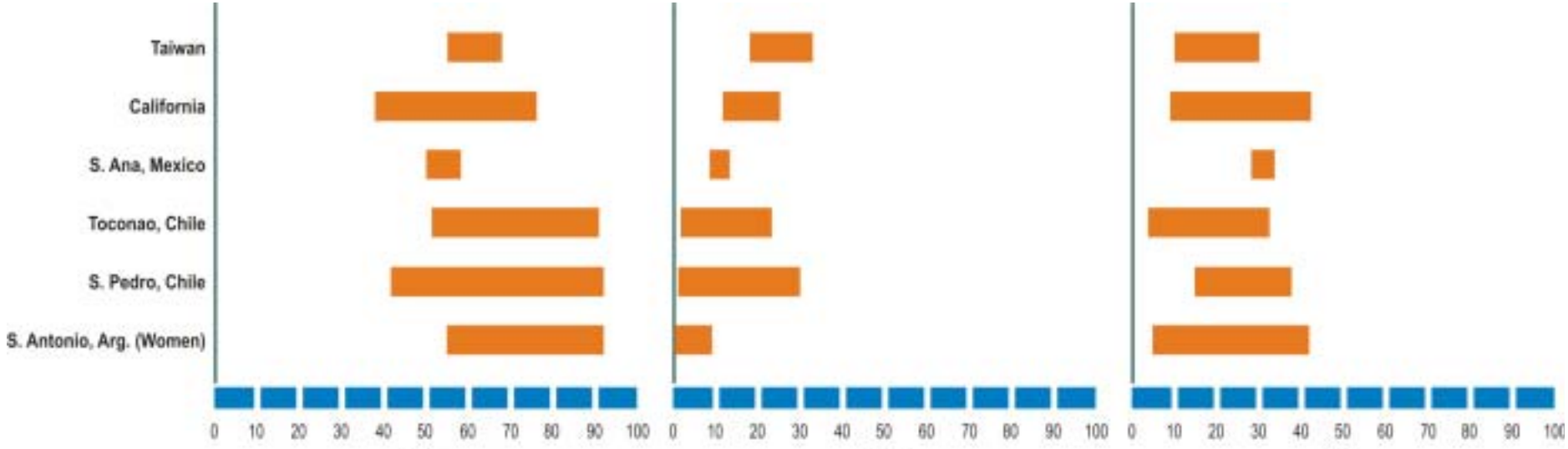
On-Going Work

- Evaluation and refinement of models for individual and population exposure assessments
  - *incorporation of dermal uptake (water, soil, dust, etc.)*
  - *refinement of dietary and incorporation of non-dietary ingestion*
  - *incorporation of bioavailability and variability in human metabolism*
- Systematic comparisons of individual-based to population-based modeling
- Continuing implementation/refinement of As-EXIS (Exposure Information System) with interactive access to multimedia (geo)databases and models

Planned Work

- Studies of geographic/regional variability
  - *for different pathways*
  - *in relation to drinking water and food consumption habits/patterns*
- Studies of temporal variability
- Systematic evaluations of the effect of database resolution on exposure/dose
- Expansion of geographic domains under consideration; intercomparisons

Population Variability in Observed Percentages of Various Arsenic Metabolites in Urine



(a) Percentage of DMA

(b) Percentage of MMA

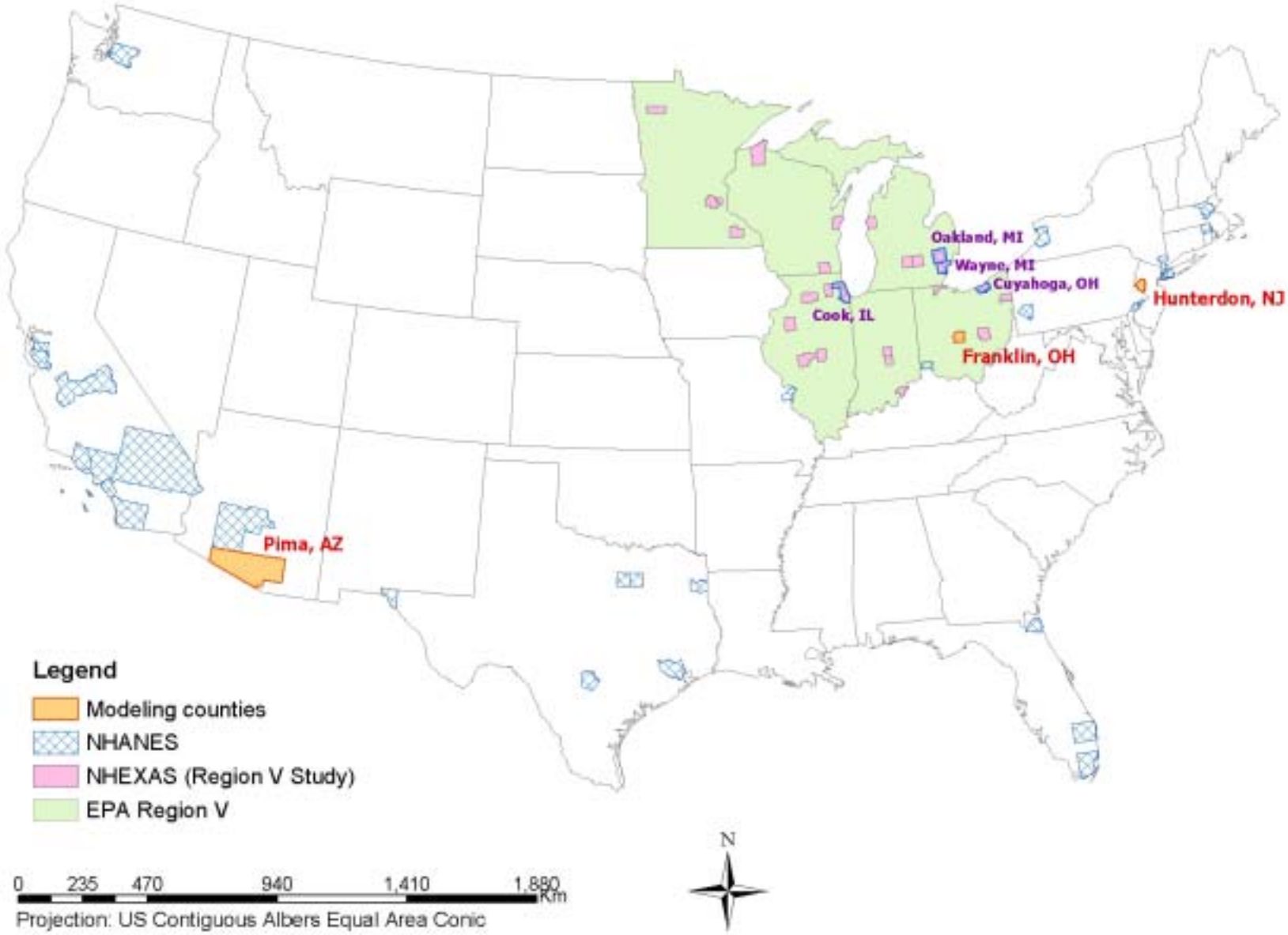
(c) Percentage of Inorganic Arsenic

adapted from Vahter, 2000

Available Individual-Specific Data for Franklin County, Ohio (NHEXAS Region V Arsenic Measurements)

Franklin County, Ohio			NHEXAS Measurements in Region V			
Age Group	Gender	Number of Individuals	Personal Air Conc. (ng/m^3)	Drinking Water Conc. (µg/L)	Food Intake (µg/day)	Urine Conc. (µg/L)
0-4 yr	M	350	5	5	4	0
	F	370	6	7	4	2
5-19 yr	M	1020	9	16	11	7
	F	1080	12	16	11	3
20-34 yr	M	1249	10	16	17	7
	F	1321	20	29	22	9
35-54 yr	M	1409	18	26	15	10
	F	1491	30	39	27	19
55-64 yr	M	355	5	8	2	5
	F	375	4	5	5	2
65+ yr	M	476	7	9	7	6
	F	504	9	22	11	6

Focus Areas of On-Going and Planned MENTOR Applications for Dource-to-Dose Exposure Studies of Multimedia Contaminants



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- Andrew Schullman (U.S. EPA): AOED
- Karen Feld (NJDEP): municipal water databases
- Eric Vowinkel (USGS): groundwater databases

Other research collaborators on Arsenic effort:

- EOHSI-CCL: V. Vyas, H. Tan, C. Efstathiou, L. Everett
- Other EOHSI: C. Weisel, M. Gochfeld (dermal uptake)
- U. Arizona: B. Williams (water consumption)