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

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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

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

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)
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

EPA-UPA Review 2002

Projection: Albers-Equal Area Conic

Computational Chemodynamics Laboratory - EOHSI
Locations of AIRS Monitoring Stations that Measured Arsenic Compounds in 2001
Average and Maximum Arsenic Concentrations Measured in PM2.5 at AIMS 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)

As Annual Total Amb. Conc. (10E-6 ug/m3)
- 1 - 30
- 31 - 59
- 60 - 100
- 101 - 152
- 153 - 11200

EPA-UPA Review 2002
Computational Chemodynamics Laboratory - EOHSI
Total Arsenic (mg/kg) Measured in 12 Major Food Groups Generated 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

Draw Distribution Network (junctions, reservoir, tank, pipes, pump and control valve)

Junction:
Elevation, water demand, initial water & source quality, demand pattern & categories, emitter coeff

Reservoir:
Hydraulic head, initial water quality, head pattern, source quality

Tank:
Bottom elevation, diameter, initial minimum & maximum water levels & water quality, minimum volume, volume curve, mixing model, reaction coeff, source quality

Pipes:
Start & End nodes, diameter, length, roughness coeff, status (open/closed/with check valve), bulk reaction coeff, wall reaction coeff

Pump:
Start & End nodes, pump curve, speed, pattern, initial status, efficiency curve, energy price, price pattern, power

Control Valve:
Start & End nodes, diameter, setting, status

Edit Curve (pump, volume, head loss, efficiency), Source Quality, Pattern & Controls

Select hydraulic, quality, reactions, times or energy option from the browser

EPANET

Hydraulic simulation model (solves flow continuity and head loss equation by gradient method)

Water quality simulation model (uses lagrangian time-based approach)

Water quality reactions (bulk reaction & wall reaction)

Water age & source tracing

Graphical representation

Map representation

Tabular representation

Junctions: Hydraulic head, pressure, water quality
Tank: Hydraulic head, water quality
Pipes: Flow Rate, velocity, head loss, Darcy-Weisbach friction factor, avg. reaction rate & water quality

Control Valves: Flow rate, head loss
Pumps: Flow, head gain

Draw Distribution Network

Graphical representation

Map representation

Tabular representation
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:**

<table>
<thead>
<tr>
<th></th>
<th>Yu’s model</th>
<th>Mann’s model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model structure</td>
<td>8 tissue compartments</td>
<td>5 tissue compartments</td>
</tr>
<tr>
<td>Exposure route</td>
<td>Oral only</td>
<td>Oral and inhalation</td>
</tr>
<tr>
<td>Distribution</td>
<td>Flow-limited</td>
<td>Diffusion-limited</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Reduction reaction of inorganic arsenic in all compartments, and biotransformation in liver and kidney.</td>
<td>Reduction/oxidation of inorganic arsenic in plasma and kidney, and bio-transformation in liver.</td>
</tr>
<tr>
<td>Excretion</td>
<td>Renal and Fecal excretion</td>
<td>Renal, Fecal and Dermal excretion.</td>
</tr>
</tbody>
</table>
Alternative Arsenic PBPK Model Output Comparisons

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

User-defined information on original model:
- number of input variables (n)
- distributions (or ranges) of input variables
- order of HDMR
- resolution (mesh)

HDMR input processing module for sampling point generation: defines series expansion form of I/O relationship

(m x n) matrix of input values for original model
- m: number of simulations (depends on HDMR order and resolution)

HDMR-reduced model

Interpolation routines

HDMR core calculation (produces output series expansion terms used to build look-up tables)

(m x p) matrix of model outputs
- p: number of model outputs

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\textsuperscript{III} Dose, for an individual (female, 50 years old)

Exposure Scenario:
Air-conc. = 8x10\textsuperscript{-5} (µmol/L), DW-conc. = 7.8x10\textsuperscript{-2} (µmol/L)
Food Intake = 1.2x10\textsuperscript{-2} (µmol/L), DW-rate = 7x10\textsuperscript{-4} (L/min)

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

Exposure Scenario:
Air-conc. = 8x10\textsuperscript{-5} (µmol/L), DW-conc. = 7.8x10\textsuperscript{-2} (µmol/L)
Food Intake = 1.2x10\textsuperscript{-2} (µmol/L), DW-rate = 7x10\textsuperscript{-4} (L/min)
FEOM Development via HDMR
Example: Arsenic PBPK Modeling for Populations

Comparison of $\text{As}^{III}$ 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

START

- Census tract demographic data
- Outdoor air concentrations

- Obtain random realizations from uncertainty distributions of statistical parameters (that specify variability in model parameters)
- Select a census tract and generate a hypothetical population comprised of N individuals that match the characteristics of the population in census tract
- STRF or BME interpolation

- Obtain estimates of 1-hr averaged outdoor concentrations in census tract
- Generate random realizations of exposure model parameters for an individual in the generated population from variability distributions (specified by uncertain statistical parameters)

- Obtain the matching diary record for each individual based on the characteristics of the individual
- Obtain activity events and associated METs values for each individual based on CHAD-ID

- Calculate dose for each activity event of an individual based on concentration intake rate and time duration of each activity event
- Calculate microenvironmental air concentrations in each activity location of the activity event sequence using the exposure model parameters

- Calculate inhalation rates for each activity event of an individual based on age, gender, and METs values
- Estimate food and drinking water concentrations

- Calculate food and drinking water concentrations

- On-line data importing module

CHAD database (consolidated human activities)
- Food and drinking water consumption and food composition (CSFII, NHEXAS)
- Food and drinking water concentrations

- MENTOR/SHEDS

END

- Obtained dose estimate for all N individuals in population?
- Obtained dose for all census tracts in area of interest?
- Completed all uncertainty iterations?
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

EXPLANATION
Arsenic, in ug/L
> 50
10-50
5-10
< 5
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 NJ DEP’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
(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)
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

Franklin County, Ohio

- Inhalation Route (Inorganic Arsenic)
- Drinking Water Route (Inorganic Arsenic)
- Food Intake Route (Inorganic Arsenic)
- Food Intake Route (Total Arsenic)

Arsenic Exposure (µg/day)

Percentiles
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 Measurements 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)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Gender</th>
<th>Number of Individuals</th>
<th>Personal Air Conc. (ng/m³)</th>
<th>Drinking Water Conc. (µg/L)</th>
<th>Food Intake (µg/day)</th>
<th>Urine Conc. (µg/L)</th>
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</thead>
<tbody>
<tr>
<td>0-4 yr</td>
<td>M</td>
<td>350</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>0</td>
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<tr>
<td></td>
<td>F</td>
<td>370</td>
<td>6</td>
<td>7</td>
<td>4</td>
<td>2</td>
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<tr>
<td>5-19 yr</td>
<td>M</td>
<td>1020</td>
<td>9</td>
<td>16</td>
<td>11</td>
<td>7</td>
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<td></td>
<td>F</td>
<td>1080</td>
<td>12</td>
<td>16</td>
<td>11</td>
<td>3</td>
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<tr>
<td>20-34 yr</td>
<td>M</td>
<td>1249</td>
<td>10</td>
<td>16</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>1321</td>
<td>20</td>
<td>29</td>
<td>22</td>
<td>9</td>
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<tr>
<td>35-54 yr</td>
<td>M</td>
<td>1409</td>
<td>18</td>
<td>26</td>
<td>15</td>
<td>10</td>
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<tr>
<td></td>
<td>F</td>
<td>1491</td>
<td>30</td>
<td>39</td>
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<tr>
<td>55-64 yr</td>
<td>M</td>
<td>355</td>
<td>5</td>
<td>8</td>
<td>2</td>
<td>5</td>
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<tr>
<td></td>
<td>F</td>
<td>375</td>
<td>4</td>
<td>5</td>
<td>5</td>
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<tr>
<td>65+ yr</td>
<td>M</td>
<td>476</td>
<td>7</td>
<td>9</td>
<td>7</td>
<td>6</td>
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<tr>
<td></td>
<td>F</td>
<td>504</td>
<td>9</td>
<td>22</td>
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<td>6</td>
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</table>
Focus Areas of On-Going and Planned MENTOR Applications for Dource-to-Dose Exposure Studies of Multimedia Contaminants
Acknowledgements and Collaborations

This work has been funded by:

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Databases and other information have been provided by:

- Ted Palma (U.S. EPA): NATA, ASPEN, EMS-HAP
- Andrew Schullman (U.S. EPA): AOED
- Karen Feld (NJ DEP): 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)