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)

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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.

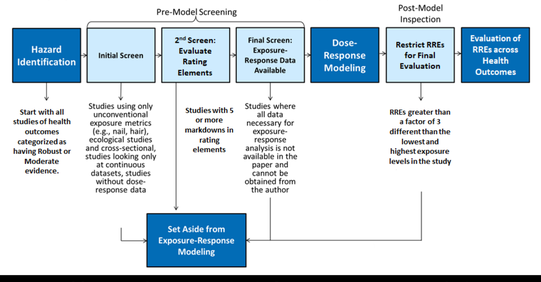


Table 1. Study Rating Criteria for Dose-Response Analysis

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

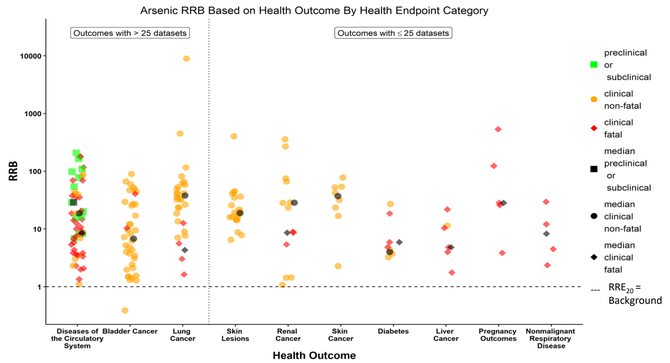
Exposure metric	Units	U.S. central tendency	Basis for U.S. estimate
Drinking water concentration	µg /L	1.5	median, 95th percentile county mean As in drinking water (USGS, 2011)
Cumulative exposure from drinking water	µg - yr/L	75	1.5 µg/L or 15.4 µg/L (above) × 50 yrs
Daily intake	µg /day (water)	1.5	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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