

Introduction to the IRIS Toxicological Review of Inorganic Arsenic

Vincent Cogliano, PhD
IRIS Director



Outline for Today's Presentations

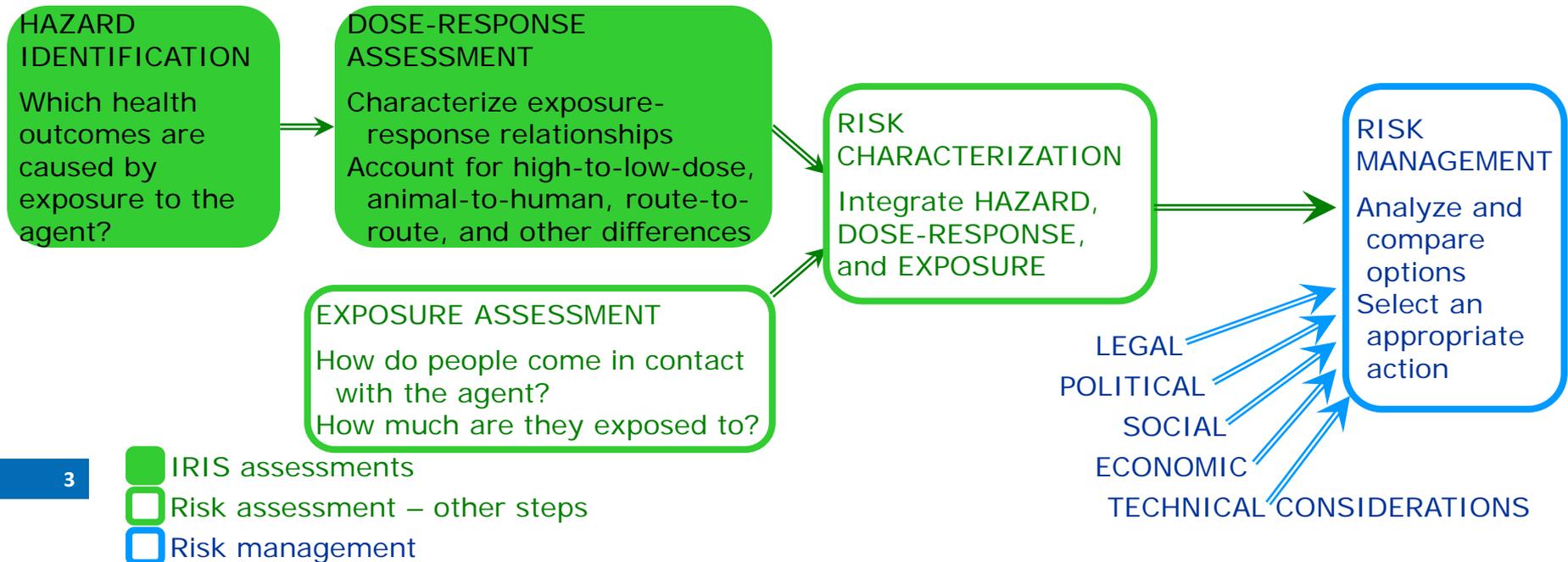
- **Introduction**
- Systematic Review
- Hazard Identification
- Adverse Outcome Pathways
- Toxicokinetics
- Dose-Response Methods

Purpose of Today's Presentations

1. Provide background on IRIS and the development process for the Toxicological Review of Inorganic Arsenic
2. Describe data and methods identified to date; and potential applications
3. Highlight how EPA is responding to NRC comments

About IRIS

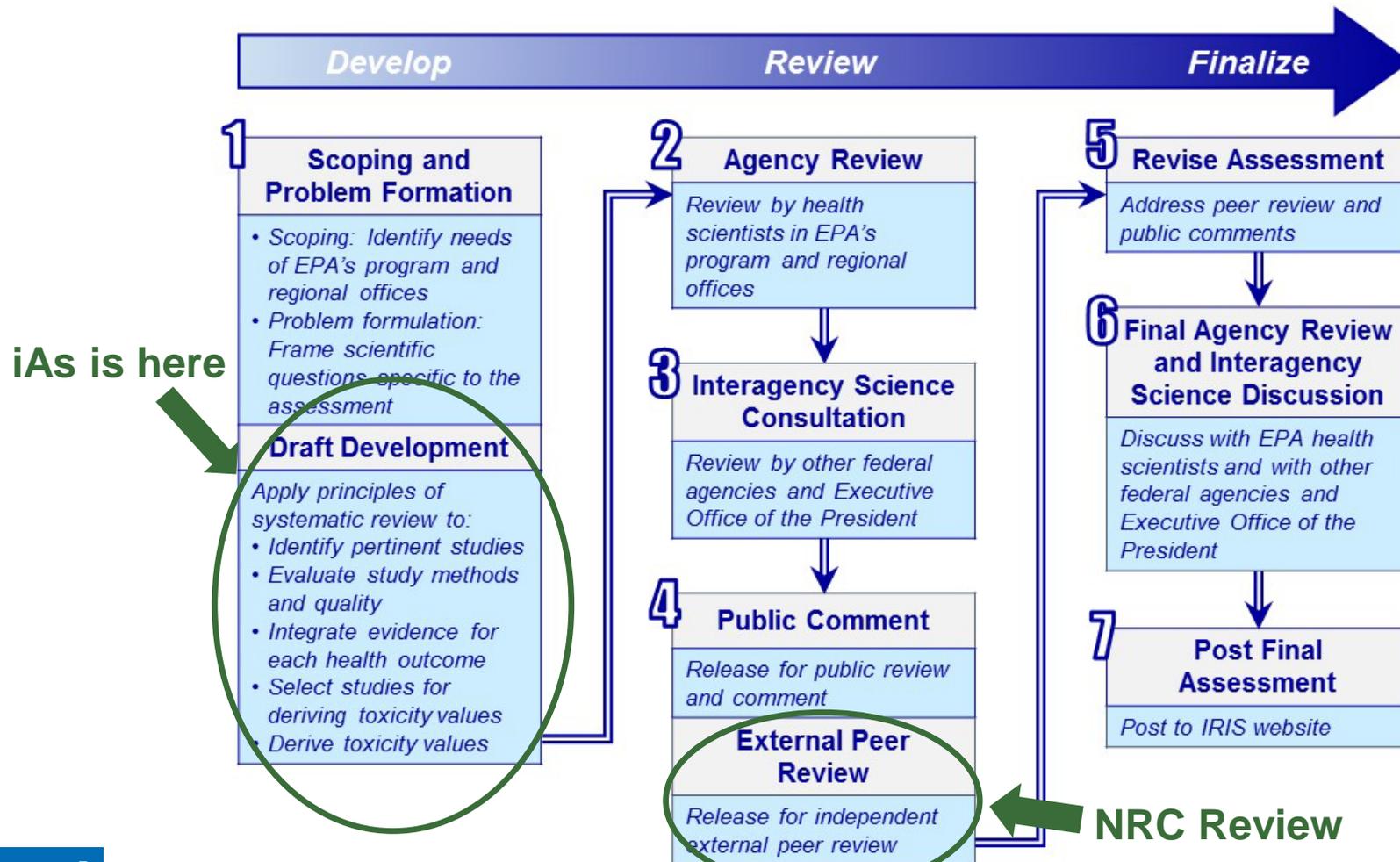
- IRIS assessments systematically review the publicly-available peer-reviewed studies to
 - Identify adverse health outcomes
 - Characterize exposure-response relationships



History of the IRIS Toxicological Review of Inorganic Arsenic

- **1988:** EPA published its current assessment of Inorganic Arsenic
- **1999, 2001:** NRC, at EPA's request, published *Arsenic in Drinking Water and Update*
- **2005:** Draft assessment released
- **2010:** Draft assessment released, reviewed by Science Advisory Board
- **2011:** Congress directed EPA to contract with NRC to review the assessment
- **2013:** EPA held public problem formulation meeting, webinars; released draft Assessment Development Plan and preliminary materials for NRC review
- **2013:** NRC released *Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic: Interim Report*; recommendations generally supported EPA's plan
- **2014:** EPA held a public science meeting to present the ADP and preliminary materials and to encourage discussion on key science issues

Current Step in the IRIS Process



NRC Interim Report

- *Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic: Interim Report (2013)*
 - Exposure considerations
 - IRIS assessment development plans: evidence evaluation, systematic review, and meta-analysis
 - Hazard identification
 - Susceptibility factors
 - Mode of action
 - Dose-response analysis

NRC Recommendations on Systematic Review Approach

- Make systematic review more transparent
- Search for studies on specific outcomes
 - Individual measures of arsenic exposure
 - Measurement of arsenic that precedes the outcome
 - “Low to moderate” exposure to inorganic arsenic (less than 100 ug/L in drinking water)
- Evaluate risk of bias using established guidelines for epidemiologic studies
- Meta-analysis should be considered for priority end points if there are three or more peer-reviewed studies

NRC Recommendations on Mode-of-Action Approach

- Develop conceptual mechanistic models
 - to provide context for data interpretation, including hazard identification
 - to inform dose-response model choice below the range of observed data
- Conduct for causal and likely causal endpoints, and endpoints that fall between two hazard descriptors for causality determination
- Better understand interhuman variability and susceptibility
- Explore exposure-response continuum for sequential progression and time dependence
- Explore biologic plausibility and evidence concordance across data sources
- Evaluate modulation by other potentially causal agents
- Inform sensitivity analyses

NRC Recommendations on Hazard Identification Approach

NRC Tier 1: Evidence of a causal association determined by other agencies and/or in published systematic reviews

- Lung cancer
- Ischemic heart disease
- Skin cancer
- Skin lesions
- Bladder cancer

NRC Tier 2: Other priority outcomes

- Prostate cancer
- Immune effects
- Nonmalignant respiratory disease
- Renal cancer
- Neurodevelopmental toxicity
- Pregnancy outcomes (infant morbidity)
- Diabetes

NRC Tier 3: Other end points to consider

- Liver cancer
- Hypertension
- Pancreatic cancer
- Stroke
- Renal disease
- Pregnancy outcomes (infant mortality)

NRC Recommendations on Dose-Response Approaches

- Quantify cancer and noncancer observed risks at US exposure levels down to background (1-5 ug/L urinary arsenic) with modest low-dose extrapolation
- Consider meta-analyses of studies with three or more exposure levels
- Estimate dose-response down to background and derive risk-specific doses with confidence limits instead of RfDs
- Incorporate more extensive consideration of uncertainty and sensitivity analyses

These Approaches May Not Be Applicable to Other IRIS Assessments

- This assessment is guided by NRC recommendations that are specific to inorganic arsenic (NRC 2013)
- There are several epidemiologic studies that investigated the association of cancer or noncancer outcomes and environmental exposures approaching—or including—background concentrations
 - It may be possible to estimate risks directly from published studies
 - NRC (2013) cited clear evidence of differential susceptibility that could lead to separate assessments for the general population and susceptible groups
 - NRC (2013) cited growing evidence—in humans and in animals—that early-life exposure may increase risks later in life
- Use of these approaches does not necessarily signal a change of approach or the availability of similar data for other IRIS assessments

Next Steps

- Public discussion
- Completion of a draft assessment
- Review by scientists in EPA's program and regional offices
- Interagency Science Consultation with other federal agencies and the Executive Office of the President
- Public comment and a public meeting on the draft assessment
- External peer review by the NRC
- Revision to address peer-review and public comments
- Final EPA Review and Interagency Science Discussion

Acknowledgments

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