Evaluation of a Physiologically-based Pharmacokinetic (PBPK) Model for Inorganic Arsenic (iAs) Exposure Using Data from Two Diverse Human Populations (Poster 3)

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Purpose and Scope

- Multiple epidemiological studies exist for some of the well-studied health endpoints associated with iAs exposure, however, results are expressed in terms of different exposure/dose metrics.
- Physiologically-based pharmacokinetic (PBPK) models may be used to obtain a common exposure metric for application in dose-response meta-analysis.
- In this study, a published human PBPK model for iAs oral intake by El-Masri and Kenyon (2008) was evaluated using data from U.S. (Churchill County, Nevada) and Bangladeshi (HEALS cohort) populations.
- Intake of iAs was examined using data on consumption of iAs-contaminated water alone or in combination with data on consumption of arsenic in food (El-Masri et al., 2018).

Methods

Epidemiological Studies of Human iAs Urine Levels

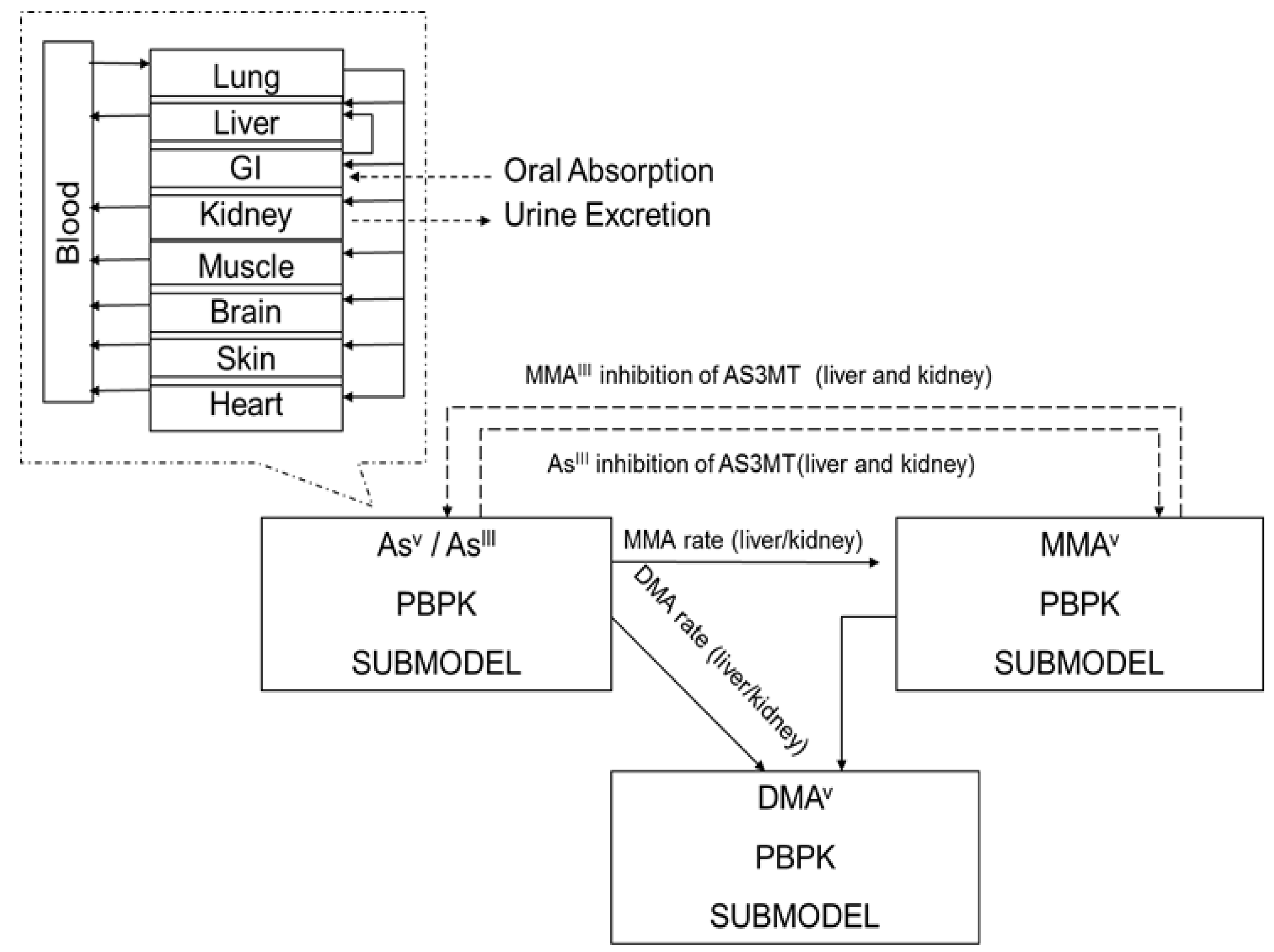
Parameter	HEALS cohort, Bangladesh[1]	Churchill County, Nevada, USA[2]
Number of observations	Total: 11,438 Male: 4,876 Female: 6,562	Total: 904 Male: 368 Female: 536
Age (years)	Range:17–75 Median: 36	Range: 45–92 Median: 61
Height (m)	Range: 1.30–1.85 Median: 1.54	Range: 1.45–1.95 Median: 1.66
Weight (kg)	Range: 24.50–100.00 Median: 46.00	Range: 44.90–165.80 Median: 79.70
Smoking status	Non-smokers: 7,405 Past-smokers: 755 Current smokers ≤10 cigarettes/day: 1,953 Current smokers >10 cigarettes/day: 1,314	Non-smokers: 755 Smokers: 149
As water conc. (μg/L)	Range: 0.1–864.0 Median: 61.0	Range: 0.86–1850.00 Median: 61.00
Total daily water consumption (mL)	Range: 175.0–10,240.0 Median: 2,850.0	Range: 0.00–25,260.00 Median: 1893.00
Urinary As conc. (μg/L)	Range: 1.0–2,273.0 Median: 87.0	Range: 0.50–856.30 Median: 39.00
Creatinine adjusted urinary As conc. (μg/g)	Range: 6.64–5,000.00 Median: 198.40	Range: 2.84–5186.00 Median: 85.44

[1]Ahsan et al. (2006); [2]Calderon et al. (2013); Hudgens et al. (2016)

PBPK Model Selection and Modification

- The PBPK model was used to estimate total arsenic levels in urine in response to oral ingestion of iAs.
- To compare predictions of the PBPK model against observations, urinary arsenic concentration and creatinine-adjusted urinary arsenic concentration were simulated.
- Both arsenic water and dietary intakes were estimated and used to generate the associated arsenic urine concentrations.

Methods (Continued)



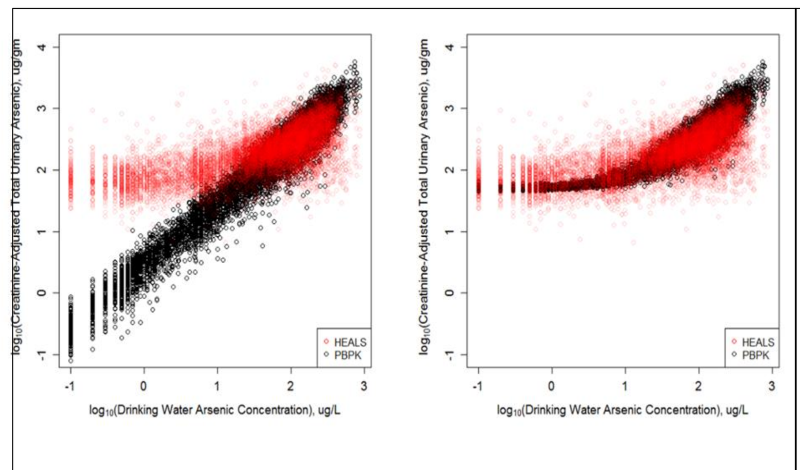
The following model inputs and outputs were adjusted for each modeled individual (based on bodyweights) during the simulation:

- Arsenic intake rate:
$$Water\ iAs\ intake = water\ iAs\ concentation\ \times water\ intake$$
- Volume of the tissue compartments:
$$BWMULT\ \times \left(\frac{Body\ weight}{70\ kg}\right)$$
- Urinary excretion rate, L/hr:
$$V_{urinary} = 0.65 \times BW \times BWMULT$$
- Creatinine excretion rate based on subject specific body weight:
$$\mathrm{MCR}=\beta_0 + \beta_1 * \mathrm{sex} + \beta_2 * \mathrm{BMI} + \beta_3 * \mathrm{age} + \beta_4 * \mathrm{age}^2$$ (Ogna et al., 2015)

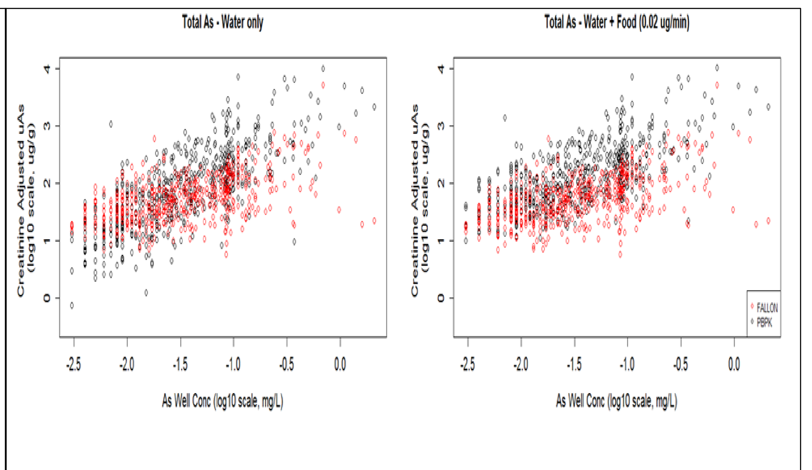
Estimation of Dietary iAs Intake to Complement iAs Exposure through Ingestion of iAs-contaminated Drinking Water

	Food type	Mean (range; μg/day)	Source
Food consumption (Bangladesh)	Rice (g/day)	• Male: 523 • Female: 300	Watanabe et al. (2004)
	Vegetable (g/day)	• Male:153.00 • Female: 146.88	Khan et al. (2009)
As levels in food (Bangladesh)	Rice (μg/kg)	• 173	Watanabe et al. (2004)
		• 150 (10–500)	Rahman et al. (2009)
		• 153 (74–301)	Rahman et al. (2011)
	Vegetable (μg/kg)	• 12.1 (1.3–22.8)	Khan et al. (2010)
		• 15 (0–136)	Khan et al. (2012)
As levels in food (U.S.)	μg/day	• 33.44 (26–40.9)	Kurzius-Spencer et al. (2014)
	μg/min	• 0.04 (0.03–0.05)	Tao and Bolger (1999)

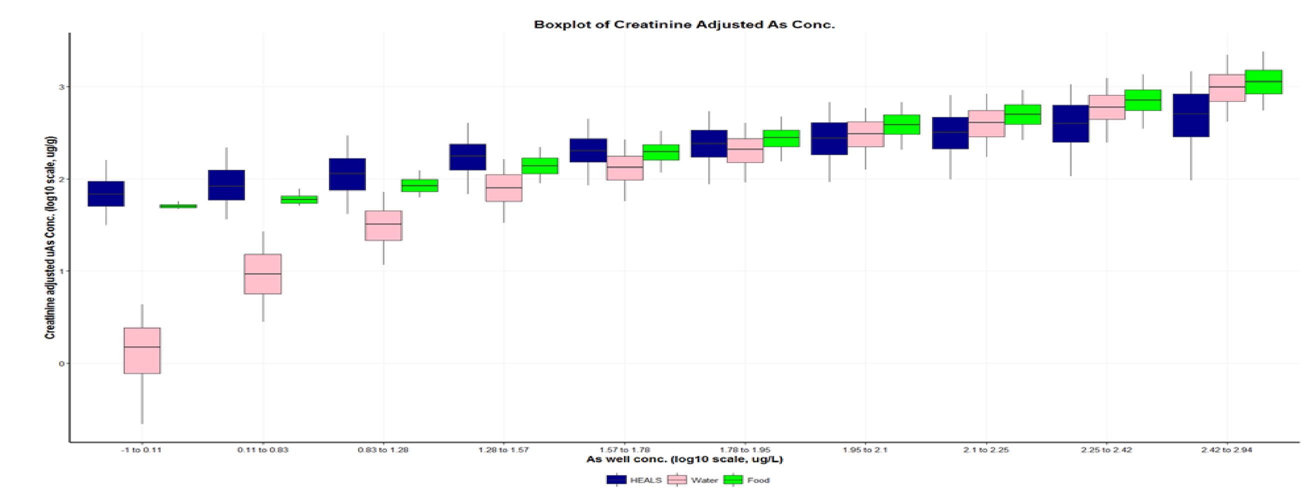
Results



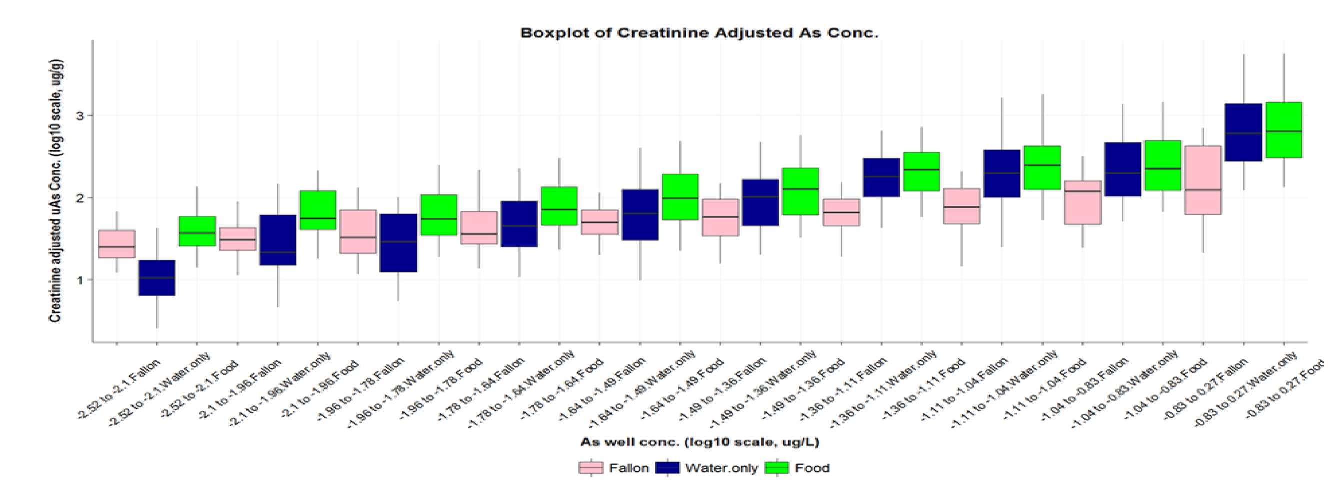
Relationship between arsenic water levels and PBPK model-predicted creatinine-adjusted urinary arsenic concentrations for the HEALS data set. Left: well water as the only arsenic intake source. Right: well-water and dietary exposure as the arsenic intake source.



Relationship between arsenic water levels and PBPK model-predicted creatinine-adjusted urinary arsenic concentrations for the Churchill County data set. Left: well water as the only arsenic intake source; Right: well-water and dietary exposure as arsenic intake source.



Creatinine-adjusted urinary As concentrations for the HEALS data set, presented by decile of As water levels.



Creatinine-adjusted urinary As concentrations for the Churchill County data set, presented by decile of As water levels.

Conclusions

- In the HEALs study, model simulations show the need for including dietary contribution of iAs exposure in addition to drinking water levels, especially at low exposure levels.
- For the Churchill County data, addition of dietary intake rates did not contribute as much to the corrections needed to bring the model's simulations closer to urinary excretion data. This may be a result of the type of foods that are consumed in two different studies; whereas rice is a major iAs dietary contributor to the HEALS study, it is not in the Churchill County study. Water intake levels in Churchill County seem to reasonably predict total arsenic urine levels.
- In both cases, the model was able to adequately relate iAs exposure to total urine concentrations in low exposure situations. Slight over-production at the higher doses may be indicative of saturable kinetics being reached more quickly than predicted by the PBPK model simulations.

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References can be found in HERO (https://hero.epa.gov/hero/index.cfm/project/page/project_id/2211)