IRIS Public Science Meeting

March 22, 2018

Office of Research and Development
NCEA, IRIS

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

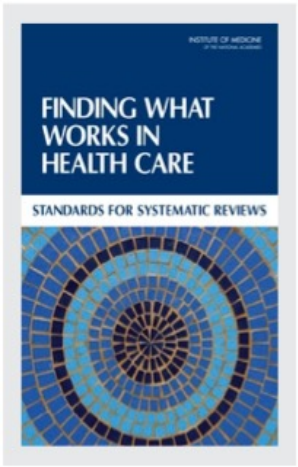
- Clean Air Act (CAA)
- Safe Drinking Water Act (SDWA)
- Food Quality Protection Act (FQPA)
- Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)
- Resource Conservation and Recovery Act (RCRA)
- Toxic Substances Control Act (TSCA)

Broad Input to Support

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

Systematic Review

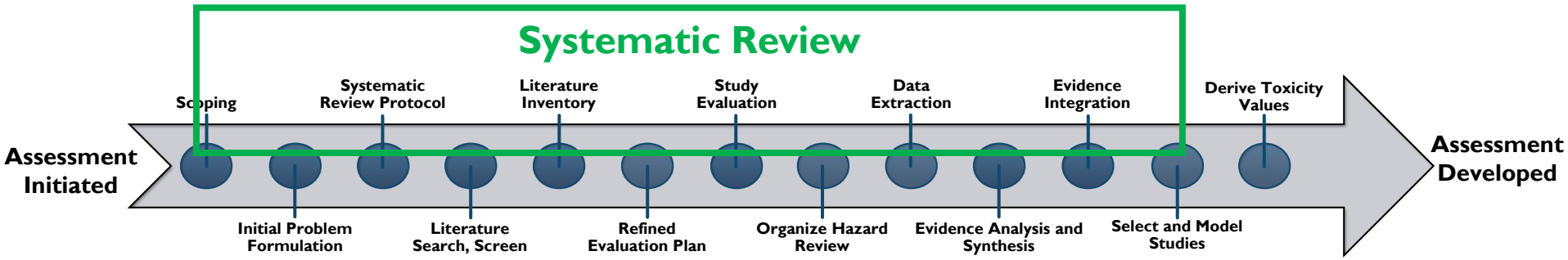
A structured and documented process for transparent literature review



"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."

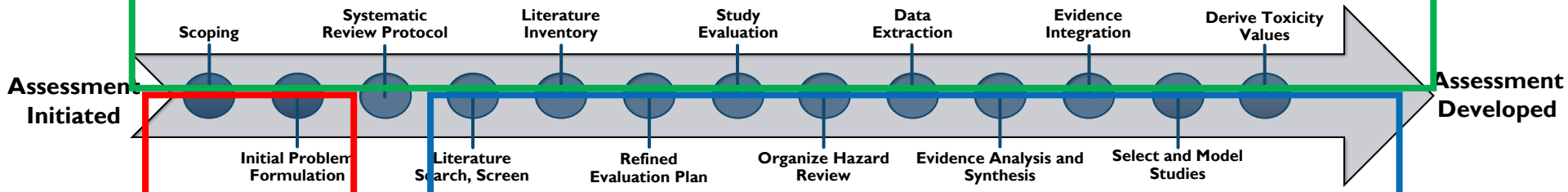
[1] Institute of Medicine. Finding What works in Health Care: Standards for Systematic Reviews. p.13-34. The National Academies Press. Washington, D.C. 2011

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)

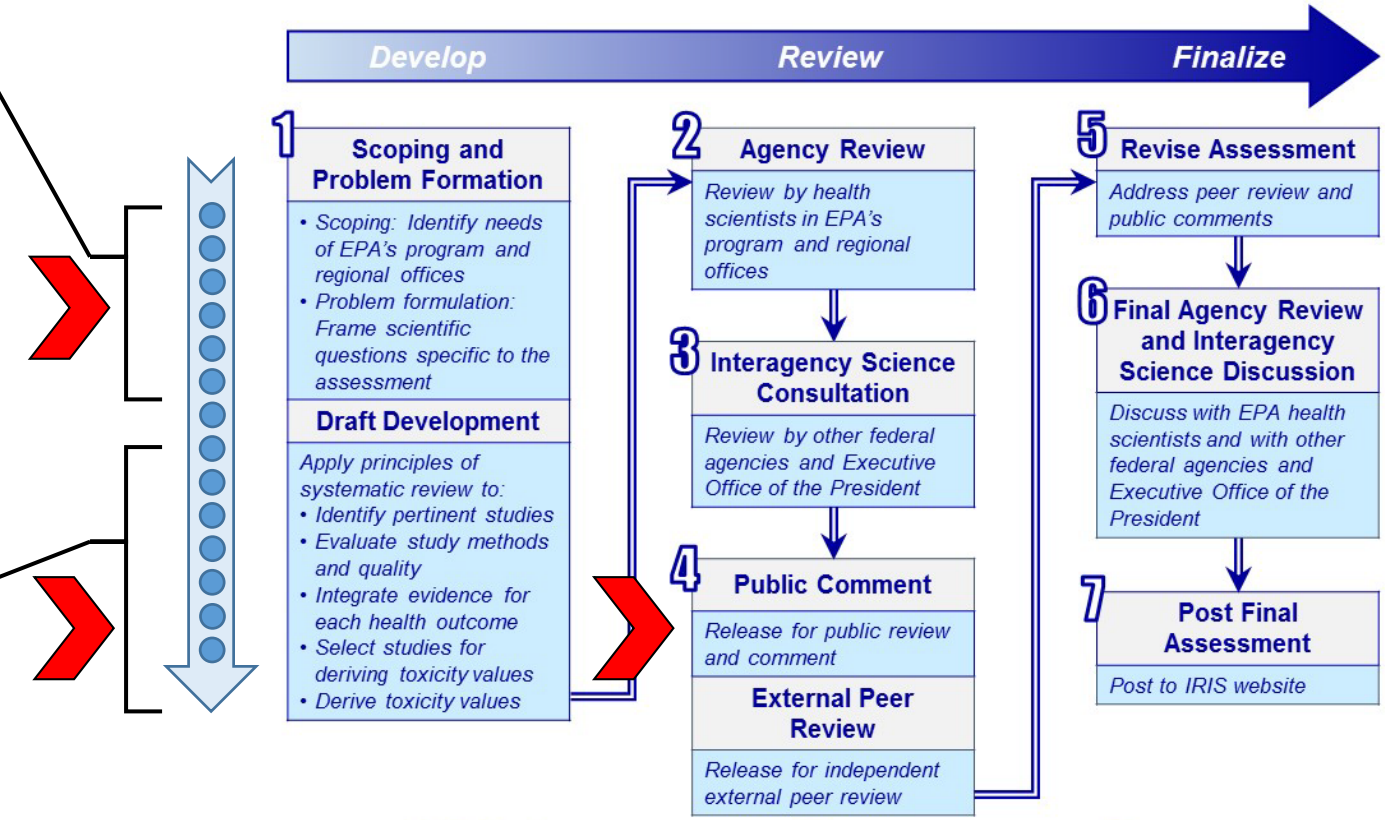
IRIS Assessment Plans, Protocols, and 7-Step IRIS Process

Early Step 1: IRIS Assessment Plans

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

Mid-Step 1: Protocols

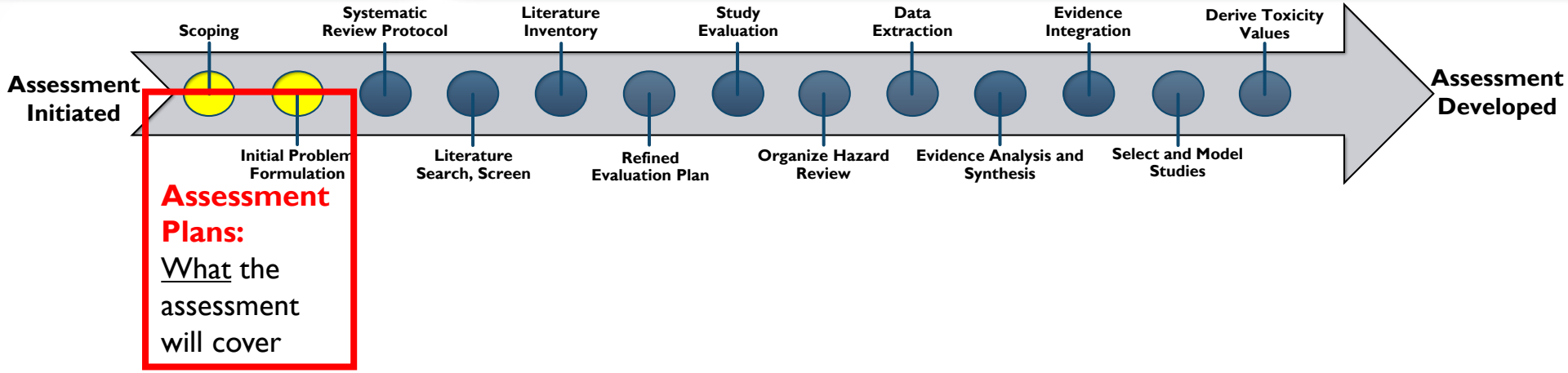
- How the assessment will be conducted
- 30-day public comment



Opportunities for Public Comment

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

IRIS Assessment Plan (IAP)



- Scoping and initial problem formulation determinations
  - Background and Agency need, exposure context, objectives and specific aims, key areas of scientific complexity
  - Includes draft PECO (Populations, Exposures, Comparators, and Outcomes) criteria which outlines evidence considered most pertinent
  - Internal review of IAP fosters early and focused Agency engagement
- Released for a 30-day public comment period + public science discussion (beginning of IRIS Step 1)
- Uranium IAP released for public comment on January 26, 2018

IRIS Assessment Plan (IAP) Content

Table 1. EPA program and regional office interest in an as… uranium

Program or regional office	Oral	Inhalation	Statutes/regulations	Anticip…
Office of Land and Emergency Management	✓		CERCLA	Uranium toxic… used to make r… response or re… short-term ren…
Region 10[a]	✓			response actio… to conduct sho… Superfund site… costs from pot… Uranium is liste… under CERCLA … National Priori…
OW	✓		Safe Drinking Water Act	Uranium toxic… used to inform risk determ… associated with contamina… found in water. The maxim… level goals of 0 µg/L and m… contaminant level of 30 µg… were published in 2000 (65…

2.4. KEY SCIENCE ISSUES

Based on the preliminary literature survey, the following key scientific issues have been identified that warrant evaluation in this assessment.

- Uranium occurs in the environment in a variety of forms to which humans may be exposed, including metallic uranium, soluble uranium salts, and poorly soluble uranium compounds. In developing the IRIS assessment, consideration will be given to the approach used by ATSDR of providing toxicity values suitable for all soluble forms of uranium versus possible alternatives, addressing specific forms of uranium (e.g., more soluble versus poorly soluble versus insoluble species). Taking into account any new research, the assessment will develop and use a rationale for the specific categories of uranium compounds assessed.

3. OVERALL OBJECTIVE, SPECIFIC AIMS, AND DRAFT PECO (POPULATIONS, EXPOSURES, COMPARATORS, AND OUTCOMES) CRITERIA

3.1. SPECIFIC AIMS

- Building on f… epidemiolog… outlined in t… ATSDR litera…
- Conduct stud… toxicological… subsequent … assessment's…
- Examine wh… toxicity valu… kidney toxici… will examine… of additional… uranium.
- If newer PEC… considered a… synthesis/in… studies used… using the me…
- Extract data … considered i…
- For the ident… (including bo… using a narra… examined by ATSDR where important new studies are *not* identified, EPA will seek to base its hazard conclusions on ATSDR's findings unless compelling reasons for further review are identified.

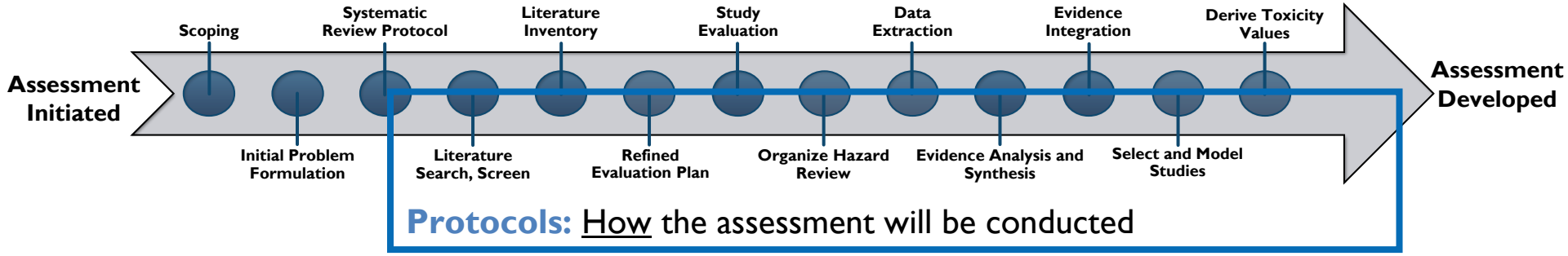
Table 2. Draft PECO (populations, comparators, exposures, and outcomes) criteria for the uranium assessment

PECO element	Evidence
Population[a]	*Human*: Any population and all life stages (e.g., children, general population, occupational, or high exposure from an environmental source). The following study designs will be considered most informative: controlled exposure, cohort, case-control, cross-sectional, and ecological. Note: Case reports and case series will be tracked during study screening but are not the primary focus of this assessment. They may be retrieved for full-text review and subsequent evidence synthesis if no or few more informative study designs are available. Case reports also can be used as supportive information to establish biologic plausibility for some target organs and health outcomes.
	Animal: Nonhuman mammalian animal species (whole organism) of any life stage (including preconception, in utero, lactation, peripubertal, and adult stages).
Exposure	Exposure based on administered dose or concentration, biomonitoring data (e.g., urine, blood, or other specimens), environmental, or occupational-setting measures (e.g., air, water levels), or job title or residence. Studies on natural uranium and depleted uranium will be included, studies on enriched uranium or those specific to radiation exposure from uranium will not be included. Mixture studies for animals will be included if they have an arm with a uranium compound only.
	Human and animal: Oral exposure will be examined. Other exposure routes, including dermal, inhalation, or injection, will be tracked during title and abstract as "supplemental information."
Comparator	*Human*: A comparison or reference population exposed to lower levels (or no exposure/exposure below detection levels) of uranium or to uranium for shorter periods.
	Animal: Quantitative exposure versus lower or no exposure with concurrent vehicle control group.
Outcomes	All noncancer health outcomes. In general, endpoints related to clinical diagnostic criteria, disease outcomes, histopathological examination, or other apical/phenotypic outcomes will be prioritized for evidence synthesis over outcomes such as biochemical measures.

[a] Evaluating individual mechanistic studies for uranium is not anticipated to be critical given the extent of the experimental animal evidence for noncancer outcomes and findings of earlier reviews. For mechanistic information, this assessment will primarily rely on other published authoritative sources, such as public health agency reports and expert review articles.

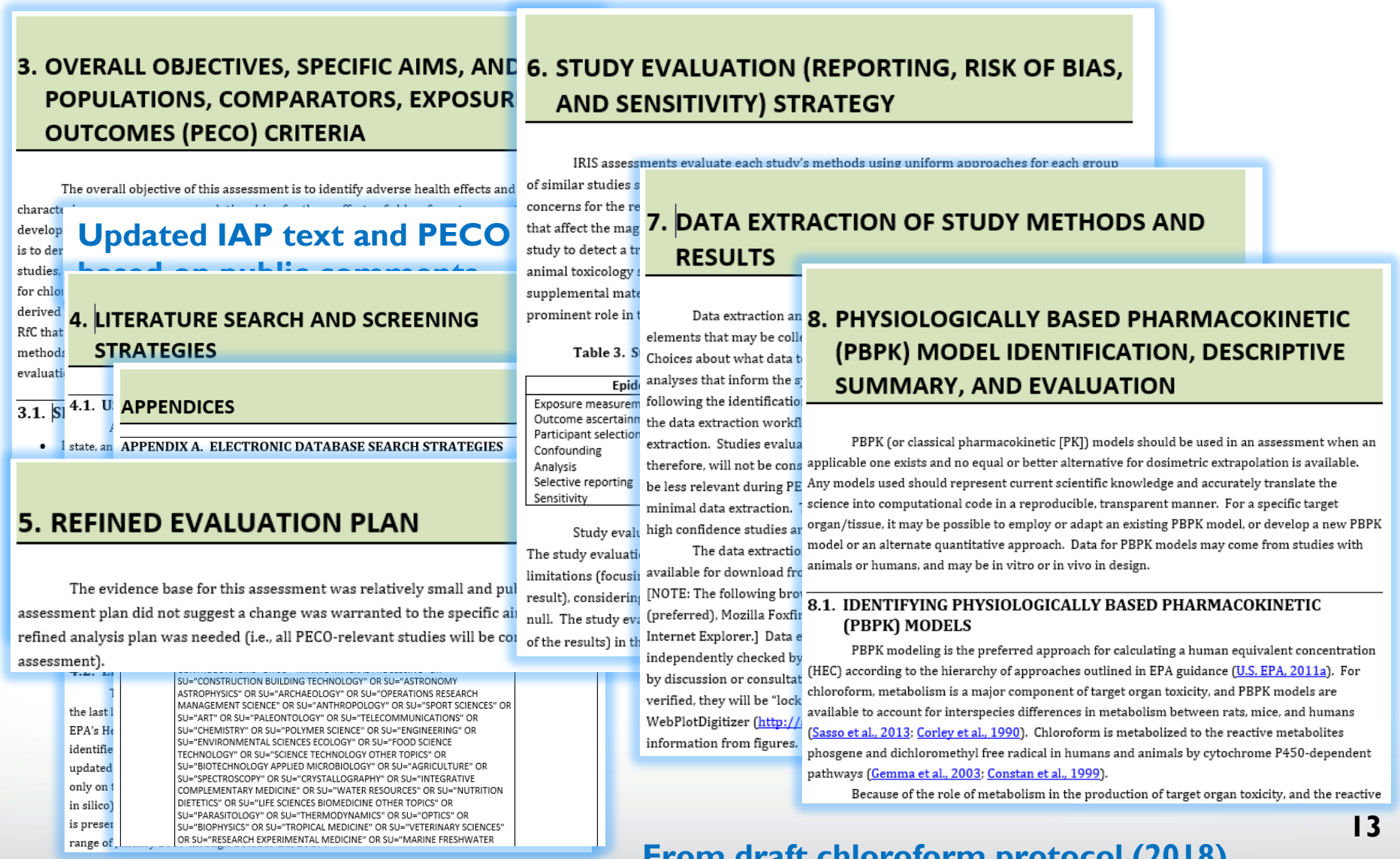
From draft uranium IAP (2018)

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 Protocol Content



From draft chloroform protocol (2018)

IRIS Protocol Content

9. SYNTHESIS WITHIN LINES OF EVIDENCE

For each potential health effect
outcomes; or a broad hazard category),
effect evidence, ar
written to empha
the evidence inte
studies or group c
association, temp
humans (U.S. EPA
Specificall
first be analyzed a
lack of data within
the available mec
chloroform, a syn
evaluation of carc

9.1. SYNTHE

To assess

Table 9. Primar
syntheses[a]

Consideration	
Consistency	Repeated exist, the "differing" *Stronger h* *Stronger c*
Biological gradient (dose-response)[b]	Increases concentrat or comple necessarily considered
Strength (effect magnitude) and precision	Given wha particularl small effec may consi other expl errors and results acr (i.e., low p
Mechanistic evidence related to biological plausibility	Supporting effects; changes in established biol evidence strength. While a lack of strength, it may do so if findings de *Human evidence:* studies in expose *Animal evidence*: studies in exposed animals
Coherence[c]	Findings across the database that fit into a co similarity in results for related effects within a dose-dependent progression of linked effects Conversely, an observed lack of changes that subsequently) with the effect of interest coul informed by the known biological developme toxicokinetic/dynamic understanding of the c
Natural experiments	*Human evidence only*: Reductions in effect th Although rare, such reductions can provide c
Temporality	*Human evidence only:* The exposure occurs be evaluation of exposure measures for each stu

10. INTEGRATION ACROSS LINES

For the analysis of most health outcomes, IRIS assessme
and mechanistic evidence. Depending on the assessment scope a
animal evidence, conclusions for mechanistic evidence may be b
mechanistic st
are drawn as f

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WITHIN STREAM CONCLUSIONS

HUMAN EVIDENCE STREAM CONCLUSION

The synthesis of evidence about health effects and mechanisms from human studies is combined (integrated) to draw a conclusion about effects within the stream

Studies and interpretation	Factors that increase confidence	Factors that decrease confidence	Summ
[Health Effect or Outcome Grouping]			
Evidence from Human Studies (Route)			
· References · Study confidence (based on evaluation of risk of bias and sensitivity) and explanation · Study design description	· Consistency · Dose-response gradient · Coherence of observed effects (apical studies) · Effect size (magnitude, severity) · Biological plausibility · Low risk of bias/ high quality · Insensitivity of null/ negative studies · Natural experiments · Temporality	· Unexplained inconsistency · Imprecision · Indirectness/ applicability · Poor study quality/ high risk of bias · Other (e.g., Single/Few Studies; small sample size) · Evidence demonstrating implausibility	Results infor affected/ una Human evid plausibility: d data influenc judgement (e precursors in Could be multiple rows (e.g study confidence or popul informs results hetero
Evidence for an Effect in Animals (Route)			
· References · Study confidence (based on evaluation of risk of bias and sensitivity) and explanation · Study design description	· Consistency and Replication · Dose-response gradient · Coherence of observed effects (apical studies) · Effect size (magnitude, severity) · Biological plausibility · Low risk of bias/ high quality · Insensitivity of null/ negative studies	· Unexplained inconsistency · Imprecision · Indirectness/ applicability · Poor study quality/ high risk of bias · Other (e.g., Single/Few Studies; small sample size) · Evidence demonstrating implausibility	Results information (gene affected/ unaffected) acro Evidence informing biolo plausibility for effects in a discuss how mechanistic influenced the within stream judgement (e.g., evidence of coherent molecular changes in animal studies) Could be multiple rows (e.g., by study confidence, species, or exposure duration) if this informs results heterogeneity

+ + + Strongestevidence
+ + ○
+ ○ ○ Weakest evidence
○ ○ ○ Inadequate
– – – Convincing evidence of no effect

Figure 4. Evidence profile table template.

11. DOSE-RESPONSE ASSESSMENT: STUDY SELECTION AND QUANTITATIVE ANALYSIS

The previous sections of this protocol describe how systematic review principles are applied to support transparent identification of health outcomes (or hazards) associated with exposure to the chemical of interest in conjunction with evaluation of the quality of the studies considered during hazard identification. Selection of specific data for dose-response assessment and performance of the dose-response assessment is conducted after hazard identification is complete, and builds off this step in developing the complete IRIS assessment. The dataset selection process involves database- and chemical-specific biological judgments that are beyond the scope of this protocol, but are discussed in existing EPA guidance and support documents. This section of the protocol provides an overview of points to consider when conducting the dose-response assessment, particularly statistical considerations specific to dose response analysis that support quantitative risk assessment. Importantly, the considerations outlined in this protocol do not supersede existing EPA guidance. Several EPA guidance and support documents provide more detailed considerations for the development of EPA's traditional dose-response values, especially EPA's *Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002), EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012b), *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), and *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b).

For IRIS toxicological reviews, dose-response assessments are typically performed for both

12. PROTOCOL HISTORY

Release date: (January 2018 [*chloroform protocol version 1*])

From draft chloroform protocol (2018)

March 22, 2018

IRIS Assessment Plan for Uranium

Presentation for the IRIS Public Meeting
Paul White
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency

The purpose of this IRIS Public Science Meeting is to discuss the science that informs the Public Comment Draft of the Uranium Assessment Plan. The draft plan and this presentation do not represent and should not be construed to represent any Agency determination or policy.

Uranium Focus

- EPA's existing IRIS evaluation of uranium dates from 1989 and includes an oral RfD of 3 x 10^{-3} mg/kg/day based on kidney toxicity and body weight loss. A considerable literature on uranium toxicology has since been published.
- ATSDR developed a comprehensive Toxicological Profile for uranium (2013) which provides an intermediate-duration oral MRL of 2 x 10^{-4} mg /kg-d. The ATSDR value is also based on kidney toxicity using a more recent study than the 1989 IRIS assessment.
- This assessment will draw upon ATSDR (2013), supplemented by an new literature search for more recent studies. Systematic review will examine new and key prior studies (slide 3).
- This assessment will address programmatic needs, focusing on oral exposure to natural or depleted uranium. It will address non-radiological effects, hence, for uranium focus on non-cancer effects.

Uranium exposures

- Soils
  - Uranium is naturally present in many soils (Average 3 ppm, locally higher)
  - Uranium mining, milling, and processing operations have caused soil contamination
  - Phosphate ore deposits can contain uranium
- Water
  - Drinking water uranium concentrations are prevalent, but generally low (average about 1 µg U/L), but local ground water can be higher. (EPA MCL 30 µg U/L)
  - Large aquifers in central US and California have locally elevated uranium, exceeding MCL
- US diet typically 0.9 - 1.5 µg U/day; uranium is adsorbed onto root crops.
- Soil ingestion and locally grown or foraged food can be important.
  - These routes can be important at a number of contaminated sites in tribal lands.
  - Regions 9 and 10 addressing important contamination on tribal lands.

For comparison, ATSDR intermediate-duration oral MRL is equivalent to an intake of 14 µg/d for a 70 kg person.

Specific assessment approach

- Literature search to identify new epidemiological and experimental animal studies of the health hazards of ingested uranium (i.e., publications from 2012-2017).
- Conduct study evaluations (risk of bias and sensitivity) for individual epidemiological and toxicological studies identified in the literature search.
- Does newly available data indicate a need to update health outcome conclusions and toxicity values from the ATSDR Toxicological Profile (i.e., kidney toxicity, and reproductive and developmental effects of uranium). Are new outcomes identified? Conduct systematic review including the new data and key prior studies identified based on ATSDR (2013).
- Integrate results across evidence streams (human and animal) to human health hazards. Biological support from mechanistic studies will be summarized primarily by relying on other published sources and targeted literature searches if needed.
- Derive an RfD as supported by the available data. System and organ specific RfD values will be derived where supported by the database.

Science Issues

- New literature available: Expect to make a judgement, based on systematic review, about important uranium health effects including kidney toxicity and reproductive and developmental effects.
- Uranium occurs in a variety of forms of varying solubility in the environment. This assessment will determine optimal approach to different uranium compounds given extent of available data and assessment needs.

Today's Science Topic

An IRIS Assessment Plan, or IAP, communicates to the public the plan for assessing each individual chemical and includes summary information on the IRIS Program's scoping and initial problem formulation, objectives and specific aims for the assessment, and the PECO (Populations, Exposures, Comparators, and Outcomes) criteria that outlines the evidence considered most pertinent to the assessment; and identification of key areas of scientific complexity. The PECO provides the framework for developing literature search strategies and inclusion/exclusion criteria, particularly with respect to evidence stream (i.e., human, animal, mechanistic), exposure measures and outcome measures.

The IRIS program is seeking a discussion with the public aimed at improving or clarifying the IAP. Below are questions to facilitate the discussion of this science topic:

- Are the assessment objectives and specific aims articulated clearly?
- Does the background information and context that is provided support the objectives for the assessment presented in plan?
- Does the proposed PECO (Population, Exposure, Comparators, Outcomes) framework identify the most pertinent evidence to address the stated needs of the Agency programs and regions?