



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

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

- 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: $\mu(\delta)$ (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 $\mu\text{g/kg-day}$ was assumed (0.05 $\mu\text{g/kg-day}$ from dietary sources, 0.021 $\mu\text{g/kg-day}$ from drinking water, and 0 $\mu\text{g/kg-day}$ from inhalation) (Xue et al., 2010; Mendez et al., 2017).

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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 $\mu\text{g/kg}$)	Adjusted RR or OR (LC – UCL)	Raw Counts Cases	Expected Controls ²	Effective Counts Cases	Expected Controls ²
Cohort Studies							
Chen et al. (2010) (cumulative water exposure, $\mu\text{g/L-years}$)	<400 400-1000 1000-5000 5000-10000 >10000	0.80 1.05 1.89 4.24 19.56	1 1.11 (0.27-4.54) 2.33 (0.86-6.36) 3.77 (1.13-12.6) 7.49 (2.7-20.8)	6 3 12 5 11	6.00 2.70 5.15 1.35 1.47	6.00 2.84 10.65 4.72 9.56	6.00 2.56 4.57 1.25 1.28
Sawada et al. (2013) Males ¹ (water concentration, $\mu\text{g/L}$)	40.5 54.7 63.5 99.1	0.85 1.15 1.33 2.08	1 1.45 (0.89-2.37) 0.89 (0.51-1.55) 1.56 (0.95-2.55)	28 41 26 46	28.00 28.28 29.21 29.49	28.00 28.00 25.14 36.06	28.00 25.82 25.14 23.12
Sawada et al. (2013) Females ¹ (water concentration, $\mu\text{g/L}$)	37.1 51.2 64.2 107.6	1.07 1.42 1.65 2.79	1 1.96 (0.7-5.53) 2.06 (0.75-5.87) 1.54 (0.5-4.73)	6 10 10 7	6.00 5.10 4.85 4.55	6.00 4.58 4.34 6.18	6.00 4.58 4.05 4.01
Case-Control Studies							
Steinmaus et al. (2013) ($\mu\text{g/d}$ from water)	<41 41-135 137-307 >307	0.92 1.64 3.20 10.40	1 1.08 (0.62-1.87) 3.06 (1.75-5.35) 5.85 (3.41-10.05)	32 39 64 97	197 194 154 95	32.00 39.23 57.22 99.06	83.52 94.59 48.69 44.09
Wu et al. (2013) ($\mu\text{g/m}$ Creatinine)	<11.74 11.74-20.94 >20.94	0.28 0.55 1.23	1 1.42 (0.9-2.25) 4.13 (2.69-6.35)	44 63 192	196 196 202	44.00 108.33 166.80	108.33 120.54 99.44
Bates et al. (1995) (cumulative water (kg intake, mg)	<19 19-33 33-53 ≥53	0.091 0.097 0.105 0.121	1 1.56 (0.8-3.2) 0.95 (0.4-2.3) 1.41 (0.7-2.9)	14 21 17 19	47 36 38 38	14.00 18.98 9.50 16.49	40.24 34.98 28.14 33.62
Steinmaus et al. (2003) (cumulative intake, mg)	<6.4 6.4-82.8 >82.8	0.09 0.10 1.09	1 0.77 (0.48-1.24) 0.73 (0.45-1.17)	66 57 58	101 111 116	66.00 56.96 54.29	73.03 81.85 82.29
Bates et al. (2004) (water concentration, $\mu\text{g/L}$)	0-50 51-100 101-200 ≥200	0.39 1.17 2.12 7.98	1 1.11 (0.3-3.7) 0.81 (0.3-2) 0.28 (0.1-1.4)	87 8 13 3	87 8 13 10	87.00 7.58 11.67 5.49	51.35 4.03 8.51 7.36
Meliker et al. (2010) (water intake, $\mu\text{g/d}$)	<1 1-10 ≥10	0.11 0.13 0.36	1 0.83 (0.62-1.11) 1.01 (0.62-1.64)	189 162 43	252 234 48	189.00 145.13 37.01	210.37 194.62 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.

- 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 $\mu\text{g/kg-day}$ iAs (~14-fold average background exposure) is highly likely to result in $1.0001 < \text{OR} < 20$.
 - 1st and 99th percentiles of gamma distribution ($f(x) = ae^{-\alpha x}(\alpha x)^{b-1} / \Gamma(b)$) 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					Effective Sample Size	Rhat
β_{mean}	0.2018	0.0002	0.1775	2.50%	25%	50%	75%	97.50%	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

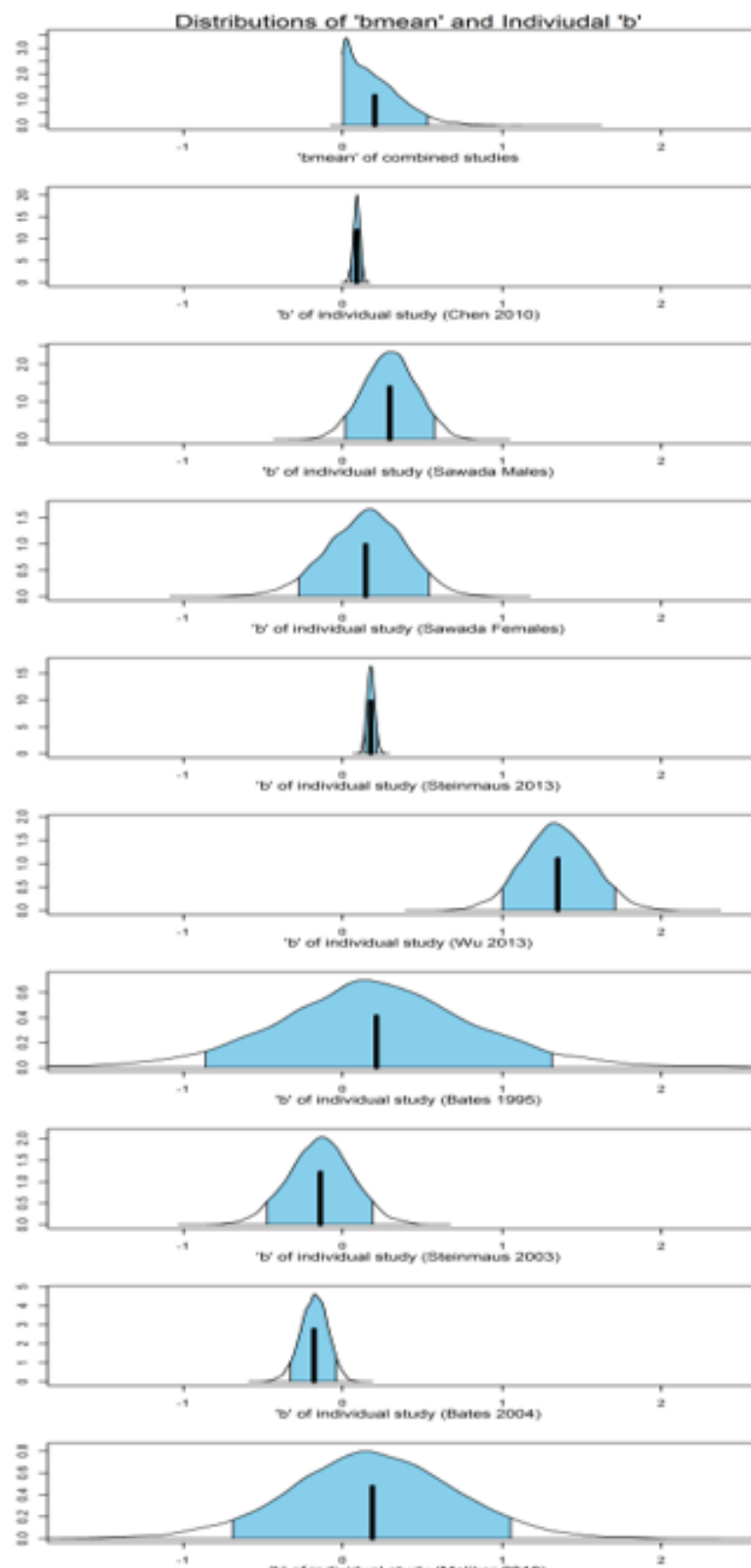
Extra Lifetime Risk ^{a, b}	Average Daily Arsenic Dose ($\mu\text{g/kg-day}$)					
	0.071 ^a	0.12	0.19	0.26	0.33	1.45
	Average Daily Arsenic Drinking Water Concentration ($\mu\text{g/L}$)					
	1.5	5	10	15	20	100
0	2.0 (0.01 - 6.3)	4.8 (0.02 - 16)	7.7 (0.03 - 25)	11 (0.04 - 35)	29 (0.1 - 106)	64 (0.2 - 271)

^a U.S. daily background dose is estimated at 0.071 $\mu\text{g/kg}$ from diet (Xue et al. 2010), 0.021 $\mu\text{g/kg}$ from water, 1.5 $\mu\text{g/L}$ median U.S. water level (Mendez et al., 2017) $\times$ 0.014 L/day mean U.S. water consumption rate (U.S. EPA, 2011, Table 3-1, "All Ages") and 0 $\mu\text{g/kg}$ from air. Thus, 1.5 $\mu\text{g/L}$ in water is associated with a background dose of 0.071 $\mu\text{g/kg}$ 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 $10,000 \times (1-b) \times x$. Thus, additional cases of bladder cancer at an extra risk of 2/10,000 (0.02%) would be $10,000 \times (1-2\%) \times 0.02\% = 1.96$.

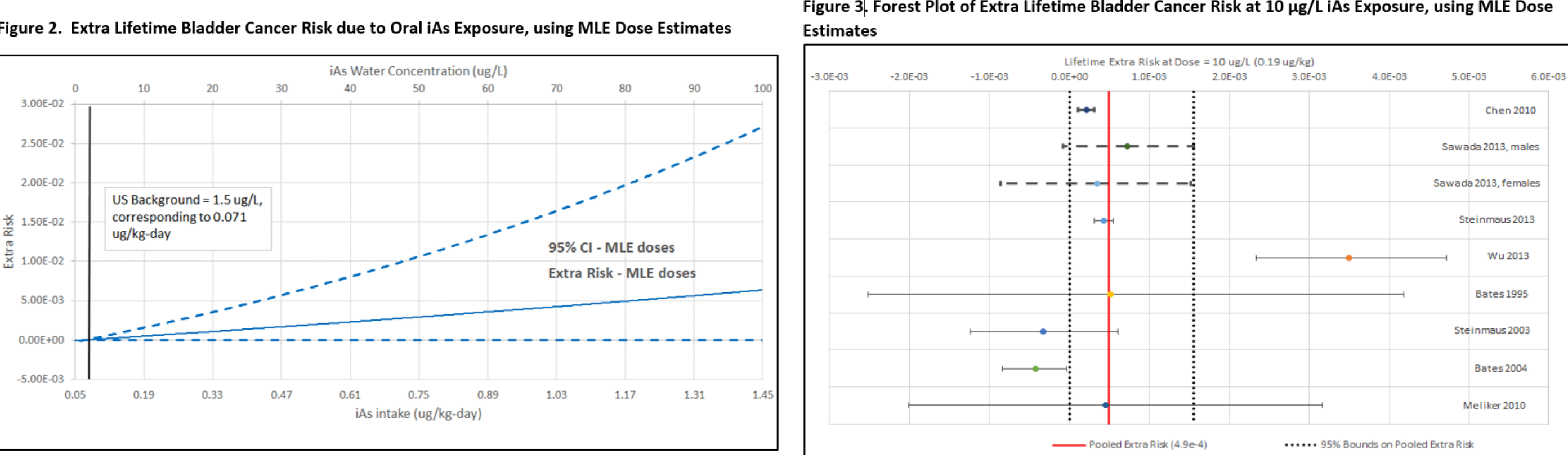
^c Mean, 2.5% and 97.5% of Bayesian posterior slope distributions were used with US lifetables to estimate mean and credible intervals for extra risk above average background risks.

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.



- 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 $\mu\text{g/day}$ decreased mean extra risk estimates from 4.88×10^{-4} $\mu\text{g/kg-day}$ to 4.68 or 4.51×10^{-4} $\mu\text{g/kg-day}$
 - 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 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 $\mu\text{g/L}$ (0.19 $\mu\text{g/kg}$)		
	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

Table 6. Posterior β_{mean} distribution values resulting from various prior Gamma distributions

Alternative Prior	2.5 th percentile	Mean	97.5 th 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, $\text{logit}(p(x)) = \alpha^* + \beta_1(x^{p1}) + \beta_2(x^{p2})$, 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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