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 determination.
- 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.

Prioritizing Health Outcomes

- NRC prioritized health outcomes into three tiers (NRC, 2013): Tier 1 (evidence of a causal association determined by other agencies and/or in published reviews); Tier 2 (other priority outcomes); Tier 3 (other endpoints to consider).
- EPA considered the strength of the epidemiological evidence for each health outcome.
- Relying on conclusions from assessments conducted by other health agencies (ATSDR, LARC, WHO, NTP) or
- Conducting new systematic reviews of the existing literature.
- Epidemiology studies will be the focus of the assessment, consistent with prior NRC input.
- Animals are not as sensitive to arsenic compared to humans due to interspecies metabolism differences.
- 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 EPA, NRC evaluated mechanistic evidence (Appendix A) and conducted M&G analyses to assess utility for reducing uncertainties in dose-response analysis (Poster 2). The analyses did not identify a clear relationship between the mechanistic evidence given the abundance of human studies.

Evidence Profile Table (diabetes example)

- An evidence profile table summarizes evidence integration conclusions.
- Approach supported in the National Academy of Sciences (NAS) review of implementation of systematic reviews in the IRIS Program (NAS, 2018).
- Tables are organized by study design (prioritizing designs with higher confidence studies) because studies of similar design generally possessed the same parameters that increased or decreased the confidence in the evidence base.

Study Evaluation for Epidemiological Studies

- Risk of bias (RoB) was evaluated using questions adapted from OHAT (NTP, 2013) which considers study design, selection bias, confounding, exposure misclassification, outcome measures, and selective reporting.
- Roll was assessed for each study question using a four-point scale that includes ratings of definitely low bias, probably low bias, probably high bias, and definitely high bias.

Strength of Evidence Judgements

- Robust and Moderate describe epidemiological evidence that supports a hazard. These terms are differentiated by the quantity and quality of information available to rule out alternative explanations for the results.
- Slight evidence includes situations in which there is no epidemiological evidence available for that evidence stream or the evidence is inconsistent and of low confidence, and cannot provide a basis for making a conclusion in either direction.
- Compelling evidence of no effect represents a situation where extensive epidemiological evidence across a range of populations and exposures identified no association. This scenario is rare.
- Both slight and indeterminate represent situations where the epidemiological evidence is insufficient to support a hazard, as uncertainty is too large.
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 Mode 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 frameworks to address:
  - Human relevance of animal tumor responses: MOA analyses are usually applied for chemicals with insufficient human data. iAs is a chemical with a large amount of epidemiological evidence. Hence, iAs 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 organismal tissues to culminate in an adverse outcome (AO). 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, principally derived from epidemiological, in vivo, and in vitro studies that analyzed effects of iAs or its metabolites (e.g., monomethylarsonous acid (MMAIII) and dimethylarsonous 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 oncoproteins, as well as activation of the ErbB2 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 arsensic-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 ErbB2 receptor and lead to cell proliferation, angiogenesis and metastasis. Rac 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://hero.epa.gov/hero/index.cfm/project/page/project_id/2213).
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. 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</td>
<td>Total: 904</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Male: 4,676</td>
<td>Male: 368</td>
</tr>
<tr>
<td>Height (m)</td>
<td>Female: 6,562</td>
<td>Female: 536</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Median: 36</td>
<td>Median: 61</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Median: 1.54</td>
<td>Median: 1.66</td>
</tr>
<tr>
<td>As water conc. (µg/L)</td>
<td>Median: 2.850</td>
<td>Median: 1.865</td>
</tr>
<tr>
<td>Total daily water consumption (mL)</td>
<td>Median: 25,260</td>
<td>Median: 4,490</td>
</tr>
<tr>
<td>Urinary As conc. (µg/L)</td>
<td>Median: 1.54</td>
<td>Median: 1.865</td>
</tr>
<tr>
<td>Creatinine-adjusted urinary As conc. (µg/g)</td>
<td>Median: 198.40</td>
<td>Median: 198.40</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 concentrations.

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:
    \[
    V = \frac{BWMULT \times \text{Body weight (70 kg)}}{122}
    \]
  - Urinary excretion rate, L/hr:
    \[
    U_{iAs,\text{urinary}} = 0.65 \times BW \times BWMULT
    \]
  - Creatinine excretion rate based on subject specific body weight:
    \[
    \text{MCR} = \beta_0 + \beta_1 \times \text{sex} + \beta_2 \times \text{BMI} + \beta_3 \times \text{age} + \beta_4 \times \text{age}^2
    \] (Ogus 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>As levels in food (Bangladesh)</td>
<td>Male: 153.0</td>
<td>Rahman et al. (2011)</td>
</tr>
<tr>
<td>As levels in food (Bangladesh)</td>
<td>Female: 146.88</td>
<td>Rahman et al. (2011)</td>
</tr>
<tr>
<td>As levels in food (U.S.)</td>
<td>173</td>
<td>Rahman et al. (2009)</td>
</tr>
<tr>
<td>As levels in food (Bangladesh)</td>
<td>150 (10-500)</td>
<td>Rahman et al. (2009)</td>
</tr>
<tr>
<td>As levels in food (Bangladesh)</td>
<td>153 (74-301)</td>
<td>Rahman et al. (2011)</td>
</tr>
<tr>
<td>As levels in food (Bangladesh)</td>
<td>12.1 (1.3-22.8)</td>
<td>Khan et al. (2010)</td>
</tr>
<tr>
<td>As levels in food (Bangladesh)</td>
<td>15 (0-136)</td>
<td>Khan et al. (2012)</td>
</tr>
<tr>
<td>As levels in food (U.S.)</td>
<td>3.34 (26.4-89)</td>
<td>Karrino-Spencer et al. (2014)</td>
</tr>
<tr>
<td>As levels in food (U.S.)</td>
<td>0.04 (0.03-0.05)</td>
<td>Tai and Bolger (1999)</td>
</tr>
</tbody>
</table>

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://archive.epa.gov/hero/index/indexes/prj/proj/pagpjdl/2211)
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 Davis1, Kan Shao1, Cara Henning1, William Mendez Jr.1, Janice S. Lee1, Ila Cote1, Ingrid Drewes2, Jeff Gift4
1ICF International, 2EPA, Office of Research and Development, National Center for Environmental Assessment – Cincinnati, 3Indiana University, 4EPA, Office of Research and Development, National Center for Environmental Assessment – Research Triangle Park.

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 epidemiologic 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 (RRE). The RRE is divided by the 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-performed trend tests.
- **Dose pre-processing:** Adjusting 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). Following of RRBs dividing RREs, values by estimates of U.S. background (RBE). Exposure units for U.S. background estimates differ to match RRE units, but are based on similar water and dietary intake assumptions (see Table 2).

Selecting 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 RR 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.

Exposure Response Modeling

- **Case-control studies:** Adjusted case and control numbers were fit by a logistic model: f(dose) = 1/(1 + exp(-a × dose)). Use of a logistic model allows for analysis of case-control studies with prospective follow-up, both having the same biomimetic-based likelihood contributions from their exposure groups (Prentice and Pyke, 1979).
- **Cohort studies:** counts of cases in each exposure group follow a Poisson distribution: Ωi = Poisson(ξi × f(dose)) where ξi and Ωi are observed cases and expected cases in the ith exposure group, respectively. Seven continuous dose-response models used for f(xi), including the linear model, power model, power-2d polynomial 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 x2 p-values, estimates of model parameters, and predicted risks (ORs for 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 epidemiologic 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., J. Allen Davis, Kan Shao, Janice S. Lee, Ila Cote, Ingrid Druwe, Jeff Gill
11 ICF, 12 EPA, Office of Research and Development, National Center for Environmental Assessment – Cincinnati; 13 Indiana University, 14 EPA, Office of Research and Development, National Center for Environmental Assessment – Research Triangle Park.

Results
- In the range of the data, similar mean absolute risks, 2.5th and 97.5th percentiles are derived from unconstrained and constrained 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

Figure 1. Summary of dose-response methodology for bladder and lung cancer. Note: BIC = Bayesian Information Criterion

Figure 2. Predicted lifetime probability of bladder cancer versus all-doses (upper plot) and low doses (lower plot) using constrained model averaging. The 95% confidence intervals are shown with gray shaded areas for iAs intake from adjusted relative risks reported in Chen et al. (2010a).

Figure 3. Predicted lifetime probability of lung cancer versus all-doses (upper plot) and low doses (lower plot) using constrained model averaging. The 95% confidence intervals are shown with gray shaded areas for iAs intake from adjusted relative risks reported in Chen et al. (2010b).

Figure 4. Predicted lifetime excess risk of bladder cancer from Chen et al. (2010a) using constrained and unconstrained model averaging.

Figure 5. Predicted lifetime excess risk of lung cancer from Chen et al. (2010b) using constrained and unconstrained model averaging.
Bayesian Hierarchical Meta-Regression of Epidemiologic Studies: Dose and Response Pre-Analysis (Poster 6)

Bruce Allen¹, Jeff Gift², Kan Sha³, Kevin Hobbit⁴, William Mendez Jr.⁵, Janice S. Lee⁶, Ila Cote⁷, Ingrid Druwe⁸, J. Allen Davis⁵

¹ Independent Consultant, ² EPA, Office of Research and Development, National Center for Environmental Assessment – Research Triangle Park, ³ Indiana University, ⁴ ICF International, ⁵ EPA, Office of Research and Development, National Center for Environmental Assessment – Cincinnati

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 IRIS assessment of inorganic arsenic (NRC, 2013).
- This poster is the first of two (see also Poster 7) 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 pre-analysis steps described here employ methods to:

- address how doses are commonly reported in epidemiological studies;
- calculate a common dose metric across all epidemiological studies;
- calculate “effective counts” from reported effect measures in human studies to provide counts used in subsequent dose-response analyses to account for confounders. (see section on “Calculating Effective Counts”)

Group Means and Uncertainty

- For dose-response analysis, a point estimate of dose is needed for each dose group, but epidemiological data is often interval censored with an open ended reported for the high dose group (e.g., > 10,000 µg/L-yrs).
- We assumed a log-normal distribution for exposures in the population of interest and calculated μ and σ as the log-scale mean and standard deviation using likelihood maximization.
- Given μ and σ, the mean within a exposure interval [(μ₁, μ₂)]:

  \[ \text{mean}(g) = e^{(μ)^2/2} × θ(μ)(g) - θ(μ)(g) - μ(θ(μ)(g) - θ(μ)(g)) \]

  where μ(θ) = (θ(μ₂) - θ(μ₁)) / (ln(μ₂) - ln(μ₁)) and θ is the cumulative distribution function for the standard normal distribution

- Group-specific means computed via this equation are used as the “MLE” doses

- “High-end” and “low-end” doses were also estimated maximizing or minimizing the mean for the highest exposure group

- These “high-end” and “low-end” estimates correspond to a chi-squared-based 95% confidence interval around the maximum likelihood (MLE) estimate for the highest exposure group

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-year), etc.
- For this analysis, we converted all reported studies into iAs daily intakes (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:

  \[ \text{dose} = DI = f (WC × WE) + (1 − f) × (WC × LE) \]

- Where DI = daily intake (µg/L), f = fraction of lifetime exposed to the study reported iAs levels (WE), WC = 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), and 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 – a distribution of values was assumed over the individuals in the study to address interindividual variability and dose-group values were then averaged.

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 epidemiologic studies in the context of dose-response analyses, including:
  - Reporting of interval-censored exposure data;
  - Use of divergent measures of iAs exposure across studies;
  - Only reporting adjusted effect measures.

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

References

Bayesian Hierarchical Meta-Regression of Epidemiologic Studies: Dose-Response Modeling and Target Population Predictions (Poster 7)
Bruce Allen, Jeff Gifford, Kan Shaw, Kevin Hobbs, William Mendez Jr, Janice S. Lee, Ila Coe, Ingrid Druwe, J. Allen Davis
1 Independent Consultant, 2 EPA, Office of Research and Development, National Center for Environmental Assessment – Research Triangle Park, 3 Indiana University, 4 ICF, 5 EPA, Office of Research and Development, National Center for Environmental Assessment – Cincinnati

Purpose and Scope

- National Research Council (NRC) has recommended the application of a flexible logistic model to cohort and case studies, 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 ICRP 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 $X_1, ..., X_p$.

$$
\text{logit}(P(Y = 1|X)) = \alpha + \beta^T x
$$

- 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: $\beta$ (slope parameter) and $\lambda$ (true proportion of doses in a dose-level).
    - Cohort studies: $\mu$ (expected number of cases in the referent group).
    - Calculated the parameter $\alpha$ or $\alpha^*$.
    - 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 inhalation) (Xue et al., 2010; Mendez et al., 2017).

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.

- The gamma distribution for $\mu_{mean}$ reflects determination that iAs is causally associated with the development of bladder cancer.
- Prior judgement that exposure to 1 µg/kg-day (~40-fold average background exposure) is highly likely to result in 1.0001 < OR < 20.
- 1% and 99% percentiles of gamma distribution ($f(x) = \text{exp}(\mu_{mean})x^{-\mu_{mean}}/\Gamma(\mu_{mean})$) set to equal $\ln(1.0001)$ 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 $\beta$ 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.

For the purpose of dose-response modeling, the $\alpha^*$ parameter was assumed to be independent for each dataset.
- Methods also assume study-specific $\beta$ values that are normally distributed around a mean of $\beta_{mean}$, with standard deviation $\beta_{sigma}$. Both $\beta_{mean}$ and $\beta_{sigma}$ were assigned priors and updated (Table 2).

The sensitivity of the hierarchical model and its outputs were examined regarding four sources of uncertainty:
- Characterization of exposure levels used in the modeling: this was addressed using the "high" and "low" dose estimates discussed in Poster 6; using different estimates of dose did not result in pooled $\beta_{mean}$ that differed greatly (0.19, 0.20, or 0.21).
- Choice of datasets: a leave-one-out analysis was performed which showed that no one study had a disproportionately large influence on the final pooled $\beta_{mean}$ value (Table 5).
- Zero background inhalation assumption: assuming background inhalation exposures of 0.2 to 0.6 µg/day decreased mean extra risk estimates from 4.88 × 10^-4 µg/kg-day (Table 5, no data set excluded) to 4.68 to 4.51 × 10^-4 µg/kg-day.
- The consideration of alternative prior distributions for $\beta_{mean}$: alternative distributions that considered different 1% or 99% percentile values did not overly influence final risk estimates (Table 6).

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, $logit(p(x)) = \alpha^* + \beta_1 x^{1/3} + \beta_2 x^{2/3}$, 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