IRIS Public Science Meeting

May 15, 2019

Welcome and Logistics

- Keep your phone **muted** throughout the webinar.
- **To ask a question or provide a comment**, use the “Q&A” pod of the Adobe Connect Webinar to inform the meeting host of your question. Questions and comments (webinar) will be posed at the end of each issue discussion.
- **To report technical difficulties or webinar issues to the meeting host,** use the “chat” pod of the Adobe Connect Webinar.

INTRODUCTION AND ROLE OF ASSESSMENT PLANS IN THE IRIS PROCESS

Kris Thayer
Director, Integrated Risk Information System (IRIS)
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency

- **Created in 1985 to foster consistency in the evaluation of chemical toxicity across the Agency.**
- **IRIS assessments contribute to decisions across EPA and other health agencies.**
- **Toxicity values**
  - Noncancer: Reference Doses (RfDs) and Reference Concentrations (RfCs).
  - Cancer: Oral Slope Factors (OSFs) and Inhalation Unit Risks (IURs).
- **IRIS assessments have no direct regulatory impact until they are combined with**
  - Extent of exposure to people, cost of cleanup, available technology, etc.
  - Regulatory options.
  - Both of these are the purview of EPA's program offices.

IRIS Provides Scientific Foundation for Agency Decision Making

IRIS

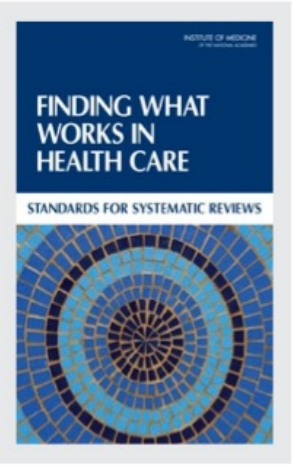
- Clean Air Act (CAA)
- Safe Drinking Water Act (SDWA)
- Food Quality Protection Act (FQPA)
- Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)
- Resource Conservation and Recovery Act (RCRA)
- Toxic Substances Control Act (TSCA)

Broad Input to Support

- Agency Strategic Goals
- Children's Health
- Environmental Justice

Systematic Review

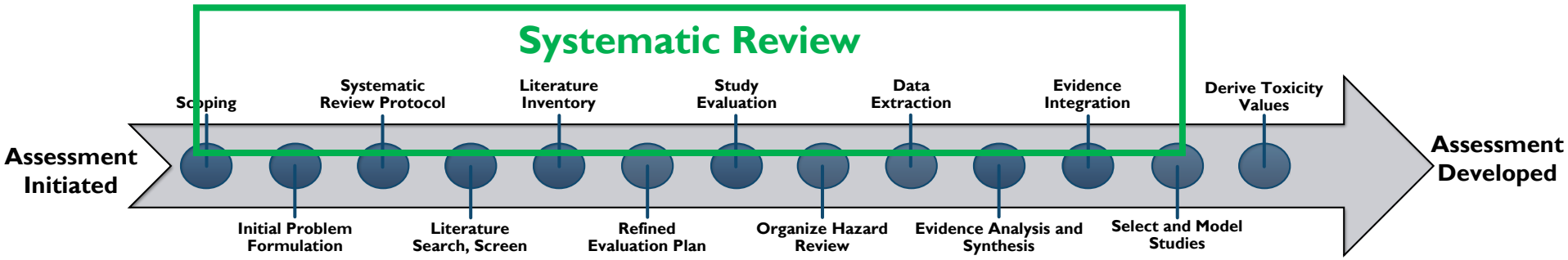
A structured and documented process for transparent literature review



"As defined by IOM [Institute of Medicine][1], systematic review 'is a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies."

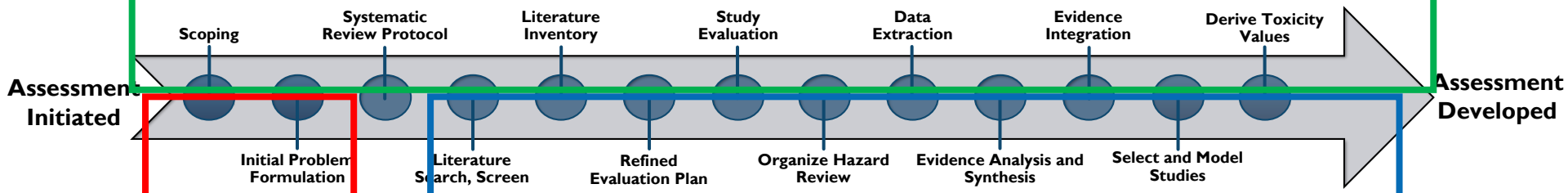
[1] Institute of Medicine. Finding What works in Health Care: Standards for Systematic Reviews. p.13-34. The National Academies Press. Washington, D.C. 2011

Systematic Review in IRIS Assessments



IRIS Systematic Review Documents

IRIS Handbook: Approaches and considerations for applying principles of systematic review to IRIS assessments, general frameworks, and examples.

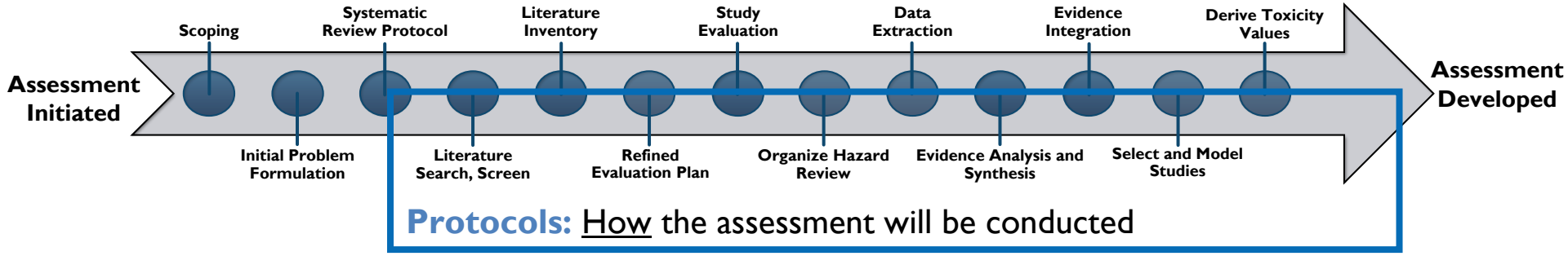


Assessment Plans: What the assessment will cover

Protocols: How the assessment will be conducted (specific procedures and approaches for each assessment component, with rationale where needed)

What we are presenting today

IRIS Protocol



- In IRIS, comments received on IAP are considered when preparing the protocol (updated IAP text is included in the protocol) and protocols are released for 30-day public comment period
- Protocol is iterative – Public comment and knowledge gained during implementation may result in revisions to the protocol to focus on the best available evidence. Major revisions are documented via updates, e.g., changes to specific aims or PECO
- List of included, excluded, and studies tagged as supplemental are disseminated through protocols (either during initial release or as an update)

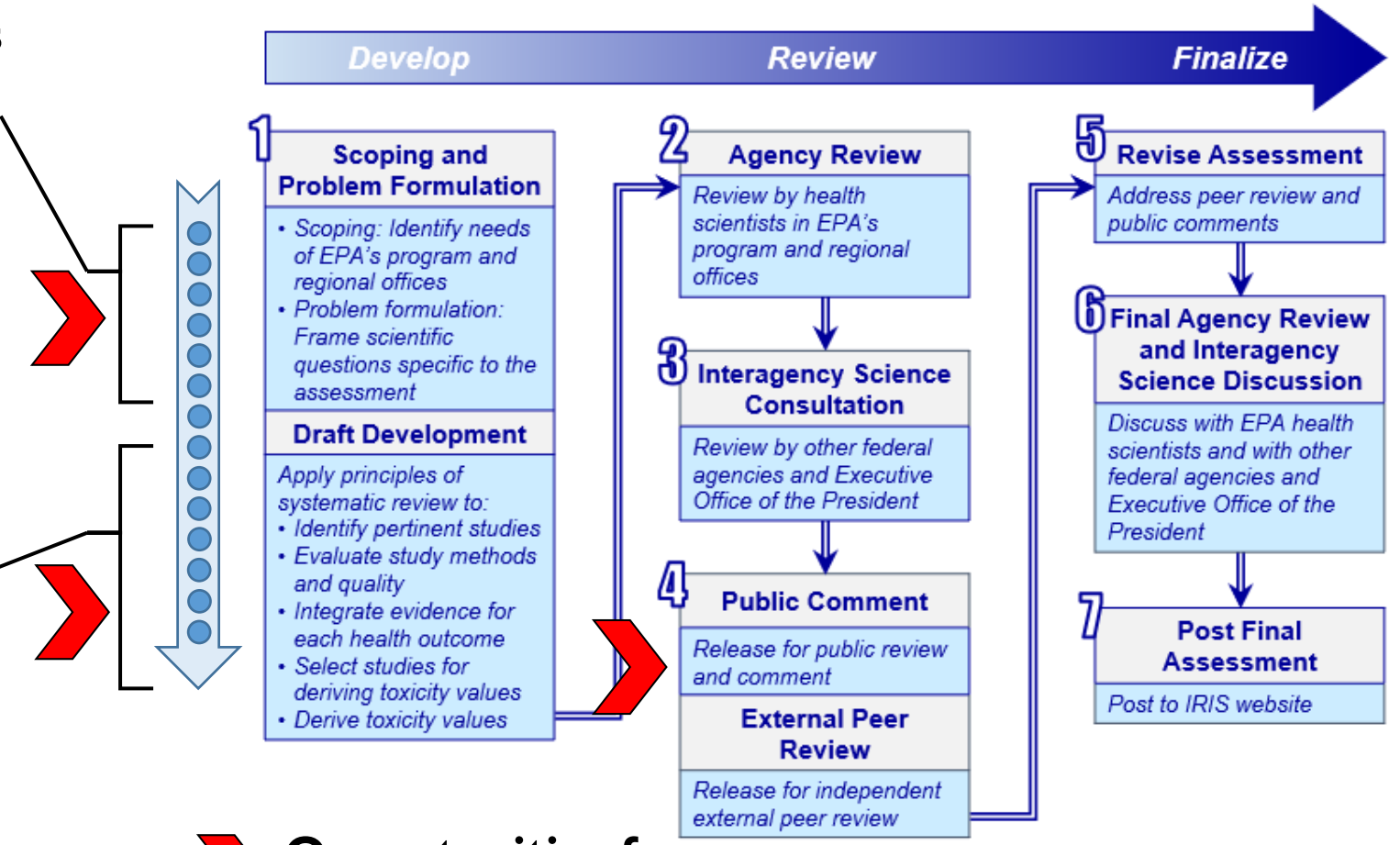
IRIS Assessment Plans, Protocols, and 7-Step IRIS Process

Early Step 1: IRIS Assessment Plans

- What the assessment covers
- 30-day public comment period + public science meeting

Mid-Step 1: Protocols

- How the assessment will be conducted
- 30-day public comment



https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#process

IRIS Assessment Plan (IAP) for MethylMercury (MeHg)

May 15, 2019

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This presentation is on a draft IAP on which the Agency is seeking public comment. As a draft, the IAP is not formally disseminated by EPA and should not be construed to represent an Agency determination or policy.

Outline of the Presentation

- Background
- Scoping and initial problem formulation
  - Scoping summary
  - Problem formulation
  - Health outcomes to be evaluated
- Overall objective, specific aims, and draft PECO (Populations, Exposures, Comparators, Outcomes) criteria
- Assessment approach
- Key science issues

Background

- Developmental neurotoxicity (DNT) hazard of MeHg is widely accepted.
- Existing IRIS RfD for MeHg published in 2001 was based on 2000 NAS report.
- Multiple DNT outcomes supported the 2001 RfD of 0.1 µg/kg-day.
- RfD is specifically based on neuropsychological impairment in Faroe Islands cohort of children prenatally exposed to MeHg.
- MeHg is formed when inorganic Hg is methylated by bacteria in soil & water.
- The primary route of exposure is through consumption of fish & seafood.
- Women & children in subsistence fishing communities are the most vulnerable to MeHg DNT.
- MeHg crosses the placenta & concentrates in cord blood (~1.7x higher than maternal blood)

Scoping Summary

- IRIS program met with EPA Programs and Regions with an interest in MeHg to discuss their specific needs
- Although the Office of Land and Emergency Management (OLEM) indicated that they needed both oral and inhalation noncancer toxicity values, at the present time, insufficient data exists to derive an inhalation value.

EPA Program or Regional Office	Oral	Inhalation	Anticipated Uses / Interest
Regions 1-10 OLEM	✓	✓	Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) Resource Conservation and Recovery Act (RCRA) Clean Water Act (CWA)

Initial Problem Formulation Continued

DNT was the basis of previous IRIS MeHg RfDs and is an established hazard. Therefore, this assessment will focus on:

- DNT exposure-response.
- Oral exposure; main route of exposure through fish/seafood consumption.
- Human studies; large epidemiology database available evaluating relationship between MeHg exposure & DNT.
- DNT outcomes resulting from exposure to fetus, infants, children, or teens.
- Potential impact of genetic polymorphisms on exposure-response relationship.

Initial Problem Formulation

- Based on NAS report and opinion of other organizations, the following are established or potential hazards of MeHg exposure:

- **DNT**
- Non-developmental nervous system outcomes
- Developmental outcomes (other than nervous system effects)
- Cardiovascular outcomes
- Immune system outcomes
- Reproductive outcomes

Health Outcomes To Be Evaluated

Developmental Neurotoxicity (DNT)

- Cognition
- Executive Function
- Personality/Emotionality Variables
- Motor Function
- Sensory/Perception

Overall Objective

Overall Objective:

To characterize the exposure-response relationship between MeHg exposure & DNT outcomes & to use the exposure-response relationship to update the RfD.

Specific Aims

- Identify epidemiological studies published since 1998 examining effects of exposure to MeHg as outlined in PECO criteria through literature search.
- Use predefined criteria to identify epidemiological studies from literature search that provide exposure-response information for DNT outcomes.
- Conduct study quality evaluations (risk of bias & sensitivity) for identified epidemiological studies. Studies with critical deficiencies generally will not be considered further.
- Summarize study methods & results from epidemiological studies on DNT outcomes.
- Identify & discuss issues concerning susceptible populations & life stages.

Specific Aims Continued

- Determine if dose conversion [PBPK modeling] is needed. Depending on biomarker, review literature to determine if calculations used in previous assessment (to convert from cord blood to oral exposure) need updating. If necessary, PBPK models will be evaluated using predefined criteria & their strengths/uncertainties will be summarized.
- Derive RfD for DNT outcomes as supported by available data.
- Characterize uncertainties & identify key data gaps/research needs.
- Determine if available data support derivation of an exposure-response relationship for DNT outcomes that could be used for cost-benefit analyses to quantify health benefits of actions to reduce exposures to MeHg.

Draft PECO Criteria

PECO element	Evidence
Populations	Human populations exposed during life stages ranging from fetus through adolescence.
Exposures	Any quantitative exposure to MeHg based on biomonitoring data (e.g., hair, nails, blood), or, possibly, food consumption (e.g., fish/seafood, rice) expressed as daily intake (e.g., mg/kg/d). Measurements must be either direct MeHg measurements or measurements of total Hg.
Comparators	Referent populations exposed to lower (within study) levels of MeHg will be used to examine specific effects. Results of comparisons must be presented with sufficient detail of quantitative modeling (e.g., regression coefficients presented with statistical measure of variation).
Outcomes	DNT outcomes measured at any age, including, but not limited to, tests or measures of cognition, motor function, behavior, vision, & hearing.

Assessment Approach

- Assessment will use modular approach--EPA will first evaluate most important route of exposure (oral) and associated selected health outcome--DNT.
- Once completed, an assessment addressing the DNT exposure-response relationship for oral exposure will be released.
- While completing this module, EPA will evaluate available hazard information for other potential adverse health outcomes.
- EPA will determine whether evidence exists to develop systematic review module(s) that assess hazard and/or derive reference values for other health outcomes.
- If additional module(s) are initiated, appropriate IAP(s) will be developed and disseminated for public comment.

Note: A separate IAP for mercury salts is currently being developed.

Key Science Issues

- Consider accuracy of different biomarkers (e.g., hair, maternal blood, cord blood) to measure MeHg exposure. Consider reliability & utility of different measures of MeHg exposure, including whether different biomarkers provide useful data for developing exposure-response relationship for MeHg exposure & DNT.

- Some epidemiological studies measure MeHg directly in human blood, hair or nails. Other studies rely on measures of total Hg to estimate MeHg exposure. Consider how best to use all biomarkers that were used in PECO-relevant epidemiology studies to inform estimates of relationship between MeHg exposure & DNT.

Key Science Issues Continued

- Consider how potential confounding in studies is accounted for in analysis. Many fish that contain MeHg also have nutrients, such as Se & PUFAs. Fish could also contain other harmful contaminants to brain development, e.g, PCBs.

- Account for differences in DNT evaluation methods. For example, developmental scores are consistently higher for both term & preterm infants when using Bayley III test vs Bayley II test. Some suggest using adjustment factor to compare scores.

Thank you! We welcome all comments.