Inorganic Arsenic IRIS Dose-Response Analyses
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Dose-Response: Methods Overview

D-R Methods Outlined in Protocol for Cancer and Non-cancer Outcomes

• Relative Risk Exposure to Background (RRB) Screening
  – Purpose – identify studies and endpoints suitable for dose-response modeling
  – Approach:
    – Focused on single study, single best model to derive point of departure
    – Attempted to derive RRB values for all 12 robust & moderate outcomes

• Model Averaging:
  – Purpose – Evaluate low dose extrapolation model uncertainty
  – Approach:
    – Applied multiple models with model averaging to Chen et al. (2010a,b) Taiwan data
    – Modeled data for bladder and lung cancer

• Bayesian Meta-Regression
  – Purpose – Use best possible approach for evaluation of low dose responses pooling information from multiple studies
  – Approach:
    – Convert all exposures to common study-specific estimate of intake (µg/kg-day)
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    – Investigate low-dose non-linearity with fractional logistic model
    – Lifetable analyses if possible
    – Best possible single study analyses if Bayesian meta-regression is not feasible
RRB Screening of Epidemiological Exposure-Response Data

• **Purpose of Screening**
  – Evaluate health outcome studies and datasets *qualitatively* and *quantitatively*
  – Compare iAs potency across hundreds of datasets for dozens of health outcomes
  – Maximize resources

• **Qualitative Systematic Review of the Literature**
  – Risk of bias evaluations conducted to inform confidence in individual studies
  – Evidence profile tables for each hazard transparently summarizes considerations underlying EPA judgments regarding strength of the human evidence
  – Additional review of study relevance for dose-response (next slide)

• **Quantitative Screening**
  – Exposure-response analysis to compare potency estimates across hundreds of studies and datasets
  – Identify health endpoints for more sophisticated analyses
Qualitative Review of Dose-Response Feasibility

- Initial Screen: focused on cohort and case-control studies
- Secondary Screen: scored dataset on a number of rating criteria; datasets with a total score ≥ 5 were excluded
- Final Screen: studies with inadequate or conflicting dose-response were excluded if issues couldn’t be resolved through communication with authors

| Table 1. Study Rating Criteria for Dose-Response Analysis |
|---------------------------------------------|--------------------------------------------------|
| **Rating Element**                        | **Criteria**                                    |
| Health outcome                            | Incidence data generally preferred over mortality data only |
| Exposure ascertainment method              | Location of residence/exposure or large group averages instead of individual measurement or small group averages |
| Exposure reporting                         | Reported as ranges without summary statistics such as averages and measures of dispersion/variance |
| Estimates control for smoking, gender, age and other key covariates | Adjusted estimates do not include important covariates |
| Number of exposure groups                  | Less than two in addition to referent precludes exposure-response modeling, more groups support more complex models |
| Number of subjects & cases reported        | One or both elements missing; only statistical summaries (RR, SMRs, etc.,) are reported |
| Exposure/dose metric                       | Worst = historical exposure measurement only, better = cumulative exposure, best = cumulative intake (no markdown for urinary As) |
| Exposure timing and duration               | Exposure histories (timing, duration) not adequately ascertained or reported |
| Representativeness of referent group/controls | Not documented or differs from exposed groups, without reported adjustment (case-control only) |
| Sufficient number of subjects, cases       | Too few cases to conduct reliable statistical analyses (most applicable to cohort cancer studies, desirable to have >~ 5 cases/exposure group |
RRB Screening Approach

• More than 250 data sets identified as suitable for RRB modeling

• EPA’s Benchmark Dose Software was used to model data and estimate the exposure that would increase risk estimate by 20% (RRE_{20})
  – Case-control studies modeled with the logistic model – under logistic regression model, results from case-control studies can be analyzed as if they were collected prospectively
  – Cohort study data assumed to follow a Poisson distribution – relative risk modeled with continuous dose-response models (single best model selected using standard practices)
  – RRE_{20} values are maximum likelihood estimates, not lower bound estimates (i.e., akin to BMDs, not BMDLs)
  – EPA considered multiple BMRs and ultimately decided 20% increase in RR was most appropriate across all endpoints
**RRB Screening – Background Estimates of Exposure**

- **RRE\textsubscript{20}** estimates then divided by estimate of US background exposure to generate RRB values
  - Background estimates of exposure drawn from multiple sources
  - RRB values closer to 1 possibly indicate clinically significant health effects at background exposure levels

### U.S. central tendency and “high” arsenic estimates for different exposure and dose metrics

<table>
<thead>
<tr>
<th>Exposure metric</th>
<th>Units</th>
<th>U.S. central tendency</th>
<th>U.S. &quot;High&quot;</th>
<th>Basis for U.S. estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinking water concentration</td>
<td>µg /L</td>
<td>1.5</td>
<td>15.4</td>
<td>median, 95th percentile county mean As in drinking water (USGS, 2011)</td>
</tr>
<tr>
<td>Cumulative exposure from drinking water</td>
<td>µg - µg/L</td>
<td>75</td>
<td>770</td>
<td>1.5 µg/L for 30 years, 15.4 µg/L for 50 years</td>
</tr>
<tr>
<td>Daily intake</td>
<td>µg /day (water)</td>
<td>1.5</td>
<td>15.4</td>
<td>1.5, 15 µg/L (above), 1.0 L/day (U.S. EPA, 2011)</td>
</tr>
<tr>
<td>Dietary intake</td>
<td>µg /day (food)</td>
<td>3.5</td>
<td>13.3</td>
<td>Mean, 95th percentile adult intake (Xue et al., 2010); 0.05, 0.19 µg/kg - d, 70-kg adult</td>
</tr>
<tr>
<td></td>
<td>µg /day (food + water)</td>
<td>5</td>
<td>28.7</td>
<td>Sum of food and water</td>
</tr>
<tr>
<td>Cumulative intake</td>
<td>mg (cumulative intake, water)</td>
<td>27.4</td>
<td>281</td>
<td>50 years intake @ 1.5, 15.4 µg/day</td>
</tr>
<tr>
<td></td>
<td>mg (cumulative intake, food + water)</td>
<td>91.3</td>
<td>524</td>
<td>50 years intake @ 5, 28.7 µg/day</td>
</tr>
<tr>
<td>Urine concentration (cr. Adj.)</td>
<td>µg As excretion / g creatinine</td>
<td>7.4</td>
<td>18.4</td>
<td>NHANES (2013-2014) median, 95th percentile (CDC, 2016)</td>
</tr>
<tr>
<td>Urine concentration</td>
<td>µg As excretion / L urine</td>
<td>5</td>
<td>16.8</td>
<td>NHANES (2013-2014) median, 95th percentile (CDC, 2016)</td>
</tr>
<tr>
<td>Air</td>
<td>µg /m\textsuperscript{2}</td>
<td>0.00075</td>
<td>0.0015</td>
<td><a href="https://cfpub.epa.gov/roe/indicator.cfm?i=90#8">https://cfpub.epa.gov/roe/indicator.cfm?i=90#8</a>: EPA's ambient monitoring archive, arsenic data averaged between 2010 and 2013</td>
</tr>
<tr>
<td>Cumulative air</td>
<td>µg /m\textsuperscript{2}-years</td>
<td>0.0375</td>
<td>0.078</td>
<td>50 years of inhalation</td>
</tr>
</tbody>
</table>
RRB Screening Approach and Results

• RRB value = 5.74

• Means that, for clinical fatal lung cancer datasets, the exposure level that would result in an RR = 1.2 is ~6-fold higher than U.S. background exposure level
RRB Screening Conclusions

- All endpoints other than immune and developmental neurocognitive effects supported RRB modeling
- All modeled health outcomes considered for further dose-response modeling
- Developmental neurotoxicity is identified as an important endpoint for EPA Program Offices; alternative modeling strategies will be pursued for this endpoint

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Preclinical or Subclinical</th>
<th>Clinical Non-Fatal</th>
<th>Clinical Fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range of RRBs</td>
<td>Median</td>
<td>Range of RRBs</td>
</tr>
<tr>
<td>Bladder Cancer</td>
<td>N/A</td>
<td>N/A</td>
<td>0.386 - 89.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>N/A</td>
<td>N/A</td>
<td>3.25 - 27.1</td>
</tr>
<tr>
<td>DCS</td>
<td>6.86 - 209</td>
<td>29.0</td>
<td>1.10 - 87.5</td>
</tr>
<tr>
<td>Liver Cancer</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>N/A</td>
<td>N/A</td>
<td>7.06 - 8920</td>
</tr>
<tr>
<td>Nonmalignant Resp. Disease</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Pregnancy Outcomes</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Renal Cancer</td>
<td>N/A</td>
<td>N/A</td>
<td>1.07 - 357</td>
</tr>
<tr>
<td>Skin Cancer</td>
<td>N/A</td>
<td>N/A</td>
<td>2.27 - 77.7</td>
</tr>
<tr>
<td>Skin Lesion</td>
<td>N/A</td>
<td>N/A</td>
<td>6.52 - 402</td>
</tr>
</tbody>
</table>
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Model Averaging

• Focused on bladder and lung cancer observed in Chen et al. (2010a,b) – large prospective cohort study in northeast Taiwan
• Bootstrap approach (n = 1,000) used to estimate iAs intake (µg/kg-day) and adjusted outcome (cases of cancer)
• Nine dose-response models fit to each bootstrap dataset and Bayesian Information Criterion used to average maximum likelihood estimates across models
• Constrained and unconstrained models used
• Lifetime cancer risks calculated for the general US population at a series of doses of 0 – 40 ug/kg-day
Model Averaging: Bladder Cancer Results for NE Taiwan

Comparing Unconstrained and Constrained Models

![Graph comparing lifetime bladder cancer risk against inorganic arsenic intake. The graph shows the relationship between cancer risk and arsenic intake, with lines indicating mean values and confidence intervals. The x-axis represents inorganic arsenic intake in μg/kg-day, while the y-axis represents lifetime bladder cancer risk. The graph includes data points for mean (C) and mean (U) exposure, with 95% confidence intervals.](image-url)

- **US background**: 0.071 μg/kg-d
- **US DW standard**: 0.19 μg/kg-d
- **Observed US DW standard = 0.19 μg/kg-d**

- **Mean (C)**
- **95% Confidence Interval (C)**
- **Mean (U)**
- **95% Confidence Interval (U)**
- **Observed**
Model Averaging: Bladder Cancer Results for NE Taiwan

Comparing Unconstrained and Constrained Models

![Graph showing lifetime extra bladder cancer risk vs. iAs intake (µg/kg-day)]

- US background = 0.071 µg/kg-day
- US DW standard = 0.19 µg/kg-day
- Referent group intake = 0.8 µg/kg-day
- Lowest exposure group intake = 2.0 µg/kg-day

**Risk at 10 ug/L (0.19 µg/kg-day):**
- 1.2x10^-4 (c)
- 4.8x10^-4 (uc)

Chen et al. (2010b), Unconstrained

Chen et al. (2010b), Constrained
Model Averaging: Conclusions

• Model averaging showed substantial model uncertainty when extrapolating from Taiwanese iAs doses to US relevant doses

• NRC (2013) recommended only “modest” low dose extrapolation (~ 1 order of magnitude) from the lowest exposure group of a candidate study, suggesting Chen et al. (2010a,b) is not appropriate for estimating US risk

• Mode of action analyses could be used to inform low-dose extrapolation in the absence of other dose-response modeling approaches

• However, a meta-regression method utilizing multiple low-, mid-, and high-dose studies is considered a preferable approach and was recommended, where feasible, by the NRC (2013)
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Bayesian Meta-Regression: Effective Counts

• Need a method that allows for combining as many study types as possible and makes use of adjusted risk and confidence limit values reported by authors

• Cohort and case-control studies typically report relative risks (RR) and odds ratios (OR) adjusted for confounders

• EPA implemented an approach to calculate “effective counts” - i.e., the counts of cases and controls that would have been observed if the covariates in all exposure groups were equal to those observed in the referent group

• Allows reported risk values to be modeled with logistic model as incidence data
Bayesian Meta-Regression: Exposure Group Means

- Exposures in epidemiologic studies often reported as a range, whereas dose-response software requires a point estimate for modeling

- Estimating a point estimate is relatively straightforward except for high doses which are often reported as open-ended ranges (e.g., > 10,000 µg/L-year)

- EPA used a maximum likelihood (ML) approach to estimate group-specific means
  - Exposures were assumed to be log-normally distributed
  - ML estimates were considered “best” estimates

- Then, to characterize exposure uncertainty, the high exposure group mean was maximized or minimized, subject to constraints on the log-likelihood, yielding a set of group means consistent with the 95% confidence bounds on the high-group mean
In order to maximize the set of studies included in EPA’s meta-regression, study-specific exposure metrics were converted into a single measure of iAs intake in units of µg/kg-day.

Previous meta-regressions have relied mainly on studies that using drinking water concentration as dose metric.

However, some studies have observed stronger associations when using alternative exposure metrics.

For example, Baris et al. (2016) found no association for drinking water concentrations but a statistically significant association for average daily arsenic intake (µg/day) and cumulative exposure (mg).

Baris et al. (2016) ultimately concluded that “[t]he contrast in our findings for cumulative arsenic intake and average arsenic concentration underscores the importance of incorporating water intake when estimating an individual’s total arsenic exposure in low to moderately exposed populations...”
Bayesian Meta-Regression: Dose Conversions

• Urinary iAs data were converted using El-Masri and Kenyon (2008) PBPK model
• Studies reporting exposures in µg/L, µg/L-year, ug/day, or mg were converted using dose conversion equations
• Cumulative measures of exposure were preferred over drinking water concentrations because of the incorporation of individual-specific durations of exposure
• However, some cumulative metrics possibly reflect short periods of high-dose exposure rather than more consistent average exposures
• EPA will take these aspects of exposure ascertainment into consideration when selecting the specific exposure metrics to use in the meta-regression
Bayesian Meta-Regression: Dose Conversions

• For example, Baris et al. (2016) reported exposures as cumulative intake in units of mg; to calculate intake in units of µg/kg-day, the following equation was used with study- or population-specific exposure factors:

\[
dose = DI + f \times \left( \frac{CI}{AGE \times BW} \right) + \left(1 - f\right) \times (WCR \times LE)
\]

<table>
<thead>
<tr>
<th>Variable (units)</th>
<th>Mean</th>
<th>SD</th>
<th>Justification for Value and Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI – Lifetime Cumulative Intake (mg)</td>
<td></td>
<td></td>
<td>Estimated from lifetime cumulative intake (mg) ranges provided by authors.</td>
</tr>
<tr>
<td>f – ADWE/AAD.</td>
<td>1</td>
<td>--</td>
<td>Assumed to be 1 when iAs well levels were not mitigated (restricted to be &lt;= 1 for MC analysis).</td>
</tr>
<tr>
<td>ADWE – Assumed average duration of well exposure (yrs)</td>
<td>66</td>
<td>--</td>
<td>Assumed to be lifetime when iAs levels in wells of the area studied were not broadly mitigated and author CI (mg) estimates are for lifetime intake.</td>
</tr>
<tr>
<td>AAD – Average age at diagnosis (yrs)</td>
<td>66</td>
<td>--</td>
<td>Estimated from reported age frequencies for cases.</td>
</tr>
<tr>
<td>LE – Low water exposure (µg/L)</td>
<td>1.5</td>
<td>4</td>
<td>Mean US county iAs USGS measurements (Mendez et al. 2016).</td>
</tr>
<tr>
<td>WCR – Water consumption rate (ml/kg-day)</td>
<td>34.5</td>
<td>23.2</td>
<td>Estimated from reported rates and confidence intervals for all age groups given in EPA Exposure Factors Handbook. Lognormal distribution assumed for MC analysis.</td>
</tr>
<tr>
<td>DI – Dietary intake (µg/kg-day)</td>
<td>0.65</td>
<td>0.33</td>
<td>US dietary intake estimate (Xue, 2010). Assumed to be lognormally distributed for MC analysis.</td>
</tr>
<tr>
<td>BW – Body weight (kg)</td>
<td>42</td>
<td>3.33</td>
<td>From EPA Exposure Factors Handbook. Assumed to be lognormally distributed with low BW of 38kg.</td>
</tr>
<tr>
<td>AGE - Average age of study participants (yrs)</td>
<td></td>
<td></td>
<td>Estimated from reported age frequencies for all study participants. Assumed to be normally distributed for MCMC.</td>
</tr>
</tbody>
</table>
Bayesian Meta-Regression: Dose Conversions

• Factors for conversions were treated as distributions and estimates were generated for each subject within a dose-group

• Individual estimates of intake dose were then calculated for the MLE, low-, and high-exposure estimates and averaged

• Markov Chain Monte Carlo (MCMC) methods were then used to characterize and account for study/population-specific interindividual differences in factors (e.g., water consumption rates, body weights, dietary intake) that influence the conversion of exposure to µg/kg-day intake dose estimates
  – Individual group dose estimations were repeated 1,000 times to derive a distribution of dose values
  – The median for the MLE, 5th percentile for the “low”, and 95th percentile for the “high” dose values were then used in the Bayesian meta-regression
Bayesian Meta-Regression: Logistic Modeling

• Purpose is to combine data from multiple cohort and case-control studies

• EPA assumes the prospective likelihood is given by a logistic equation, with arsenic intake, $X$, as the explanatory variable

$$\text{logit}\{\Pr(D = 1|X)\} = \alpha^* + \beta(X)$$

• Allows estimation of prospective likelihood from case-control studies (which are by definition retrospective) and thus inclusion with cohort studies in meta-regression

• Logistic model flexible enough to represent nonlinear “sigmoidal” dose-response relationships expected at a population level for toxicants with widely differing individual sensitivities (e.g., due to human heterogeneity and/or multiple iAs MOAs) (NRC, 2006, 2009, 2014).

• This type of sigmoidal shape is possible at the population level “even if the dose-response relationship has a clear threshold in a single rodent species or cell line” (NRC, 2014)
Bayesian Meta-Regression: Use of MOA Information

- For ubiquitous toxicants such as iAs, where multiple studies exist that reflect the biological diversity & low levels of exposures in U.S. populations:
  - “...extrapolation below the level of observations ... is less important than for compounds for which evidence is derived from animal bioassays or occupational (high dose) epidemiology” (NRC, 2009)
  - “it is impossible to determine the correct functional form of the population dose-response curve solely from mechanistic information derived from animal studies and in vitro systems.” (NRC, 2014)
  - “the existence of individual dose-response thresholds does not necessarily imply the existence of a population dose-response threshold” given individual differences in the threshold due to environmental or genetic factors (NRC, 2006)

\[
\begin{align*}
\pi_i &= 0, \text{if } d < \theta_i \\
\pi_i &= 1 - \exp[-\beta(d - \theta_i)], \quad \text{if } d > \theta_i
\end{align*}
\]

If \( \Theta \) has a logit distribution

Individual dose-response curve

Logistic population dose-response curve
Bayesian Meta-Regression: Logistic Modeling

- Hierarchical model assumes study-specific $\beta$ values are normally distributed around mean = $\beta_{\text{mean}}$ with standard deviation = $\beta_{\text{sigma}}$
- $\beta_{\text{mean}}$ and $\beta_{\text{sigma}}$ are both assigned priors and updated

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prior Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta(i)^1$</td>
<td>Normal ($\beta_{\text{mean}}, \beta_{\text{sigma}}$)</td>
</tr>
<tr>
<td>$\beta_{\text{mean}}$</td>
<td>Gamma (a=0.52, b=0.89)</td>
</tr>
<tr>
<td>$\beta_{\text{sigma}}$</td>
<td>Half-Cauchy (scale=5)</td>
</tr>
</tbody>
</table>

$^1 \beta(i)$ is the dose coefficient for data set $i$.

- Hierarchical structure of analysis explicitly accounts for heterogeneity across studies
  - A random-effects model is used, where no “true” association between iAs exposure and disease is assumed (i.e., fixed effects), but rather a distribution of effects is estimated, reflecting that individual studies can be considered to be random samples from the true population
  - The magnitude of heterogeneity across studies can be characterized by evaluation of the coefficient of variation for the pooled estimate of effect
Bayesian Meta-Regression: Gamma Prior for Pooled Slope

• The Gamma distribution for $\beta_{\text{mean}}$ reflects the determination that iAs is causally associated with bladder cancer (i.e., prior does not allow negative slopes)

• Prior judgment is that exposure to 1 µg/kg-day iAs (~14-fold above average background exposure) is highly likely to result in $1.0001 < \text{OR} < 20$

• 1st and 99th percentiles of Gamma distribution set equal to ln(1.0001) and ln(20)

• Gamma distribution is right skewed
  – it 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
Bayesian Meta-Regression: Modeling Results

Summary of Bayesian Meta-Regression Outputs, Including Parameters Important for Risk Estimation in the Target Population

<table>
<thead>
<tr>
<th>β Parameter</th>
<th>Mean</th>
<th>SE of the Mean</th>
<th>SD</th>
<th>Percentiles</th>
<th>Effective Sample Size</th>
<th>Rhat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.5%</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>β_mean</td>
<td>0.2018</td>
<td>0.002</td>
<td>0.1775</td>
<td>0.0008</td>
<td>0.0572</td>
<td>0.1636</td>
</tr>
<tr>
<td>β_sigma</td>
<td>0.6232</td>
<td>0.0026</td>
<td>0.2315</td>
<td>0.3198</td>
<td>0.4679</td>
<td>0.5767</td>
</tr>
<tr>
<td>Chen et al. (2010)</td>
<td>0.0879</td>
<td>0.0002</td>
<td>0.0212</td>
<td>0.0434</td>
<td>0.0742</td>
<td>0.0885</td>
</tr>
<tr>
<td>Sawada et al. (2013) - males</td>
<td>0.2968</td>
<td>0.0017</td>
<td>0.1686</td>
<td>-0.0322</td>
<td>0.1823</td>
<td>0.2972</td>
</tr>
<tr>
<td>Sawada et al. (2013) - females</td>
<td>0.1455</td>
<td>0.0026</td>
<td>0.2497</td>
<td>-0.3659</td>
<td>-0.0196</td>
<td>0.1545</td>
</tr>
<tr>
<td>Steinmaus et al. (2013)</td>
<td>0.1774</td>
<td>0.0003</td>
<td>0.0246</td>
<td>0.1303</td>
<td>0.1607</td>
<td>0.1771</td>
</tr>
<tr>
<td>Wu et al. (2013)</td>
<td>1.349</td>
<td>0.0023</td>
<td>0.2164</td>
<td>0.9246</td>
<td>1.2018</td>
<td>1.3461</td>
</tr>
<tr>
<td>Bates et al. (1995)</td>
<td>0.2135</td>
<td>0.0075</td>
<td>0.6862</td>
<td>-1.1259</td>
<td>-0.1985</td>
<td>0.1969</td>
</tr>
<tr>
<td>Steinmaus et al. (2003)</td>
<td>-0.1389</td>
<td>0.0021</td>
<td>0.2004</td>
<td>-0.5335</td>
<td>-0.2717</td>
<td>-0.1366</td>
</tr>
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<td>Bates et al. (2004)</td>
<td>-0.1787</td>
<td>0.0009</td>
<td>0.0875</td>
<td>-0.3562</td>
<td>-0.2359</td>
<td>-0.1764</td>
</tr>
<tr>
<td>Meliker et al. (2010)</td>
<td>0.1869</td>
<td>0.0058</td>
<td>0.5348</td>
<td>-0.8819</td>
<td>-0.1539</td>
<td>0.181</td>
</tr>
</tbody>
</table>

Summaries of Stan model runs: 4 chains were run, each with 10000 iterations; the “warm-up” (number of iterations before results were tabulated) was 5000; remaining 5000 iterations per chain were thinned by 2 (every other iteration was dropped). Therefore, the total number of post-warmup draws = 10,000.

Effective samples is the effective sample size used to estimate the parameters and Rhat is the potential scale reduction factor on split chains, a measure of convergence (at convergence Rhat = 1). Effective sample sizes are large enough and the convergence criterion is satisfied for all parameters.
Bayesian Meta-Regression: Lifetable Analysis

- Lifetable analysis methods, including consideration of background exposure to iAs used to estimate extra risk of disease in the target population (i.e., general US population)
  - Background rates of disease assumed to represent zero extra risk from iAs
  - A mean background iAs dose of 0.071 µg/kg-day assumed: 0.05 µg/kg-day from dietary exposures, 0.021 µg/kg-day from drinking water, and 0 µg/kg-day from inhalation

Pooled Meta-Regression Estimates of Extra Lifetime Bladder Cancer Incidence Risk at Various Doses (per 10,000) and Drinking Water Exposures using MLE Dose Estimates

<table>
<thead>
<tr>
<th>Average Daily Arsenic Dose (µg/kg-day)</th>
<th>0.071</th>
<th>0.12</th>
<th>0.19</th>
<th>0.26</th>
<th>0.33</th>
<th>0.75</th>
<th>1.45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Daily Arsenic Drinking Water Concentration (µg/L)</td>
<td>1.5</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Extra Lifetime Risk*</td>
<td>0</td>
<td>2.0 (0.01 - 6.3)</td>
<td>4.8 (0.02 - 16)</td>
<td>7.7 (0.03 - 25)</td>
<td>11 (0.04 - 35)</td>
<td>29 (0.1 - 106)</td>
<td>64 (0.2 - 271)</td>
</tr>
</tbody>
</table>

*These extra risk estimates assume a mean U.S. background rate for bladder cancer of 2%. Predicted additional cases in a cohort of size 10,000 for extra risk, x, when the background rate is b, would be 10,000*(1-b)*x. Thus, additional cases of bladder cancer at an extra risk of 2/10,000 (0.02%) would be 10,000*(1-0.02%)*0.02% = 1.96.

*Mean, 2.5% and 97.5% of Bayesian posterior slope distributions were used with US lifetables to estimate mean and credible intervals for extra risk above average background risks.
Bayesian Meta-Regression: Sensitivity Analyses

- Multiple sensitivity analyses indicate final modeling results not overly sensitive to modeling decisions

- Dose conversions/intake estimates: \( \beta_{\text{mean}} \) reasonably similar between high, MLE, and low intake estimates (0.19, 0.2018, 0.21)

- Incorporation of background iAs inhalation component only decreased extra risk estimates 4%-7%

- Leave-one-out analysis showed no study had undue influence on final results; leaving out Wu et al. (2013) reduced extra risk 3-fold

- Assumption of different Gamma priors didn’t result in large differences in posterior distributions
  - Alternative priors with different 1st percentiles resulted in greatest differences
Bayesian Meta-Regression: Fractional Logistic Model

• Using a fractional logistic model can allow for J-shaped dose-response curves (i.e., negative slopes in the low dose region); possibly more in line with iAs toxicological effects and/or MOAs.

• A case study using bladder cancer data has shown that monotonically increasing dose-response curves are preferred over low-dose negative curves.

• Even for dose-response curves with low-dose negative slopes, slopes are monotonically increasing above iAs background exposure levels.

![Figure 2. Middle Dose Range for Best Model](image1)

![Figure 16. Middle Dose Range for 2nd Best Model](image2)
iAs Dose-Response Methods: Summary

• EPA’s proposed approach for modeling epidemiologic data for inorganic arsenic improves upon previous approaches:
  – Screening analysis systematically identified health endpoints with databases suitable for further dose-response
  – Uses a multi-study meta-regression approach and thereby avoids issues relating to selecting a single study to base analysis on
  – Combines evidence from case-control and cohort studies
  – Converts disparate measures of exposure into a single metric to allow for incorporation of as many studies as possible
  – Logistic model flexible enough to fit many dose-response curves, including threshold-like curves
  – Possibility of non-monotonic dose-responses investigated via fractional logistic model
  – Extrapolates risk to population of interest – US general population
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• Kan Shao (Indiana University)
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