EPA
United States
Environmental Protection
Agency

Approach to Systematic Review for the IRIS Toxicological Review of Inorganic Arsenic

Janice S. Lee, PhD
Assessment manager
U.S. EPA

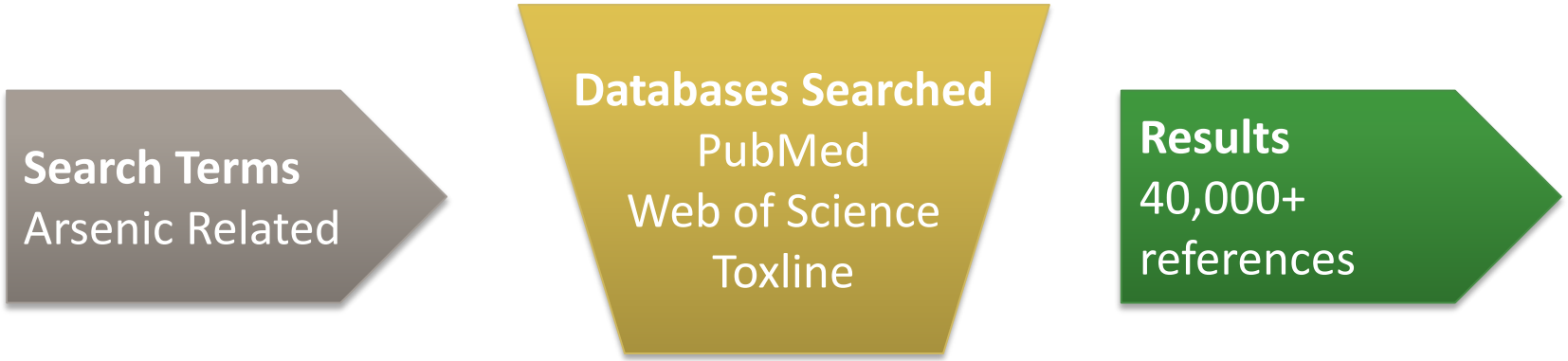
EPA United States Environmental Protection Agency

Outline for Today's Presentations

- Background
- **Approach to Systematic Review**
- Adverse Outcome Pathways
- Hazard Identification
- Toxicokinetics
- Dose-Response Methods

EPA United States Environmental Protection Agency

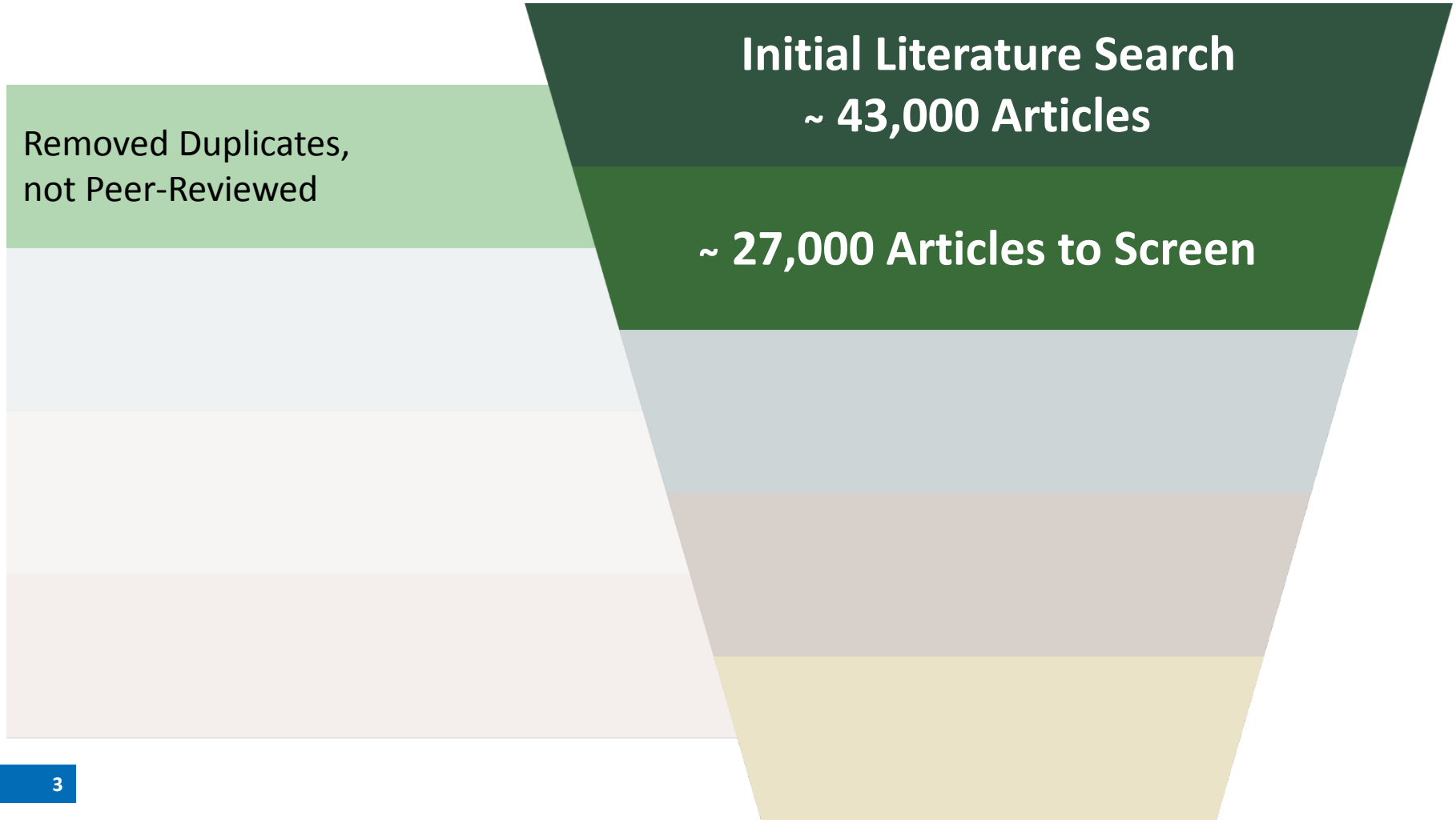
Literature Identification



- Initial literature search completed January 2013
  - Monthly updates using same search terms and databases

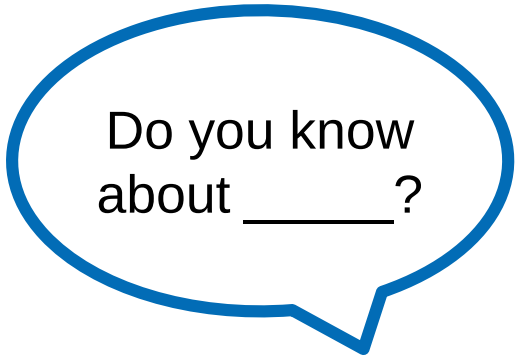
EPA United States Environmental Protection Agency

Comprehensive Literature Search



EPA United States Environmental Protection Agency

Two Approaches for Finding Relevant References



Clustering

Mathematical algorithms applied to create groups of similar references based on text similarities; type of natural language processing

- Does not depend on pre-existing knowledge of references, just natural divisions

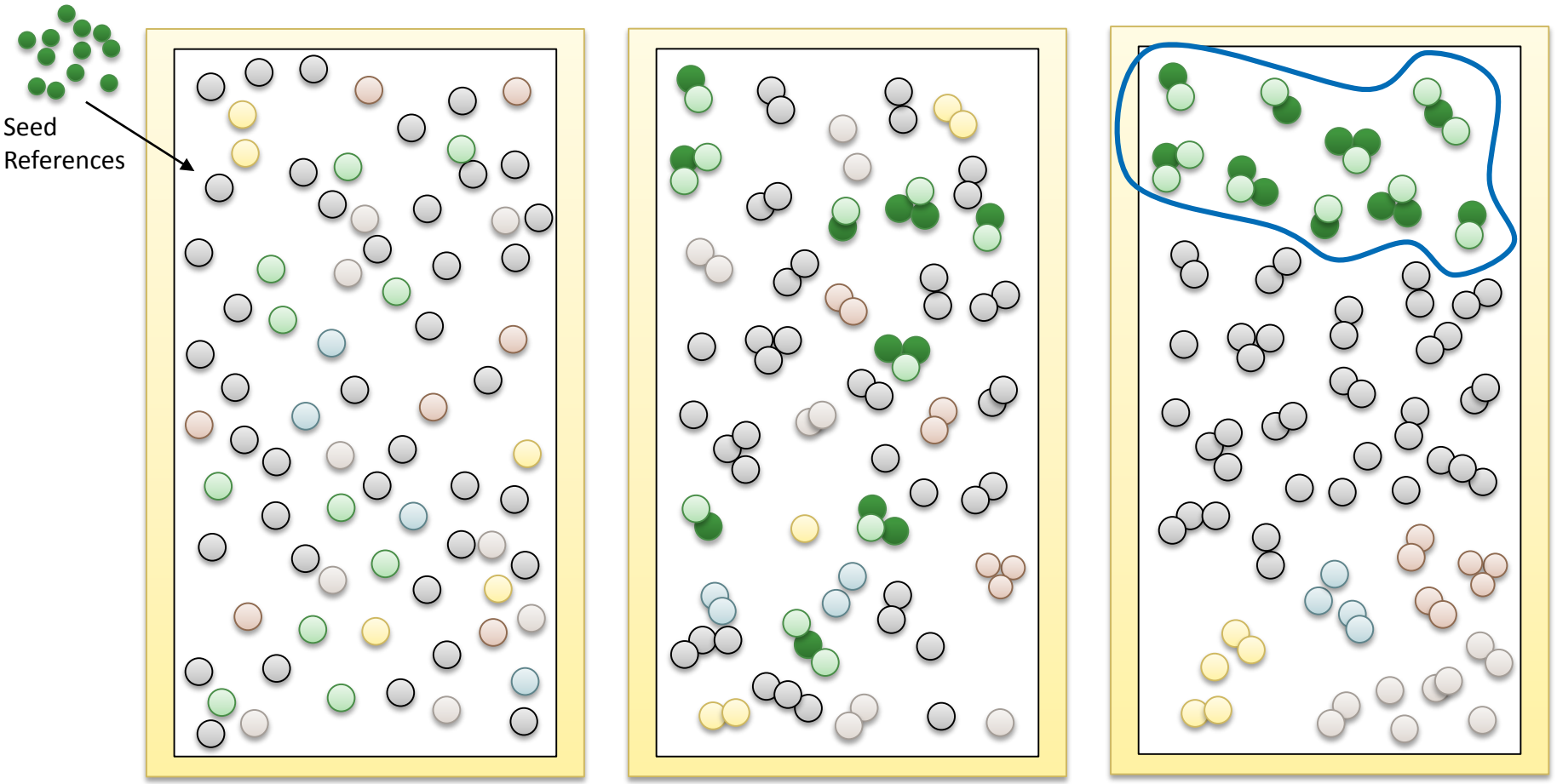
Key Word Search

User-specified list of terms and topics applied to identify groups of similar references

- Depends on user's knowledge of all potential topics of interest

EPA United States Environmental Protection Agency

Use Clustering to Identify Health Effects Literature

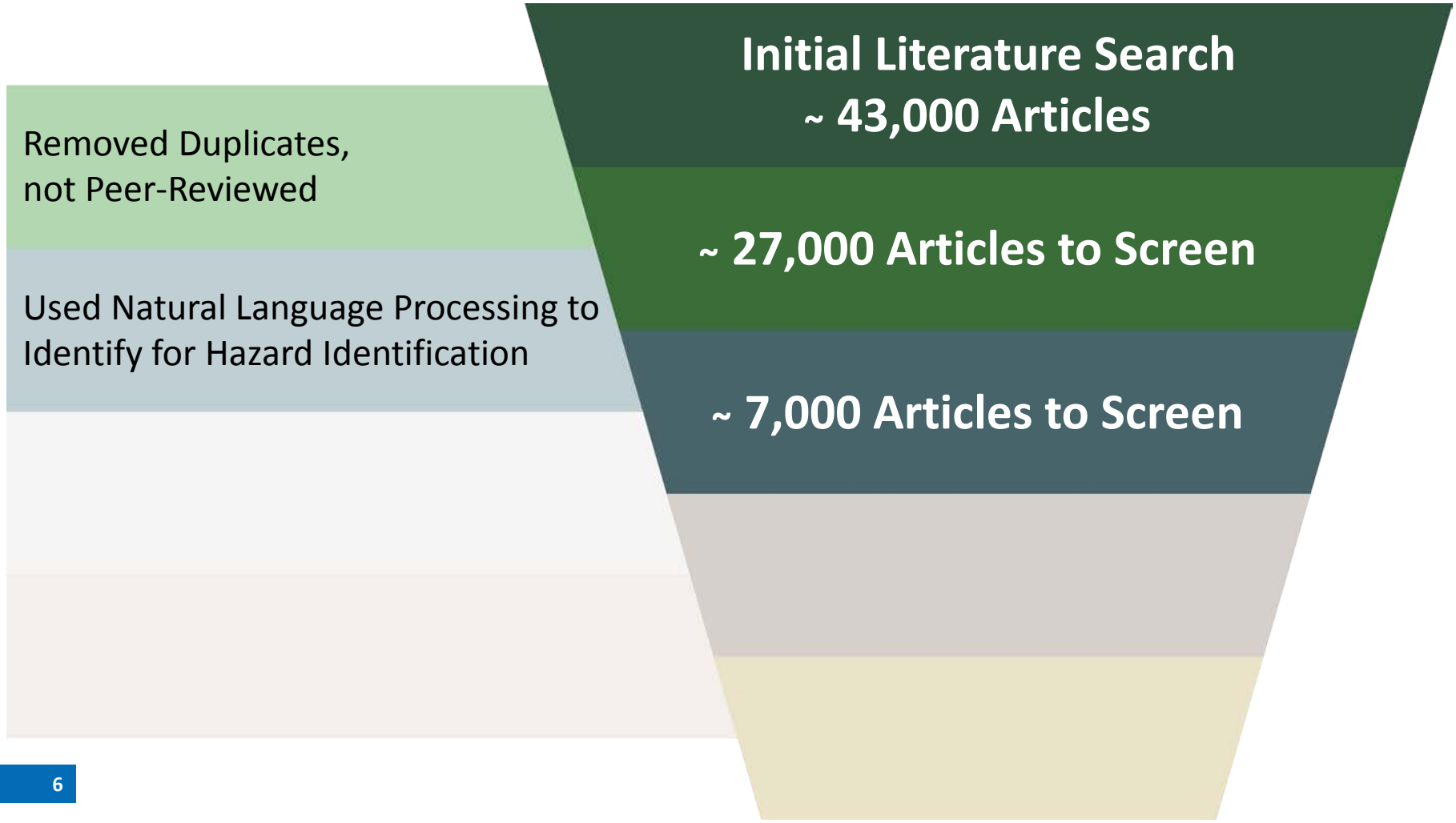


Add seed references to literature search results

Cluster references based on text similarities in titles and abstracts

Further review all clusters containing at least one seed reference

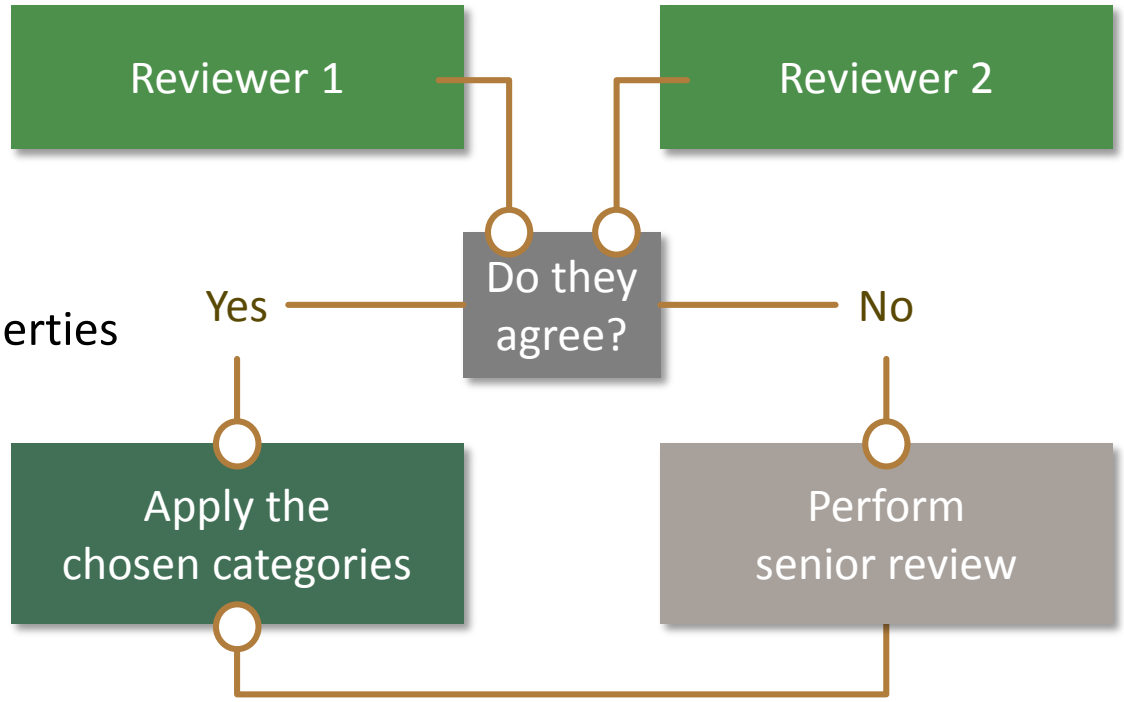
Hazard Identification Clustering Results



Screening to Determine Relevance

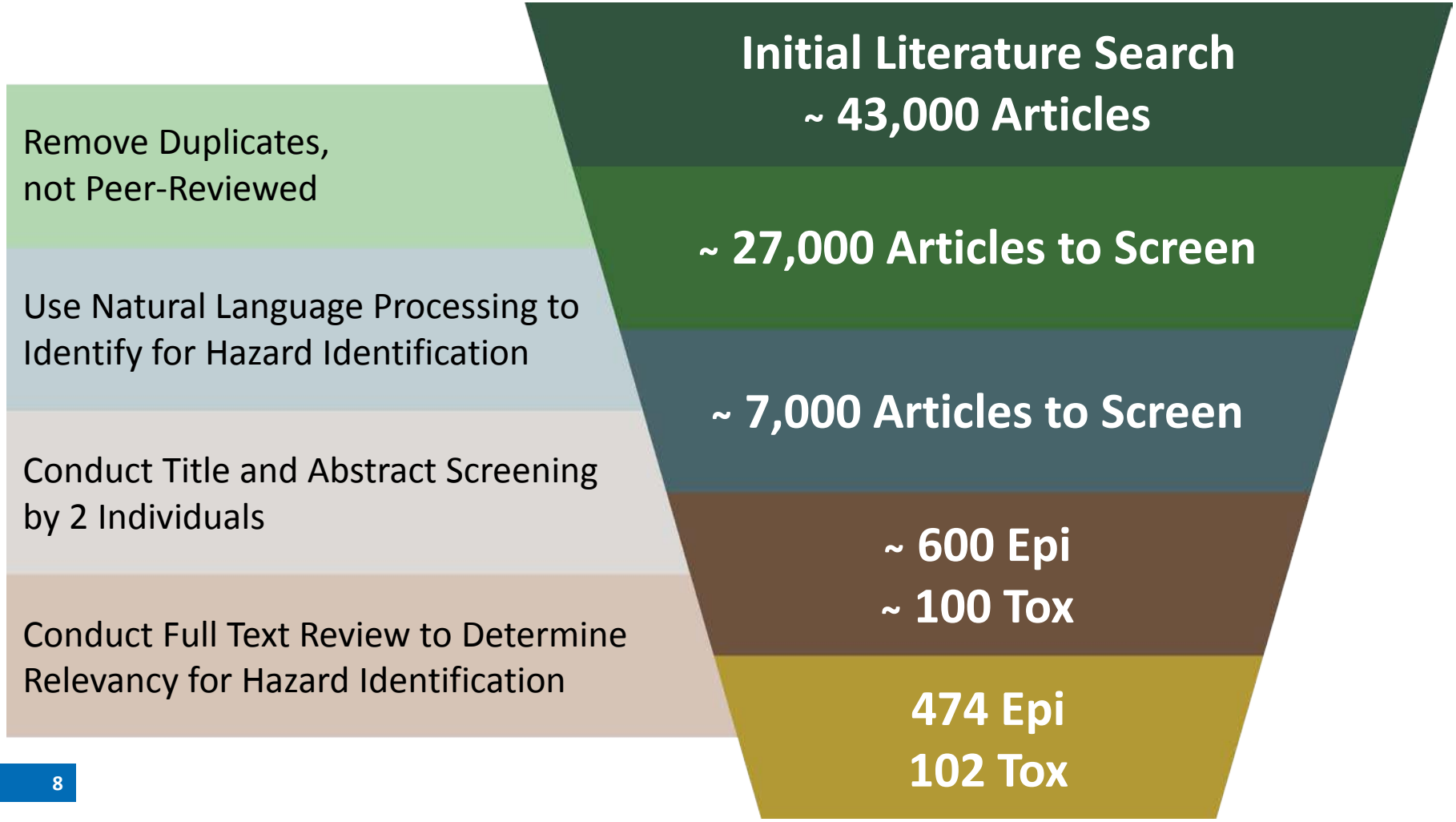
Review title and abstract of each article

- **Epidemiology**
- **Toxicology**
- Susceptibility
- MOA
- PBPK/TK
- Acute Exposure
- Physical/Chemical Properties
- Exposure only
- Ecology
- Non-Arsenic
- Review
- Other



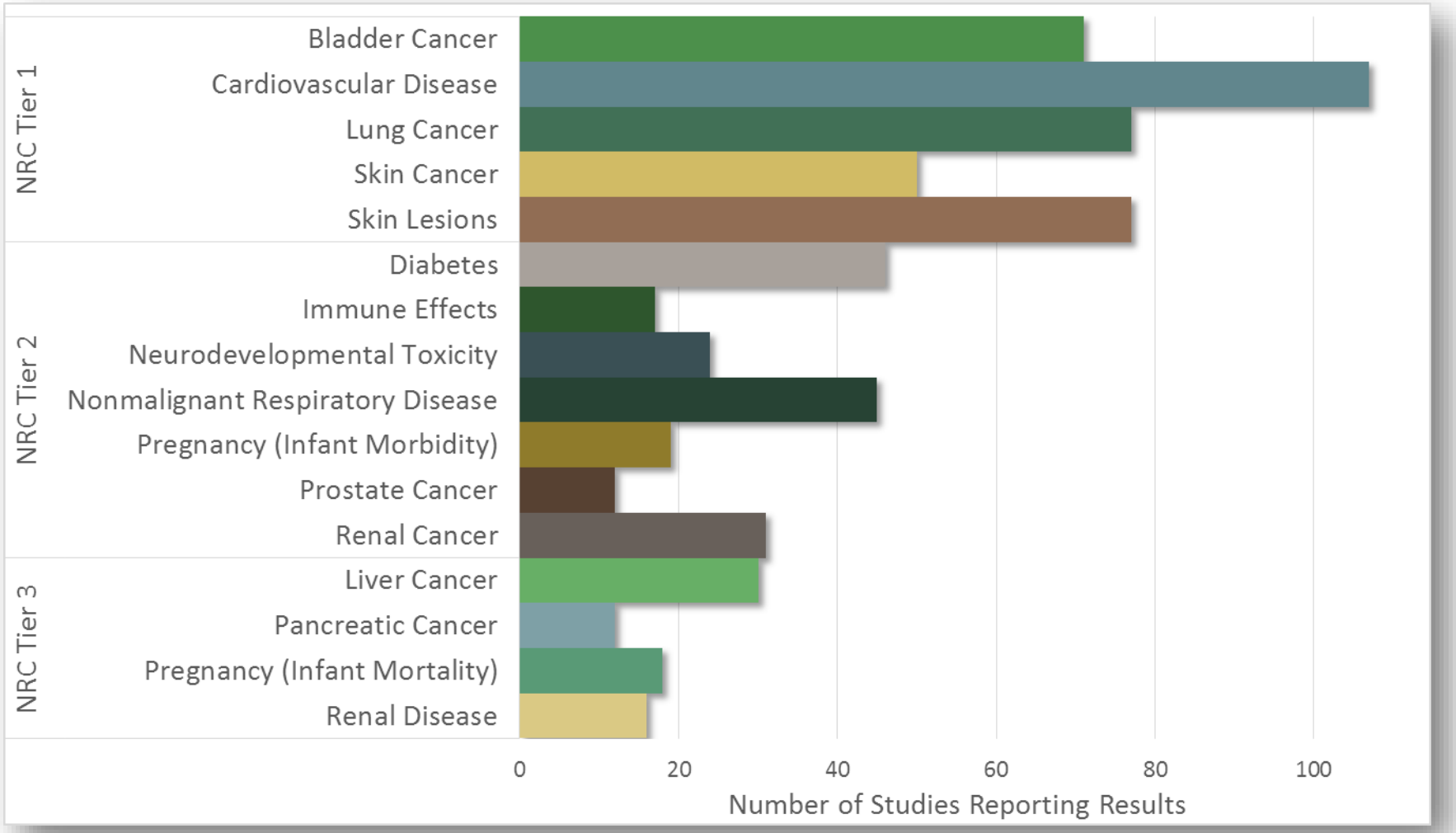
EPA United States Environmental Protection Agency

Systematic Literature Search



EPA United States Environmental Protection Agency

Full-Text Screening Results by Health Effect



EPA United States Environmental Protection Agency

Why Evaluate Risk of Bias?

- NRC recommended:
  - Evaluate risk of bias (ROB) using established methods
    - Bias – "systematic error, or deviation from the truth, in results or inferences"
- Allows us to characterize strengths and weaknesses of individual studies transparently, systematically, and consistently
  - Not a checklist
  - Not inclusion/exclusion criteria
  - Informs hazard identification and dose-response analyses
- Many approaches exist for evaluating ROB with general focus on 6 domains:
  - Selection
  - Confounding
  - Performance
  - Attrition
  - Detection
  - Reporting Bias

EPA United States Environmental Protection Agency

Evaluation of Potential Risk of Bias

- Used approach from the Office of Health Assessment and Translation (OHAT) at National Institute of Environmental Health Sciences (NIEHS)
- For arsenic, developed risk of bias evaluation protocol:
  - Questions under 6 domains
  - Implemented with 2 independent reviewers
  - Rationales and ratings determined for individual questions
  - No overall score or rating assigned to a study
- Risk of bias is useful for selecting studies for dose-response

Elements of the ROB Protocol

- Six **domains** or types of bias:
  - Selection
  - Confounding
  - Performance
  - Attrition
  - Detection
  - Reporting Bias
- One or more **questions** per domain
  - Some questions not applicable to epi or tox studies
  - 4 possible **ratings** for each question
- **Considerations** for each rating specific to study design
  - Further informed by arsenic-specific **clarifications** added to OHAT protocol

EPA United States Environmental Protection Agency

Implementation of the ROB Protocol

- Each question answered with rating AND written rationale

++	**Definitely low risk of bias** - direct evidence of low risk of bias practices
+	**Probably low risk of bias** - indirect evidence OR deviations would not appreciably bias results, including consideration of direction and magnitude of bias
–	**Probably high risk of bias** - indirect evidence of high risk of bias practices OR insufficient information provided about relevant risk of bias practices
– –	**Definitely high risk of bias** - direct evidence of high risk of bias practices

Example of Risk of Bias Question, Considerations, and As-Specific Clarifications*

DOMAIN: DETECTION

Question: **Can we be confident in the outcome assessment?**

Considerations: (for cohort studies)

++ **Direct evidence** of well-established methods such as objectively measured with diagnostic methods, measured by trained interviewers, obtained from registries

As-Specific Clarifications: Cancer cases histologically confirmed; self-reported data validated with medical records

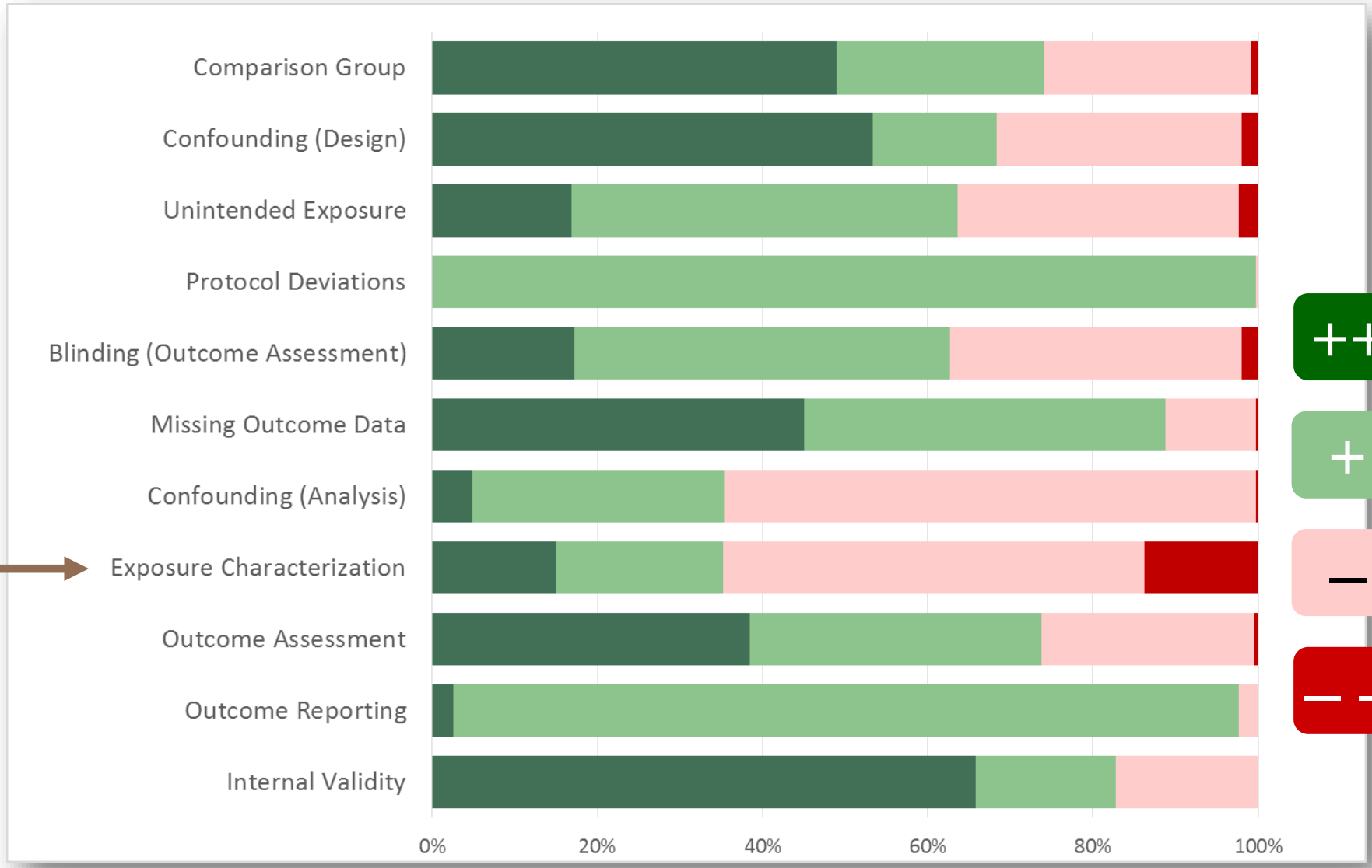
\+ **Indirect evidence** of well-established methods or acceptable methods such as proxy reporting of outcomes, mining of data collected for other purposes

As-Specific Clarifications: Death certificates used but not certified by nosologist; or information on accuracy, validity, and completeness of death certificates not described

* Information presented is incomplete due to space limitations of slide. Complete details recorded in protocol.

EPA
United States
Environmental Protection
Agency

Risk of Bias Results for 474 Epi Studies



EPA United States Environmental Protection Agency

Observations Following Risk of Bias Evaluations

- **Perfect set of questions does not exist:** Does not eliminate need for expert judgement
- **Refinements needed:** Environmental health community needs to develop questions tailored to environmental exposure and epidemiology studies
- **Increased quality:** Two independent reviewers provide confidence in conclusions
- **Increased consistency:** All studies evaluated based on same considerations
- **Increased transparency:** Rationales documented
- **Increased time:** Average ~3 hours per study (1.5 hours per reviewer)

Data Extraction for Summary Evidence Tables

- Extracted data from all studies into evidence tables
- Use risk of bias, evidence tables, full-text publications, and expert judgement to develop hazard identification sections

Reference and study design	Exposure measures	Results
Bates et al. (2004) **Study Type:** case-control **Location:** Argentina (Cordoba Province) **Population:** residents in region with high arsenic water concentrations n cases: 114 n control: 114	**Exposure Surrogate:** drinking water **Exposure Description:** average arsenic water concentration estimated for 6-40 years prior to interview based on samples collected from wells near individual's current and past residences **Population-Level Exposure:** 164 ug/L mean	**Outcome: bladder cancer** ***arsenic concentration (excluding proxy wells) (quartiles), ug/L*** Exp. Level / N / adjOR / (CI) 0-50 / 87 / 1 / n/a 51-100 / 8 / 1.11 / 0.3, 3.7 101-200 / 13 / 0.81 / 0.3, 2.0 >200 / 3 / 0.28 / 0.1, 1.4 Stat Method: multivariate conditional logistic regression ***arsenic concentration, including proxy wells, all subjects (quartiles), ug/L*** Exp. Level / n / adjOR / (CI) 0-1.0 / 34 / 1 / n/a 1.1-17 / 21 / 0.35 / 0.10, 0.90 18-80 / 32 / 0.9 / 0.30, 2.30 >80 / 27 / 0.46 / 0.20, 1.30 Stat Method: conditional logistic regression ***consumption of well water over past 61-70 years, smokers only, ug/L*** Exp. Level / N / adjOR / (CI) No / 37 / 1 / n/a Yes / 30 / 2.54 / 1.0, 6.4 Stat Method: multivariate unconditional logistic regression (adjusted for highest daily number of cigarettes ever smoked)

Literature Search Approach for MOA/AOPs

- Purpose: Find information to support MOA/AOP analyses
- Used clustering with seed references from previous assessments
- Identified data related to key events with key words

EPA United States Environmental Protection Agency

Literature Search Approach for Susceptibility

- Purpose: Find information on susceptible populations and factors
- Used Key Word Search approach for these topic areas
  - Polymorphisms
  - Lifestages
  - Smoking
  - Alcohol consumption
  - Sex
  - Microbiome
  - Pre-existing disease
  - Co-exposure
  - Nutrition
  - Socioeconomic factors
  - MOA

EPA United States Environmental Protection Agency

Summary: Systematic review

- Broad **literature search** followed by **categorization** and **screening for relevance**
  - Epidemiologic and toxicologic health effects data
  - Susceptibility data
  - Mechanistic information to evaluate adverse outcome pathways
- **Risk of bias evaluation** of epidemiology and toxicology studies
- **Extraction** of study characteristics and results compiled into database

EPA United States Environmental Protection Agency

Acknowledgments

- Ila Cote, Jeff Gift, Glinda Cooper, Ellen Kirrane, Tom Luben, Ryan Jones, Vince Cogliano, members of NCEA Epidemiology Workgroup, members of NCEA Systematic Review Workgroup, and others at U.S. EPA
- Audrey Turley, Robyn Blain, Sorina Eftim, Cara Henning, Michelle Cawley, Bryan Luukinen, Susan Goldhaber, Pam Ross, Courtney Skuce, Dave Burch, and others at ICF International
- Andy Rooney and Kris Thayer at NIEHS

Supplemental Information

EPA United States Environmental Protection Agency

Risk of Bias Domains and Questions for Epidemiology Studies

- Selection Bias
  - Were the comparison groups appropriate?
- Confounding
  - Did the study design or analysis account for important confounding and modifying variables?
  - Did researchers adjust or control for other exposures that are anticipated to bias results?
- Performance
  - Did researchers adhere to the protocol?
- Attrition
  - Were outcome data complete without attrition or exclusion from analysis?

EPA United States Environmental Protection Agency

Risk of Bias Domains and Questions for Epidemiology Studies (cont.)

- Detection
  - Were the outcome assessors blinded to study group or exposure level?
  - Were confounding variables assessed consistently across groups using valid and reliable measures?
  - Can we be confident in the exposure characterization?
  - Can we be confident in the outcome assessment?
- Selective Reporting
  - Were all measured outcomes reported?
- Other
  - Were there no other potential threats to internal validity (e.g., statistical methods were appropriate)?