Purpose and Scope

- National Research Council (NRC) recommended that health outcomes be tiered and further prioritized given the volume of data on iAs, particularly human data (NRC, 2013).
- The 2019 updated problem formulation includes the refined scope that specifies which health outcomes are prioritized for dose-response analyses and toxicity value derivation.
- The protocol includes the methods and approaches proposed for use in developing the assessment, including systematic review and hazard characterization methods used to prioritize health outcomes.
- This poster presents diabetes as an illustrative example.

Evidence Profile Table (diabetes example)

<table>
<thead>
<tr>
<th>tier</th>
<th>factor that increases confidence</th>
<th>factor that decreases confidence</th>
<th>summary of evidence</th>
<th>strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Consistent positive association observed in populations at risk, primarily ≥ 10 μg/L/day</td>
<td></td>
<td>Weak evidence</td>
<td>Tier 1: Evidence of causality</td>
</tr>
<tr>
<td>2</td>
<td>Consistent positive association observed in populations at risk, primarily ≥ 10 μg/L/day</td>
<td></td>
<td>Weak evidence</td>
<td>Tier 1: Evidence of causality</td>
</tr>
<tr>
<td>3</td>
<td>Consistent positive association observed in populations at risk, primarily ≥ 10 μg/L/day</td>
<td></td>
<td>Weak evidence</td>
<td>Tier 1: Evidence of causality</td>
</tr>
</tbody>
</table>

Characterization of Hazard

<table>
<thead>
<tr>
<th>Health outcome</th>
<th>NRC Tier</th>
<th>EPA strength of evidence judgment of human evidence of a causal association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>Par 1</td>
<td>Robust, based on Tier 1 conclusions of “carcinogenic” for lung cancer from other assessments (Cheng et al., 2017)</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>Par 1</td>
<td>Robust, based on Tier 1 conclusions of “carcinogenic” for bladder cancer from other assessments (Kauppinen et al., 2016)</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>Tier 1</td>
<td>Based on systematic review conducted by EPA on evidence of carcinogenicity for skin cancer based on other assessments (ATSDR, 2004a, 2004b, 2004c), NRC Tier 1, and conclusions of “carcinogenic” for skin cancer based on other assessments (ATSDR, 2004a, 2004b, 2004c, 2004d, 2004e)</td>
</tr>
<tr>
<td>Isosexual hormone system</td>
<td>Tier 1</td>
<td>Moderated, based on systematic review conducted by EPA on evidence of endocrine disruption, based on evidence noted in other assessments (ATSDR, 2004a, 2004b, 2004c, 2004d, 2004e) and meta-analysis (NRC, 2010)</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>Tier 1</td>
<td>Moderated, based on systematic review conducted by EPA, which is similar to associations noted in other assessments (ATSDR, 2004a, 2004b, 2004c, 2004d, 2004e) and meta-analysis (NRC, 2010)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Par 2</td>
<td>Robust, based on systematic review conducted by EPA on pregnancy and birth outcomes (fetal loss, stillbirth, and neonatal mortality) (fetal loss and neonatal mortality in the first 5 yr of life), which is similar to associations noted in other assessments (ATSDR, 2004a, 2004b, 2004c, 2004d, 2004e) and meta-analysis (NRC, 2010)</td>
</tr>
<tr>
<td>Hematological/immune</td>
<td>Tier 1</td>
<td>Moderated, based on systematic review conducted by EPA on evidence of immunological effects, which is similar to associations noted in ATSDR (2012, 2014, 2016) and NRC (2014)</td>
</tr>
<tr>
<td>Nephrological/urinary</td>
<td>Par 2</td>
<td>Robust, based on systematic review conducted by EPA on evidence of urinary effects, which is similar to associations noted in ATSDR (2012, 2014, 2016) and NRC (2014)</td>
</tr>
<tr>
<td>Neurodevelopmental effects</td>
<td>Tier 2</td>
<td>Moderated, based on systematic review conducted by EPA, which is similar to associations noted in ATSDR (2012, 2014, 2016) and NRC (2014)</td>
</tr>
<tr>
<td>Immune effects</td>
<td>Tier 2</td>
<td>Moderated, based on systematic review conducted by EPA, which is similar to associations noted in ATSDR (2012, 2014, 2016) and NRC (2014)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Par 1</td>
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<td>Isosexual hormone system</td>
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<tr>
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<td>Tier 1</td>
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<td>Moderated, based on systematic review conducted by EPA, which is similar to associations noted in ATSDR (2012, 2014, 2016) and NRC (2014)</td>
</tr>
</tbody>
</table>

Conclusions

- Health outcomes with robust or moderate evidence were prioritized for dose-response.
- Prostate cancer, pancreatic cancer, and renal cancer were not prioritized (slight evidence).
- Immune effects not prioritized (no suitable data sets for analysis).
- Prioritization of health outcomes for dose-response analysis is summarized in Table 5.3 of the protocol.
Purpose and Scope

➢ 2015 Inorganic Arsenic (iAs) Assessment Development Plan laid out plans to:
  - Develop network analyses for endpoints considered to be causally or likely causally associated with specific adverse outcomes. Based on National Research Council (NRC) recommendations, extensive use of Action (MOA) analysis were also conducted for bladder cancer to better understand human variability and the possible use of mechanistic data to inform low dose extrapolation.
  - The utility of these analyses were evaluated in the context of EPA’s 2005 Cancer Guidelines recommendations on use of MOA framework to address:
    - Human relevance of animal tumor responses: MOA analyses are usually applied for chemicals with insufficient human evidence. iAs is a chemical with a large amount of epidemiological evidence. Hence, MOA is not needed for establishing human relevance.
    - Differences in anticipated response among humans: extensive information of risk modifiers in humans are available in the epidemiologic database. Hence, a MOA analysis to address potential differences in response across human populations was not considered essential.
    - Decisions about the anticipated shape of the dose-response relationship: given the availability of low dose epidemiological studies, mechanistic data (which is largely based on animal and in vitro studies) is not considered critical for low dose extrapolation. However, as recommended by NRC, EPA inventoried mechanistic evidence (Protocol, Appendix A) and conducted a case study MOA analysis for idiopathic bladder cancer to assess its utility for reducing uncertainties in dose-response analysis. Bladder cancer was selected due to its extensive evidence base as compared to other priority iAs health outcomes.

Adverse Outcome Pathway Network (AOPn) Development

In order to develop network analyses we decided to use the Adverse Outcome Pathway (AOP) framework. AOPs are chemically agnostic representations that identify the sequence of biochemical events required to produce an adverse effect or outcome. AOPs begin with a molecular initiating event (MIE) and link to a series of key events (KE) that traverse biological complexity starting at the molecular level, through cellular, organ and organism effects and culminate in an adverse outcome (AO).

Step 1: Establishing the Disease-Based Biological Pathway for Bladder Cancer Development in Humans

➢ To delineate a postulated mode of action for arsenic-induced bladder cancer, the molecular basis for bladder tumor development, irrespective of a specific chemical insult, was first established.
  - The information for building this AOPn was predominantly derived from current literature reviews.
  - Several key events were identified in the progression of bladder cancer, including activation of the Ras-MAPK, PI3K and JAK-STAT pathways. Activation of these pathways was associated with genetic alterations in the HRAS and FGFR oncogenes that induced constitutive activation of these genes. (see Figure 1).
  - Inactivation of key tumor suppressor genes, p53 and RB1, were identified as key events (KE) in the progression of bladder carcinomas (Figure 1).
  - The AOPn was compared to the KEGG (Kyoto Encyclopedia of Genes and Genomes) database for bladder carcinoma in humans to ensure concordance (see Figure 2).

Step 2: Identifying Arsenic-specific Modification in the Bladder Cancer Network

➢ After establishing a general disease-based network for bladder cancer, information on arsenic-specific alterations in the pathway was integrated from published literature on arsenic-induced bladder cancer, primarily derived from epidemiological, in vivo, and in vitro studies that analyzed effects of iAs or its metabolites (e.g., monomethylarsonic acid (MMAIII) and dimethylarsonic acid (DMAIII)) in vitro when the test system is known not to have metabolizing capability at concentrations ≤ 100 µM.

➢ The postulated bladder cancer AOPn. (Figure 3) indicates activation of the FGFR and HRAS oncogenes, as well as activation of the ERK2 receptor as molecular initiating events (MIE) in the progression of bladder carcinoma. Activation of Ras was identified as a key event (KE). Activation of Ras triggers a number of molecular events such as stimulation of the MAPK, VEGF, PI3K-AKT, and JAK/STAT pathways which culminate in cell proliferation, angiogenesis, cell survival, and ultimately bladder tumor formation.

➢ Evaluating the arsenic-specific evidence in relation to the disease-based bladder cancer AOPn, we identified several KE in iAs-induced bladder carcinoma. Specifically, iAs may activate Ras signaling through production of reactive oxygen species (ROS), imbalance of oxidative signaling, or through activation of the ERK2 receptor and lead to cell proliferation, angiogenesis and metastasis. Ras activation was also identified as a KE in the progression of idiopathic bladder carcinoma.

➢ Additionally, iAs-produced ROS can damage DNA and lead to p53 dysregulation, stimulation of matrix metalloproteinases (MMPs), and ultimately angiogenesis and metastasis (Figure 3, Table 1).

Conclusions

➢ The bladder cancer-based AOPn framework to support the iAs MOA was created using literature reviews of bladder cancer idiopathic disease as a starting point.

➢ Information from published literature on arsenic induced bladder cancer was integrated into the bladder cancer AOPn and nodes in the network that arsenic acted upon were identified. In this way, we created a bladder cancer-based AOP analysis of iAs MOA (Figure 3; Table 1).

➢ While the MOA evaluation identified arsenic-specific mechanisms and risk modifiers likely to increase risk of human bladder cancer, the impact and utility of mechanistic information on dose-response analyses was minimal.

➢ Much of the primary MOA evidence is based on in vitro studies which raises concerns about their applicability to informing low-dose effects.

➢ Ample epidemiological data is available for dose-response, and many studies included observations down to US background exposure levels.

➢ Conducting a similar analysis for other prioritized outcomes is hindered by the lack of a complete MOA for any health outcome and the likelihood that most, if not all, health outcomes associated with arsenic exposure involve multiple interactive MOAs.

References can be found in HERO (https://herose.epa.gov/hero/index.cfm/project/page/project_id_22313).
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 Jr3, Edward Hudgens1, David Thomas1, and Janice S. Lee4

1EPA, Office for 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., 2015).

Methods

Epidemiological Studies of Human iAs Urine Levels

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HEALS cohort, Bangladesh1</th>
<th>Churchill County, Nevada, USA3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of observations</td>
<td>Total: 11,438</td>
<td>Total: 904</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Male</td>
<td>6,876</td>
<td>Male: 368</td>
</tr>
<tr>
<td>Female</td>
<td>4,562</td>
<td>Female: 536</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Range: 17-75</td>
<td>Median: 45.92</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: 4.90-10.00</td>
<td>Median: 4.99-16.50</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Non-smokers: 7,405</td>
<td>Median: 79.70</td>
</tr>
<tr>
<td></td>
<td>Past-smokers: 755</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current smokers ≤10 cig/day: 1,953</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current smokers &gt;10 cig/day: 1,341</td>
<td></td>
</tr>
<tr>
<td>As water conc. (μg/L)</td>
<td>Range: 0.1-8.64.0</td>
<td>Median: 0.86-1850.00</td>
</tr>
<tr>
<td></td>
<td>Median: 6.1</td>
<td>Median: 6.1</td>
</tr>
<tr>
<td>Total daily water consumption</td>
<td>Range: 175.0-240.0</td>
<td>Median: 25.26-260</td>
</tr>
<tr>
<td>(mL)</td>
<td>Median: 2.850</td>
<td>Median: 1893.00</td>
</tr>
<tr>
<td>Urinary As conc. (μg/L)</td>
<td>Range: 1.0-227.40</td>
<td>Median: 0.50-856.30</td>
</tr>
<tr>
<td></td>
<td>Median: 87.0</td>
<td>Median: 39.00</td>
</tr>
<tr>
<td>Creatinine adjusted urinary As</td>
<td>Range: 6.6-5,000.00</td>
<td>Median: 2.84-5186.00</td>
</tr>
<tr>
<td>conc. (μg/g)</td>
<td>Median: 198.40</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 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 concentration × water intake
- Volume of the tissue compartments:
  \( \text{BWMULT} \times \left( \frac{\text{Body weight}}{70 \text{ kg}} \right) \)
- Urinary excretion rate, L/hr:
  \( V_{\text{urinary}} = 0.65 \times BW \times \text{BWMULT} \)
- Creatinine excretion rate based on subject specific body weight:
  \( \text{MCR} = \beta_0 + \beta_1 \times \text{sex} + \beta_2 \times \text{BMI} + \beta_3 \times \text{age}^2 \) (Ong et al., 2015)

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

<table>
<thead>
<tr>
<th>Food type</th>
<th>Mean (range; μg/day)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice (g/day)</td>
<td>Male: 523</td>
<td>Watanabe et al. (2004)</td>
</tr>
<tr>
<td>Vegetable (g/day)</td>
<td>Female: 300</td>
<td>Khan et al. (2009)</td>
</tr>
<tr>
<td></td>
<td>Male: 153.00</td>
<td>Khan et al. (2009)</td>
</tr>
<tr>
<td></td>
<td>Female: 146.88</td>
<td>Khan et al. (2009)</td>
</tr>
<tr>
<td></td>
<td>173</td>
<td>Rahman et al. (2011)</td>
</tr>
<tr>
<td></td>
<td>150 (10-500)</td>
<td>Rahman et al. (2009)</td>
</tr>
<tr>
<td></td>
<td>153 (74-301)</td>
<td>Rahman et al. (2011)</td>
</tr>
<tr>
<td></td>
<td>12.1 (13-22.8)</td>
<td>Khan et al. (2010)</td>
</tr>
<tr>
<td></td>
<td>15 (0–136)</td>
<td>Khan et al. (2012)</td>
</tr>
<tr>
<td></td>
<td>4.6 (1.9–7.9)</td>
<td>Karmir Spencer et al. (2014)</td>
</tr>
<tr>
<td></td>
<td>33.44 (26-48.9)</td>
<td>Tasi and Bolger (1999)</td>
</tr>
</tbody>
</table>

References can be found in HERO [https://hero.epa.gov/hero/index/indexes/project/pag/project_id/2311].

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.
Analyzing Study-Specific Estimates of Exposures Associated with a Defined Relative Risk vs U.S. Background Exposure (RRBs) for Inorganic Arsenic (iAs) Health Outcomes (Poster 4)

Kevin Hobble1, J. Allen Davis2, Kan Shao1, Cara Henning1, William Mendez Jr.1, Janice S. Lee3, Ilia Cote4, Ingrid Druwe1, Jeff Gift4


Purpose and Scope

- National Research Council (NRC) recommended that EPA derive risk estimates for iAs for health effects with adequate epidemiologic evidence (NRC, 2013).
- EPA developed an approach to provide an efficient, yet also effective, means of focusing dose-response analysis efforts given the extent of the epidemiological evidence base, and the variance in data quality across health outcomes.

Relative Risk Exposure vs Background Exposure (RRB)

EPA developed an approach that allows for comparison of relative risk estimates across studies that use various exposure metrics. Dose-response modeling is used to estimate exposures associated with a given increase in relative risk (RR). The RRE is divided by an estimate of the U.S. background level for that exposure metric. This approach involves:

- **Selection of datasets:** starting from health outcomes with robust/moderate databases, and considering author-prepared trend tests.
- **Data preprocessing:** estimating group-level means, adjusting incidence rates for covariates, categorizing outcomes, and considering author-performed trend tests.
- **Exposure-response modeling:** case-control and cohort studies were modeled to predict exposures where relative risk (RR) changed by 20% (regardless of endpoint severity or prevalence) compared to the RR estimated at U.S. background (Table 2) (RRE). RREs were divided into Risk Estimation values for other key covariates (including age, gender, and smoking status).
- **Derivation of RRBs:** values by estimates of U.S. background (RRE) (US Background). Exposure units for U.S. background estimates differ from match RRB units, but are based on similar water and dietary intake assumptions (see Table 2).

Selection of Datasets

- **Hazard Identification:** focused on epidemiological studies of iAs health outcomes having robust/moderate databases (see Poster 1).
- **Initial screen:** focused on datasets from cohort and case-control studies. Ecological, cross-sectional and continuous (e.g., neurocognitive response measures) datasets not considered for purposes of RRE derivation for purposes of the RRB analysis.
- **Secondary screen:** each dataset received a score of 0, 1, or 2 for each rating element (Table 1). Datasets for which the sum of scores was >= 5 were excluded.
- **Final screen:** studies with inadequate or conflicting dose-response data were removed if issue(s) could not be resolved through communications with authors.

Data Preprocessing

- **Estimating Group-Level Mean Exposures:** Exposure ranges were fit to lognormal distributions using maximum likelihood (MLE) methods. Group mean estimates were derived by drawing large Monte Carlo samples (10 million) from fitted distributions, and sampling randomly in each exposure range for appropriate numbers of subjects.
- **Adjusting Incidence to Account for Covariates:** “Effective counts” derived from reported ORs that were adjusted for covariates (see Poster 1).
- **Identifying Background Exposure for the U.S. Population:** For RRE and RRB derivations, relative risk for central tendency background exposures (Table 2) set to 1.0, thus, the RRE is exposure or dose, the calculated relative risk is 1.2. This allows for comparison of U.S.-specific risk results across studies.
- **Categorizing Outcomes:** To facilitate comparing across RRBs, outcomes categorized by types (clinical, fatal, clinical-non fatal, preclinical, subclinical and control only). See Table 3 for details.

Exposure Response Modeling

- **Case-control studies -** adjusted case and control numbers were fit by a logistic model: f(dose) = 1/(1 + exp(−(a − b × dose))). Use of a logistic model allows for analysis of case-control studies with prospective studies, both having the same binomial likelihood contributions from their exposure groups (Prentice and Pyke, 1979).
- **Cohort studies:** counts of cases in each exposure group follow a Poisson distribution: \( \lambda = \alpha \times \exp(β × dose) \). The estimated case-generating parameter is an estimate of the cumulative dose-response models used for \( f(c) \), including the linear model, power model, log-linear model, Michaelis-Menten model, and the Exponential 2, 3, and 4 models.
- **Model Fit Assessment and Model Selection:** for each dataset, the model generated estimates of log likelihood, AIC and \( \chi^2 \) p-value, estimates of model parameters, and predicted risks (ORs for case-control; RRs for cohort) at each exposure level, with confidence limits. EPA (2012) BMD modeling methods were used to select a best fitting model from the multiple models used to fit cohort study data.
- **Selection of a Benchmark Relative Risk:** for this comparative analysis, a 20% relative risk dose, or RRE, is estimated. The 20% effect level was chosen to avoid extrapolating far outside the range of data and because, for the bulk of the epidemiological data sets, an increase in odds ratio or relative risks of about 20% was near the smallest increase that could be resolved based on the data.

Conclusions

As indicated in Poster 1, all of the outcomes in this RRB analysis, as well as neurocognitive effects for which RRB values could not be derived, were identified as having Robust or Moderate evidence overall and will therefore be considered for dose-response analysis. However, NRC (2013) identified priority health outcomes for EPA to focus on and recommended that EPA further prioritize. EPXs RRB analysis approach supports this prioritization effort by providing a method for comparing the results of diverse studies of health outcomes, and identifying key endpoints and datasets that are suitable for use in more detailed dose-response analyses (see Posters 5, 6, and 7). Consistent with key outcomes identified by the NRC (NRC, 2013), DCS, bladder cancer and lung cancer were identified as having the largest databases of adequate dose-response datasets, increasing confidence in the RRB summary statistics (e.g., median estimates), as well as low RRB values relative to most outcomes. RRB values for diabetes and liver cancer data are also low, but are associated with smaller databases and a lower degree of certainty in the RRB summary statistics.

References


The Application of Model Averaging Methods to Assess the Suitability of Taiwanese Studies for Predicting U.S. Bladder and Lung Cancer Risk from Inorganic Arsenic (IAs) Intake (Poster 5)

William Mendez Jr.1, J. Allen Davis2, Kan Shao3, Janice S. Lee4, Ila Cote5, Ingrid Druwe6, Jeff Gift7

1 ICF, 2 EPA, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, 3 Indiana University, 4 EPA, Office of Research and Development, National Center for Environmental Assessment – Research Triangle Park.

Purpose and Scope

- National Research Council (NRC) recommended that EPA focus on high-quality epidemiologic studies that assess inorganic arsenic (IAs) exposures commonly experienced in the U.S., where mean background intake is estimated to be 0.071 µg IAs/kg-day (see Posters 6 and 7) and where intake levels above 1 µg IAs/kg-day are extremely rare (NRC, 2013).
- An analysis was performed to assess the suitability of two studies of bladder and lung cancer risk in a large Taiwanese population (Chen et al., 2010a,b) that:
  - meet EPA study quality criteria (see Poster 1).
  - form the basis of arsenic risk assessments performed by other international organizations (FDA, 2016, WHO, 2011), and
  - are associated with high IAs exposure levels relative to the U.S. (IAs intake for the reference group of these studies is >0.9 µg/kg-day, more than 10× higher than the estimated U.S. background intake level).

Modeling Approach - Overview

A model averaging approach was applied in an attempt to extrapolate lifetime bladder and lung cancer probabilities estimated at µg/kg-day intake doses estimated for a large prospective cohort study of residents in northeastern Taiwan (Chen et al., 2010a,b) to relevant U.S. doses. The approach is illustrated in Figure 1 and builds upon dose-response model averaging methods developed by the FDA. It involves:

- Estimation of water and dietary intake variability for the Taiwanese population to represent the variability in the input variables to the bootstrap model.
- Bootstrap simulation to incorporate uncertainty in the estimation of adjusted outcomes (cases of cancer) and dietary arsenic intake.
- Model Averaging to extrapolate to U.S. relevant doses and assess model dependence.

Estimation of water and dietary intake variability

Multiple data sources and methods were used to derive inputs for the bootstrap estimation of arsenic intake. In summary:

- IAs Drinking water intake was estimated by fitting a mixed lognormal distribution to the drinking water concentration data from the Chen et al. cohort. Distributions of drinking water consumption were estimated based on age-specific survey data from the Taiwan Department of Health (TDOH, 2007).
- IAs food intake was estimated using food consumption from Taiwan Department of Health survey data (TDOH, 2007) and IAs concentration distributions (for rice and leafy vegetables) or central tendency estimates (tubers, pulses, meats and fish) estimated from multiple studies of Taiwanese and other Asian countries.

Bootstrap simulation

- A “bootstrap” methodology was applied to simulate the variability in arsenic intake and in outcome measures, and their impacts on risk estimates. As shown in Figure 1, the estimated arsenic intake doses from water and diet were summed for each subject in each bootstrap iteration, and average total daily intake doses were estimated across each exposure group. The 1,000 sets of group average arsenic intake dose served as inputs, along with the outcome data sets, to the dose-response estimation.

Model Averaging

- Nine dose-response models available in EPA’s Benchmark Dose Software (BMDS) were fit to each bootstrap data set (Table 1). A diverse set of models was chosen to cover “model space” and explore “model uncertainty” as fully as possible.
- Models were estimated by maximizing binomial likelihood with varying constraints.
- Outputs from the bootstrap analysis included 1,000 sets of maximum likelihood parameter estimates and model log likelihoods derived for each input data set.
- Bayesian InformationCriterion (BIC) values were calculated as:
  \[ \text{BIC} = -2 \times \log(\text{likelihood}) + k \times \text{log}(n) \]
  where \( k \) = number of parameters estimated and \( n \) = number of observations.
- The weights employed in model averaging were based on the calculated average BIC values for each model. For each model (i), the Bayes weights were calculated as:
  \[ \text{Weight}_i = \frac{1}{1 + \text{BIC}_i - \alpha} \]
  where “Prior” model weights were assumed to be 1/9 (i.e., no a priori preferred model).
- Weibull, log logistic, log probit, Gamma, and dichotomous Hill models were run with power or slope terms both unconstrained and constrained to be >1.0 to better assess model dependence in the low dose region.
- Weighted estimates of lifetime bladder and lung cancer probabilities were calculated for a series of doses from 0 to 40 µg/kg-day, corresponding to the range of mean total arsenic intakes observed in the bootstrap data set.

![Figure 1. Summary of dose-response methodology for bladder and lung cancer. Note: BIC = Bayesian Information Criterion](image1)

![Figure 2. Predicted lifetime probability of bladder cancer versus all doses (upper plot) and low doses (lower plot) using constrained (C) and unconstrained (U) models compared to adjusted observed incidence from adjusted relative risks reported in Chen et al. (2010b).](image2)

![Figure 3. Predicted lifetime probability of lung cancer versus all doses (upper plot) and low doses (lower plot) using constrained (C) and unconstrained (U) models compared to adjusted observed incidence from adjusted relative risks reported in Chen et al. (2010b).](image3)

![Figure 4. Predicted lifetime probability of lung cancer versus all doses (upper plot) and low doses (lower plot) using constrained (C) and unconstrained (U) models compared to adjusted observed incidence from adjusted relative risks reported in Chen et al. (2010b).](image4)

![Figure 5. Predicted lifetime probability of lung cancer versus all doses (upper plot) and low doses (lower plot) using constrained (C) and unconstrained (U) models compared to adjusted observed incidence from adjusted relative risks reported in Chen et al. (2010b).](image5)

Results

- In the range of the data, similar mean absolute risk, 2.5th and 97.5th percentiles are derived from constrained and unconstrained models (Figures 2 & 3; upper plots).
- At lower doses, absolute risks derived from the unconstrained models curve sharply downward compared to those from constrained models (Figures 2 & 3; lower plots).
- Differences in extra risk (i.e., the increase in risk relative to estimated “background risk”) are more substantial, particularly in the low-dose range (see Figures 4 and 5).

Conclusions

As reflected in Figures 2 through 5, EPA’s model averaging analysis shows substantial model uncertainty in extrapolating from the IAs doses estimated for the Taiwan cohort to the estimated U.S. background IAs dose of 0.071 µg/kg-day. This result, combined with the NRC (2013) recommendation to perform only “modest” (e.g., 1 order of magnitude) extrapolation from the lowest exposure group of a candidate study, suggests that the Chen et al. (2010a,b) studies should not serve as the sole basis for U.S.-specific cancer risk estimates. As a result, EPA has developed a multiple study Bayesian meta-regression approach that has the potential to better inform dose-response and provide more reliable risk estimates at U.S.-relevant arsenic dose levels (see Posters 6 and 7).

References

Jeff Gift gift@epa.gov | 919-541-4828

Jeff Gift gift@epa.gov | 919-541-4828
Dose Conversions and Uncertainty

For meta-analysis, it is imperative that all studies are expressed using a common dose metric, but iAs studies often report exposures in drinking water concentrations (µg/L), cumulative exposure (µg/kg-day), etc. For this analysis, we converted all reported studies into iAs daily intake values (µg/kg-day).

For example, for a study that reports average iAs exposure (µg/L) or cumulative iAs exposure (µg/L/year), daily intake (µg/kg-day) was calculated via:

\[ \text{dose} = DI = f \times (WCR \times WE) + (1 - f) \times (WCR \times LE) \]

Where DI = dietary intake (µg/kg), f = fraction of lifetime exposed to the study reported iAs levels (WE), WCR = water consumption rate (L/kg), WE = arsenic exposure level (µg/L), if exposure is given in terms of cumulative exposure [CE, WE is estimated by dividing CE by the reported duration of exposure (RDWE)], LE = low exposure value (µg/L).

Parameters necessary for conversion determined on a study-by-study basis, according to study population.

Factors for conversion were not treated as single values according to study population. The Bayesian dose response meta-regression model calculates sensitivity uncertainty to investigate the degree of dose that exist across studies used in the analysis (Figure 1) (full set of sensitivity analyses discussed in Poster 7).

After averaging over all individuals within a dose-group, a Monte Carlo simulation was run with 1,000 iterations to derive a distribution of group-specific dose values.

The median, 2.5%, and 97.5% percentiles from this distribution were used to characterize the "best", "low-end", and "high-end" estimates of dose (Table 3).

Calculation of Effective Counts

For both cohort and case-control studies, published manuscripts almost always report relative risks (RR) or odds ratios (OR) that have been adjusted for some set of confounders.

The Bayesian dose-response meta-regression method described here is based on the likelihood of observing a particular number of cases.

The goal of computing "effective" counts of cases and controls is to construct of set of counts that reflect only the effect of exposure to iAs (Table 1).

Essentially, the calculation results in counts of cases and controls that would have been calculated had all the covariates (other than dose) in all groups been the same as those observed in the referent group.

The methods employed to calculate these "effective counts" are based on those of Greenland and Longnecker (1992), Hamling et al. (2008), and Orsini et al. (2012).

Studies included in the subsequent Bayesian dose-response meta-regression included incidence rate cohort, cumulative incidence cohort, and case-control studies.

Conclusions

The methods described herein were used to account for commonly encountered limitations in epidemiological studies in the context of dose-response analyses, including:

- Reporting of interval censored exposure studies
- Use of divergent measures of iAs exposure across studies
- And only reporting adjusted effect measures

With respect to calculation of doses for use in a meta-regression, the current method calculates multiplicative exposure meta effect estimates and facilitates sensitivity uncertainty to investigate the degree of dose that exist across studies used in the analysis (Figure 1) (full set of sensitivity analyses discussed in Poster 7).

References


### Purpose and Scope

- National Research Council (NRC) has recommended the application of meta-analytical approaches, including Bayesian approaches, to well-studied health outcomes for the development of point estimates of risk and confidence intervals (NRC, 2013; NRC, 2014).
- NRC specifically recommended that EPA conduct dose-response meta-analysis for arsenic-related diseases in the IIS assessment of inorganic arsenic (NRC, 2013).
- This poster is the second of two (see also Poster 6) that describe a case study highlighting an application of Bayesian hierarchical dose-response meta-regression to the analysis of arsenic exposure and human bladder cancer.

### Case Study: Inorganic Arsenic (iAs) & Bladder Cancer

The dose-response and target population prediction steps described here employ methods to:

- Apply a flexible logistic model to cohort and case-control epidemiological studies of inorganic arsenic (iAs) in a hierarchical Bayesian framework to estimate study-specific and pooled slopes.
- Extrapolate predictions of risk to a target population of interest using lifetable methods.
- This method explicitly uses as inputs the results of the pre-analysis steps described in Poster 6.

### Dose-Response Modeling and Lifetable Analysis

**The purpose** the dose-response analysis described herein is to perform a meta-regression to combine multiple studies for two kinds of epidemiological studies: case-control and cohort studies.

We assume that the **prospective likelihood** is given by a logistic equation applied to a vector of p explanatory variables X = (X1, ..., Xp):

\[
\text{logit}(P(Y = 1|X)) = \beta_0 + \beta^T x(X)
\]

- Due to the differing designs of case-control and cohort studies, methods were developed for each study type independently in order to predict the **prospective likelihood** of each study.
- For the Bayesian implementation of the meta-regression:
  - All analyses were conducted in the Stan programming language
  - Defined necessary parameters for modeling and set priors:
    - Case-control studies: \(\beta^T \) (slope parameters) and \(\lambda \) (true proportion of doses in a dose interval)
    - Cohort studies: \(\mu^T \) (expected number of cases in the referent group)
  - Calculated the parameter \(\alpha^T \)
  - Defined the log-likelihood contribution for each dose group
- Typical lifetable analysis methods, including consideration of background exposure to iAs, were used to estimate extra risk of disease in the target population:
  - Background rates of disease assumed to represent zero extra risk from iAs
  - A mean background iAs dose of 0.071 µg/kg-day was assumed (0.05 µg/kg-day from dietary sources, 0.021 µg/kg-day from drinking water, and 0 µg/kg-day from inhalation) (Xue et al., 2010; Mendez et al., 2017).

### Dose-Response Modeling and Lifetable Analysis cont.

Table 1 summarizes the data used in the case study of iAs and bladder cancer, including the estimated intake values and effective counts calculated as described in the Poster 6.

For the purpose of dose-response modeling, the \(\alpha^T \) parameter was assumed to be independent for each dataset.

Methods also assume study-specific \(\beta^T \) values that are normally distributed around a mean of \(\mu_{\beta} \), with standard deviation \(\sigma_{\beta} \). Both \(\mu_{\beta} \) and \(\sigma_{\beta} \) were assigned priors and updated (Table 2).

The gamma distribution for \(\mu_{\beta} \) reflects determination that iAs is causally associated with the development of bladder cancer.

Prior judgement that exposure to 1 µg/kg-day iAs (<14-fold average background exposure) is highly likely to result in \(1.0001 < \alpha < 20 \).

1st and 99th percentiles of gamma distribution \(f(x) = \frac{1}{\Gamma(a)\beta^a} e^{-(\beta x)^a} \) set equal to \(\ln(1.0001)\) and \(\ln(20)\), results in parameters listed in Table 2.

Important to note that gamma distribution gives greatest weight to values of \(x \) closest to zero (hence, prior assumption is weaker association with iAs unless data are sufficient to override prior).

Estimates of pooled and study-specific \(\beta^T \) values derived from the hierarchical model and estimated lifetime extra risks in the target population are summarized in Tables 3 and 4 and Figures 1-3.

### Conclusions

- These Bayesian meta-regression methods (Posters 6 and 7) allow for inclusion of more studies than other meta-regression methods by reconciling different study designs and exposure metrics, and could potentially be applied to any endpoint for which multiple studies and incidence/mortality/morbidity lifetables are available.
- The logistic dose-response model used could be extended to consider fractional-polynomial forms of the logistic model, \(\text{logit}(p(x)) = \alpha^T + \beta_1 (x^p)^1 + \beta_2 (x^p)^2 \) to allow more flexibility in fitting datasets for the investigation of whether the data suggest a J-shaped dose-response (e.g., negative slopes in the low dose region).

### References

2. The views expressed in this poster are those of the author(s) and do not necessarily represent the views or the policies of the U.S. Environmental Protection Agency.

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