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

Hisham El-Masri1, Tao Hong2, Cara Henning2, William Mendez Jr2, Edward Hudgens3, David Thomas1, and Janice S. Lee1

1EPA, Office of Research and Development – Research Triangle Park, 2ICF International

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., 2019).

Methods

Epidemiological Studies of Human iAs Urine Levels

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HEALS cohort, Bangladesh</th>
<th>Churchill County, Nevada, USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of observations</td>
<td>Total: 11,438 Male: 6,876</td>
<td>Total: 904 Male: 368</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Range: 17–75 Male: 536</td>
<td>Median: 45–92 Female: 536</td>
</tr>
<tr>
<td>Height (m)</td>
<td>Median: 1.30–1.85</td>
<td>Median: 1.45–1.95</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Median: 1.54</td>
<td>Median: 1.66</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Male: 368</td>
<td>Female: 536</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Non-smokers: 7,405</td>
<td>Non-smokers: 755</td>
</tr>
<tr>
<td>Past-smokers: 755</td>
<td>Current smokers ≤10 cigarettes/day: 1,953</td>
<td>Smokers: 149</td>
</tr>
<tr>
<td>Current smokers &gt;10 cigarettes/day: 1,314</td>
<td>Median: 36</td>
<td>Median: 44.90–165.80</td>
</tr>
<tr>
<td>As water conc. (µg/L)</td>
<td>Range: 0.86–1850.00</td>
<td>Median: 87.0</td>
</tr>
<tr>
<td>Total daily water consumption (mL)</td>
<td>Range: 175.0–1,240.0</td>
<td>Median: 25,260.00</td>
</tr>
<tr>
<td>Urinary As conc. (µg/L)</td>
<td>Range: 0.50–856.30</td>
<td>Median: 28.40</td>
</tr>
<tr>
<td>Creatinine-adjusted urinary As conc. (µg/L)</td>
<td>Median: 85.44</td>
<td>Median: 85.44</td>
</tr>
</tbody>
</table>

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 urinary concentration.

Results

- The following model inputs and outputs were adjusted for each modeled individual (based on bodyweights) during the simulation:
  - Arsenic intake rate:
    \[
    \text{Water iAs intake} = \text{water iAs concentration} \times \text{water intake}
    \]
  - Volume of the tissue compartments:
    \[
    \text{BWMULT} = \text{Body weight} \times (70 \text{ kg})
    \]
  - Urinary excretion rate, L/hr:
    \[
    \text{U\text{_{wash}}} = 0.65 \times \text{BW} \times \text{BWMULT}
    \]
  - Creatinine excretion rate based on subject specific body weight:
    \[
    \text{MCR} = \beta_0 + \beta_1 \times \text{sex} + \beta_2 \times \text{BMI} + \beta_3 \times \text{age} + \beta_4 \times \text{age}^2
    \]

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

- In the HEALS study, model simulations show the need for including dietary exposure as arsenic intake source. Right: well-water and dietary exposure as the arsenic intake source.

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.

References can be found in HERO (https://heroes.epa.gov/heroindex/dmsproject/page/projectid/2311).