EPA
United States
Environmental Protection
Agency

Systematic Review Methods Used to Prioritize Health Outcomes

Janice Lee, Ellen Kirrane, and Tom Luben

Office of Research and Development
National Center for Environmental Assessment, IRIS

July 16, 2019

Outline for Today's Presentations

- Introduction and Role of the Protocol in the IRIS Systematic Review Process
- Updated Problem Formulation and Scoping
- **Systematic Review Methods Used to Prioritize Health Outcomes**
- Dose-Response Assessment and Derivation of Slope Factors and Reference Values

Specific Aims

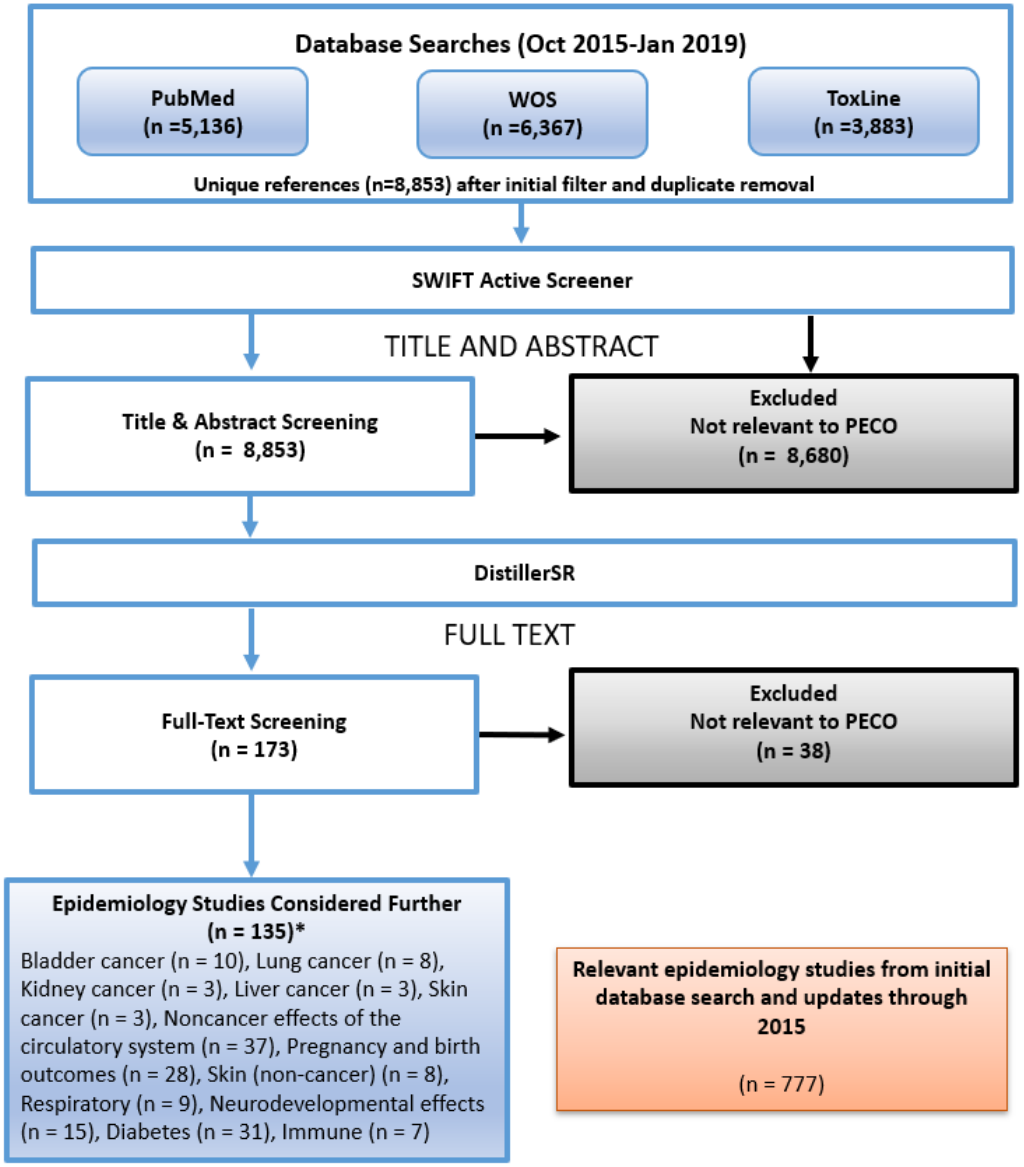
- Identified human studies reporting effects of exposure to iAs, focusing on health outcomes suggested by the NRC (2013):
  - Tier 1 (Bladder cancer, lung cancer, skin cancer, skin lesions, ischemic heart disease)
  - Tier 2 (Diabetes, birth weight, neurodevelopmental effects, immune effects, renal cancer, prostate cancer, nonmalignant respiratory disease)
  - Tier 3 (Hypertension, stroke, fetal loss/stillbirth/neonatal mortality, liver cancer, pancreatic cancer, renal disease)
- Conducted study evaluations (risk of bias) using OHAT approach
- Strength of evidence synthesis conclusions across epidemiology studies expressed by relying on conclusions from other assessments or conducting new systematic review evidence synthesis analysis
  - Because bladder cancer, lung cancer, skin cancer, and skin lesions are accepted hazards, the strength of evidence for these outcomes was considered *robust* and no new evidence synthesis was conducted. Focus on studies considered suitable for dose-response analysis.
  - For other health outcomes, new systematic review evidence synthesis analysis was conducted to characterize the strength of evidence for potential hazard

NRC (National Research Council). (2013). Critical aspects of EPA's IRIS assessment of inorganic arsenic: Interim report. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/18594/critical-aspects-of-epas-iris-assessment-of-inorganic-arsenic-interim

Populations, Exposures, Comparators, and Outcomes (PECO)

PECO element	Evidence
Populations	This assessment focuses on human studies only to include any population and life stage (occupational or general population, including children and other sensitive life stages or populations).
Exposures	Subchronic- or chronic-duration studies of interest provide quantitative estimates of exposure with measurements based on biomonitoring data (e.g., hair, nails, urine, or blood), inhalation (air exposures [$\mu g/m^3$]), drinking water exposures ($\mu g/L$), cumulative exposures ($\mu g/m^3$-yr; $\mu g/L$/-yr), and doses expressed as $\mu g/d$ and $\mu g/kg$-d. Studies with episodic or acute exposures will be excluded (i.e., poisonings or other short-term exposures that last up to 30 d). Studies using arsenicals, primarily arsenic trioxide and Fowler's solution will be excluded because chemotherapeutic agents are not within the scope of this review. Studies using arsenide (As^{3-}), an inorganic form of arsenic, also will be excluded. Exposures usually occur via the gas arsine and result in a different, distinctive toxicological profile based on binding to hemoglobin and red blood cell lysis.
Comparators	A comparison or reference population with no detectable exposure or exposure to lower levels of inorganic arsenic. Exposure-response quantitative results are presented in sufficient detail (e.g., odds ratios or relative risks with associated confidence intervals, numbers of cases/controls, etc.).
Outcomes	Screening of health outcomes prioritized for inclusion in the assessment: cancers of the bladder, lung, kidney, liver, and skin; noncancer effect of inorganic arsenic on the circulatory system (ischemic heart disease, hypertension, and stroke), reproductive system (including pregnancy and birth outcomes), developmental outcomes (including neurodevelopmental toxicity), endocrine system (including diabetes), immune system, respiratory system, and skin Note: A broad outcome search strategy was retained during the different phases of outcome prioritization. Epidemiological studies on other health outcomes not prioritized are tagged during screening to monitor for new studies that may affect the problem formulation decisions described above.
PBPK models	Studies describing PBPK models for inorganic arsenic will be included. Studies describing quantitative models or data for understanding kinetics in biological media will be tracked as "potentially relevant supplemental material."

Literature Search and Screening



*Studies may be in multiple categories

Study Evaluation Overview of Epidemiological Studies

Individual study level domains (OHAT)
Epidemiological
Selection
Confounding
Performance
Attrition
Detection
Selective reporting bias
Other (internal validity)

Risk of bias evaluation protocol:

- Questions under 6 domains
- Further informed by arsenic-specific clarifications added to OHAT protocol (Appendix C)
- Implemented with 2 independent reviewers

ROB rating	
++	Definitely low
+	Probably low
-	Probably high
--	Definitely high

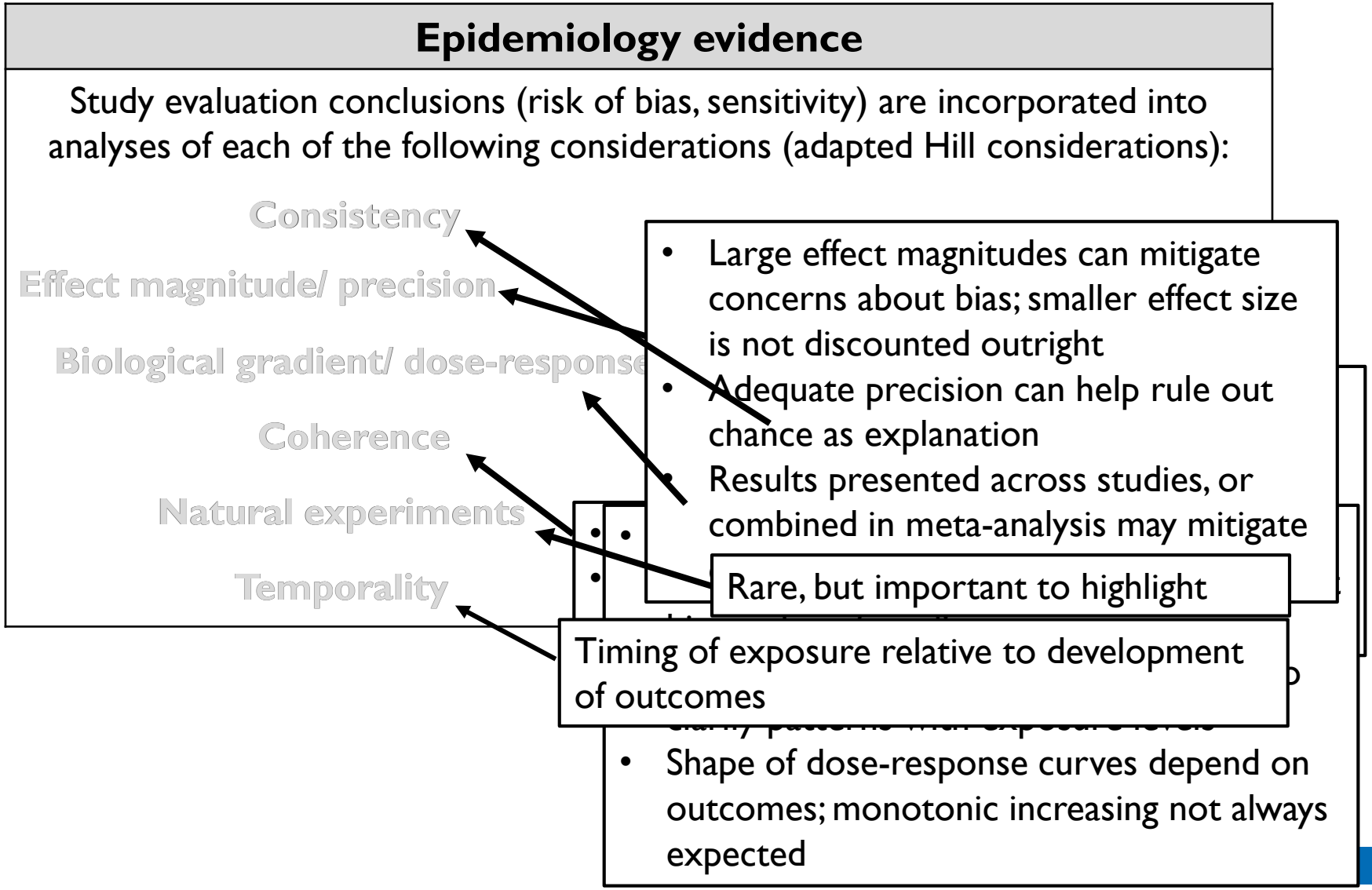
Rationales and ratings determined for individual questions

Overall Study Rating
High
Medium
Low
Uninformative → excluded

Risk of bias conclusions considered along with strengths and limitations to reach study classification

Evidence Synthesis

A description of the types of human evidence, and an analysis and presentation of that information to facilitate strength of evidence judgments for a given health effect



Evidence Profile Table – Inorganic Arsenic and Pancreatic Cancer

	Studies (by design) and study confidence (i.e. based on risk of bias and sensitivity considerations[1])	Factors that increase confidence	Factors that decrease confidence	Summary of findings	Strength of evidence judgment
Case-control Studies	Study was well-designed with well-characterized exposure leading to general interpretation of *high* confidence Spain: Amaral et al. (2012)	• Authors adjusted for potential confounders, including age, gender, region, smoking status, past history of diabetes, and education level • Study accounted for other trace elements in toenail samples	• No discussion on missing toenail samples • Environmental exposure levels not defined for subjects, but expected to be low with the source of drinking water to be the same for cases and controls	Positive association reported at the highest quartile of arsenic (>0.1061 µg/g) compared with the other quartiles (<0.0518-0.1061 µg/g)	⊕ SLIGHT Supported primarily by inconsistent evidence in different populations across the world.
Cohort Studies	Studies from the United States, Asia, and Turkey with a range of confidence that includes *high* or *medium* United States: García-Esquinas et al. (2013); Lewis et al. (1999); Japan: Sawada et al. (2013); Taiwan: Hsu et al. (2013)	• Adequate sample sizes reduce risk of chance and some biases • Well-characterized exposure reduces risk of confounding and other biases • Authors adjusted for potential confounders • Consistent no associations observed in diverse populations across the world	• Uncertainty due to one study that reported a positive association	No associations observed in all but one cohort study The failure to detect an effect might have been due to insufficient follow-up time for the development of pancreatic cancer or low numbers of pancreatic cancer cases.	
Ecological Studies	Studies possessed some limitations in the quantitative characterization of exposure, leading to general interpretations of *medium* confidence United States: Liu-Mares et al. (2013); Japan: Yorifuji et al. (2011); Taiwan: Tsai et al. (1999)	• Temporality demonstrated in Japanese study with exposure in early life from contaminated milk powder and development of pancreatic cancer later in life	• Some concern for risk of bias across the set of studies, due largely to deficiencies in exposure assessment and inability to account for potential confounding from individual-level variables	Studies report generally inconsistent associations	

Evidence Profile Table – Inorganic Arsenic and Pancreatic Cancer

	Studies (by design) and study confidence (i.e. based on risk of bias and sensitivity considerations[1])	Factors that increase confidence	Factors that decrease confidence	Summary of findings	Strength of evidence judgment
Case-control Studies	Study was well-designed with well-characterized exposure leading to general interpretation of *high* confidence Spain: Amaral et al. (2012)	• Authors adju confounders, i region, smokin elements in to	drinking water to be the same for cases and controls	on at the quartile c µg/g) d with r quartiles (<0.0518-0.1061 µg/g)	⊕ SLIGHT Supported primarily by inconsistent evidence in different populations across the world.
Cohort Studies	Studies from the United States, Asia, and Turkey with a range of confidence that includes *high* or *medium* United States: García-Esquinas et al. (2013); Lewis et al. (1999); Japan: Sawada et al. (2013); Taiwan: Hsu et al. (2013)	• Adequate sample sizes reduce risk of chance and some biases • Well-characterized exposure reduces risk of confounding and other biases • Authors adjusted for confounders across the world	• Uncertainty due to one study that reported a positive association	No associations observed in all but one cohort study t r of pancreatic cancer or low numbers of pancreatic cancer cases.	
Ecological Studies	Studies possessed some limitations in the quantitative characterization of exposure, leading to general interpretations of *medium* confidence United States: Liu-Mares et al. (2013); Japan: Yorifuji et al. (2011); Taiwan: Tsai et al. (1999)	• Temporality demonstrated in Japanese study with exposure i early life from contaminated m	individual-level variables		

"**well-designed** with **well-characterized exposure** leading to general interpretation of **high confidence**"

"range of confidence that includes **high or medium**"

"Studies possessed **some limitations in the quantitative characterization of exposure**, leading to general interpretations of **medium confidence**"

Evidence Profile Table – Inorganic Arsenic and Pancreatic Cancer

	Studies (by design) and study confidence (i.e. based on risk of bias and sensitivity considerations[1])	Factors that increase confidence	Factors that decrease confidence	Summary of findings	Strength of evidence judgment
Case-control Studies	Study was well-designed with well-characterized exposure leading to general interpretation of *high* confidence Spain: Amaral et al. (2012)	• Authors adjusted for potential confounders, including age, gender, region, smoking status, past history of diabetes, and education level • Study accounted for other trace elements in toenail samples	• No discussion on missing toenail samples • Environmental exposure levels r defined for subje but expected to h the same for case controls	Positive association reported at the highest quartile	⊕ SLIGHT different populations
Cohort Studies	Studies from the United States, Asia, and Turkey with a range of confidence that includes *high* or *medium* United States: García-Esquinas et al. (2013); Lewis et al. (1999); Japan: Sawada et al. (2013); Taiwan: Hsu et al. (2013)	• Adequate sample sizes reduce risk of chance and some biases • Well-characterized exposure reduces risk of confounding and other biases • Authors adjusted for potential confounders • Consistent no associations observed in diverse populations across the world	• Uncertainty due to one study that reported a positive association	cases.	
Ecological Studies	Studies possessed some limitations in the quantitative characterization of exposure, leading to general interpretations of *medium* confidence United States: Liu-Mares et al. (2013); Japan: Yorifuji et al. (2011); Taiwan: Tsai et al. (1999)	• Temporality demonstrated in Japanese study with exposure in early life from contaminated milk powder and development of pancreatic cancer later in life	• Some concern for risk of bias across the set of studies, due largely to deficiencies in and inability to account for potential confounding from individual-level variables	Studies report	

- Adjusted for potential confounders
- Accounted for other trace elements in toenail samples

- **Adequate sample sizes** reduce risk of chance and some biases
- **Well-characterized exposure** reduces risk of confounding and other biases
- Adjusted for potential confounders

- **Temporality**; exposure in early life and development of pancreatic cancer later in life

Evidence Profile Table – Inorganic Arsenic and Pancreatic Cancer

Studies (by design) and study confidence (i.e. based on risk of bias and sensitivity considerations[1])		Factors that increase confidence	Factors that decrease confidence	Summary of findings	Strength of evidence judgment
Ca	Study was well-designed with well-characterized exposure leading to general	• Authors adjusted for potential confounders, including age, gender, n, smoking status, past history abetes, and education level dy accounted for other trace	• No discussion on missing toenail samples • Environmental exposure levels not defined for subjects, but expected to be low with the source of drinking water to be the same for cases and controls	Positive association reported at the highest quartile of arsenic (>0.1061 µg/g) compared with the other quartiles (<0.0518-0.1061 µg/g)	⊕ SLIGHT Supported primarily by inconsistent evidence in different populations across the world.
Cohort Studies	Studies from the United States, Asia, and Turkey with a range of confidence that	• Adequate sample sizes reduce risk of chance and some biases aracterized exposure risk of confounding and ers ent no associations observed in diverse populations across the world	• Uncertainty due to one study that reported a positive association	No associations observed in all but one cohort study The failure to detect an effect might have been due to insufficient follow-up time for the development of pancreatic cancer or low numbers of pancreatic cancer cases.	
Ecological Studies	[1999]	orality demonstrated in e study with exposure in tic cancer later in life	• Some concern for risk of bias across the set of studies, due largely to deficiencies in exposure assessment and inability to account for potential confounding from individual-level variables	Studies report generally inconsistent associations	

- No discussion of missing samples
- Environmental exposure levels not defined; source of drinking water same for cases and controls

- **Uncertainty**; results inconsistent across studies

Some concern of **risk of bias** across body of evidence; deficiencies in **exposure assessment** and **potential for confounding**

Evidence Profile Table – Inorganic Arsenic and Pancreatic Cancer

	Studies (by design) and study confidence (i.e. based on risk of bias and sensitivity considerations[1])	Factors that increase confidence	Factors that decrease confidence	Summary of findings	Strength of evidence judgment
Case-control Studies	Study was well-designed with well-characterized exposure leading to general interpretation of *high* co Spain: Amaral et al. (20	• Authors adjusted for potential confounders, including age, gender, y	• No discussion on missing toenail samples • Environmental defined for subjects, but expected to be low with the source of drinking water to be the same for cases and controls	Positive association reported at the highest quartile of arsenic (>0.1061 µg/g) compared with the other quartiles (<0.0518-0.1061 µg/g)	⊕ SLIGHT Supported primarily by inconsistent evidence in different populations across the world.
Cohort Studies	Studies from the United States, Asia, and Turkey with a range of confidence that includes *high* or *mediu* United States: García-E; Lewis et al. (1999); Jap (2013); Taiwan: Hsu et	• Adequate sample sizes reduce risk of chance and some bias • Consistent no associations observed in diverse populations across the world	• Uncertainty due to one study that reported a positive association	No associations observed in all but one cohort study The failure to detect an effect might have been due to insufficient follow-up time for the development of pancreatic cancer or low numbers of pancreatic cancer cases.	
Ecological Studies	Studies possessed some quantitative characteriz leading to general inter confidence United States: Liu-Mares et al. (2013); Japan: Yorifuji et al. (2011); Taiwan: Tsai et al. (1999)	pancreatic cancer later in life	• Some concern for ris studies, due largely t deficiencies in exposure assessment and inability to account for potential confounding from individual-level variables	Studies report generally inconsistent associations	

"Positive association reported in highest quartile"; limited number of studies

"Null associations observed in all but 1 cohort study" ; limited number of studies

"Generally inconsistent associations" ; limited number of studies

Evidence Profile Table – Inorganic Arsenic and Pancreatic Cancer

	Studies (by design) and study confidence (i.e. based on risk of bias and sensitivity considerations)	Factors that increase confidence	Factors that decrease confidence	Summary of findings	Strength of evidence judgment
Case-control Studies	Study was wel characterized interpretation Spain: Amaral		discussion on ing toenail bles vironmental	Positive association reported at the highest qua le	⊕ SLIGHT Supported primarily by inconsistent evidence in different populations across the world.
			king water to be ame for cases and rols	quartiles (<0.0518-0.1061 µg/g)	
Cohort Studies	Studies from the United States, Asia, and Turkey with a range of confidence that includes *high* or *medium* United States: García-Esquinas et al. (2013); Lewis et al. (1999); Japan: Sawada et al. (2013); Taiwan: Hsu et al. (2013)	• Adequate sample sizes reduce risk of chance and some biases • Well-characterized exposure reduces risk of confounding and other biases • Authors adjusted for potential confounders • Consistent no associations observed in diverse populations across the world	• Uncertainty due to one study that reported a positive association	No associations observed in all but one cohort study The failure to detect an effect might have been due to insufficient follow-up time for the development of pancreatic cancer or low numbers of pancreatic cancer cases.	
Ecological Studies	Studies possessed some limitations in the quantitative characterization of exposure, leading to general interpretations of *medium* confidence United States: Liu-Mares et al. (2013); Japan: Yorifuji et al. (2011); Taiwan: Tsai et al. (1999)	• Temporality demonstrated in Japanese study with exposure in early life from contaminated milk powder and development of pancreatic cancer later in life	• Some concern for risk of bias across the set of studies, due largely to deficiencies in exposure assessment and inability to account for potential confounding from individual-level variables	Studies report generally inconsistent associations	

Slight: signal of a possible effect, but evidence is conflicting or weak

- Inconsistent evidence in different populations across the world from limited number of studies

Evidence Profile Table – Diseases of the Circulatory System

Studies (by design) and study confidence (i.e. based on risk of bias and sensitivity considerations[2])		Factors that increase confidence	Factors that decrease confidence	Summary of findings: Diseases of the Circulatory System	Strength of evidence judgment: Diseases of the Circulatory System
Coronary Heart Disease					
Cohort Studies	Multiple well-designed cohort studies with individual level data, including prospective studies. Most studies described methods employed to validate outcomes consider important covariates in the analysis. Multiple studies were conducted in areas where a large proportion of the population was exposed to concentrations of iAs in drinking water of <100 ug/L. In addition, several studies considered both dose and exposure metrics in their analyses. Thus, studies were generally interpreted with *high* or *medium* confidence. US: Farzan et al. (2015a);Moon et al. (2013) Bangladesh: Chen et al. (2011); Sohel et al. (2009) China: Wade et al. (2009) Europe: D'Ippoliti et al. (2015) S.W. Taiwan: Pu et al. (2007); Chen et al. (1996)	• **Generally consistent** positive associations observed high quality s… U.S. and in Bangladesh… substantial proportion… exposed to <100 ug/L • **Exposure-dependent** … most studies • Studies generally repo… **associations,** many of… significance at higher exposure levels[4]. • **Low risk of bias** (i.e., risk of confounding, exposure misclassification and other sources of bias) across the set of studies, due in part to the comprehensive collection of information on covariates in large well conducted cohort studies and well-characterized exposure based on multiple dose and exposure metrics. • **Coherence** with findings for related endpoints/CHD risk factors such as hypertension, atherosclerosis • Case control and case cohort studies conducted in established cohorts in Bangladesh, China and the US extend analyses to support **biologically plausible** increased CHD-related mortality among those with lower methylation capacity and explore **refined or alternative exposure assessment strategies**.	• Some concern for residual …other …sts for …ngs …in …W. …al …may differ relative to US populations may be limited.	A set of large, well-conducted studies report generally consistent, positive associations with CHD morbidity and mortality. Studies of diverse populations (Figure 1-9) use various metrics of iAs exposure. Positive associations with hypertension are also observed in many studies. Evidence for exposure-dependent changes within and across studies is evident (Figures 1-9 and 1-10), Findings are further supported by studies showing the effect of iAs exposure across related endpoints or with CVD risk factors for CVD. Evidence base for stroke is limited. Some well-conducted studies report positive associations at higher exposure levels.	⊕⊕⊕ ROBUST Supported primarily by consistent evidence from high or medium confidence cohort studies that rule out chance, confounding, and other biases with reasonable confidence. The strongest evidence derives from studies of IHD and hypertension. This evidence is supported by studies reporting associations of arsenic exposure with related CVD endpoints including atherosclerosis and repolarization abnormalities (e.g. QT prolongation). The judgment is based on a large body of evidence including studies of populations with exposure gradients spanning relatively low (<100 ug/L) concentrations of iAs in drinking water.
Ecological and Cross-sectional Studies	Ecologic studies in areas such as SW Taiwan where iAs poisoning was endemic report increased CVD-related morbidity or mortality and declines in mortality post-intervention. Blackfoot disease, a PVD characterized by gangrene in the extremities is also documented in SW Taiwan. Findings from ecologic studies in locations with relatively low drinking-water concentrations and occupational studies are not entirely consistent. S.W. Taiwan: Wu et al. (1989); Chang et al. (2004); Chang et al. (2004)	• The **strength** of the associations observed in studies of the population of S.W Taiwan is notable. • Post-intervention analysis that approximates a **natural experiment** indicates a reduction in CVD-related mortality in SW Taiwan after drinking water source containing high levels of iAs (700-960 ug/L) was discontinued.	Potential **risk of bias** across the set of studies, due largely to deficiencies in exposure assessment and inability to account for potential confounding from individual-level variables. This concern is mitigated by the large body of studies with individual data that were conducted since the initial ecological studies.		

More than 100 Studies

Evidence Profile Table – Diseases of the Circulatory System

Studies (by design) and study confidence (i.e. based on risk of bias and sensitivity considerations[2])		Factors that increase confidence	Factors that decrease confidence	Summary of findings: Diseases of the Circulatory System	Strength of evidence judgment: Diseases of the Circulatory System
Coronary Heart Disease					
Cohort Studies	Multiple well-designed cohort studies with individual level data, including prospective studies. Most studies described methods employed to validate outcomes consider important covariates in the analysis. Multiple studies were conducted in areas where a large proportion of the population was exposed to concentrations of iAs in drinking water of <100 ug/L. In addition, several studies considered both dose and exposure metrics in their analyses. Thus, studies were generally interpreted with *high* or *medium* confidence. US: Farzan et al. (2015a);Moon et al. (2013) Bangladesh: Chen et al. (2011); Sohel et al. (2009) China: Wade et al. (2009) Europe: D'Ippoliti et al. (2015) S.W. Taiwan: Pu et al. (2007); Chen et al. (1996)	•**Generally consistent** positive associations observed high quality s U.S. and in Bangladesh substantial proportion exposed to <100 ug/L •**Exposure-dependent** most studies •Studies generally repo **associations,** many of significance at higher exposure levels[4]. •**Low risk of bias** (i.e. risk of confounding ex bi co st or •**Co** er hypertension, atherosclerosis •Case control and case cohort studies conducted in established cohorts in Bangladesh, China and the US extend analyses to support **biologically plausible** increased CHD-related mortality among those with lower methylation capacity and explore **refined or alternative exposure assessment strategies**.	•Some concern for residual other sts for ngs in W. al may differ relative to US populations may be limited	A set of large, well-conducted studies report generally consistent, positive associations with CHD morbidity and mortality. Studies of diverse populations (Figure 1-9) use various metrics of iAs exposure. Positive associations with hypertension are also n many studies. r exposure-changes within studies is gures 1-9 and ings are further by studies e effect of iAs exposure across related endpoints or with CVD risk factors for CVD. Evidence base for stroke is limited. Some well-conducted studies report positive associations at higher exposure levels.	⊕⊕⊕ ROBUST Supported primarily by consistent evidence from high or medium confidence cohort studies that rule out chance, confounding, and other biases with reasonable confidence. The strongest evidence derives from studies of IHD and hypertension. This evidence is supported by studies reporting associations of arsenic exposure with related CVD endpoints including atherosclerosis and repolarization abnormalities (e.g. QT prolongation). The judgment is based on a large body of evidence including studies of populations with exposure gradients spanning relatively low (<100 ug/L) concentrations of iAs in drinking water.
Ecological and Cross-sectional Studies	Ecologic studies in areas such as SW Taiwan where iAs poisoning was endemic report increased CVD-related morbidity or mortality and declines in mortality post-intervention. Blackfoot disease, a PVD characterized by gangrene in the extremities is also documented in SW Taiwan. Findings from ecologic studies in locations with relatively low drinking-water concentrations and occupational studies are not entirely consistent. S.W. Taiwan: Wu et al. (1989); Chang et al. (2004); Chang et al. (2004)	•The **strength** of the associations observed in studies of the population of S.W Taiwan is notable. •Post-intervention analysis that approximates a **natural experiment** indicates a reduction in CVD-related mortality in SW Taiwan after drinking water source containing high levels of iAs (700-960 ug/L) was discontinued.	Potential **risk of bias** across the set of studies, due largely to deficiencies in exposure assessment and inability to account for potential confounding from individual-level variables. This concern is mitigated by the large body of studies with individual data that were conducted since the initial ecological studies.		

More than 100 Studies

• Coronary (Ischemic) Heart Disease (Tier 1)

Evidence Profile Table – Diseases of the Circulatory System

Hypertension					
Cohort Studies	Some, but not all, well-designed cohort studies report positive associations of iAs exposure with hypertension. Results are sensitive to the choice of exposure metric. Studies were generally interpreted with *high* or *medium* confidence. S.W. Taiwan: Wang et al. (2011), Bangladesh: Rahman et al. (1999); Islam et al. (2012); Chen et al. (2007); Guha Mazumder et al. (2012); China: Li et al. (2013a); Li et al. (2013b), U.S.: Jones et al. (2015); Gong and O'Bryant (2012) Some studies report increased blood pressure with iAs exposure among subgroups including those with low nutrient intake, pregnant women and children. U.S.: Farzan et al. (2015b), Bangladesh: Hawkesworth et al. (2013); Chen et al. (2007), China: Kwok et al. (2007)	• **Consistent positive associations** with metrics indicating recent exposure to iAs (or cumulative exposure in currently exposed populations) are generally reported. This observation is compatible with the understanding that hypertension can resolve in the absence of exposure. • Large well conducted study reporting no association with hypertension found small **increases in SBP, DBP and PP** in association with iAs exposure. • **Exposure-dependent associations** observed in many studies • **Coherence** across related endpoints including QT prolongation • **Low risk of bias** in many studies • The evidence base includes some that evaluate both dose and exposure metrics.	• Positive associations with hypertension are not entirely consistent across studies, e.g. no association with hypertension observed in large prospective study in Bangladesh • Generalizability of findings from studies conducted in Bangladesh, China and S.W. Taiwan where nutritional status or other factors may differ relative to US populations may be limited.		
Supporting Evidence from Ecological and Cross-sectional Studies	Arsenic-associated increases in blood pressure found in cross sectional and ecological studies with supporting evidence from studies that examine endpoints that indicate sympathetic hyperactivity.	• The st studie • Post-i natur relate sourc was			
Stroke					
	Stroke: Some but not all well-designed cohort studies, including prospective studies report positive associations with stroke. Bangladesh: Rahman et al. (2014); Chen et al. (2011), Europe: D'Ippoliti et al. (2015) U.S. Farzan (2015)	• Exposure dependent associations more consistently positive in populations with higher (>50) concentrations of iAs in drinking water but not in all studies[3].	• Evidence remains limited • Associations not entirely consistent across studies		

- Coronary (Ischemic) Heart Disease (Tier 1)
- Hypertension and Stroke (Tier 2)

[1] Because numerous studies interpreted with medium-high confidence were available, this table includes the most informative studies and does not include those interpreted with low confidence (see Appendix XX for documentation of the study evaluations and the supporting rationale for these judgments)

[2] Risk of bias and sensitivity-related criteria were evaluated for all studies, with overall study judgments placing an emphasis on the appropriate and sensitive conduct of methods relating to exposure characterization, blinding of outcome assessment, and analysis of potential confounding (see Appendix XX)

[3] Positive associations with IHD and stroke not reported in US study (mean = 2.6 ug/L drinking water) although increased risk of IHD among current smokers and with increasing pack-years observed (Farzan, 2015).

[4] Meta analyzed relative estimate for studies in high exposure areas (>50) was precise and significant while a weaker association was observed in low to moderate exposure areas (<50); however, recent studies

Evidence Profile Table – Diseases of the Circulatory System

Strength-of-evidence judgement	Description
Robust (⊕⊕⊕) … evidence in human studies	A set of *high*- or *medium*-confidence independent studies reporting an association between the exposure and the health outcome, with reasonable confidence that alternative explanations, including chance, bias, and confounding, can be ruled out across studies. The set of studies is primarily consistent, with reasonable explanations when results differ; an exposure-response gradient is demonstrated; and the set of studies includes varied populations. Additional supporting evidence, such as associations with biologically related endpoints in human studies (coherence) or large estimates of risk, may increase confidence but are not required.

Evidence Profile Table – Diseases of the Circulatory System

Strength-of-evidence judgement	Description
Robust (⊕⊕⊕) … evidence in human studies	A set of *high-* or *m* … ies reporting an assoc … e health outcome, w … alternative explana … confounding, can b … of studies is primarily … explanations when … e gradient is demons … es varied populations … ch as associations wit … human studies (coherence) or large estimates of risk, may increase confidence but are not required.

Set of high- or medium-confidence studies:

- iAs concentrations in water spanned low (<100 µg/L) to higher concentrations
- Several studies have exposure and dose metrics (e.g. cumulative water exposure and urine)

Evidence Profile Table – Diseases of the Circulatory System

Strength-of-evidence judgement	Description
Robust (⊕⊕⊕) … evidence in human studies	A set of *high-* c…es reporting an as… health outcome… alternative exp… confounding, c…f studies is prima… explanations w… gradient is dem…s varied populati…n as associations with biologically related endpoints in human studies (coherence) or large estimates of risk, may increase confidence but are not required.

Rule out chance, bias and confounding with reasonable confidence:

- Large, adequately powered studies
- Validated outcomes
- Consideration of important covariates that could potentially confound the associations
- Generally high participation rates

Evidence Profile Table – Diseases of the Circulatory System

Strength-of-evidence judgement	Description
Robust (⊕⊕⊕) … evidence in human studies	A set of *high*- or *medium*-confidence independent studies reporting an association between the exposure and the health ou[illegible]ble confidence that alternativ[illegible]ding chance, bias, and confounding, can be ruled out across studies. The set of studies is primarily consistent, with reasonable explanations when results differ; an exposure-response gradient is demonstrated; and the set of studies includes varied populations. Additional supporting evidence, such as associations with biologically related endpoints in human studies (coherence) or large estimates of risk, may increase confidence but are not required.

Consistent

Evidence Profile Table – Diseases of the Circulatory System

Strength-of-evidence judgement	Description
Robust (⊕⊕⊕) … evidence in human studies	A set of *high*- or *medium*-confidence independent studies reporting an association between the exposure and the health ou[illegible]ble confidence that alternativ[illegible] confounding, can be ruled out[illegible] studies is primarily consistent,[illegible] explanations when results diff[illegible] gradient is demonstrated; and[illegible] varied populations. Additional [illegible] as associations with biologically related endpoints in human studies (coherence) or large estimates of risk, may increase confidence but are not required.

Consistent

Exposure-response gradient

Evidence Profile Table – Diseases of the Circulatory System

Strength-of-evidence judgement	Description
Robust (⊕⊕⊕) … evidence in human studies	A set of *high*- or *medium*-confidence independent studies reporting an association between the exposure and the health ou…ble confidence that alternativ… confounding, can be ruled out… studies is primarily consistent,… explanations when results diff… gradient is demonstrated; and… varied populations. Additional … as a… related endpoints in hum… arge estimates of risk, may… e not required.

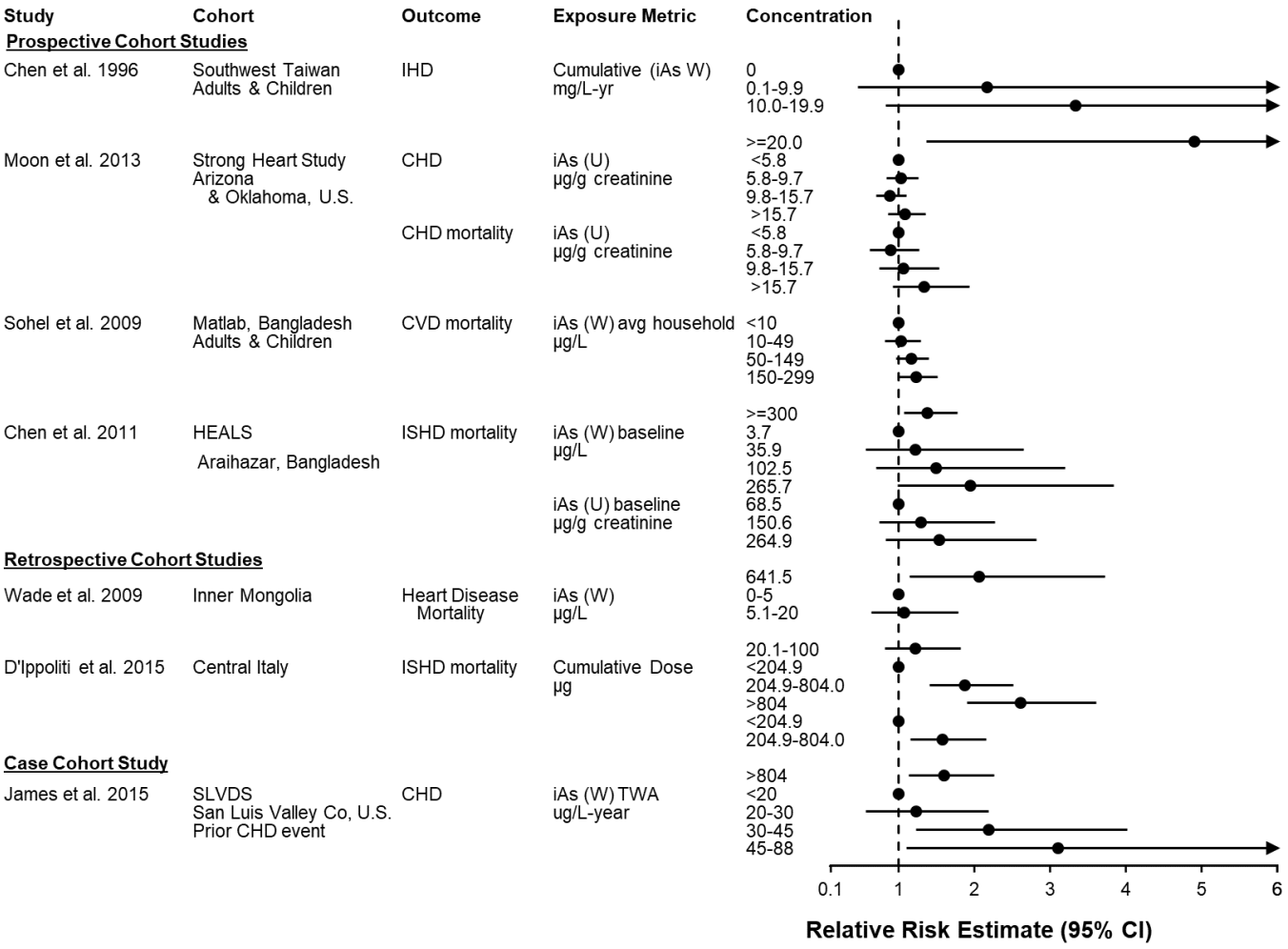
Consistent

Exposure-response gradient

Varied Populations

U.S., Europe, Asia

Evidence Profile Table – Diseases of the Circulatory System



Studies of Cardiovascular Disease and Mortality

CHD=Coronary Heart Disease; CVD= Cardiovascular Disease; HEALS=Health Effect of Arsenic Longitudinal Study; IHD=Ischemic Heart Disease; SLVDS=San Luis Valley Diabetes Study; TWA=Time Weighted Average U=Urinary; W=Water

Evidence Profile Table – Diseases of the Circulatory System

Strength-of-evidence judgement	Description
Robust (⊕⊕⊕) … evidence in human studies	A set of *high*- or *medium*-confidence independent studies reporting an association between the exposure and the health outcome, with reasonable confidence that alternative explanations, including chance, bias, and confoun… studies i… explanat… gradient… varied p… as assoc… human s… may increase confidence but are not required.

Coherence

- Hypertension/increased blood pressure
- Repolarization abnormalities (e.g. QT prolongation)
- Atherosclerosis
- Circulating markers of cardiovascular disease risk (e.g. inflammation, endothelial dysfunction)

Acknowledgments

- Kris Thayer, Jeff Gift, Ellen Kirrane, Tom Luben, Ryan Jones, Ingrid Druwe, Allen Davis, Andrew Kraft, Tina Bahadori, Belinda Hawkins, members of NCEA Epidemiology Workgroup, members of NCEA Systematic Review Workgroup, and others at U.S. EPA
- Ali Goldstone, Nicole Vetter, Katie Duke, Audrey Turley, Robyn Blain, Sorina Eftim, Michelle Cawley, Susan Goldhaber, and others at ICF International
- Andy Rooney at NIEHS