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Dose-Response Methods for the IRIS Toxicological Review of Inorganic Arsenic

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Outline for Today's Presentations

- Background
- Approach to Systematic Review
- Hazard Identification
- Mechanistic Conceptual Models
- Toxicokinetics
- **Dose-Response Methods**

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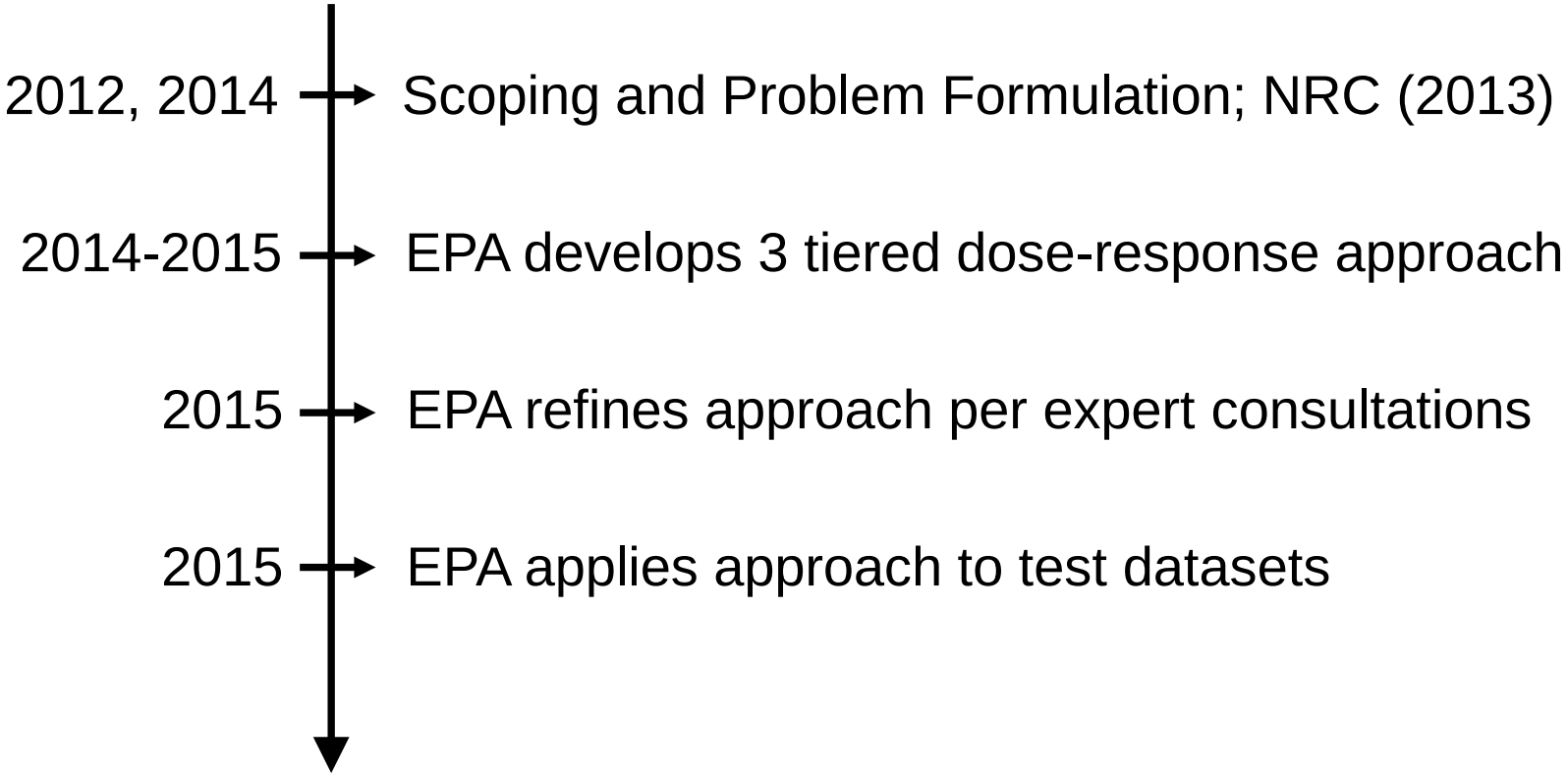
Background



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EPA Methods

- Preparations for Dose-response Modeling
  - Tiered approach
  - Study selection
  - Dose considerations
  - Response considerations
- Methods for Dose-response Modeling
  - Low dose extrapolation
  - Quantifying uncertainty/variability; Sensitivity analyses
- Interpretation of Dose-response Modeling Results
  - Extrapolate to target population
  - Derive risk-specific doses

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Responding to NRC Recommendations (and Other Technical Challenges)

- Preparations for Dose-response Modeling
  - **Tiered Approach** (see Supplemental Information for details)
    - Tier 1 – Standard dose-response models for individual datasets; screen studies for application of more complex methods
    - Tier 2 – More detailed evaluation of data sets (e.g., meta-analysis, model averaging) & sources of uncertainty (e.g., bootstraps, sensitivity analyses); extrapolate risk-based doses to U.S. population
    - Tier 3 – More extensive probabilistic risk and uncertainty analyses using mechanistic data and Bayesian models

Tiered Approach (continued)

Tier 1 – Standard dose-response models for individual data sets

- Start with relatively simple screening methods to get a general idea of dose-response for individual data sets
- Generally applied to grouped (summary) data
- Estimation based on author-reported exposure metrics and adjusted responses
- Conventional frequentist models (linear, Poisson, logistic regression, etc.) fit by maximum likelihood (MLE) methods

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Tiered Approach (continued)

Tier 1 – Standard dose-response models for individual data sets

Tier 2 – Detailed evaluation of data sets & sources of uncertainty

- Modeling of individual data where available
- More complex models where needed; meta-analysis, meta-regression where feasible
- Use MOA information when low dose shape is not well-defined
- Use of empirical relationships, PBPK models to compare exposure/dose metrics

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Tiered Approach (continued)

Tier 1 – Standard dose-response models for individual data sets

Tier 2 – Detailed evaluation of data sets & sources of uncertainty

Tier 3 – More extensive probabilistic risk analysis

- Incorporate major sources of uncertainty in exposure, intake and dose-response
- Apply Bayesian models fit by MCMC estimation, to characterize uncertainty
- Incorporate mechanistic information into dose-response (if possible)

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Responding to NRC Recommendations (and Other Technical Challenges)

- Preparations for Dose-response Modeling
  - Tiered Approach
  - **Study Selection**
    - Focus on epidemiological studies; human studies preferred and abundant
    - Prefer studies that include well-defined, low exposures
    - Prefer individual data; use group data if necessary

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Study Selection

Key considerations

- Endpoint characterization
- Exposure ascertainment and uncertainty
- Estimates control for important covariates
- Adequate number of exposure groups
- Sufficient numbers of subjects and cases
- Exposure/dose metric
- Exposure timing and duration
- Representativeness of referent group
- Separate risk estimates for sensitive groups

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Responding to NRC Recommendations (and Other Technical Challenges)

- Preparations for Dose-response Modeling
  - Tiered Approach
  - Study Selection
  - **Dose considerations**
    - Account for total inorganic arsenic dose
    - Use biomarkers of exposure when available
    - Prefer individual data; use group data when necessary
    - Use PBPK modeling to characterize the relationship between internal dose and external exposure metrics
    - Prioritize studies that use multiple exposure metrics

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Responding to NRC Recommendations (and Other Technical Challenges)

- Preparations for Dose-response Modeling
  - Tiered Approach
  - Study Selection
  - Dose considerations
  - **Response considerations**
    - Focus on endpoints determined to be causal or likely causal
    - Identify covariates affecting risks

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Responding to NRC Recommendations (and Other Technical Challenges)

- Methods for Dose-response Modeling of Exposed Population
  - **Low dose extrapolation**
    - Attempt to characterize dose–response down to background for U.S. population (equivalent to 1-5 µg/L urinary As excretion) using observed data when possible
    - "Modest extrapolation" (order of magnitude) from observed to background levels of exposure when necessary
    - Starting point for low-dose risk estimation = statistical confidence bounds derived from study population data and dose-response models
    - Incorporate potential differences in exposure patterns, sensitivity between study population and target populations
    - Use mechanistic considerations to inform dose-response below observation range, where possible

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Responding to NRC Recommendations (and Other Technical Challenges)

- Methods for Dose-response Modeling of Exposed Population
  - **Low dose extrapolation**
  - **Quantifying uncertainty/variability; Sensitivity analyses**
    - Assess model uncertainty, possibly via model averaging in conjunction with derivation of bootstrap confidence intervals
    - Assess model parameter uncertainty via sensitivity analyses
    - Meta-analyses for priority endpoints with ≥ 3 comparable studies
    - Consider life-stage sensitivity
    - Conduct sensitivity analyses on covariate impact (e.g., smoking)

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Responding to NRC Recommendations (and Other Technical Challenges)

- Interpretation of Dose-response Modeling Results
  - **Extrapolate dose-response results** to target (U.S.) population considering mechanistic data and population differences, (e.g., background level, dietary, genetic, environment, social, cultural differences)
  - **Derive risk-specific doses** to address "needs of analyses that would typically use a RfD"

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Areas Mechanistic Information Can Impact Dose-Response Analyses

- Dose metric selection – e.g., to determine importance of cumulative vs maximum dose (duration vs concentration), target organ, life stage
- Response metric selection – e.g., for the identification of key precursor effects and selection of appropriate BMR level
- Model weighting – For assigning prior weights to model forms (e.g., low dose linear vs. nonlinear; saturable vs non-saturable) in a Bayesian model averaging approach
- Parameter priors – For assigning prior probability distributions to parameters in a Bayesian analysis
- Sensitivity analyses – For informing sensitivity analyses of factors such as background exposure, dosimetry from drinking water arsenic intake, nutrition, and genetics that could affect differences in sensitivity to arsenic between study and target populations

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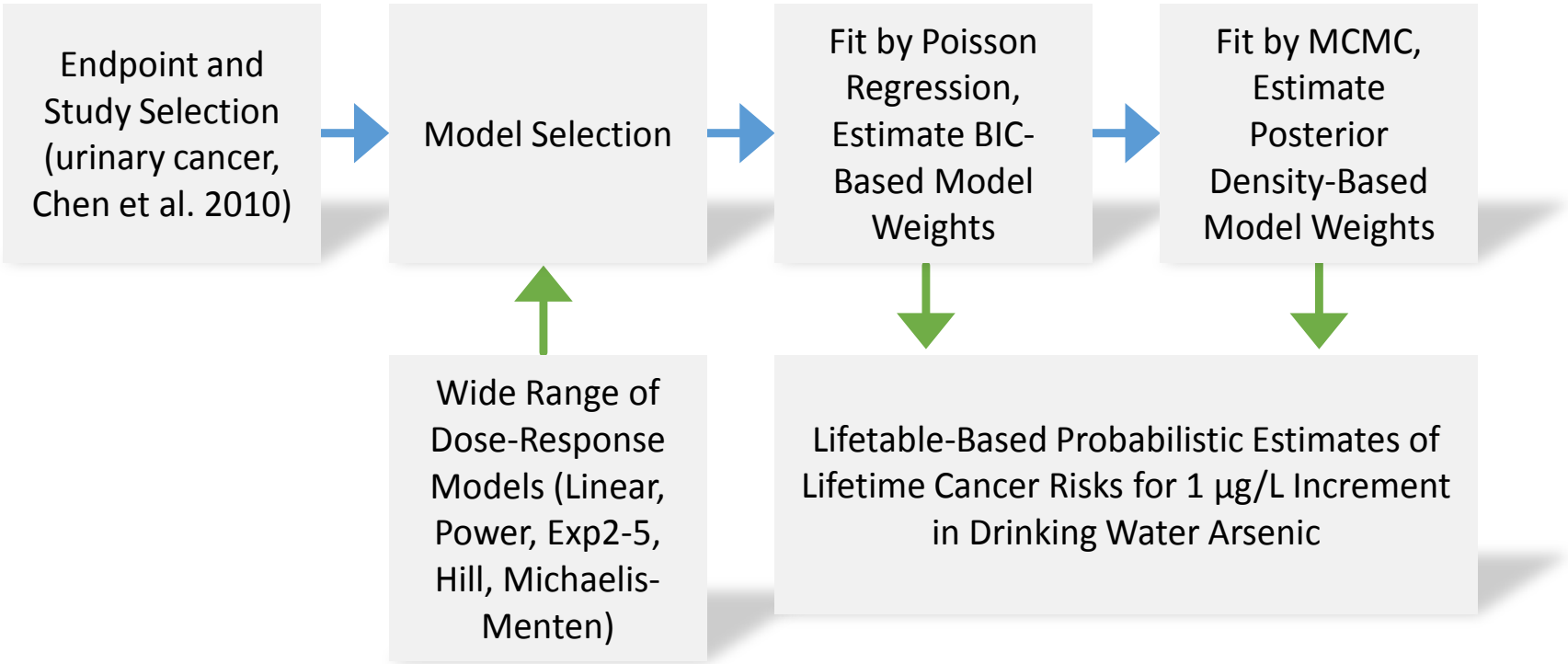
Example of Model Averaging for a Dichotomous Endpoint



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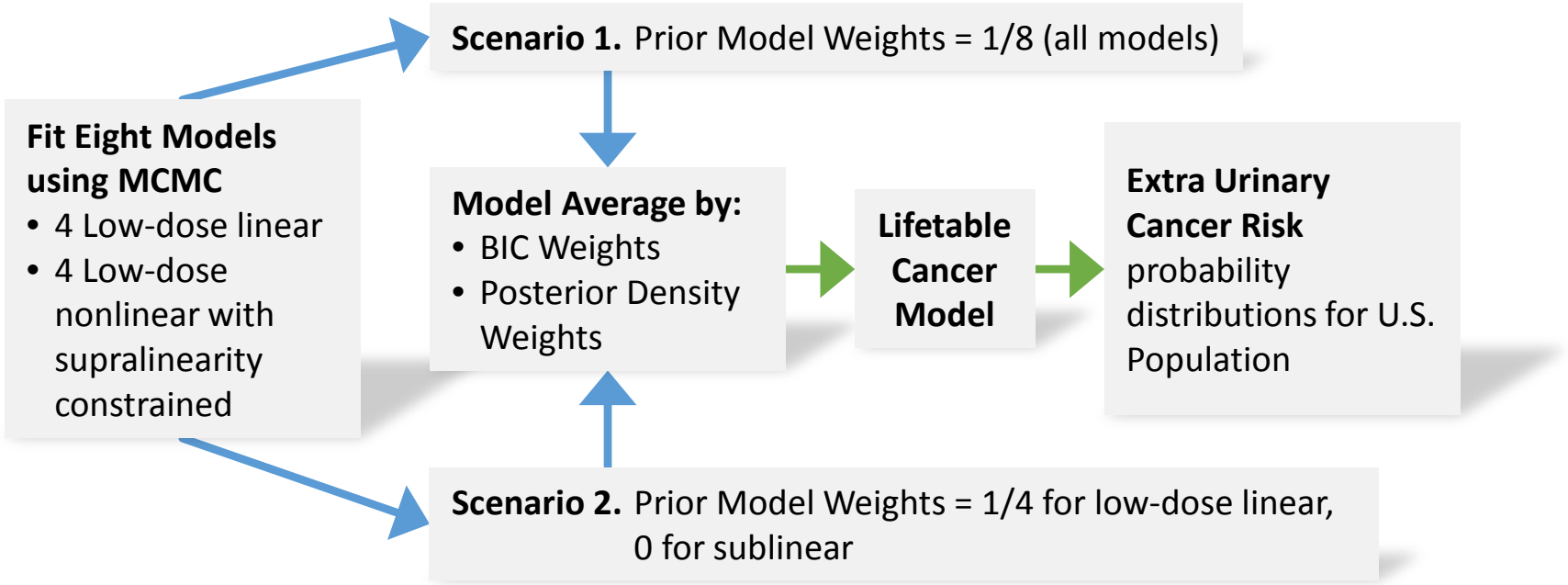
Weighting Schemes for Model Averaging



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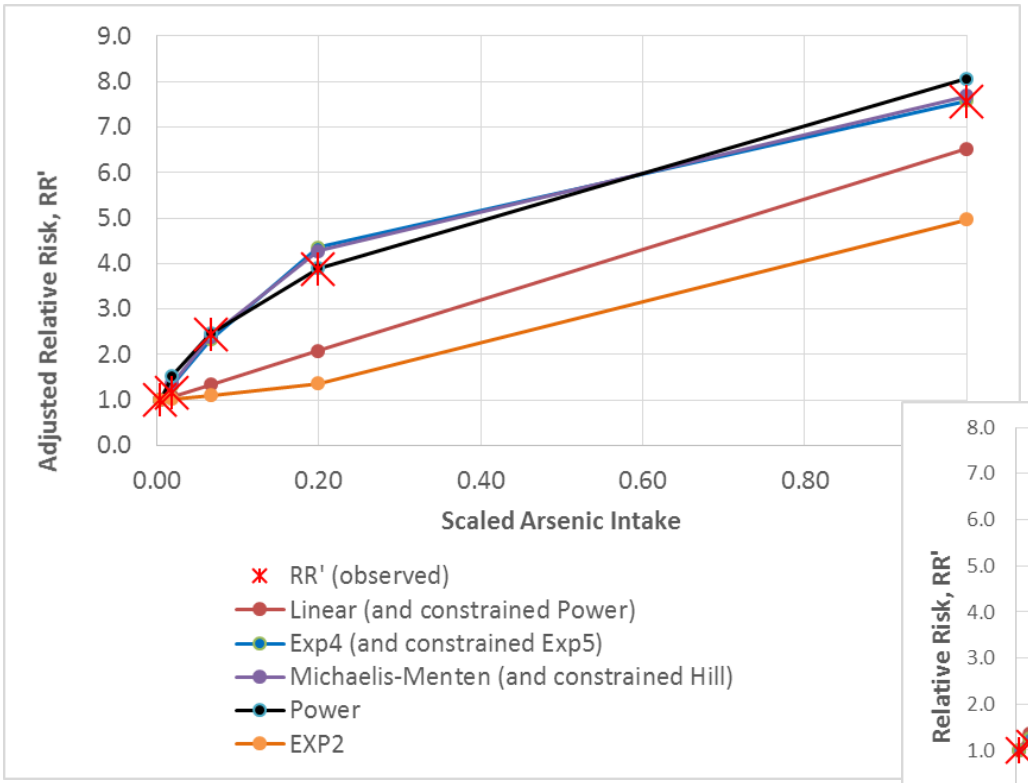
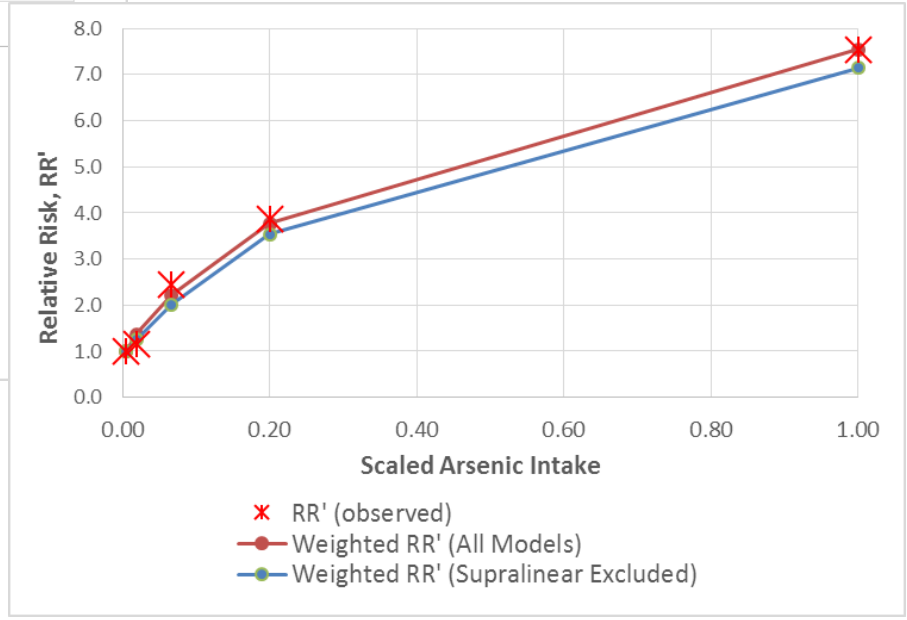
iAs Dose-Response – Model Averaging





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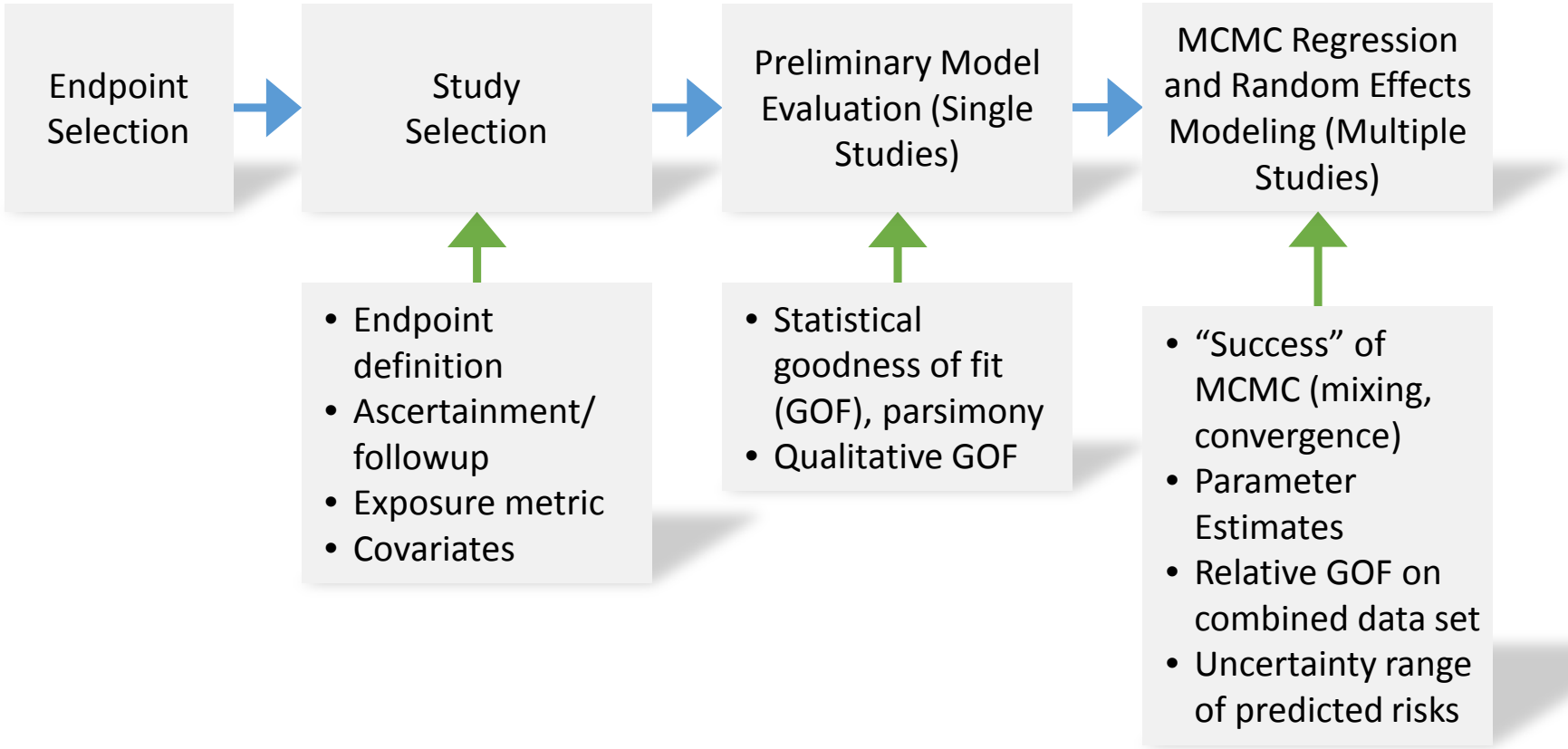
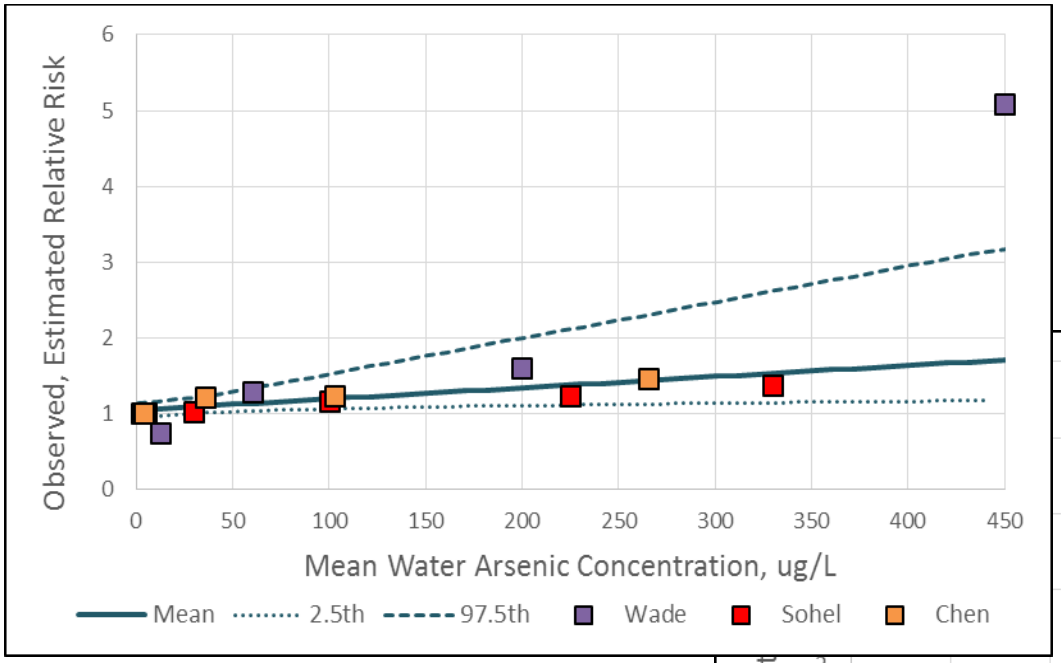
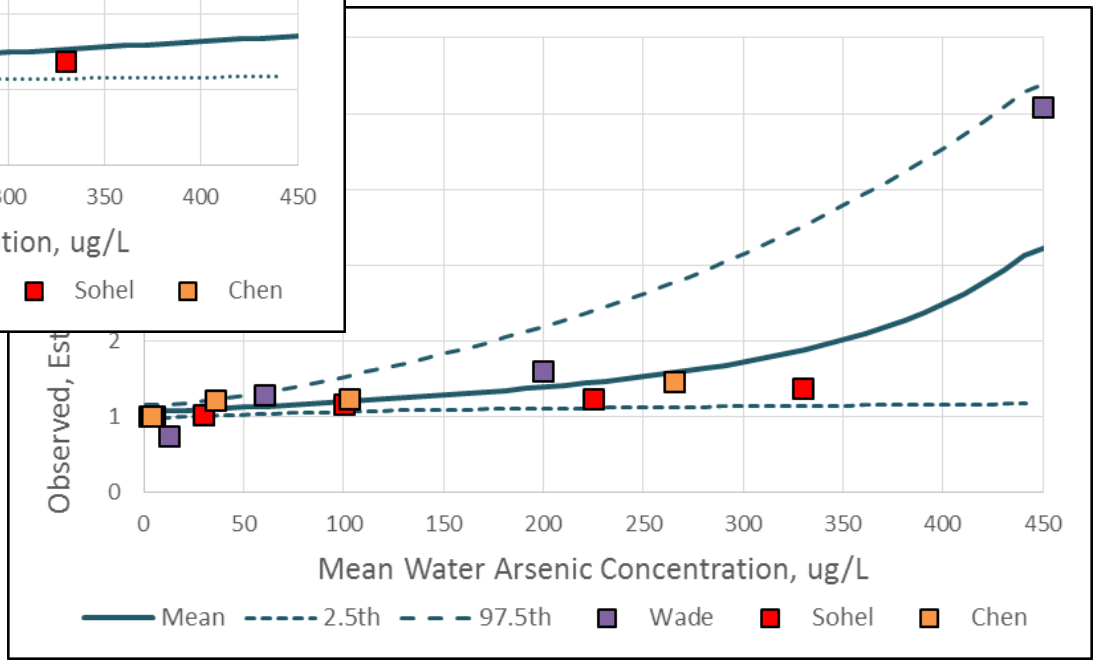
Example of Bayesian Regression Approach (Data from Multiple Studies)



Bayesian Regression - CVD mortality, linear and Exponential 2 random effects models





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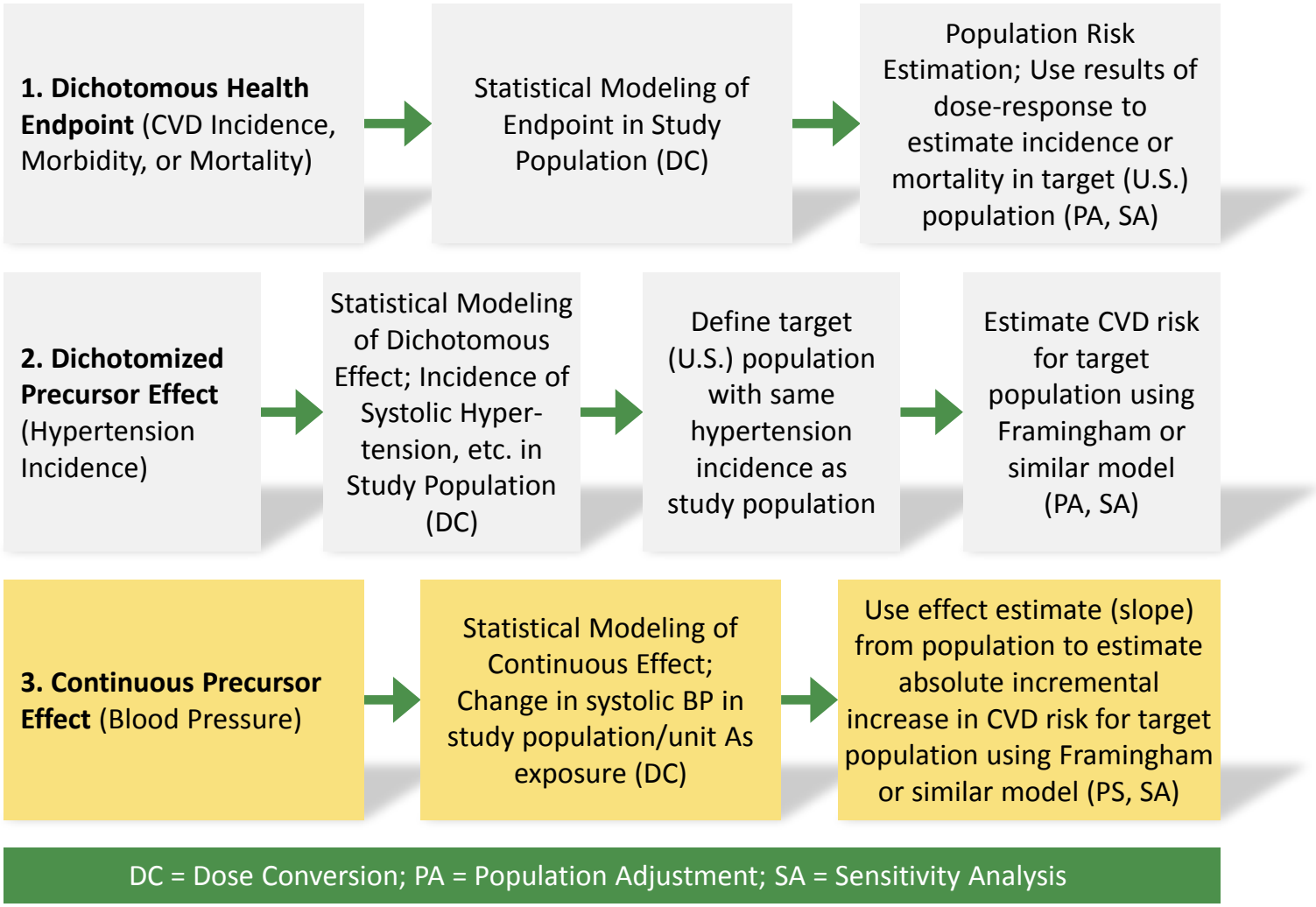
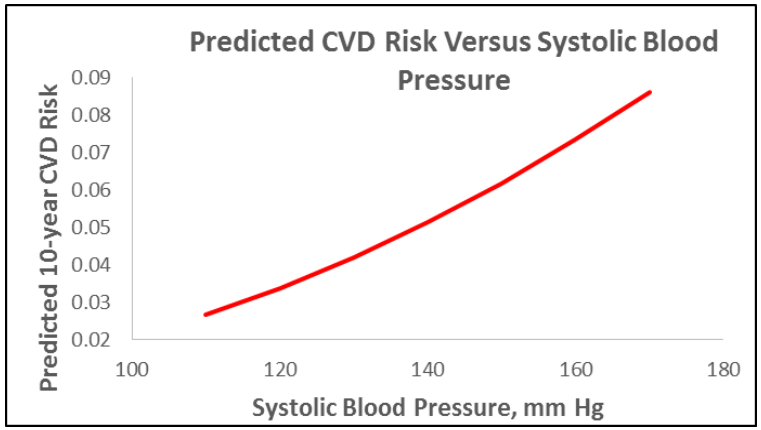
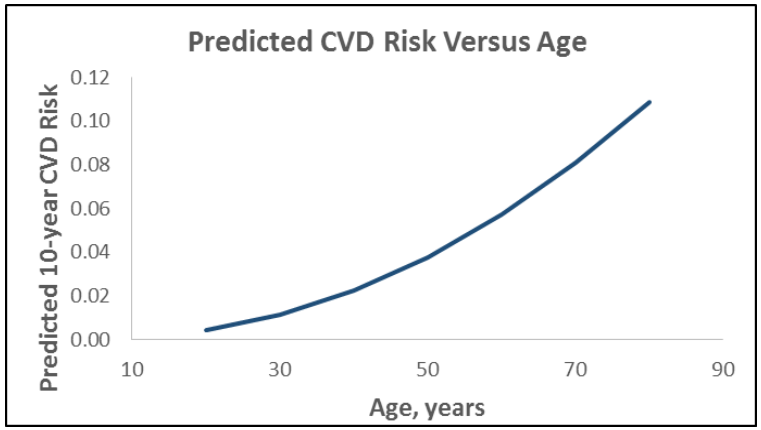
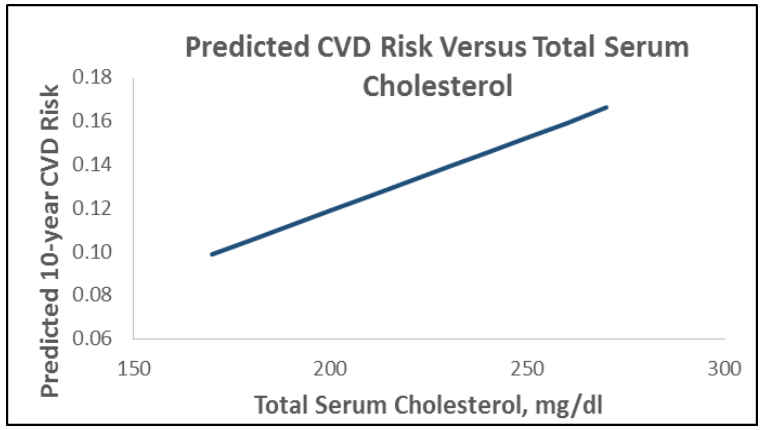
Risk Estimation Strategies for Cardiovascular Endpoints

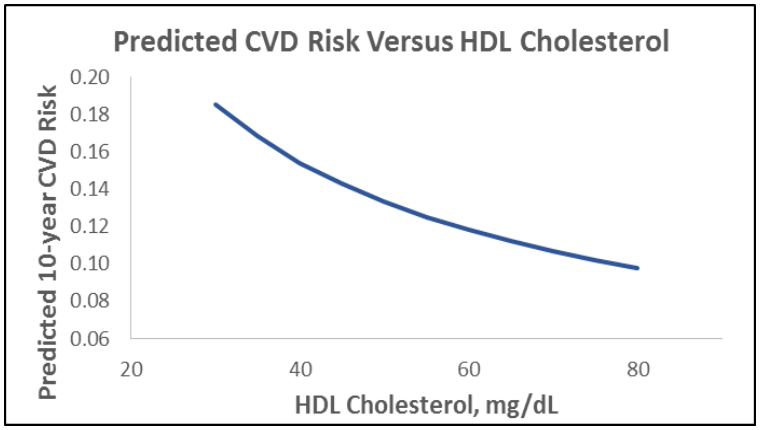


Risk Estimation Strategies for Cardiovascular Endpoints



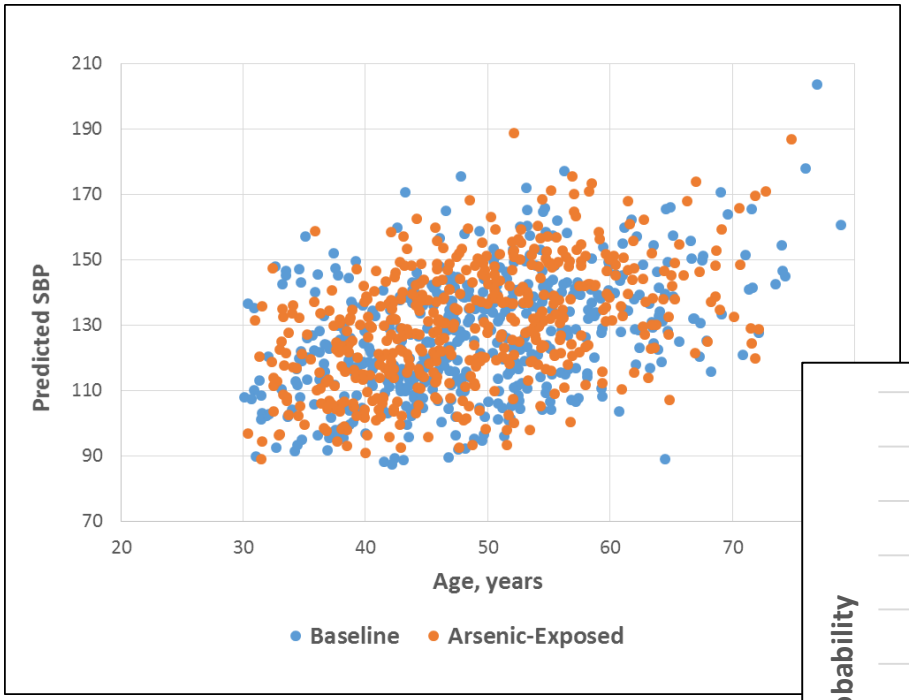




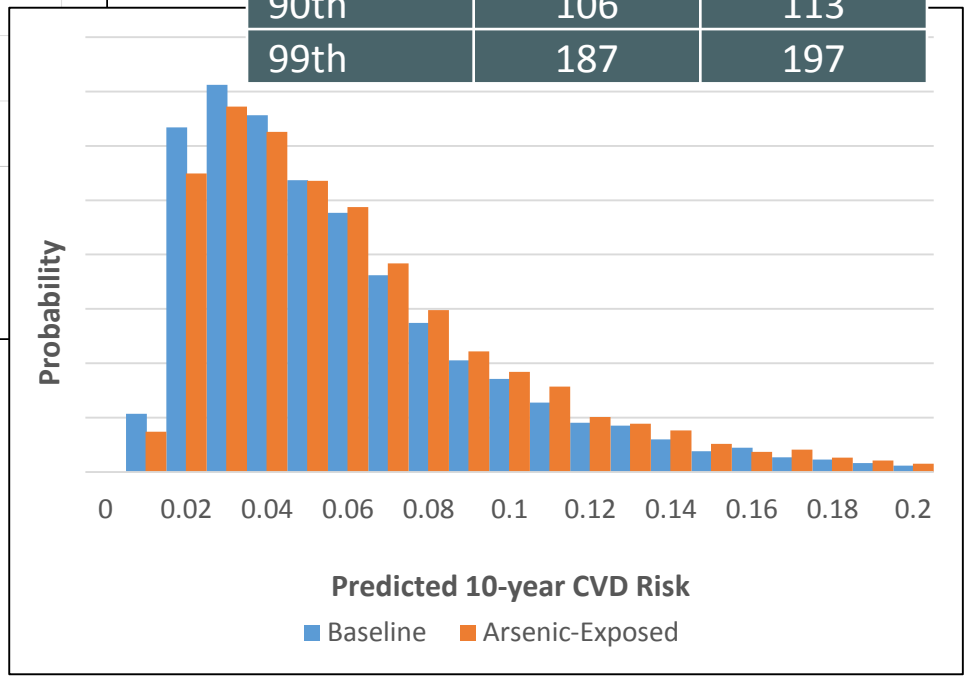


(Estimates for female nonsmokers not treated for hypertension; non-varying parameters are held at their mean values.)

Estimated Change in Blood Pressure, CVD Risks



Predicted 10-Yr. CVD Risk/1,000		
Percentile	Baseline	As-Exposed
1st	8	9
10th	16	18
Median	44	48
Mean	54	58
90th	106	113
99th	187	197



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Summary of Method Examples

Method	Example Endpoints
Dichotomous response measures	Urinary Cancer
Continuous Response Measures	CVD (blood pressure)
Meta-regression	CVD (mortality)

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Summary: Dose-Response

- **Study Selection** – All studies undergo risk-of-bias and study quality review; minimal data required for Tier 1 analysis; Tier 1 results inform study selection for Tier 2/3 analysis
- **Exposure Characterization** – Preference for individual data and exposures < 100 µg/L in water; PBPK model to convert to common dose metric for meta-analyses if possible
- **Response Characterization** – Use author reported responses adjusted for covariates (use individual data if available); endpoints must be similar across studies for meta-analyses
- **Mechanistic Considerations** – Consider in selecting studies, dose, outcome metrics, weighting models for model averaging, assigning prior probabilities to model parameters, and informing sensitivity analyses
- **Meta-Analysis** – Consider whenever sufficient number of low-ROB studies available. Fixed and random effects models may be used to evaluate study heterogeneity
- **Sensitivity Analyses** – Likely subjects of sensitivity analyses include dose-response model form, assignment of parameter priors, exposure concentration, timing, and duration; individual differences in sensitivity, extrapolation of risks to target populations

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Supplemental Information

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Dose-Response Analysis Tiers

Dose-Response Element	Approach	Tier		
		1	2	3
Type of Study Data	Grouped exposure or outcome, or both	✓	✓	✓
	Individual exposure, outcome, covariates		✓	✓
# of Studies Evaluated	One at a time	✓	✓	✓
	Multiple (classical and Bayesian meta-analysis, pooled estimates, where feasible)		✓	✓
Dosimetry	Exposure or intake metrics as reported by authors (e.g., point estimates or ranges)	✓		
	Intake from multiple sources, estimates of exposure uncertainty; from individual exposure data where available		✓	✓
	Biomarker data	✓	✓	✓
	Intraconversion of intake/biomarker metrics using empirical relationships and PBPK models		✓	✓
Dose-Response Model Forms	Standard parametric models (may include benchmark dose-type, etc.)	✓		
	Complex parametric and non-parametric models (random effects, etc.) as appropriate		✓	✓
Dose-Response Modeling Methods	Conventional (primarily maximum likelihood)	✓	✓	
	Markov Chain Monte Carlo estimation of model parameters		✓	✓
	Model averaging		✓	✓
Output Risk Metrics	Dose-response relationships based on grouped data and reported statistical significance	✓		
	Model-based risk estimates (calculated from individual data where available)		✓	✓
	Fully probabilistic risk estimates			✓
Uncertainty and Variability Analyses	Primarily qualitative, evaluation of risk differences across models, studies	✓		
	Sensitivity analyses of variations in exposure, kinetic factors, and response covariates as allowed by data		✓	✓
	Probabilistic modeling of exposure, pharmacokinetic, and prior distribution uncertainty			✓
Low-Dose Extrapolation	Within range of study data	✓		
	Statistical confidence limits on predicted risks		✓	✓
	Risk predictions for target populations considering MOA, individual variability			✓