EPA
United States
Environmental Protection
Agency

Inorganic Arsenic IRIS Dose-Response Analyses

by Allen Davis and Jeff Gift
National Center for Environmental Assessment

July 16, 2019

Dose-Response: Methods Overview

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

- **Relative Risk Exposure to Background (RRB) Screening**
  - **Purpose – identify studies and endpoints suitable for dose-response modeling**
  - **Approach:**
    - Focused on single study, single best model to derive point of departure
    - Attempted to derive RRB values for all 12 robust & moderate outcomes
- **Model Averaging**:
  - **Purpose – Evaluate low dose extrapolation model uncertainty**
  - **Approach:**
    - Applied multiple models with model averaging to Chen et al. (2010a,b) Taiwan data
    - Modeled data for bladder and lung cancer
- **Bayesian Meta-Regression**
  - **Purpose – Use best possible approach for evaluation of low dose responses pooling information from multiple studies**
  - **Approach:**
    - Convert all exposures to common study-specific estimate of intake (µg/kg-day)
    - Multiple study, hierarchical dose-response analysis using logistic model
    - Investigate low-dose non-linearity with fractional logistic model
    - Lifetable analyses if possible
    - Best possible single study analyses if Bayesian meta-regression is not feasible

RRB Screening of Epidemiological Exposure-Response Data

- **Purpose of Screening**
  - Evaluate health outcome studies and datasets ***qualitatively*** and ***quantitatively***
  - Compare iAs potency across hundreds of datasets for dozens of health outcomes
  - Maximize resources
- **Qualitative Systematic Review of the Literature**
  - Risk of bias evaluations conducted to inform confidence in individual studies
  - Evidence profile tables for each hazard transparently summarizes considerations underlying EPA judgments regarding strength of the human evidence
  - Additional review of study relevance for dose-response (next slide)
- **Quantitative Screening**
  - Exposure-response analysis to compare potency estimates across hundreds of studies and datasets
  - Identify health endpoints for more sophisticated analyses

Qualitative Review of Dose-Response Feasibility

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

Table 1. Study Rating Criteria for Dose-Response Analysis

Rating Element	Criteria
Health outcome	Incidence data generally preferred over mortality data only
Exposure ascertainment method	Location of residence/exposure or large group averages instead of individual measurement or small group averages
Exposure reporting	Reported as ranges without summary statistics such as averages and measures of dispersion/variance
Estimates control for smoking, gender, age and other key covariates	Adjusted estimates do not include important covariates
Number of exposure groups	Less than two in addition to referent precludes exposure-response modeling, more groups support more complex models
Number of subjects & cases reported	One or both elements missing; only statistical summaries (RR, SMRs, etc.,) are reported
Exposure/dose metric	Worst = historical exposure measurement only, better = cumulative exposure, best = cumulative intake (no 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

RRB Screening Approach

- More than 250 data sets identified as suitable for RRB modeling
- EPA's Benchmark Dose Software was used to model data and estimate the exposure that would increase risk estimate by 20% (RRE_{20})
  - Case-control studies modeled with the logistic model – under logistic regression model, results from case-control studies can be analyzed as if they were collected prospectively
  - Cohort study data assumed to follow a Poisson distribution – relative risk modeled with continuous dose-response models (single best model selected using standard practices)
  - RRE_{20} values are maximum likelihood estimates, not lower bound estimates (i.e., akin to BMDs, not BMDLs)
  - EPA considered multiple BMRs and ultimately decided 20% increase in RR was most appropriate across all endpoints

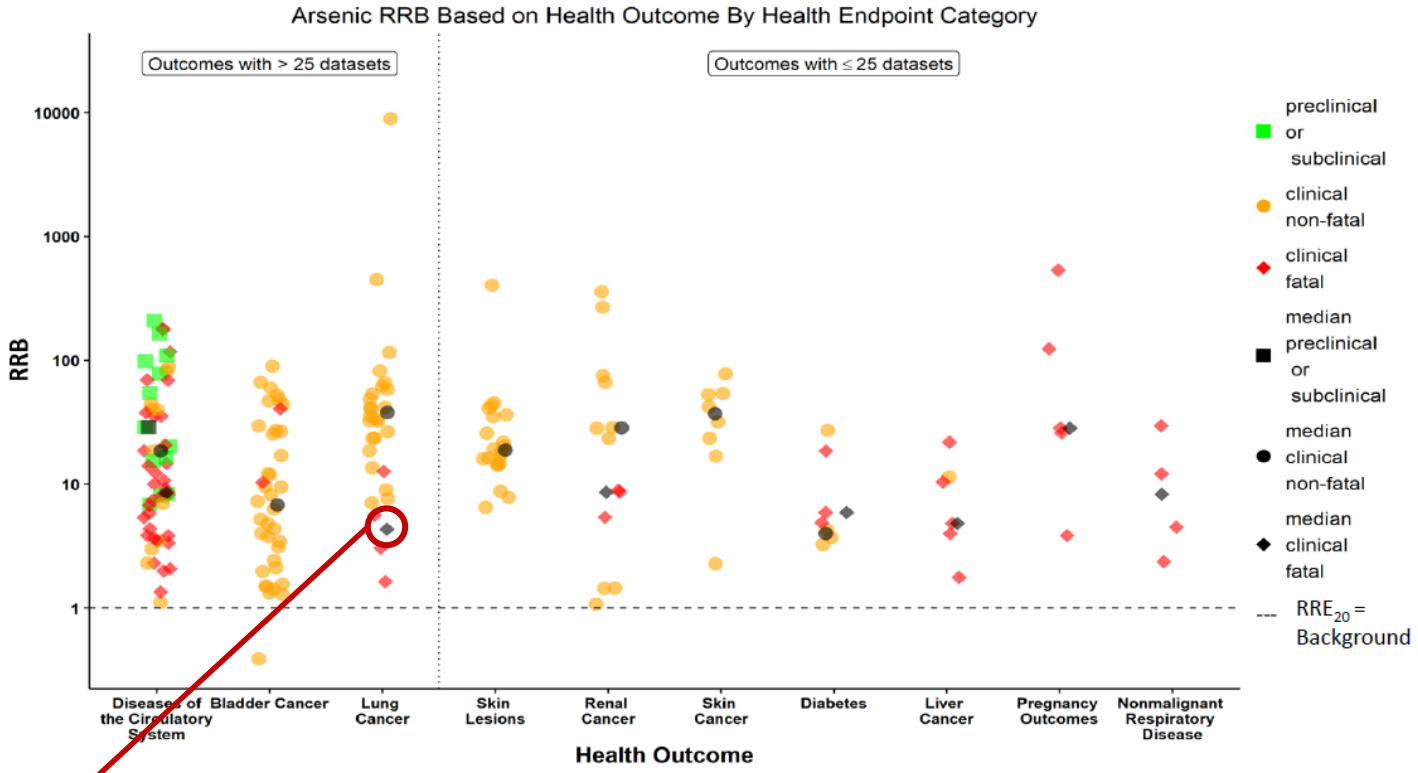
RRB Screening – Background Estimates of Exposure

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

U.S. central tendency and "high" arsenic estimates for different exposure and dose metrics

Exposure metric	Units	U.S. central tendency	U.S. "High"	Basis for U.S. estimate
Drinking water concentration	µg /L	1.5	15.4	median, 95th percentile county mean As in drinking water (USGS, 2011)
Cumulative exposure from drinking water	µg - yr/L	75	770	1.5 µg/L for 30 years, 15.4 µg/L for 50 years
Daily intake	µg /day (water)	1.5	15.4	1.5, 15 µg/L (above), 1.0 L/day (U.S. EPA, 2011)
Dietary intake	µg /day (food)	3.5	13.3	Mean, 95th percentile adult intake (Xue et al., 2010); 0.05, 0.19 µg/kg-d), 70-kg adult
	µg /day (food + water)	5	28.7	Sum of food and water
Cumulative intake	mg (cumulative intake, water)	27.4	281	50 years intake @ 1.5, 15.4 µg/day
	mg (cumulative intake, food + water)	91.3	524	50 years intake @ 5, 28.7 µg/day
Urine concentration (cr. Adj.)	µg As excretion / g creatinine	7.4	18.4	NHANES (2013-2014) median, 95th percentile (CDC, 2016)
Urine concentration	µg AS excretion / L urine	5	16.8	NHANES (2013-2014) median, 95th percentile (CDC, 2016)
Air	µg /m^3	0.00075	0.00156	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 /m^3-years	0.0375	0.078	50 years of inhalation

RRB Screening Approach and Results



** 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.

- RRB value = 5.74
- Means that, for clinical fatal lung cancer datasets, the exposure level that would result in an RR = 1.2 is ~6-fold higher than U.S. background exposure level

RRB Screening Conclusions

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

Table 2. 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

Dose-Response: Methods Overview

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

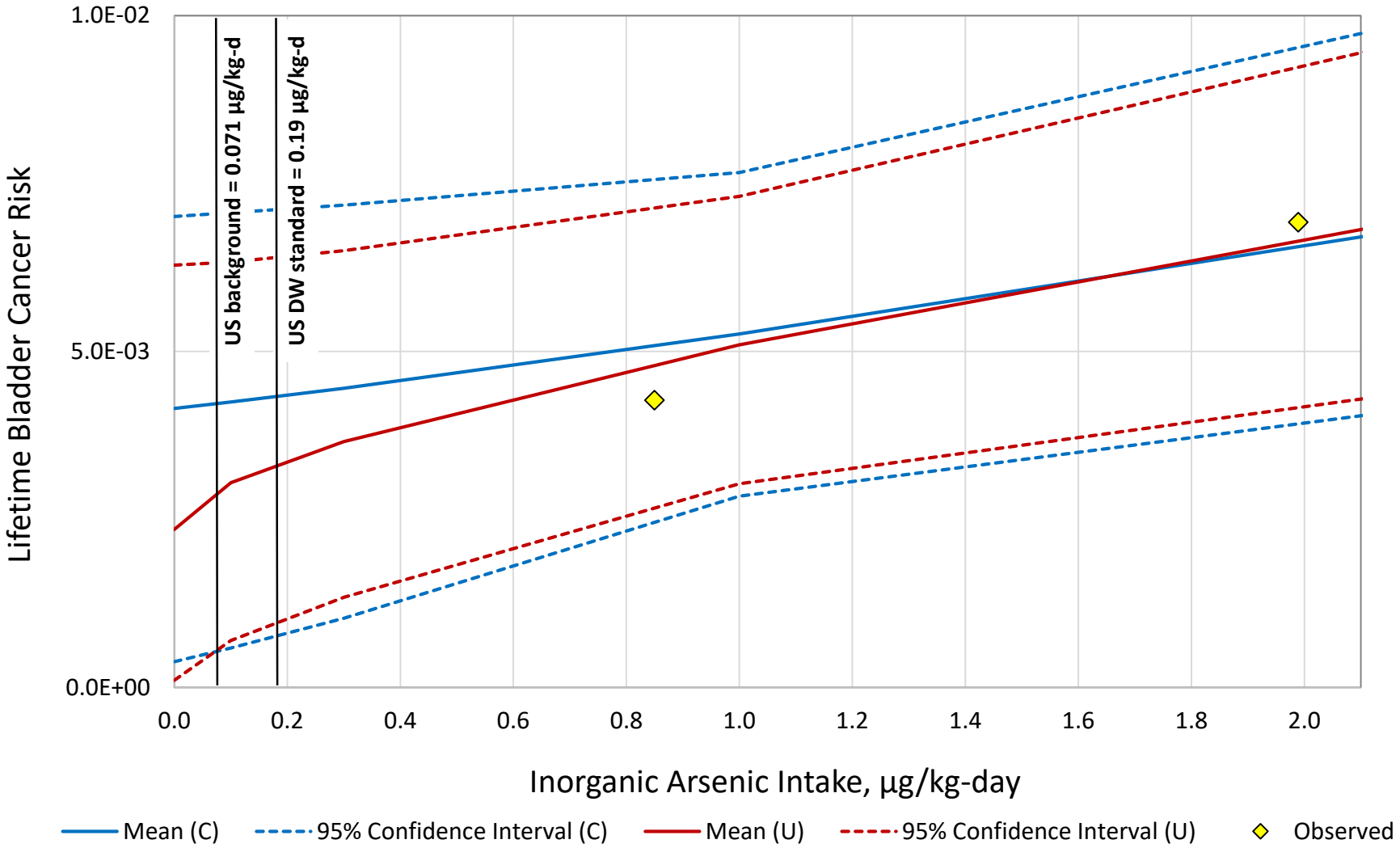
- **Relative Risk Exposure to Background (RRB) Screening**
  - **Purpose – identify studies and endpoints suitable for dose-response modeling**
  - **Approach:**
    - Focused on single study, single best model to derive point of departure
    - Attempted to derive RRB values for all 12 robust & moderate outcomes
- **Model Averaging**:
  - **Purpose – Evaluate low dose extrapolation model uncertainty**
  - **Approach:**
    - Applied multiple models with model averaging to Chen et al. (2010a,b) Taiwan data
    - Modeled data for bladder and lung cancer
- **Bayesian Meta-Regression**
  - **Purpose – Use best possible approach for evaluation of low dose responses pooling information from multiple studies**
  - **Approach:**
    - Convert all exposures to common study-specific estimate of intake (µg/kg-day)
    - Multiple study, hierarchical dose-response analysis using logistic model
    - Investigate low-dose non-linearity with fractional logistic model
    - Lifetable analyses if possible
    - Best possible single study analyses if Bayesian meta-regression is not feasible

Model Averaging

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

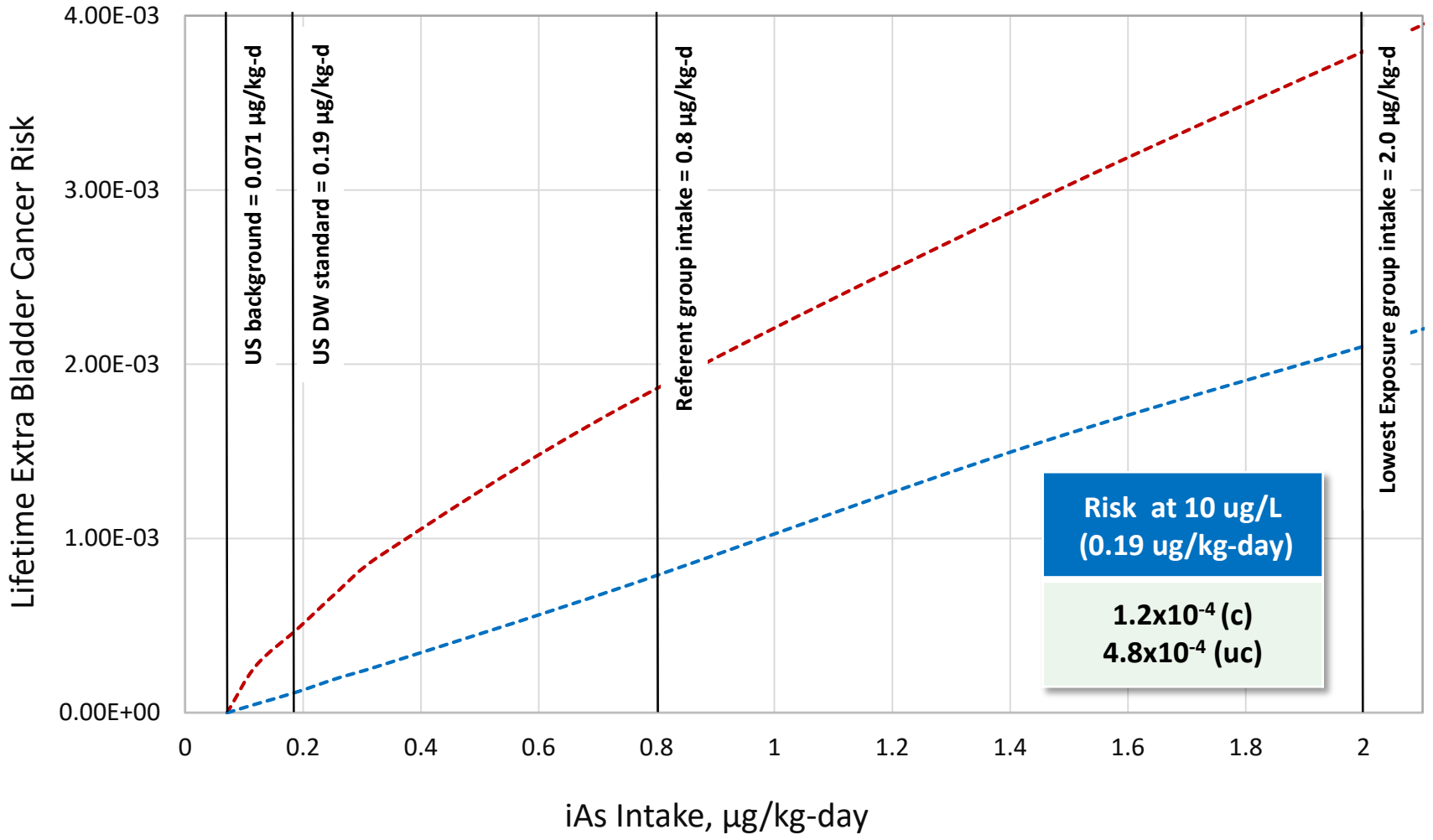
Model Averaging: Bladder Cancer Results for NE Taiwan

Comparing Unconstrained and Constrained Models



Model Averaging: Bladder Cancer Results for NE Taiwan

Comparing Unconstrained and Constrained Models



Model Averaging: Conclusions

- Model averaging showed substantial model uncertainty when extrapolating from Taiwanese iAs doses to US relevant doses
- NRC (2013) recommended only “modest” low dose extrapolation (~ 1 order of magnitude) from the lowest exposure group of a candidate study, suggesting Chen et al. (2010a,b) is not appropriate for estimating US risk
- Mode of action analyses could be used to inform low-dose extrapolation in the absence of other dose-response modeling approaches
- However, a meta-regression method utilizing multiple low-, mid-, and high-dose studies is considered a preferable approach and was recommended, where feasible, by the NRC (2013)

Dose-Response: Methods Overview

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

- **Relative Risk Exposure to Background (RRB) Screening**
  - **Purpose – identify studies and endpoints suitable for dose-response modeling**
  - **Approach:**
    - Focused on single study, single best model to derive point of departure
    - Attempted to derive RRB values for all 12 robust & moderate outcomes
- **Model Averaging**:
  - **Purpose – Evaluate low dose extrapolation model uncertainty**
  - **Approach:**
    - Applied multiple models with model averaging to Chen et al. (2010a,b) Taiwan data
    - Modeled data for bladder and lung cancer
- **Bayesian Meta-Regression**
  - **Purpose – Use best possible approach for evaluation of low dose responses pooling information from multiple studies**
  - **Approach:**
    - Convert all exposures to common study-specific estimate of intake (µg/kg-day)
    - Multiple study, hierarchical dose-response analysis using logistic model
    - Investigate low-dose non-linearity with fractional logistic model
    - Lifetable analyses if possible
    - Best possible single study analyses if Bayesian meta-regression is not feasible

Bayesian Meta-Regression: Effective Counts

- Need a method that allows for combining as many study types as possible and makes use of adjusted risk and confidence limit values reported by authors
- Cohort and case-control studies typically report relative risks (RR) and odds ratios (OR) adjusted for confounders
- EPA implemented an approach to calculate “effective counts” - i.e., the counts of cases and controls that would have been observed if the covariates in all exposure groups were equal to those observed in the referent group
- Allows reported risk values to be modeled with logistic model as incidence data

Bayesian Meta-Regression: Exposure Group Means

- Exposures in epidemiologic studies often reported as a range, whereas dose-response software requires a point estimate for modeling
- Estimating a point estimate is relatively straightforward except for high doses which are often reported as open-ended ranges (e.g., > 10,000 µg/L-year)
- EPA used a maximum likelihood (ML) approach to estimate group-specific means
  - Exposures were assumed to be log-normally distributed
  - ML estimates were considered "best" estimates
- Then, to characterize exposure uncertainty, the high exposure group mean was maximized or minimized, subject to constraints on the log-likelihood, yielding a set of group means consistent with the 95% confidence bounds on the high-group mean

Bayesian Meta-Regression: Dose Conversions

- In order to maximize the set of studies included in EPA's meta-regression, study-specific exposure metrics were converted into a single measure of iAs intake in units of µg/kg-day
- Previous meta-regressions have relied mainly on studies that using drinking water concentration as dose metric
- However, some studies have observed stronger associations when using alternative exposure metrics
- For example, Baris et al. (2016) found no association for drinking water concentrations but a statistically significant association for average daily arsenic intake (µg/day) and cumulative exposure (mg)
- Baris et al. (2016) ultimately concluded that *"[t]he contrast in our findings for cumulative arsenic intake and average arsenic concentration underscores the importance of incorporating water intake when estimating an individual's total arsenic exposure in low to moderately exposed populations…*"

Bayesian Meta-Regression: Dose Conversions

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

Bayesian Meta-Regression: Dose Conversions

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

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

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

Bayesian Meta-Regression: Dose Conversions

- Factors for conversions were treated as distributions and estimates were generated for each subject within a dose-group
- Individual estimates of intake dose were then calculated for the MLE, low-, and high-exposure estimates and averaged
- Markov Chain Monte Carlo (MCMC) methods were then used to characterize and account for study/population-specific interindividual differences in factors (e.g., water consumption rates, body weights, dietary intake) that influence the conversion of exposure to µg/kg-day intake dose estimates
  - Individual group dose estimations were repeated 1,000 times to derive a distribution of dose values
  - The median for the MLE, 5th percentile for the "low", and 95th percentile for the "high" dose values were then used in the Bayesian meta-regression

Bayesian Meta-Regression: Logistic Modeling

- Purpose is to combine data from multiple cohort and case-control studies
- EPA assumes the prospective likelihood is given by a logistic equation, with arsenic intake, X, as the explanatory variable

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

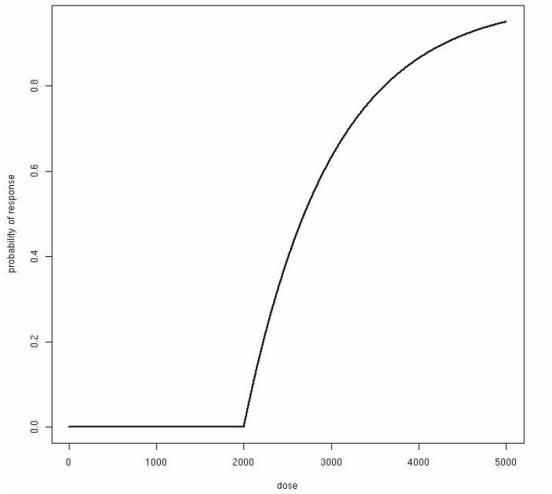
- Allows estimation of prospective likelihood from case-control studies (which are by definition retrospective) and thus inclusion with cohort studies in meta-regression
- Logistic model flexible enough to represent nonlinear "sigmoidal" dose-response relationships expected at a population level for toxicants with widely differing individual sensitivities (e.g., due to human heterogeneity and/or multiple iAs MOAs) (NRC, 2006, 2009, 2014).
- This type of sigmoidal shape is possible at the population level "even if the dose-response relationship has a clear threshold in a single rodent species or cell line" (NRC, 2014)

Bayesian Meta-Regression: Use of MOA Information

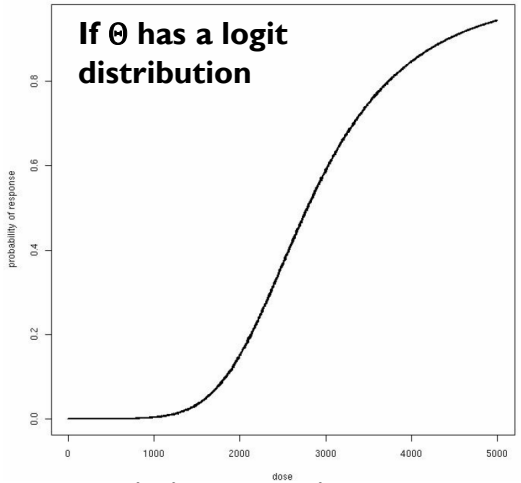
- For ubiquitous toxicants such as iAs, where multiple studies exist that reflect the biological diversity & low levels of exposures in U.S. populations:
  - "…extrapolation below the level of observations … is less important than for compounds for which evidence is derived from animal bioassays or occupational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

$\pi_i = 0, \text{if d} < \theta_i$

$\pi_i = 1 - \exp[-\beta(d - \theta_i)],$ if $\text{d} > \theta_i$



Individual dose-response curve



Logistic population dose-response curve

Bayesian Meta-Regression: Logistic Modeling

- Hierarchical model assumes study-specific β values are normally distributed around mean = β_mean with standard deviation = β_sigma
- β_mean and β_sigma are both assigned priors and updated

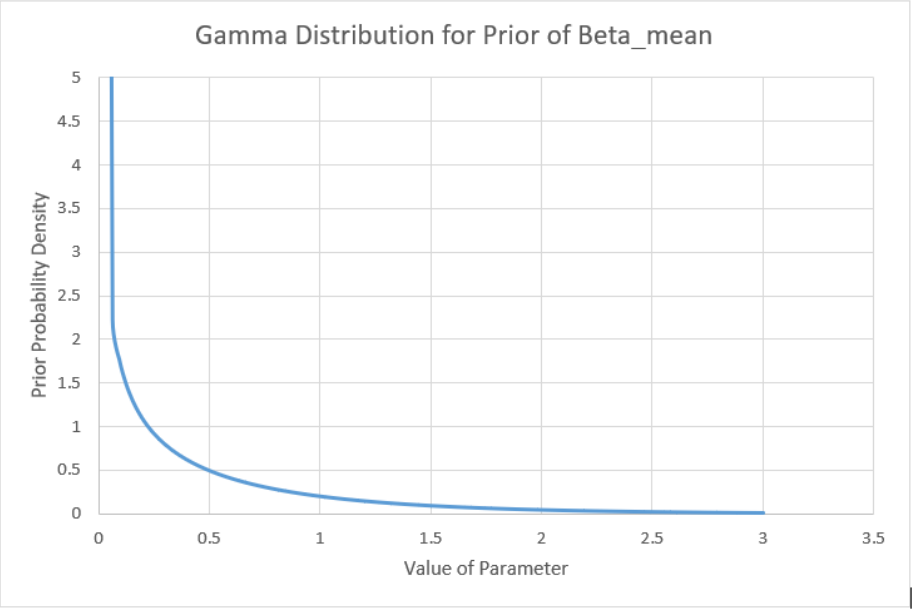
Parameter	Prior Distribution
β(i)[1]	Normal (β_mean, β_sigma)
β_mean	Gamma (a=0.52, b=0.89)
β_sigma	Half-Cauchy (scale=5)

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

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

Bayesian Meta-Regression: Gamma Prior for Pooled Slope

- The Gamma distribution for β_mean reflects the determination that iAs is causally associated with bladder cancer (i.e., prior does not allow negative slopes)
- Prior judgment is that exposure to 1 µg/kg-day iAs (~14-fold above average background exposure) is highly likely to result in 1.0001 < OR < 20
- 1st and 99th percentiles of Gamma distribution set equal to ln(1.0001) and ln(20)
- Gamma distribution is right skewed
  - it gives greatest weight to values of x closest to zero
  - Hence, prior assumption is weaker association with iAs unless data are sufficient to override prior



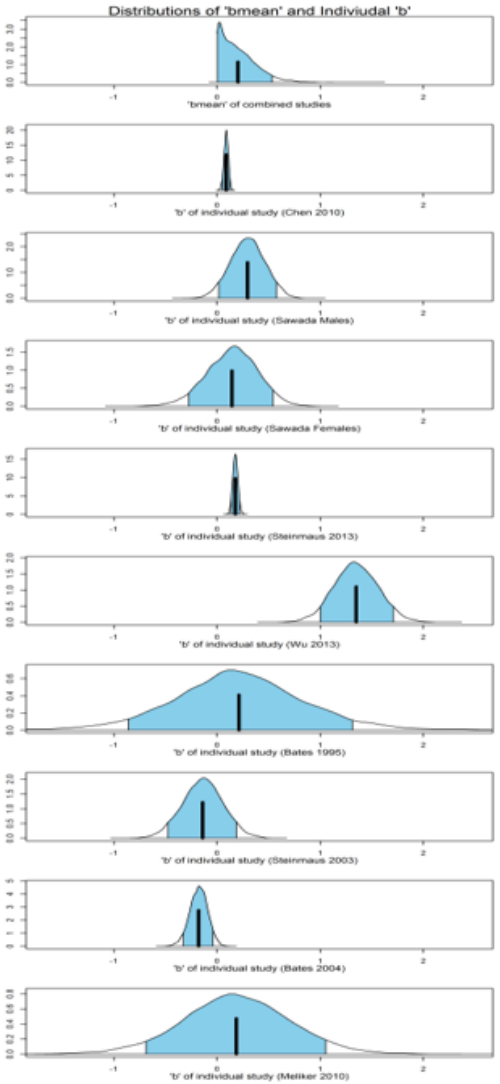
Bayesian Meta-Regression: Modeling Results

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

β Parameter	Mean	SE of the Mean	SD	Percentiles					Effective Sample Size	Rhat
				2.50%	25%	50%	75%	97.50%		
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; the "warm-up" (number of iterations before results were tabulated) was 5000; remaining 5000 iterations per chain were thinned by 2 (every other iteration was dropped). Therefore, the total number of post-warmup draws = 10,000.
Effective samples is the effective sample size used to estimate the parameters and Rhat is the potential scale reduction factor on split chains, a measure of convergence (at convergence Rhat = 1). Effective sample sizes are large enough and the convergence criterion is satisfied for all parameters.

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



Bayesian Meta-Regression: Lifetable Analysis

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

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

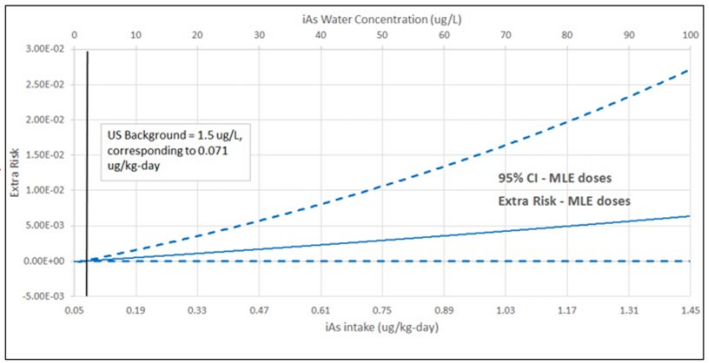
	Average Daily Arsenic Dose (ug/kg-day)						
	0.071	0.12	0.19	0.26	0.33	0.75	1.45
	Average Daily Arsenic Drinking Water Concentration (ug/L)						
	1.5	5	10	15	20	50	100
Extra Lifetime Risk [a, b]	0	2.0 (0.01 - 6.3)	4.8 (0.02 - 16)	7.7 (0.03 - 25)	11 (0.04 - 35)	29 (0.1 - 106)	64 (0.2 - 271)

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

[b] 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.

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

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



Bayesian Meta-Regression: Sensitivity Analyses

- Multiple sensitivity analyses indicate final modeling results not overly sensitive to modeling decisions
- Dose conversions/intake estimates: β_mean reasonably similar between high, MLE, and low intake estimates (0.19, 0.2018, 0.21)
- Incorporation of background iAs inhalation component only decreased extra risk estimates 4%-7%
- Leave-one-out analysis showed no study had undue influence on final results; leaving out Wu et al. (2013) reduced extra risk 3-fold
- Assumption of different Gamma priors didn't result in large differences in posterior distributions
  - Alternative priors with different 1st percentiles resulted in greatest differences

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

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**	**--**

Bayesian Meta-Regression: Fractional Logistic Model

- Using a fractional logistic model can allow for J-shaped dose-response curves (i.e., negative slopes in the low dose region); possibly more in line with iAs toxicological effects and/or MOAs
- A case study using bladder cancer data has shown that monotonically increasing dose-response curves are preferred over low-dose negative curves
- Even for dose-response curves with low-dose negative slopes, slopes are monotonically increasing above iAs background exposure levels

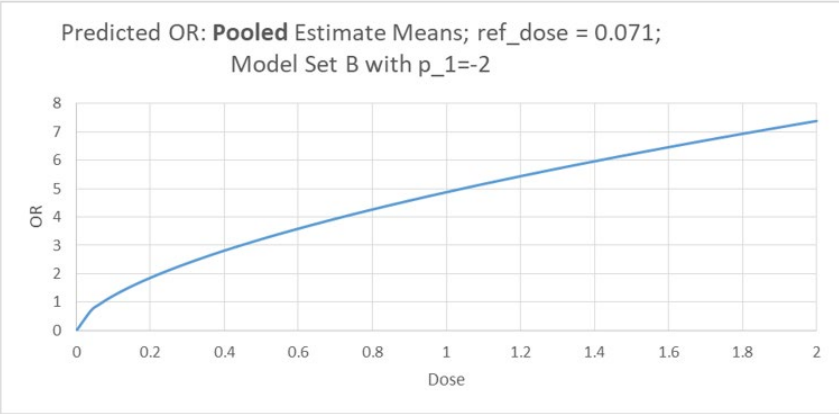


Figure 2. Middle Dose Range for Best Model

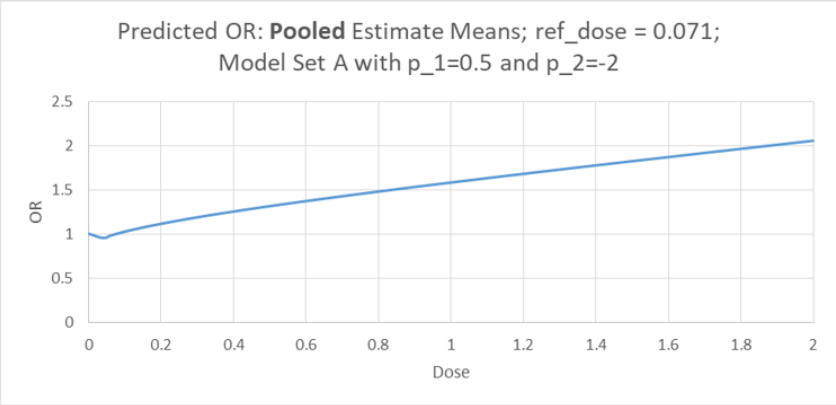


Figure 16. Middle Dose Range for 2nd Best Model

iAs Dose-Response Methods: Summary

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

Acknowledgements

- Ila Cote, Jeff Gift, Tom Luben, Ellen Kirrane, Ryan Jones, Allen Davis, Ingrid Druwe, Kris Thayer, Andrew Kraft, Tina Bahadori, Belinda Hawkins, members of NCEA Statistical Workgroup, and others at U.S. EPA
- Audrey Turley, William Mendez Jr, and others at ICF International
- Bruce Allen (Bruce Allen Consulting)
- Kan Shao (Indiana University)

References

Baris, D; Waddell, R; Beane Freeman, LE; Schwenn, M; Colt, JS; Ayotte, JD; Ward, MH; Nuckols, J; Schned, A; Jackson, B; Clerkin, C; Rothman, N; Moore, LE; Taylor, A; Robinson, G; Hosain, GM; Armenti, KR; Mccoy, R; Samanic, C; Hoover, RN; Fraumeni, JF; Johnson, A; Karagas, MR; Silverman, DT. (2016). *Elevated Bladder Cancer in Northern New England: The Role of Drinking Water and Arsenic*. J Natl Cancer Inst 108. http://dx.doi.org/10.1093/jnci/djw099

Chen, CL; Chiou, HY; Hsu, LI; Hsueh, YM; Wu, MM; Chen, CJ. (2010a). Ingested arsenic, characteristics of well water consumption and risk of different histological types of lung cancer in northeastern Taiwan. Environ Res 110: 455-462. http://dx.doi.org/10.1016/j.envres.2009.08.010

Chen, CL; Chiou, HY; Hsu, LI; Hsueh, YM; Wu, MM; Wang, YH; Chen, CJ. (2010b). Arsenic in drinking water and risk of urinary tract cancer: A follow-up study from northeastern Taiwan. Cancer Epidemiol Biomarkers Prev 19: 101-110. http://dx.doi.org/10.1158/1055-9965.EPI-09-0333

El-Masri, HA; Kenyon, EM. (2008). Development of a human physiologically based pharmacokinetic (PBPK) model for inorganic arsenic and its mono- and di-methylated metabolites. J Pharmacokinet Pharmacodyn 35: 31-68. http://dx.doi.org/10.1007/s10928-007-9075-z

NRC (National Research Council). (2006). Assessing the human health risks of Trichloroethylene: Key scientific issues. Washington, DC: The National Academies Press.

NRC (National Research Council). (2009). Science and decisions: Advancing risk assessment. Washington, DC: The National Academies Press. http://dx.doi.org/10.17226/12209

NRC (National Research Council). (2013). Critical aspects of EPA's IRIS assessment of inorganic arsenic: Interim report. Washington, D.C: The National Academies Press.

NRC (National Research Council). (2014a). Review of EPA's Integrated Risk Information System (IRIS) process. Washington, DC: The National Academies Press. http://www.nap.edu/catalog.php?record_id=18764

Wu, C, -C; Huang, Y, -K; Chung, C, -J; Huang, C, -Y; Pu, Y, -S; Shiue, H, -S; Lai, L, -A; Lin, Y, -C; Su, C, -T; Hsueh, Y, -M. (2013). Polymorphism of inflammatory genes and arsenic methylation capacity are associated with urothelial carcinoma. Toxicol Appl Pharmacol 272: 30-36. http://dx.doi.org/10.1016/j.taap.2013.05.019