Systematic Review Methods and Hazard Characterization for the Updated Problem Formulation and Protocol for the Inorganic Arsenic (iAs) IRIS Assessment (Poster 1)

United States Environmental Protection Agency

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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.

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 strength of the epidemiological evidence for hazard by
  - Relying on conclusions from assessments conducted by other health agencies (ATSDR, IARC, 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 epidemiology 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 MOA analyses to assess utility for reducing uncertainties in dose-response analysis (Poster 2). The analyses did not identify a clear application of the mechanistic evidence given the abundance of human studies.

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 measures, outcome measures, and selective reporting.
- RoB 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 some epidemiological evidence that supports a hazard, but there are substantial uncertainties in the data and a conclusion of *Moderate* does not apply.
- *Indeterminate* describes a situation where there are no epidemiological studies 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 if insufficient to support a hazard, as uncertainty is too large.

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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 review 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 factors that increased or decreased confidence in the evidence base.

	Studies (by design) and study confidence (i.e. based on risk of bias and sensitivity considerations[2])	Factors that increase confidence	Factors that decrease confidence	Summary of findings	Strength of evidence judgment
Cohort Studies	Studies were well-designed with well-characterized exposures, large number of subjects with long duration exposures, sufficient follow-up for latency, and used iterative and scientifically rigorous analyses; thus, they were generally interpreted with *high* or *medium* confidence Taiwan:Tseng et al. (2000), Chen et al. (2012), Hsu et al. (2013); United States: Ettinger et al. (2009); Denmark: Bräuner et al. (2014); Italy: D'Ippoliti et al., (2015)	• **Consistent** positive associations observed in populations across 3 continents, primarily at > 10 µg/kg-day • **Exposure-dependent** associations observed that establish **temporality** in studies in which prolonged arsenic exposure was associated with diabetes • **Low risk of bias** across the set of studies, due in part to well-characterized exposures • Exposure-response gradient observed across studies	• **Indirectness** with evaluation of metabolic syndrome and insulin sensitivity observed in one study • Small sample size in one study	The set of well-conducted studies report generally consistent, positive associations across diverse populations > 10 µg/kg-day , with some evidence for exposure-dependent changes within and across studies.	⊕⊕⊕ ROBUST Supported primarily by consistent and reliable evidence from cohort and case-control studies that rules out chance, confounding, and other biases with reasonable confidence. This evidence is based on associations generally observed above 10 µg/kg-day arsenic intake in general population studies across the world. Additional support is provided by consistent associations in both cross-sectional and ecological studies, although some uncertainties remain; this coherence across diverse study designs further strengthens the judgment.
Case-control Studies	Studies were generally well-designed with well-characterized exposures, included large population with adequate number of cases, precise case definition, and used iterative and scientifically rigorous analyses; thus, they were generally interpreted with *high* or *medium* confidence United States: James et al. (2013), Kim et al. (2013); Bangladesh: Pan et al. (2013b), Nizam et al. (2013); Mexico: Coronado-González et al. (2007);	• **Consistent** positive associations observed in populations across 3 continents, primarily at > 10 µg/kg-day	• Not all studies included individual-level exposure data	The set of well-conducted studies report generally consistent, positive associations across diverse populations at > 10 µg/kg-day, with some evidence for exposure-dependent changes	
Cross-sectional Studies	Studies were generally well-designed, with well-characterized exposures; however, some were limited by small sample size, interference of organic arsenicals in classifying exposure, or deficiency identifying cases, resulting in general interpretations of *medium* confidence United States: Gribble et al. (2012), Navas-Acien et al. (2008), Navas-Acien et al. (2009), Steinmaus et al. (2009); Korea: Rhee et al. (2013); Bangladesh: Islam et al. (2012); Mexico: Del Razo et al. (2011); Taiwan: Chen et al. (2011), Lai et al. (1994); South Korea: Kim and Lee (2011); China: Li et al. (2013), Feng et al. (2015); Canada: Feseke et al. (2015)	• **Consistent** positive associations observed in diverse populations across the world, although • **Exposure-dependent** associations observed across studies	• Series of studies conducted using NHANES data limited by authors' inability to interpret organic arsenic levels derived from seafood intake. Each author subsequently addressed it in their own way with differing results. • **Imprecision**: although consistent increases in odds ratios (or similar measures) were generally observed across studies, several did not find statistically significant increases, introducing uncertainty	A number of recent cross-sectional studies of populations across the world consistently reported a positive relationship between arsenic exposure and diabetes	
Ecological studies	Studies were limited to analyses in Taiwan and one study in United States and possessed some limitations in the quantitative characterization of exposure, leading to general interpretations of *medium* confidence Taiwan: Chiu et al. (2006); Tsai et al. (1999); Wang et al. (2003); United States: Meliker et al. (2007)	• **Consistent** positive associations observed	• Some **concern for risk of bias** across the set of studies, due largely to deficiencies in exposure assessment and inability to account for potential confounding from individual-level variables • Limited number of studies, primarily only in one population	Few ecological studies with majority looking at diabetes mortality that provide consistent positive associations.	

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

Characterization of Hazard

Health outcome	NRC Tier	EPA strength-of-evidence judgement of human evidence of a causal association
NRC Tiers: Tier 1: Evidence of causality; Tier 2: Other priority outcome; Tier 3: Other endpoints to consider		
Lung cancer	Tier 1	Robust. Based on NRC Tier 1 and conclusions of "carcinogenic" for lung cancer from other assessments (ATSDR, 2016; NTP, 2016; IARC, 2012; WHO, 2011a, b; ATSDR, 2007; IARC, 2004b).
Bladder cancer	Tier 1	Robust. Based on NRC Tier 1 and conclusions of "carcinogenic" for bladder cancer from other assessments (ATSDR, 2016; NTP, 2016; IARC, 2012; WHO, 2011a, b; ATSDR, 2007; IARC, 2004b).
Skin cancer	Tier 1	Robust. Based on 1995 EPA conclusion of "known carcinogen" based on skin cancer (U.S. EPA, 1995), NRC Tier 1, and conclusions of "carcinogenic" for skin cancer based on other assessments (ATSDR, 2016; NTP, 2016; IARC, 2012; WHO, 2011a, b; ATSDR, 2007).
Ischemic heart disease	Tier 1	Robust. Based on systematic review conducted by EPA on diseases of the circulatory system (ischemic heart disease and hypertension/stroke), which is similar to associations noted in other assessments (ATSDR, 2016; WHO, 2011a, b; ATSDR, 2007) and meta-analysis[a] (Moon et al., 2017a, b; Moon et al., 2013).
Skin lesions	Tier 1	Robust. Based on NRC Tier 1 and conclusions from other assessments (ATSDR, 2016; WHO, 2011a, b; ATSDR, 2007).
Diabetes	Tier 2	Robust. Based on systematic review conducted by EPA, which is similar to associations noted in ATSDR (2016), an expert review conducted as part of an NTP workshop (Maull et al., 2012; Thayer et al., 2012) and a meta-analysis[a] (Wang et al., 2014).
Pregnancy outcomes (fetal and infant morbidity)	Tier 2	Robust. Based on systematic review conducted by EPA on pregnancy and birth outcomes (fetal growth, prematurity, and infant growth in the first 5 yr of life), which is similar to associations noted in ATSDR (2016) and meta-analysis[a] by Quansah et al. (2015).
Pregnancy outcomes (fetal loss, stillbirth, and neonatal mortality)	Tier 3	Robust. Based on systematic review conducted by EPA on pregnancy and birth outcomes (fetal loss and infant mortality in the first 5 yr of life), which is similar to associations noted in ATSDR (2016), review by Bloom et al. (2010), and a meta-analysis[a] by Quansah et al. (2015).
Hypertension/ stroke[b]	Tier 3	Robust. Based on systematic review conducted by EPA on diseases of the circulatory system (including ischemic heart disease and hypertension/stroke), which is similar to associations noted in ATSDR (2016), review by Abhyankar et al. (2012), and meta-analysis[a] (Moon et al., 2017a, b; Moon et al., 2013).
Renal cancer	Tier 2	Moderate. Based on systematic review conducted by EPA, which is similar to associations noted in IARC (2012, 2004b) and ATSDR (2016).
Nonmalignant respiratory disease	Tier 2	Moderate. Based on systematic review conducted by EPA, which is similar to associations noted in ATSDR (2016).
Neurodevelopmental toxicity	Tier 2	Moderate. Based on systematic review conducted by EPA, which is similar to associations noted in ATSDR (2016).
Immune effects	Tier 2	Moderate. Based on systematic review conducted by EPA, which is similar to associations noted in ATSDR (2016).
Liver cancer	Tier 3	Moderate. Based on systematic review conducted by EPA, which is similar to associations noted in IARC (2012, 2004b).
Health outcomes considered to have slight evidence		
Prostate cancer	Tier 2	Slight. Based on systematic review conducted by EPA, which is similar to associations noted in IARC (2012, 2004b).
Pancreatic cancer	Tier 3	Slight. Based on systematic review conducted by EPA and associations noted in IARC (2004b).
Renal disease	Tier 3	Slight. Based on systematic review conducted by EPA.

[a]In cases of Tier 2 or 3 health outcomes, the results and conclusions of systematic reviews conducted by EPA formed the primary rationale for identifying a health outcome as having robust, moderate, or slight strength of evidence. For health outcomes that also had meta-analyses conducted by outside groups, the meta-analyses are considered supplemental information. Relevant primary studies included in the meta-analyses were considered in the systematic reviews conducted by EPA.

[b]These outcomes considered along with the larger ischemic heart disease database; the strength of the epidemiologic database was based on the full set of all studies for all endpoints.

Note: The results of the systematic reviews and hazard analyses will be included in the assessment and subject to external peer review (or cited, if published in the peer review literature).

Conclusions

- Health outcomes with robust or moderate evidence were prioritized for dose-response
- Prostate cancer, pancreatic cancer, and renal disease 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

Building an Adverse Outcome Pathway Network for Arsenic-Induced Bladder Cancer (Poster 2)

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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, *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 principally 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 carcinoma **(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).**

Adverse Outcome Pathway Network (AOPn) Development

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 oncogenes, 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 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 ErbB2 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).**

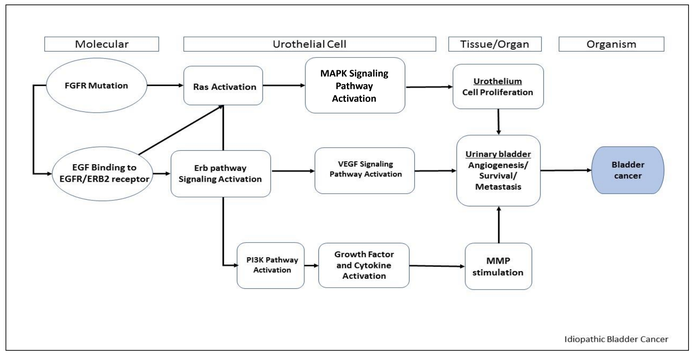

Figure 1: AOPn for idiopathic bladder cancer in humans.

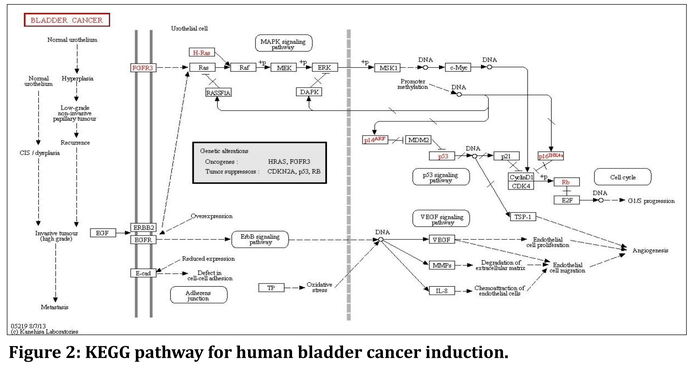

Figure 2: KEGG pathway for human bladder cancer induction.

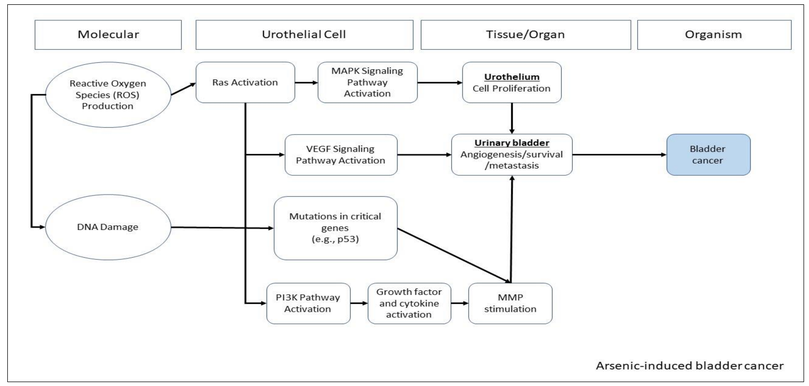

Figure 3: Postulated AOPn for iAs-induced bladder cancer in humans.

Table 1. Representative evidence and references where iAs has been shown to affect the AOPn in bladder.

Key Event	Evidence	References
EGFR, ErbB2 activation	• Upregulation of EGFR in human urothelial cell line (UROtsa) following chronic exposure to iAs metabolite MMA(III) (50nM)	• Eblin et al., 2007
	• Upregulation of EGFR in vivo	• Simeonova et al 2002 • Simeonova and Luster 2002
Oxidative stress, ROS generation; imbalance of oxidative signaling	• Activation of AP-1, NFkB in vitro	• Felix et al., 2005 • Barchowsky et al., 1996 • Kaltreider et al., 1999 • Wijeweera et al., 2001
	• ROS generation from iAs & its metabolites (eg., DMA) lead to oxidative stress in vivo	• Yamanaka et al 1990, • Yamanaka et al 1989
	• ROS generation from iAs & its metabolites (eg., DMA) lead to oxidative stress in vitro	• Liu et al., 2001, • Hei et al 1998, • Wang et al 2001
Ras signaling; MAPK activation	• Activation of MAPK signaling in human urothelial cell lines	• Bailey et al., 2012 • Wang et al., 2013 • Eblin et al., 2007
	• Increased expression of MAPK proteins in mouse bladder at 0.01% arsenite (in vivo)	• Luster and Simeonova, 2004
p53 Mutation	• Increased protein expression of p53 in vitro	• Naranmandura et al., 2011 • Huang et al., 2004 • Flora et al., 2011
Metallotheoionein activation	• Increased metallotheoionein transcriptional expression in human urothelial cell lines	• Eblin et al., 2006, • Eblin et al., 2008, • Wnek et al., 2011 • Clewell et al., 2011
Cell proliferation, cell survival, angiogenesis	• Increased gene expression related to epithelial-to-mesenchymal transition, inflammation, DNA damage, apoptosis/survival and proliferation in vitro and in vivo	• Yager et al 2013 • Clewell et al., 2011 • Flora et al., 2011 • Gentry et al., 2010 • Clewell et al., 2014 • Vizcaya-Ruiz et al., 2009

The majority of the evidence comes from research groups that examined immortalized human urothelial cell lines and human bladder cancer cell lines (UROtsa, EJ-1), although evidence for gene expression changes in rodent bladder are also available. Disruption of the pathway and signaling has been demonstrated at the level of transcriptional expression as well as protein expression. The arsenic species tested in these biological systems were varied but predominantly include iAsIII and MMAIII (to which UROtsa cell lines are particularly sensitive).

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/2211)

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

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Purpose and Scope

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

Methods

Epidemiological Studies of Human iAs Urine Levels

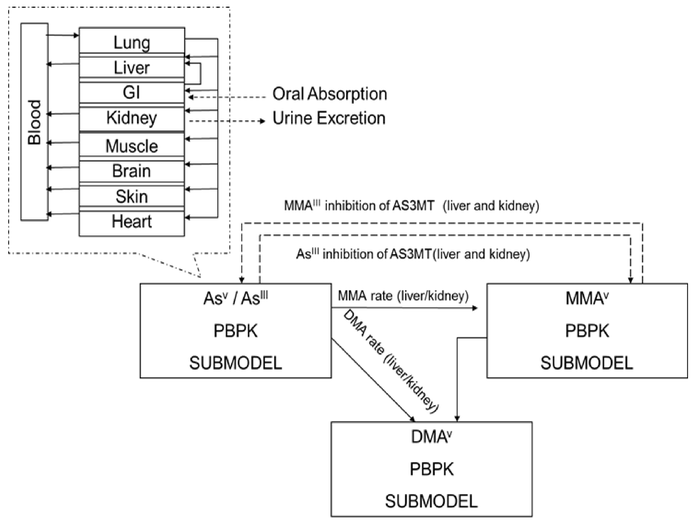
Parameter	HEALS cohort, Bangladesh[1]	Churchill County, Nevada, USA[2]
Number of observations	Total: 11,438 Male: 4,876 Female: 6,562	Total: 904 Male: 368 Female: 536
Age (years)	Range:17–75 Median: 36	Range: 45–92 Median: 61
Height (m)	Range: 1.30–1.85 Median: 1.54	Range: 1.45–1.95 Median: 1.66
Weight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

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

PBPK Model Selection and Modification

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

Methods (Continued)



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

- Arsenic intake rate:

$$Water\ iAs\ intake = water\ iAs\ concentation \times water\ intake$$

- Volume of the tissue compartments:

$$BWMULT \times \left(\frac{Body\ weight}{70\ kg}\right)$$

- Urinary excretion rate, L/hr:

$$V_{urinary} = 0.65 \times BW \times BWMULT$$

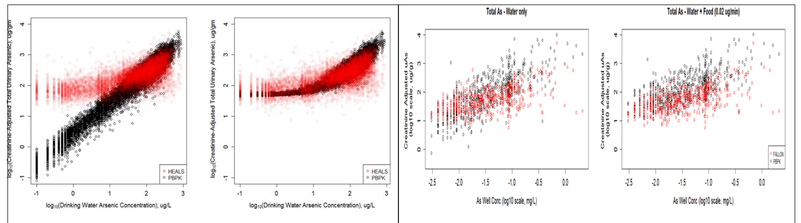
- Creatinine excretion rate based on subject specific body weight:

$$MCR = \beta_0 + \beta_1 * sex + \beta_2 * BMI + \beta_3 * age + \beta_4 * age^2$$ (Ogna et al., 2015)

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

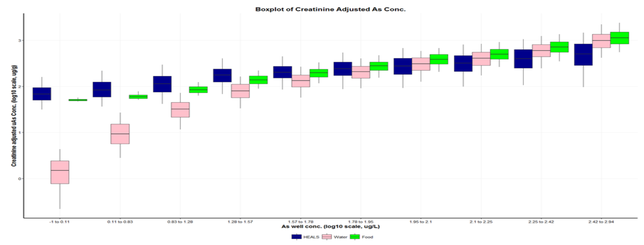
	Food type	Mean (range; µg/day)	Source
Food consumption (Bangladesh)	Rice (g/day)	• Male: 523 • Female: 300	Watanabe et al. (2004)
	Vegetable (g/day)	• Male:153.00 • Female: 146.88	Khan et al. (2009)
As levels in food (Bangladesh)	Rice (µg/kg)	• 173	Watanabe et al. (2004)
		• 150 (10–500)	Rahman et al.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

Results

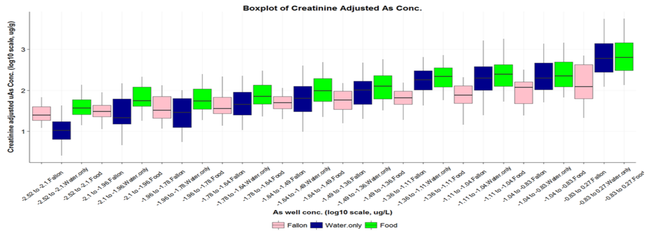


Relationship between arsenic water levels and PBPK model-predicted creatinine-adjusted urinary arsenic concentrations for the HEALS data set. Left: well water as the only arsenic intake source. Right: well-water and dietary exposure as the arsenic intake source.

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



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



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

Conclusions

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

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

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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 Hobbie[1], J. Allen Davis[2], Kan Shao[3], Cara Henning[1], William Mendez Jr.[1], Janice S. Lee[4], Ila Cote[4], Ingrid Druwe[4], Jeff Gift[4]

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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 (RRE). 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, a 3-step strategy (see below) was used to select studies for modeling.
- *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_{20}).
- *Derivation of RRBs*: dividing RRE_{20} values by estimates of U.S. background (RRE_{20}/U.S. Background). 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).

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_{20} 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.

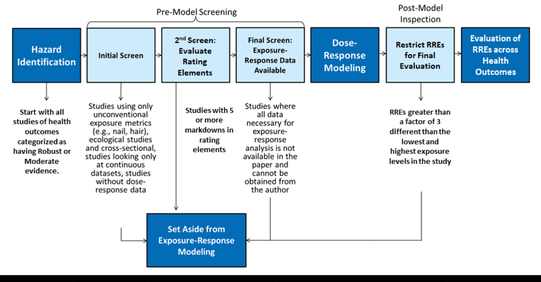


Table 1. Study Rating Criteria for Dose-Response Analysis

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 mark-down 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

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_{20} is exposure or dose for which 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 RREs, outcomes categorized by types (clinical–fatal, clinical–non fatal, preclinical, subclinical) and subcategories (e.g., fetal loss, infant mortality and stillbirths for pregnancy outcomes).

Table 2. U.S. Background Estimates for Use in RRB Derivation

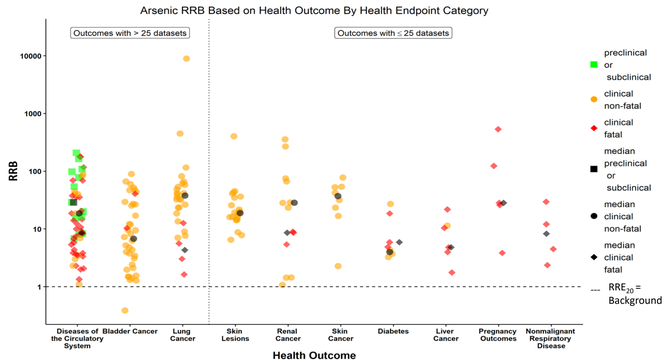
Exposure metric	Units	U.S. central tendency	Basis for U.S. estimate
Drinking water concentration	µg /L	1.5	median, 95th percentile county mean As in drinking water (USGS, 2011)
Cumulative exposure from drinking water	µg - yr/L	75	1.5 µg/L or 15.4 µg/L (above) × 50 yrs
Daily intake	µg /day (water)	1.5	1.5 µg/L or 15.4 µg/L (above) × 1.0 L/day (U.S. EPA, 2011)
Dietary intake	µg /day (food)	3.5	0.05 µg/kg-d mean or 0.19 µg/kg-d 95th percentile adult intake (Xue et al., 2010) × 70-kg adult
	µg /day (food + water)	5	Sum of food and water
Cumulative intake	mg (cumulative intake, water)	27.4	1.5 µg/day or 15.4 µg/day (above) × 50 yrs
	mg (cumulative intake, food + water)	91.3	5 µg/day or 28.7 µg/day (above) × 50 yrs
Urine concentration (cr. Adj.)	µg As excretion / g creatinine	7.4	NHANES (2013-2014) median or 95th percentile (CDC, 2016)
Urine concentration	µg AS excretion / L urine	5	NHANES (2013-2014) median or 95th percentile (CDC, 2016)
Air	µg /m³	0.00075	https://cfpub.epa.gov/roe/indicator.cfm?i=90#8; EPA's ambient monitoring archive, arsenic data averaged between 2010 and 2013
Cumulative air	µg /m³-years	0.0375	0.00075 µg /m³ or 0.00156 µg /m³ (above) × 50 yrs

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-based likelihoods contributions from their exposure groups (Prentice and Pyke, 1979).
- *Cohort studies* – counts of cases in each exposure group follow a Poisson distribution: $o_i \sim \text{Poisson}\,[e_i \times f(d_i)]$, where o_i and e_i are observed cases and expected case number in the ith exposure group, respectively. Seven continuous dose-response models used for $f(\cdot)$, including the linear model, power model, 2nd-degree polynomial model, Michaelis-Menten model, and the Exponential 2, 3, and 4 models.
- *Model Fit Assessment and Model Selection* – for each dataset, the modeling 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_{20} 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.

Results

- Final screening of studies led to the identification of 262 datasets within 68 studies.
- The figure shows individual and median preclinical/subclinical, clinical nonfatal and clinical fatal RRB results organized by most to least number of datasets.
- Table 3 presents RRB ranges, means and medians for each health outcome.



** Results reflect datasets of clinical incidence which produced RRE_{20} (the exposure associated with a 20% increase in relative risk) estimate no more than 3-fold below or above the study exposure range.
RRB is the ratio of the RRE_{20} to the typical U.S. background exposure.

Table 3. RRB Estimates by Health Outcome

Endpoint	Preclinical or Subclinical		Clinical Non-Fatal		Clinical Fatal	
	Range of RRBs	Median	Range of RRBs	Median	Range of RRBs	Median
Bladder Cancer	N/A	N/A	0.386 - 89.2	6.76	N/A	N/A
Diabetes	N/A	N/A	3.25 - 27.1	3.99	4.87 - 18.6	5.90
DCS	6.86 - 209	29.0	1.10 - 87.5	18.6	1.35 - 181	8.48
Liver Cancer	N/A	N/A	N/A	N/A	1.76 - 21.8	4.83
Lung Cancer	N/A	N/A	7.06 - 8920	37.8	1.64 – 12.7	5.74
Nonmalignant Resp. Disease	N/A	N/A	N/A	N/A	2.4 - 29.7	8.28
Pregnancy Outcomes	N/A	N/A	N/A	N/A	3.86 - 537	28.4
Renal Cancer	N/A	N/A	1.07 - 357	28.4	5.41 - 8.97	8.62
Skin Cancer	N/A	N/A	2.27 - 77.7	37.0	N/A	N/A
Skin Lesion	N/A	N/A	6.52 - 402	18.8	N/A	N/A

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. EPA's 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.

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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)

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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 observed at µg/kg-day intake doses estimated for a large prospective cohort study of residents in northeast 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 daily arsenic intake dose.
- *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.

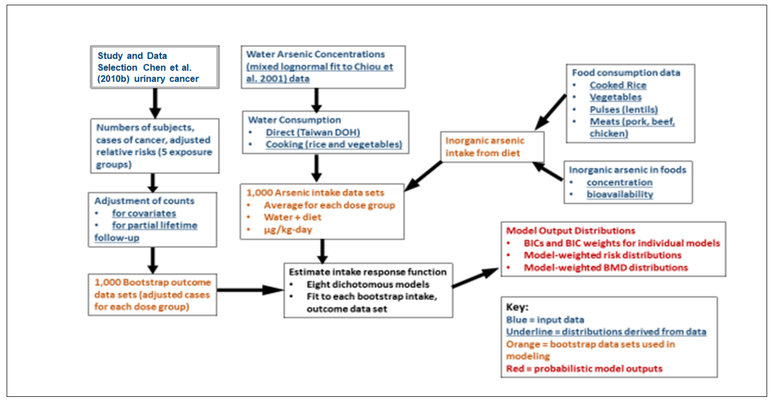

Figure 1. Summary of dose-response methodology for bladder and lung cancer. Note: BIC = Bayesian Information Criterion

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 Information Criteria (BIC) values were calculated as:

$$BIC = -2 \times \log(likelihood) + k \times \ln(n)$$

  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:

$$Weight_i = \frac{e^{(-0.5 \times BIC_i)}}{\sum_{i=1}^{9} e^{(-0.5 \times BIC_i)}}$$

- "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.

Table 1. Models included in the dose-response assessment

Model	Form	Parameters
Quantal linear	r(dose) = a + (1−a) × (1−exp(−b × dose))	2
Logistic	r(dose) = 1/(1 + exp(−a−b × dose))	2
Probit	r(dose) = pnorm(a + b × dose)	2
Weibull	r(dose) = a + (1−a) × (1−exp(−c × dose^b))	3
Multistage 2	r(dose) = a + (1−a) × (1−exp(−b × dose−c × dose^2))	3
Log logistic	r(dose) = a + (1−a)/(1+exp(−c−b × log(dose)))	3
Log probit	r(dose) = a + (1−a) × pnorm(c + b × log(dose))	3
Gamma	r(dose) = a + (1−a) × pgamma(c × dose^b)	3
Dichotomous Hill	r(dose) = v × g + (v−v × g)/(1 + exp(−c−b × log(dose)))	4

Results

- In the range of the data, similar mean absolute risk, 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).

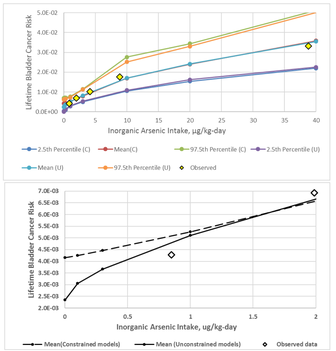

Figure 2. Predicted lifetime probability of bladder cancer versus all doses (upper plot) and low doses (lower plot) using constrained (C) and unconstrained (U) models compared to adjusted observed incidence from adjusted relative risks reported in Chen et al. (2010b).

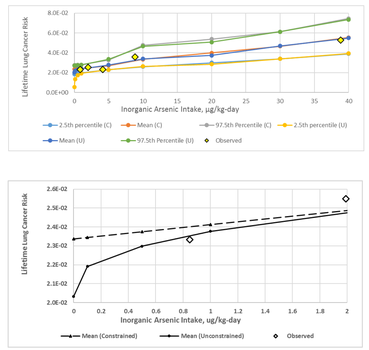

Figure 3. Predicted lifetime probability of lung cancer versus all doses (upper plot) and low doses (lower plot) using constrained (C) and unconstrained (U) models compared to adjusted observed incidence obtained from adjusted relative risks reported in (Chen et al., 2010a).

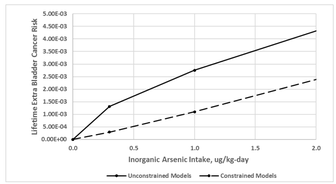

Figure 4. Predicted low dose extra risk of bladder cancer from Chen et al. (2010b) for constrained and unconstrained model averaging.

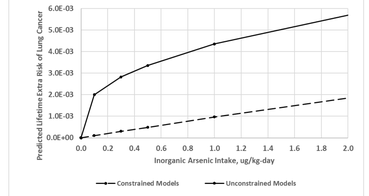

Figure 5. Predicted low dose extra risk of lung cancer from Chen et al. (2010a) using constrained and unconstrained model averaging.

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).

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Bayesian Hierarchical Meta-Regression of Epidemiologic Studies: Dose and Response Pre-Analysis (Poster 6)

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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 epidemiologic data is often interval censored with an open ended reported for the high dose group (e.g., > 10,000 µg/L-yrs, Table 1)

Table 1: Calculated Effective Cases from Selected Arsenic Epidemiology Results - Information Presented in Tables 1 and 3 of Cohort Study by Chen et al. (2010)[a]

Cumulative water exposure, µg/L: years	Cases	Adjusted RR (95% CI)	Effective Cases	Effective Expected Number
< 400	6	--	6.00	6
400–1,000	3	1.11 (0.27 – 4.54)	2.84	2.56
1,000–5,000	12	2.33 (0.86 – 6.36)	10.65	4.57
5,000–10,000	5	3.77 (1.13 – 12.6)	4.72	1.25
>10,000	11	7.49 (2.70 – 20.8)	9.56	1.28

[a] The information in the first three columns is directly from Chen et al. (2010). The last two columns are computed as described subsequently in this poster.

- 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 (c_g, c_{g+1}) is given by:

$$mean(g) = e^{\left(\mu+\frac{\sigma^2}{2}\right)} \times \frac{\theta(U_1(g)-\sigma)-\theta(U_0(g)-\sigma)}{\theta(U_1(g))-\theta(U_0(g))},$$

  - where $U_1(g) = \frac{(ln(c_{g+1})-\mu)}{\sigma}$, $U_0(g) = \frac{(ln(c_g)-\mu)}{\sigma}$, and $\theta()$ 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 values 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 intake values (µg/kg-day).
- For example, for a study that reports average iAs exposure (µg/L) or cumulative iAs exposure (µg/L-yr), daily intake (µg/kg-day) was calculated via:

$$dose = DI + f \times (WCR \times WE) + (1 - f) \times (WCR \times LE)$$

  - 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]), 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. Table 2 illustrates how this was done for one dose group.

Table 2: Example of Dose Calculations – Converting Reported cumulative exposure (µg/L-year) in Chen et al. (2010) to daily intakes (µg/kg-day) for one dose group

Variable	DI	f	WCR	RDWE	LE	WE – MLE	MLE Dose	WE - Low	Low Dose	WE - High	High Dose
Mean	0.65	0.630769	0.0345	42	5						
SD	0.333333	--	0.02319	3.333333	15						
Distribution	LogNormal	Beta	LogNormal	LogNormal	LogNormal						
Study Participant											
1	0.469875	0.739176	0.020187	47.73289	0.955895	3.29	0.524063	3.35	0.524879	3.24	0.523245
2	0.448139	0.548615	0.019016	37.84907	0.088638	4.15	0.492239	4.22	0.492959	4.09	0.491518
3	0.443911	0.525224	0.089145	37.46044	0.775256	4.20	0.673251	4.27	0.676512	4.13	0.669982
4	0.239939	0.716066	0.034483	39.79564	0.316072	3.95	0.340594	4.02	0.342213	3.89	0.338971
--	--	--	--	--	--	--	--	--	--	--	--
1000[1]	0.540283	0.868618	0.026601	45.62604	33.13435	3.45	0.735713	3.50	0.737035	3.39	0.734389
						Average	0.784552		0.785761		0.78334

[1] Assumed distributions with associated means and standard deviations are sampled a number of times equal to the dose-specific Ns, for doses with N > 1000, 1000 samples are taken to ease computational burden

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

Table 3: Results of the Monte Carlo Simulation Analysis to Calculate MLE, Low, and High Dose Estimates

Cumulative water exposure, µg/L: years	Dose Scenarios	Mean	Standard Deviation	0%	1%	5%	10%	25%	50%	75%	90%	95%	99%	100%
< 400	High	0.802	0.014	0.764	0.775	0.781	0.786	0.793	0.802	0.811	0.821	0.826	0.837	0.852
	Low	0.805	0.014	0.767	0.778	0.784	0.789	0.796	0.804	0.814	0.823	0.828	0.840	0.854
	MLE	0.804	0.014	0.765	0.776	0.783	0.787	0.794	0.803	0.813	0.822	0.827	0.838	0.853
400–1,000	High	1.052	0.016	1.008	1.017	1.027	1.033	1.042	1.051	1.062	1.072	1.078	1.091	1.111
	Low	1.052	0.016	1.008	1.017	1.027	1.033	1.042	1.051	1.062	1.073	1.078	1.091	1.111
	MLE	1.052	0.016	1.008	1.017	1.027	1.033	1.042	1.051	1.062	1.072	1.078	1.091	1.111
1,000–5,000	High	1.893	0.032	1.781	1.818	1.839	1.852	1.872	1.893	1.915	1.935	1.945	1.969	1.995
	Low	1.887	0.032	1.776	1.812	1.834	1.847	1.866	1.888	1.909	1.929	1.940	1.963	1.989
	MLE	1.890	0.032	1.779	1.815	1.837	1.849	1.869	1.891	1.912	1.932	1.943	1.966	1.992
5,000–10,000	High	4.245	0.123	3.880	3.961	4.032	4.086	4.164	4.245	4.329	4.397	4.443	4.526	4.677
	Low	4.238	0.123	3.874	3.955	4.026	4.080	4.157	4.239	4.322	4.390	4.436	4.519	4.669
	MLE	4.241	0.123	3.877	3.958	4.029	4.083	4.161	4.242	4.326	4.393	4.439	4.523	4.673
>10,000	High	20.487	0.597	18.322	19.152	19.481	19.720	20.083	20.478	20.867	21.292	21.477	21.858	22.285
	Low	18.687	0.543	16.718	17.475	17.774	17.992	18.320	18.679	19.032	19.420	19.588	19.935	20.325
	MLE	19.555	0.569	17.492	18.284	18.598	18.826	19.171	19.547	19.917	20.323	20.499	20.863	21.271

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 groups
  - 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 multiple exposure metrics and facilitates sensitivity analyses 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).

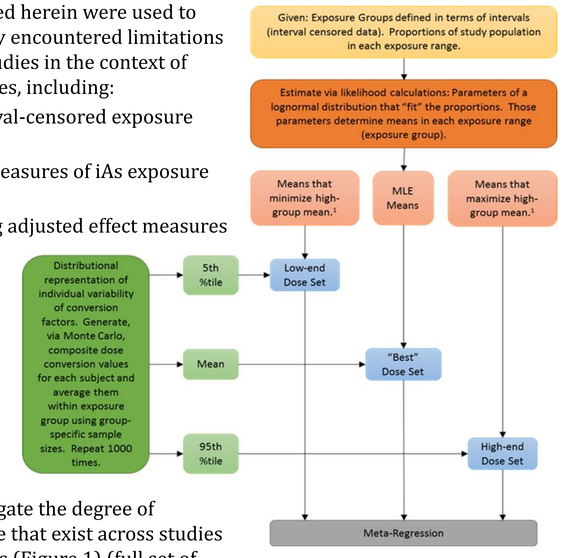

Figure 1: dose pre-analysis and uncertainty flowchart in relation to "best", "low-end", and "high-end" dose sets; [1] See Group Means and Uncertainty section

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Bayesian Hierarchical Meta-Regression of Epidemiologic Studies: Dose-Response Modeling and Target Population Predictions (Poster 7)

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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 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 $X = (X_1, \ldots, X_p)$:

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

- 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: β (slope parameter) and λ (true proportion of doses in a dose-interval)
    - Cohort studies: μ(δ) (expected number of cases in the referent group)
  - Calculated the parameter α or α*
  - 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

Table 1. Maximum Likelihood Dose Estimates, adjusted relative risks (RR) or odds ratios (OR) and Effective Counts for Bladder Cancer Studies Used in Meta-Regression

Data Set Name (Reported dose units)	Exposure Ranges (in reported dose units)	"Best" Dose Values for Analysis (avg daily μg/kg)	Adjusted RR or OR (LCL – UCL)	Raw Counts: Cases	Raw Counts: Expected or Controls[2]	Effective Counts: Cases	Effective Counts: Expected or Controls[2]
Cohort Studies							
Chen et al. (2010) (cumulative water exposure, μg/L-years)	< 400	0.80	1	6	6.00	6.00	6.00
	400-1000	1.05	1.11 (0.27-4.54)	3	2.70	2.84	2.56
	1000-5000	1.89	2.33 (0.86-6.36)	12	5.15	10.65	4.57
	5000-10000	4.24	3.77 (1.13-12.6)	5	1.33	4.72	1.25
	>10000	19.56	7.49 (2.7-20.8)	11	1.47	9.56	1.28
Sawada et al. (2013) Males[1] (water concentration, μg/L)	40.5	0.85	1	28	28.00	28.00	28.00
	54.7	1.15	1.45 (0.89-2.37)	41	28.28	37.44	25.82
	63.5	1.33	0.89 (0.51-1.55)	26	29.21	22.37	25.14
	99.1	2.08	1.56 (0.95-2.55)	46	29.49	36.06	23.12
Sawada et al. (2013) Females[1] (water concentration, μg/L)	37.1	1.07	1	6	6.00	6.00	6.00
	51.2	1.42	1.96 (0.7-5.53)	10	5.10	8.98	4.58
	64.2	1.65	2.06 (0.72-5.87)	10	4.85	8.34	4.05
	107.6	2.79	1.54 (0.5-4.73)	7	4.55	6.18	4.01
Case-Control Studies							
Steinmaus et al. (2013) (μg/d from water)	<41	0.92	1	32	197	32.00	83.32
	41-136	1.64	1.08 (0.62-1.87)	39	194	39.23	94.59
	137-307	3.20	3.06 (1.75-5.35)	64	154	57.22	48.69
	>307	10.40	5.85 (3.41-10.05)	97	95	99.06	44.09
Wu et al. (2013) (μg/gm Creatinine)	≤11.74	0.28	1	44	196	44.00	108.33
	11.74-20.94	0.55	1.42 (0.9-2.25)	63	196	69.52	120.54
	>20.94	1.23	4.13 (2.69-6.35)	192	202	166.80	99.44
Bates et al. (1995) (cumulative water iAs intake, mg)	<19	0.091	1	14	47	14.00	40.24
	19-33	0.097	1.56 (0.8-3.2)	21	36	18.98	34.98
	33-53	0.105	0.95 (0.4-2)	17	39	9.30	28.14
	>53	0.121	1.41 (0.7-2.9)	19	38	16.49	33.62
Steinmaus et al. (2003) (cumulative Intake, mg)	<6.4	0.09	1	66	101	66.00	73.03
	6.4-82.8	0.10	0.77 (0.48-1.24)	57	111	56.96	81.85
	> 82.8	1.09	0.73 (0.45-1.17)	58	116	54.29	82.29
Bates et al. (2004) (water concentration, μg/L)	0-50	0.39	1	87	80	87.00	51.35
	51-100	1.17	1.11 (0.3-3.7)	8	8	7.58	4.03
	101-200	2.12	0.81 (0.3-2)	13	13	11.67	8.51
	>200	7.98	0.28 (0.1-1.4)	3	10	3.49	7.36
Meliker et al. (2010) (water intake, μg/d)	<1	0.11	1	189	252	189.00	210.37
	1-10	0.13	0.83 (0.62-1.11)	162	234	145.13	194.62
	>10	0.36	1.01 (0.62-1.64)	43	48	37.01	40.79

[1] Sawada et al. (2013) reported medians for the exposure groups. Thus, we used those estimates (reported here) rather than working from the ranges.
[2] Expected raw and effective counts for cohort studies or control raw and effective counts for case-control studies.

- For the purpose of dose-response modeling, the α* parameter was assumed to be independent for each dataset
- Methods also assume study-specific β values that are normally distributed around a mean = β_mean, with standard deviation = β_sigma. Both β_mean and β_sigma were assigned priors and updated (Table 2)

Table 2. Prior parameter distributions used in the Bayesian Meta-Regression

Parameter	Prior Distribution
β(i)[1]	Normal (β_mean, β_sigma)
β_mean	Gamma (a=0.52, b=0.89)
β_sigma	Half-Cauchy (scale=5)

[1] β(i) is the dose coefficient for data set i.

- The gamma distribution for β_mean 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 < OR < 20.
  - 1st and 99th percentiles of gamma distribution ($f(x) = \alpha e^{-\alpha x}(\alpha x)^{b-1} / \Gamma(b)$) 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 β 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.

Table 3. Summary of Bayesian Meta-Regression Outputs, Including Parameters Important for Risk Estimation in the Target Population

β Parameter	Mean	SE of the Mean	SD	Percentiles: 2.50%	25%	50%	75%	97.50%	Effective Sample Size	Rhat
β_mean	0.2018	0.002	0.1775	0.0008	0.0572	0.1636	0.3018	0.6274	8219	1
β_sigma	0.6232	0.0026	0.2315	0.3198	0.4679	0.5767	0.724	1.2205	7788	1.0001
Chen et al. (2010)	0.0879	0.0002	0.0212	0.0434	0.0742	0.0885	0.1022	0.1284	9221	0.9998
Sawada et al. (2013) - males	0.2968	0.0017	0.1686	-0.0322	0.1823	0.2972	0.4107	0.6255	9294	1.0005
Sawada et al. (2013) - females	0.1455	0.0026	0.2497	-0.3659	-0.0196	0.1545	0.3166	0.6147	9346	0.9999
Steinmaus et al. (2013)	0.1774	0.0003	0.0246	0.1303	0.1607	0.1771	0.1936	0.2272	8530	0.9998
Wu et al. (2013)	1.349	0.0023	0.2164	0.9246	1.2018	1.3461	1.4953	1.7746	8934	0.9999
Bates et al. (1995)	0.2135	0.0075	0.6863	-1.1259	-0.1985	0.1969	0.6078	1.5945	8484	1.0004
Steinmaus et al. (2003)	-0.1389	0.0021	0.2004	-0.5335	-0.2717	-0.1366	-0.006	0.2499	8747	0.9997
Bates et al. (2004)	-0.1787	0.0009	0.0875	-0.3562	-0.2359	-0.1764	-0.1192	-0.0144	9141	1.0001
Meliker et al. (2010)	0.1869	0.0058	0.5348	-0.8819	-0.1539	0.181	0.5292	1.2308	8523	1.0001

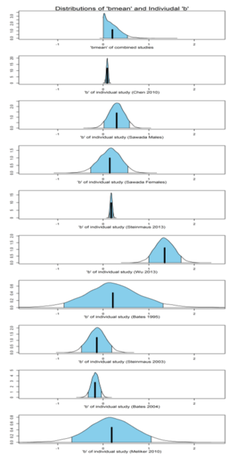
Summaries of Stan model runs: 4 chains were run, each with 10000 iterations; "warm-up" = 5000; remaining 5000 iterations per chain were thinned by 2 (every other iteration was dropped). Therefore, the total number of post-warmup draws = 10,000.
Effective samples = effective sample size used to estimate the parameters and Rhat is a measure of convergence (at convergence Rhat = 1). Effective sample sizes are large enough and the convergence criterion is satisfied for all parameters.

Table 4. 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

Extra Lifetime Risk[b,c]	Average Daily Arsenic Dose (ug/kg-day)						
	0.071[a]	0.12	0.19	0.26	0.33	0.75	1.45
	Average Daily Arsenic Drinking Water Concentration (ug/L)						
	1.5	5	10	15	20	50	100
0	2.0 (0.01 - 6.3)	4.8 (0.02 - 16)	7.7 (0.03 - 25)	11 (0.04 - 35)	29 (0.1 - 106)	64 (0.2 - 271)	

[a] U.S. daily background dose is estimated at 0.071 ug/kg, with 0.05 ug/kg from diet (Xue et al. 2010), 0.021 ug/kg from water, 1.5 ug/L median U.S. water level (Mendez et al. 2017) x 0.014 L/day mean U.S. water consumption rate (U.S. EPA, 2011, Table 3-1, "All Ages") and 0 ug/kg from air. Thus, 1.5 ug/L in water is associated with a background dose of 0.071 ug/kg and an extra risk of 0.
[b] These extra risk estimates assume a mean U.S. background rate for bladder cancer of 2% (NCI, 2017). 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*(1−2%)*0.02% = 1.96.
[c] 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.

Figure 1. Posterior Distributions for Pooled and Study-specific Logistic Slope Parameters Using the MLE Dose Estimates.



Black vertical lines indicate means of posterior distributions. 95% credible intervals for the logistic slope parameters are highlighted in blue

Dose-Response Modeling and Lifetable Analysis cont.

Figure 2. Extra Lifetime Bladder Cancer Risk due to Oral iAs Exposure, using MLE Dose Estimates

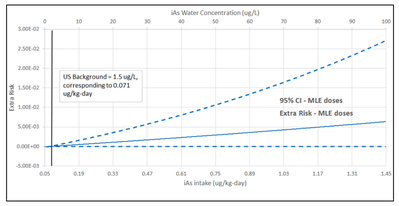
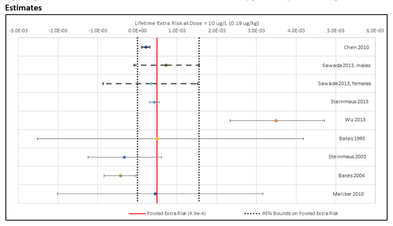


Figure 3. Forest Plot of Extra Lifetime Bladder Cancer Risk at 10 μg/L iAs Exposure, using MLE Dose Estimates



- 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 β_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 β_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 or 4.51×10^{-4} μg/kg-day

Table 5. Impact of Leave-One-Out Cross Validation (Dataset Exclusion) on Lifetime Extra Risk of Bladder Cancer

Excluded Data Set	Extra Lifetime Risk at 10 μg/L (0.19 μg/kg): 2.5 %tile	Mean	97.5 %tile
None	1.91E-06	4.88E-04	1.56E-03
Chen et al. (2010)	1.91E-06	5.48E-04	1.85E-03
Sawada et al. (2013), males	1.67E-06	4.88E-04	1.72E-03
Sawada et al. (2013), females	1.67E-06	5.17E-04	1.75E-03
Steinmaus et al. (2013)	1.44E-06	5.27E-04	1.76E-03
Wu et al. (2013)	4.78E-07	1.62E-04	5.77E-04
Bates et al. (1995)	1.91E-06	4.85E-04	1.54E-03
Steinmaus et al. (2003)	2.39E-06	5.86E-04	1.85E-03
Bates et al. (2004)	2.63E-06	6.11E-04	1.86E-03
Meliker et al. (2010)	1.44E-06	4.95E-04	1.64E-03

- The consideration of alternative gamma prior distributions for β_mean: alternative distributions that considered different 1st or 99th percentile values did not overly influence final risk estimates (Table 6)

Table 6. Posterior β_mean distribution values resulting from various prior Gamma distributions

Alternative Prior	2.5th percentile	Mean	97.5th percentile	% Mean Difference
1.0001 – 10	0.0012	0.2108	0.6512	4.46
1.0001 – 30	0.0005	0.1966	0.6311	-2.58
1.00001 -20	0.0001	0.1707	0.5922	-15.41
1.001 - 20	0.0045	0.237	0.6673	17.44
Original Prior (1.0001 – 20)	**0.0008**	**0.2018**	**0.6274**	--

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, $logit(p(x)) = \alpha^* + \beta\_1(x^{p1}) + \beta\_2(x^{p2})$, 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)

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