EPA
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Strategic Adverse Outcome Pathway Analysis to Inform Human Health Risk Assessment: An Example with Inorganic Arsenic

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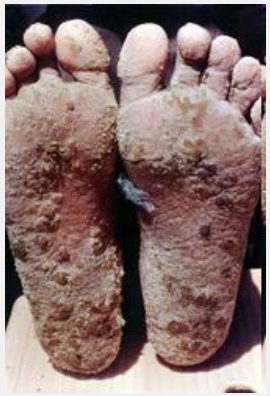
Context: Inorganic arsenic (iAs)

- Ubiquity of arsenic
  - Multiple organizations, agencies

- Potential exposures
  - Water, food, juice
  - Susceptible populations



- Health effects*

Cancer

- Lung†
- Skin†
- Bladder†
- Prostate
- Pancreatic
- Renal
- Liver

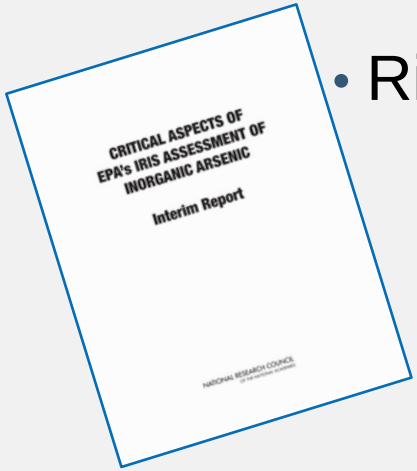
Noncancer

- Ischemic heart disease
- Skin lesions
- Diabetes
- Nonmalignant respiratory disease
- Pregnancy outcomes
- Neurodevelopmental toxicity
- Immune effects
- Renal disease
- Hypertension
- Stroke

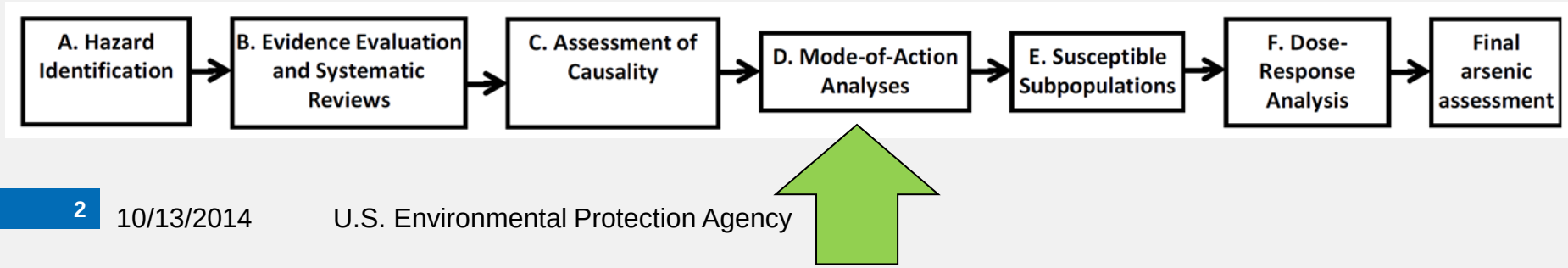
*NRC 2013, †IARC 2012

Context: Risk Assessment & Management of iAs

- Risk management
  - Guidance, restrict, label food products
  - Drinking water limits



- Risk assessment
  - FDA draft: Apple juice
  - EPA: Integrated Risk Information System
    - Hazard identification and dose-response
    - Stakeholder and partner recommendations
    - National Research Council recommendations



Approach: AOP analysis in iAs IRIS Assessment

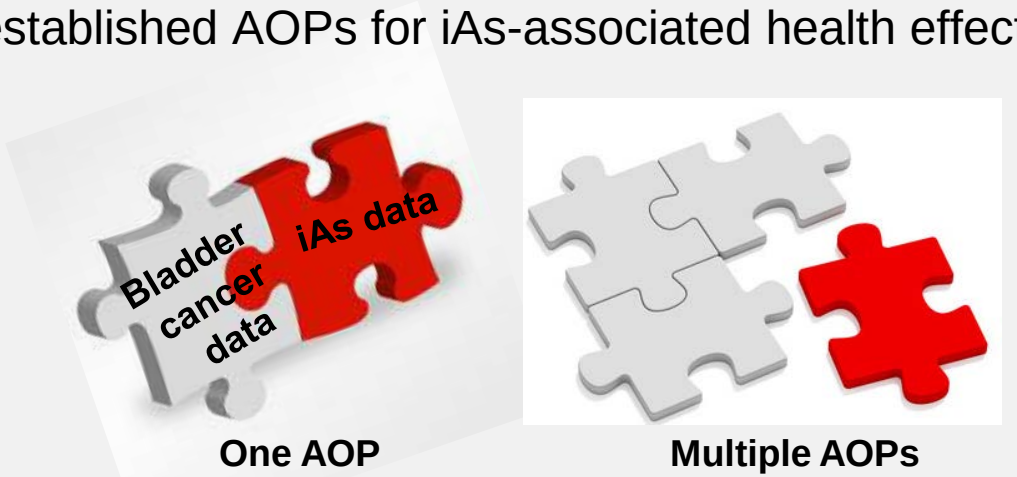
1. Provide problem formulation statement (Develop Populations, Exposures, Comparators, Outcomes [PECO] statement for AOP analysis)
2. Tabulate adverse outcome data (supporting & conflicting)
3. Provide pharmacokinetic data for each adverse outcome & its precursors (exposure & temporal ranges)
4. List modes of action for each adverse outcome (link pharmacokinetic & pharmacodynamic data to adverse outcome in exposure & temporal manner)
5. Construct concordance table (strengths, weakness of each MOA by species, population, subpopulation)

NRC, 2013

*"The **mode-of-action framework** (Boobis et al. 2006, 2008; Carmichael et al. 2011) **in conjunction with the human-relevance framework** (Meek et al. 2003) provides a transparent method of organizing information for hazard identification and risk assessment that includes exposure information, dose–response information, a clear conclusion, identified data gaps, and potentially susceptible populations."*

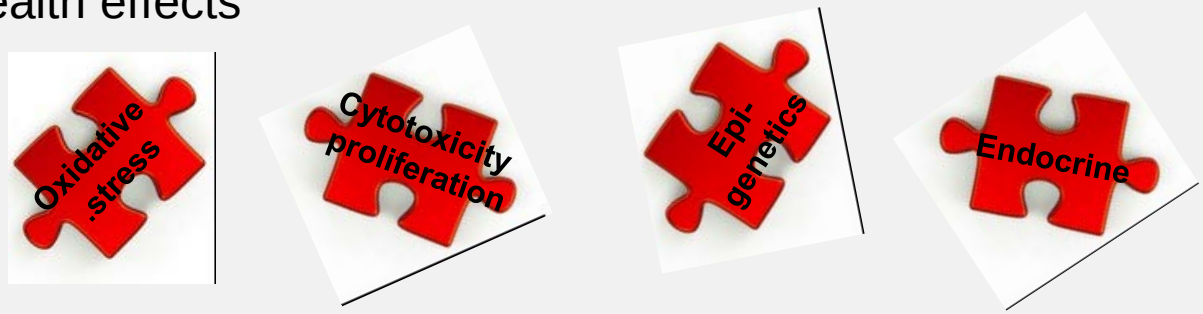
Approach:
AOP analysis in iAs IRIS Assessment

- **Ideal world:** established AOPs for iAs-associated health effects



One AOP **Multiple AOPs**

- **Reality:** many hypothesized mechanisms of action for iAs-associated health effects



- **Solutions:**
  - systematic review of mechanistic data per NRC guidance (short-term)
  - scientific community (research & regulatory) → develop & validate AOPs (long-term)

Adverse Outcome Pathway analysis: PECO statement development

Goal: Clearly define what AOP analysis can inform & how data would influence assessment

AOP Analysis Key Question: For dose-response analysis of an iAs health effect in humans (including susceptible populations), do mechanistic data **increase or decrease confidence** in the: 1) response metric selection, 2) dose-metric selection, or 3) model selection (e.g., linear low-dose, high-dose plateau), or 4) human variability?

Draft Dose-Response Confidence Evaluation:

Confidence in Dose-Response Analysis

Initial Confidence based upon Key Features of Analyses
HIGH (++++)
MODERATE (+++)
LOW (++)
VERY LOW (+)

→

Mechanistic Data Factors: ↑ / ↓ Confidence
Biological concordance Key Event Essentiality Temporal concordance Dose-response concordance Consistency

→

Confidence in Dose-Response Analysis with Mechanistic Data
HIGH (++++)
MODERATE (+++)
LOW (++)
VERY LOW (+)

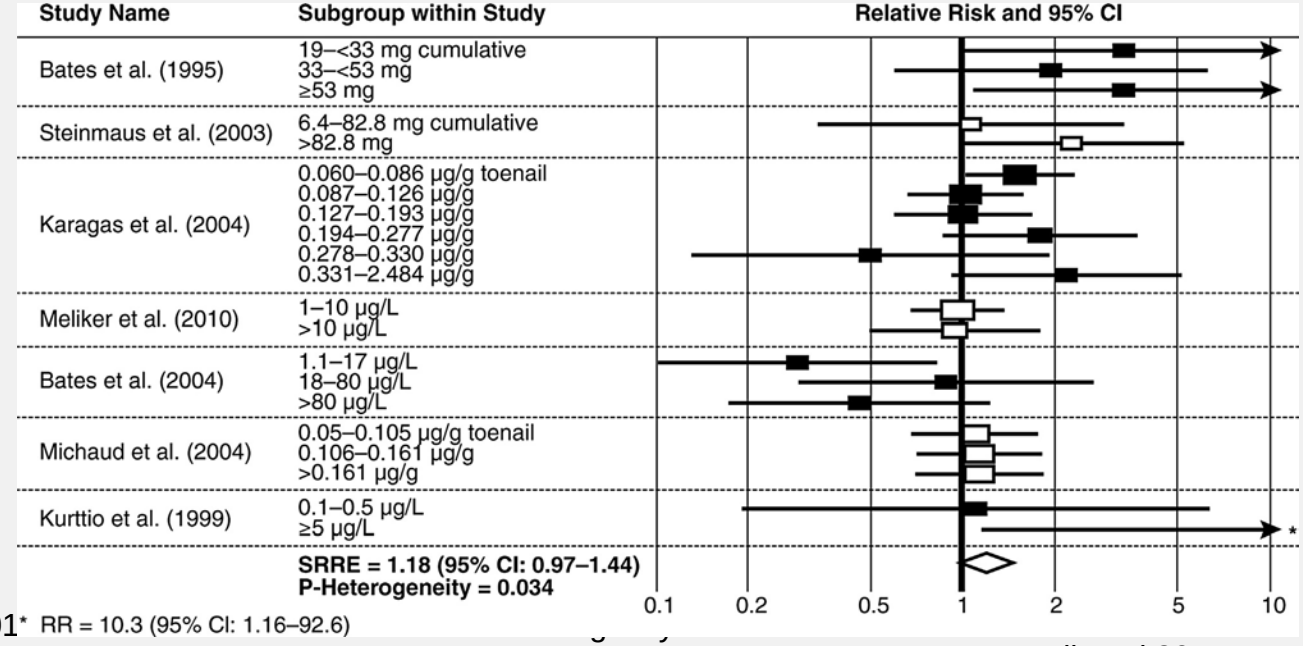
Informed by Simon et al 2014, Meek et al 2014, Rooney et al 2014

Adverse Outcome Pathway analysis: PECO statement development

iAs-induced bladder cancer example

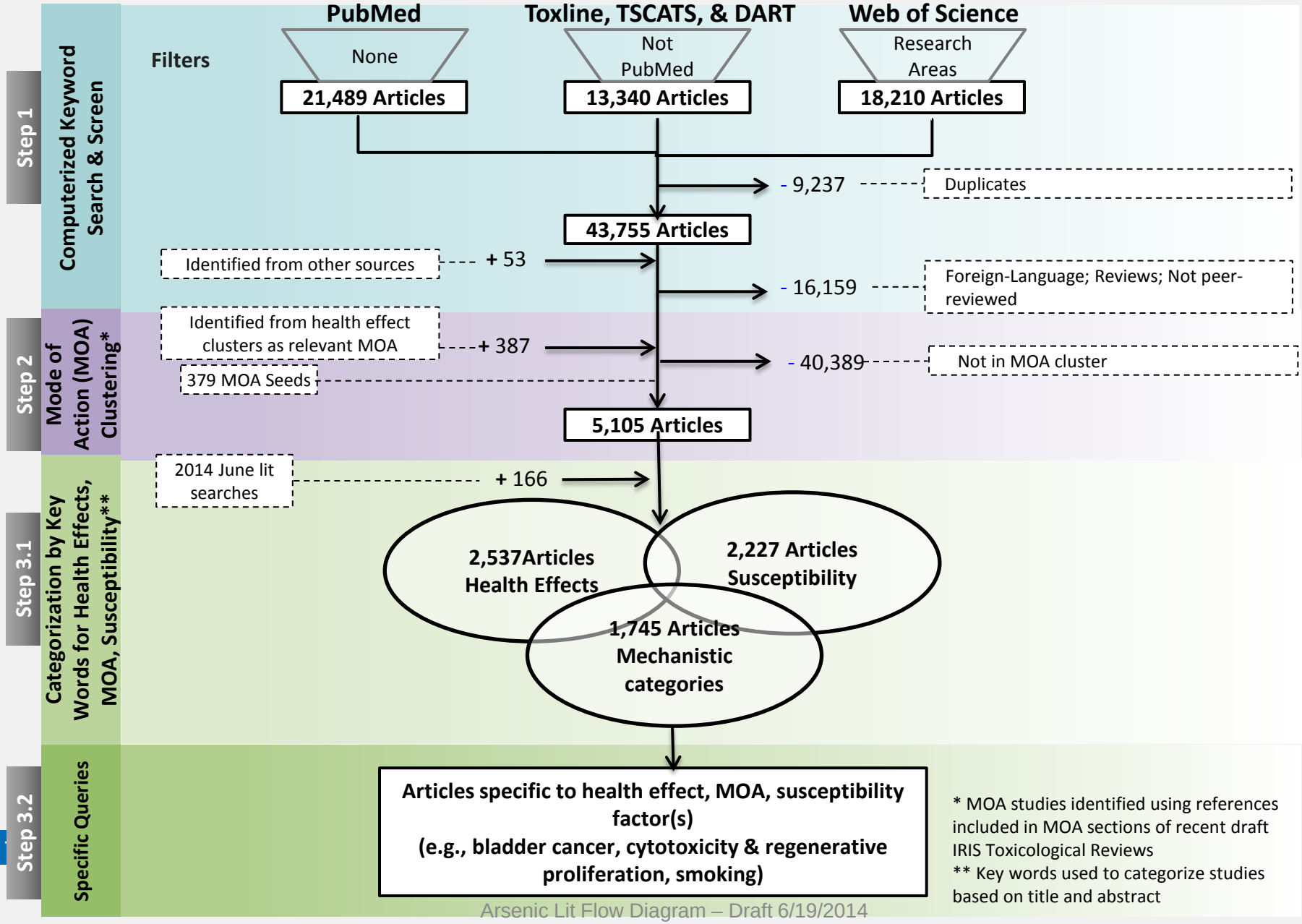
- *Example PECO Question:* Studies in human populations show mixed results when examining the relationship between low level (<10 ug/L) iAs exposures and bladder cancer in smokers. Do mechanistic data ↑/↓ confidence that iAs interacts with other causes of bladder cancer (e.g., smoking) in different populations (e.g., selection of additive vs. relative risk models)?

Example analysis of iAs bladder cancer risk in ever smokers:



Tsuji et al 2014.

AOP Analysis: PECO statement development (Literature Review)

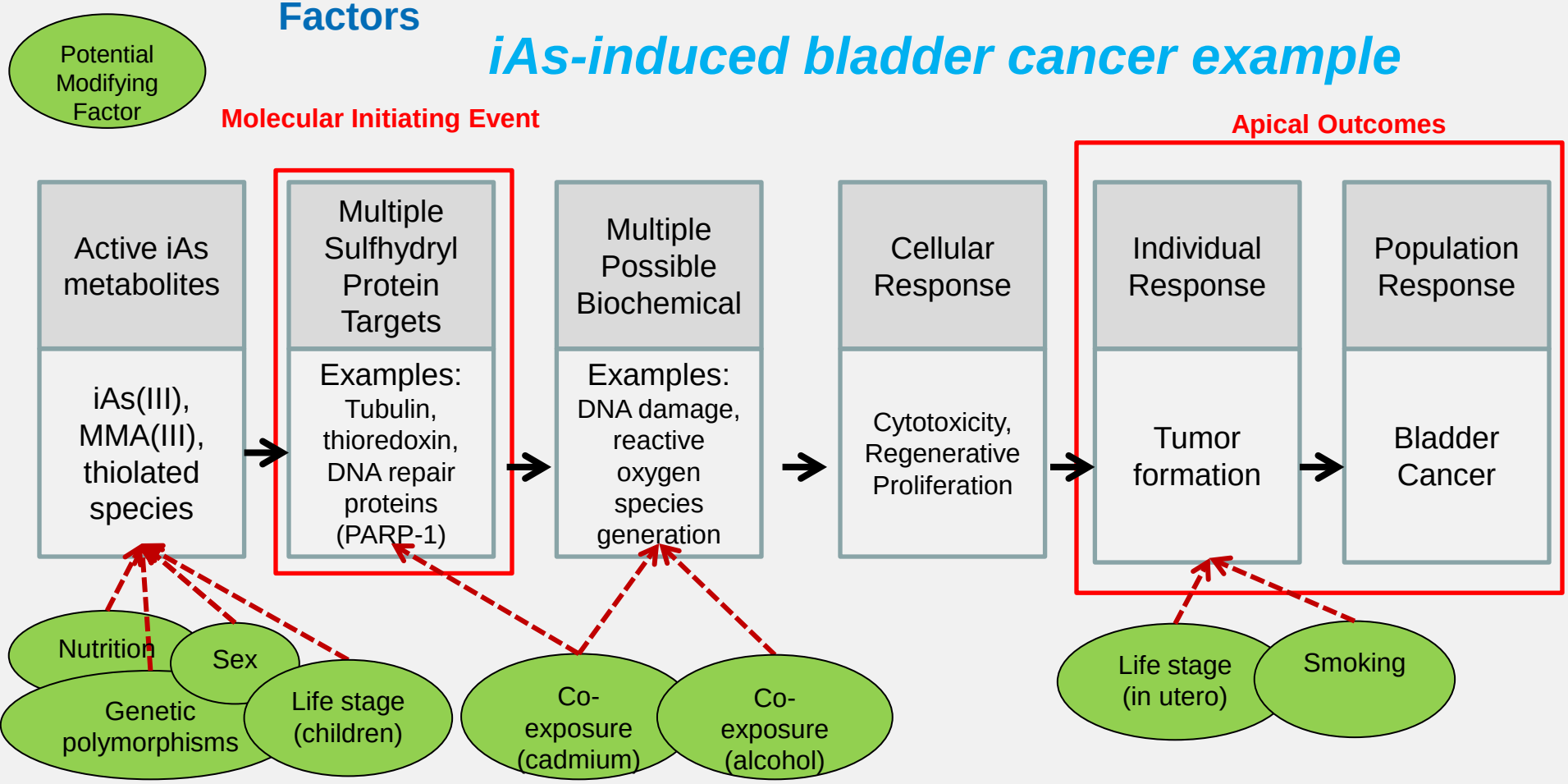


* MOA studies identified using references included in MOA sections of recent draft IRIS Toxicological Reviews

** Key words used to categorize studies based on title and abstract

Adverse Outcome Pathway analysis: Data visualization— Hypothesized Key Events & Modifying Factors

iAs-induced bladder cancer example



→ One of several hypothesized AOPs

→ Not necessarily simple progression of Key Events

→ How to consider confidence in modifying factors at relevant exposure levels?

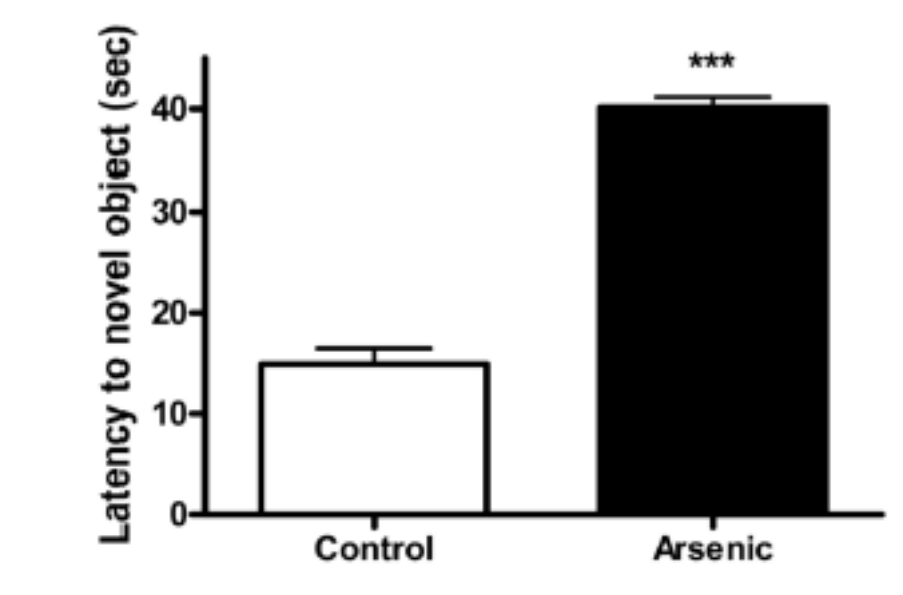
→ How to consider confidence in interactions (or lack thereof) between modifying factors?

Simon et al, 2014; See reference list for iAs references

Adverse Outcome Pathway analysis: PECO statement development

iAs-induced developmental neurotoxicity example

- *Example PECO Question:* Human and animal data suggest that early life exposures to iAs may result in developmental neurotoxicity, yet measures of exposure and response are not consistent between animal and human studies. Do mechanistic data ↑/↓ confidence in selection of IQ measures as a response metric for developmental neurotoxicity (i.e., response metric selection)?



Martinez-Finley et al 2009

Adverse Outcome Pathway analysis in iAs IRIS Assessment: Challenges for Discussion

- Developing an AOP vs. querying an AOP for relevance to assessment of a particular chemical
  - Pursuit of data for scientific vs. assessment interests
  - Confidence in data to "validate" an AOP vs. inform an assessment
  - Methods to determine confidence in key events, modifying factors, AOP, chemical-specific data relevant to KE, MFs, AOP
  - Communication tools: process and outcomes of confidence determination

- Systematic review of mechanistic literature
  - Generally larger body of studies compared to health effects
  - Terminology varies in literature
  - Lack of methods for study quality review
    - Internal validity, external validity, risk of basis

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