IRIS Public Science Meeting

December 5, 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, Chemical & Pollutant Assessment Division (CPAD)
Center for Public Health and Environmental Assessment (CPHEA)
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

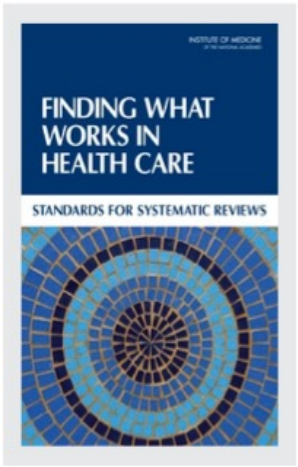
- Clean Air Act (CAA)
- Safe Drinking Water Act (SDWA)
- Food Quality Protection Act (FQPA)
- Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)
- Resource Conservation and Recovery Act (RCRA)
- Toxic Substances Control Act (TSCA)

Broad Input to Support

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

Systematic Review

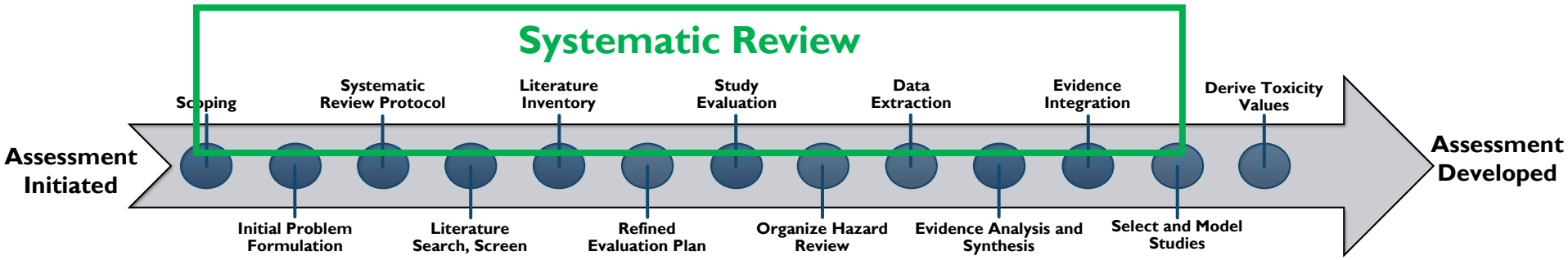
A structured and documented process for transparent literature review



"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."

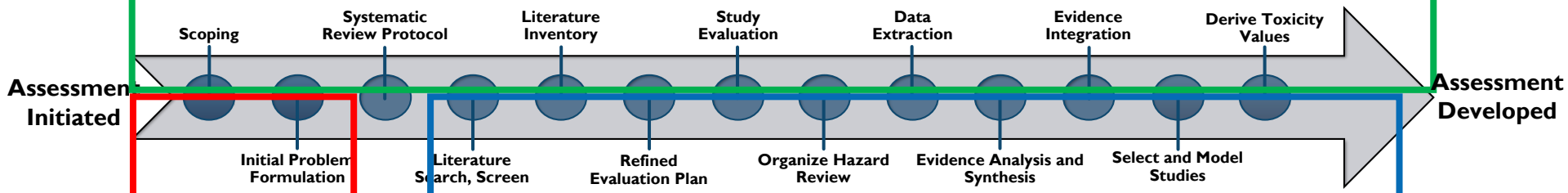
[1] Institute of Medicine. Finding What works in Health Care: Standards for Systematic Reviews. p.13-34. The National Academies Press. Washington, D.C. 2011

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.

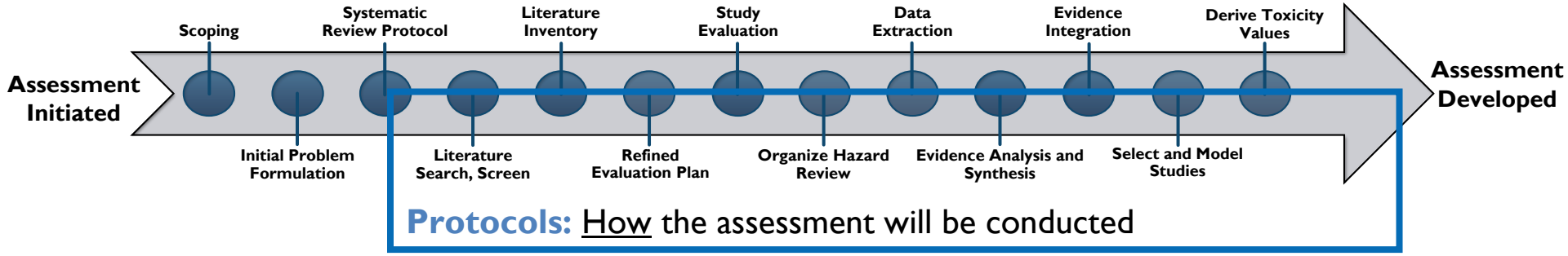


Assessment Plans: What the assessment will cover

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)

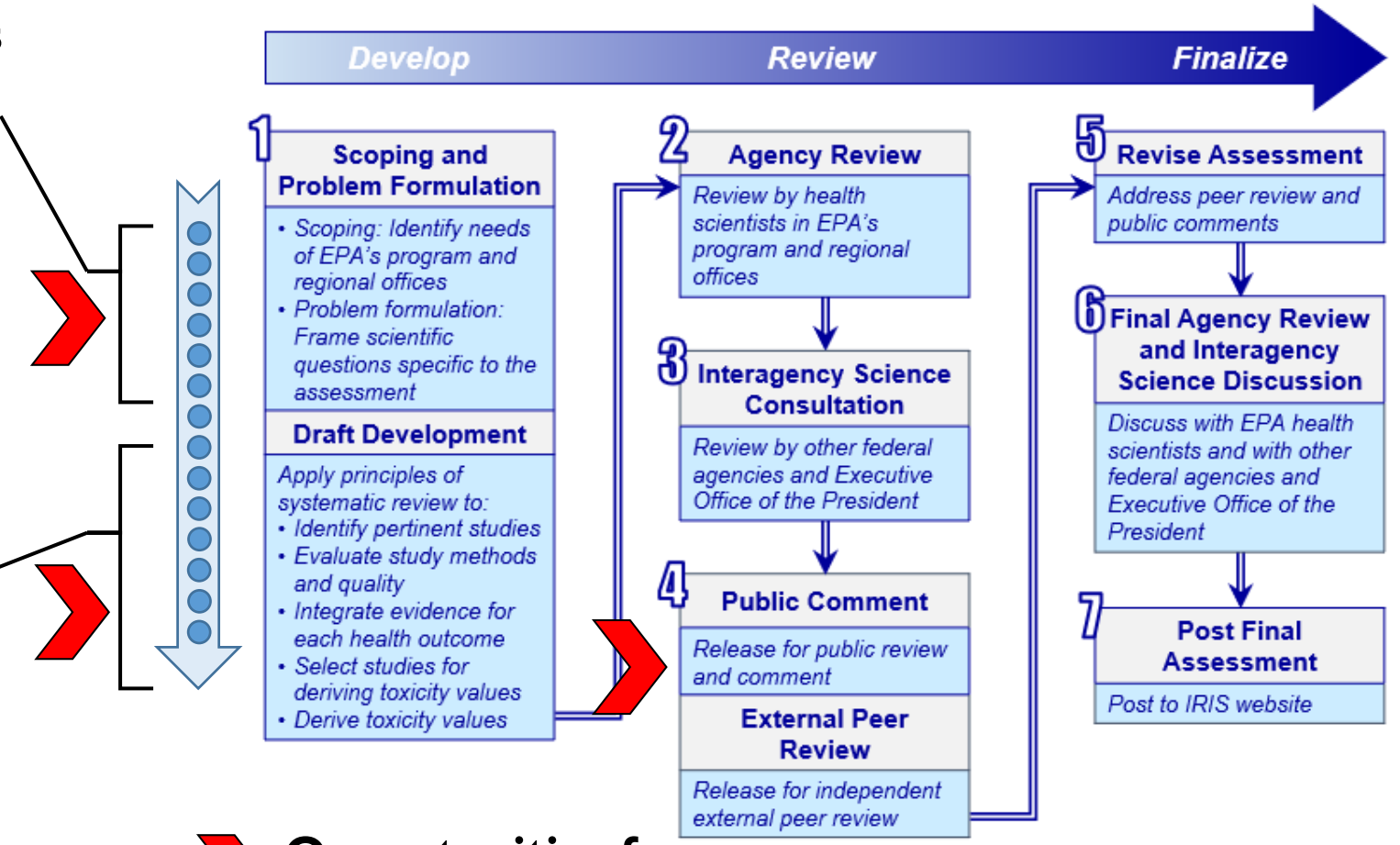
IRIS Assessment Plans, Protocols, and 7-Step IRIS Process

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

Inorganic Mercury Salts IRIS Assessment Plan Public Science Meeting

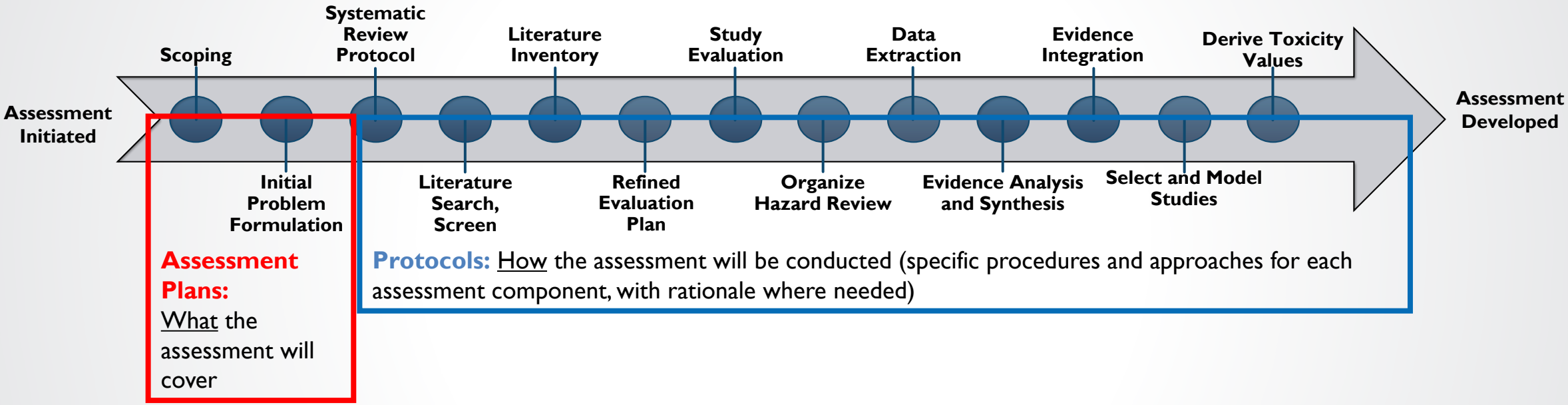
December 5, 2019

Nagu Keshava *(Assessment Manager)*
Center for Public Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency

Outline of the Presentation

- Background
- Scoping Summary
- Problem Formulation
  - Literature Search Terms and Strategy
  - Draft PECO
- Overall Objective and Specific Aims
- Preliminary Literature Survey Results
- Health Outcomes to be Evaluated
- Key Science Topics

IRIS Assessment Plan and Protocol



- A scoping and problem formulation document (IAP) is released with a public comment period; comments received on IAP are then considered when preparing the protocol.
- The protocol is a document adopted by the IRIS Program as part of its full implementation of systematic review

Background

- **Occurrence:** Elemental mercury can combine with chlorine, sulfur, and other elements to form inorganic compounds. The most common naturally occurring inorganic mercury salts include mercuric chloride ($HgCl_2$), mercuric sulfide (HgS, cinnabar), and mercurous chloride (Hg_2Cl_2, calomel).
- **Uses:** Inorganic mercury compounds are used in skin lightening soaps and creams, photography, as a topical antiseptic and disinfectant, wood preservative, and fungicide. In the past, mercurous chloride was used in medicinal products including laxatives, worming medications, teething powders.
- **Exposure:** Human exposure occurs both in occupational and environmental settings. Occupations include mining, electrical equipment manufacturing, and chemical and metal processing. In the general population, exposure can occur through the dermal, oral or inhalation route.
- **ADME:** Once in the body, inorganic mercury salts move to different tissues through the bloodstream and readily accumulate in kidneys and liver. Absorption depends on solubility and intestinal pH. Inorganic mercury salts are mainly excreted through urine or feces.

Background

- **Current EPA toxicity values for inorganic mercury salts**

  - 1995
    - IRIS derived an oral RfD value of 3×10^{-4} mg/kg-day for mercuric chloride based on autoimmune effects (autoimmune glomerulonephritis) in brown Norway rats in subchronic-duration feeding and subcutaneous studies. An RfD for mercuric sulfide or mercurous chloride is not available on IRIS at this time.
    - A cancer assessment for mercuric chloride is available. Based on the qualitative weight-of-evidence characterization, mercuric chloride was classified as a possible human carcinogen. However, no quantitative cancer values were derived for either oral or inhalation exposures because of lack of human data and limited animal carcinogenicity data.
  - 2002
    - A screening-level literature review was conducted pertinent to the RfD for mercuric chloride but did not identify any new critical studies.
  - No inhalation toxicity values (RfC) have been derived for any of the inorganic mercury salts (mercuric chloride, mercuric sulfide, or mercurous chloride).

Background

Toxicity Values across Agencies

Reference	Value (mg/kg-d)	Exposure duration	Chemical note	Endpoints/basis
U.S. EPA (1995)	3×10^{-4}	Chronic	Mercuric chloride	Autoimmune effects (autoimmune glomerulonephritis) UF = 1,000 (10 for LOAEL to NOAEL, 10 for subchronic studies and a combined 10 for both UF_A and UF_H) (U.S. EPA, 1987; Andres, 1984; Bernaudin et al., 1981; Druet et al., 1978)
ATSDR (1999)	2×10^{-3}	Intermediate	Mercurous chloride, mercuric chloride, mercuric sulfide, and mercuric acetate	Kidney-weight changes in rats UF = 100 (UF_A = 10, UF_H = 10), following 26 weeks oral exposure to mercuric chloride (NTP, 1993)
WHO (2003)	2×10^{-3}	Chronic	Mercuric chloride	Renal effects in rats UF = 100 (UF_A = 10, UF_H = 10) (NTP, 1993)

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_H = intraspecies uncertainty factor.

Scoping Summary

- During scoping, the IRIS Program met with EPA program and regional offices that had interest in an IRIS assessment for inorganic mercury salts to discuss specific assessment needs. In addition, during fiscal year 2018, the Administrator prioritized chemicals for IRIS assessments that included inorganic mercury salts as one of them to meet the-needs of EPA programs and regions.

EPA Program or Regional Office	Oral	Inhalation	Anticipated Uses / Interest
Office of Land and Emergency Management	✓	✓	Toxicological information from inorganic mercury salts may be used to make risk determinations for response actions (e.g., short-term removals, long-term remedial response actions) under CERCLA and RCRA including Subtitle I. For example, CERCLA authorizes EPA to conduct short or long-term cleanups at Superfund sites and later recover cleanup costs from potentially responsible parties under section 107.

Methyl mercury: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=343693
Elemental mercury: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=370

Overall Objective and Specific Aims

- Conduct a literature search to identify epidemiology and toxicology literature as outlined in the PECO.
- Conduct study evaluations (risk of bias and sensitivity) for individual epidemiology and toxicology studies and PBPK models, if the data are available.
- Synthesize the evidence across studies, assessing similar health outcomes using a narrative approach.
- Integrate the strength of evidence conclusions across evidence streams.
- Derive toxicity values as supported by the available data. Characterize uncertainties and identify key data gaps and research needs.

Literature Search Terms and Strategy

PubMed	Mercuric choride: ((((("Bichloride of mercury" OR "Calochlor" OR "Corrosive sublimate" OR "Dichloromercury" OR "HgCl2" OR "Mercuric chloride" OR "Mercuric perchloride" OR "Mercury bichloride" OR "Mercury chloromercurate (II)" OR "Mercury dichloride" OR "Mercury perchloride" OR "Mercury (II) chloride"))) AND ("2018/01/01"[Date - Publication] : "2019/02/15"[Date - Publication])) Mercuric sulfide: ((alpha-HgS OR Chinese red OR Cinnabar OR Ethiops mineral OR Aethiops mineral OR HgS OR Mercuric sulfide OR Mercury (II) sulfide OR Mercury (II) sulfide black OR Mercury (II) sulfide red OR Mercury sulfide OR Mercury sulphide OR Vermilion)) AND ("2018/01/01"[Date - Publication] : "2019/02/15"[Date - Publication]) Mercurous chloride: ((caloreen OR calomel OR chloromercuri OR Cl2Hg2 OR mercury dichloride OR Hg2Cl2 OR hydrochloric acid mercury salt OR mercurous chloride OR mercury (I) chloride OR mercury chloride OR mercury monochloride OR mercury protochloride OR mercury subchlorides OR mild mercury chloride)) AND ("2018/01/01"[Date - Publication] : "2019/02/15"[Date - Publication])	1997–Feb 2019 Search results: 1,997 1997–Feb 2019 Search results: 1,200 1997–Feb 2019 Search results: 2,612
WOS	Mercuric choride: TS=("Bichloride of mercury" OR "Calochlor" OR "Corrosive sublimate" OR "Dichloromercury" OR "HgCl2" OR "Mercuric chloride" OR "Mercuric perchloride" OR "Mercury bichloride" OR "Mercury chloromercurate (II)" OR "Mercury dichloride" OR "Mercury perchloride" OR "Mercury (II) chloride" OR "7487-94-7") AND PY=2018-2019 Mercuric sulfide: TS=("alpha-HgS" OR "Chinese red" OR "Cinnabar" OR "Ethiops mineral" OR "HgS" OR "Mercuric sulfide" OR "Mercury (II) sulfide" OR "Mercury (II) sulfide black" OR "Mercury (II) sulfide red" OR "Mercury sulfide" OR "Mercury sulphide" OR "Vermilion") AND PY=2018-2019 Mercurous chloride: TS=("Caloreen" OR "Calomel" OR "Chloromercuri" OR "Cl2Hg2" OR "Dimercury dichloride" OR "Hg2Cl2" OR "Hydrochloric acid mercury salt OR Mercurous chloride" OR "Mercury (I) Chloride" OR "Mercury chloride" OR "Mercury monochloride" OR "Mercury protochloride" OR "Mercury subchloride" OR "Mild mercury chloride") AND PY=2018-2019	1997–Feb 2019 Search results: 3,888 1997–Feb 2019 Search results: 3,862 1997–Feb 2019 Search results: 2,150
TOXLINE	Mercuric choride: @OR+("Bichloride+of+mercury"+Calochlor+"Corrosive+sublimate"+Dichloromercury+HgCl2+"Mercuric+chloride"+"Mercuric+perchloride"+"Mercury+bichloride"+"Mercury+chloromercurate+(II)"+"Mercury+dichloride"+"Mercury+perchloride"+"Mercury+(II)+chloride"+@TERM+@rn+7487-94-7)+@NOT+@org+pubmed+pubdart+@AND+@RANGE+yr+2018+2019 Mercuric sulfide: @OR+("alpha-HgS"+"Chinese+red"+"Cinnabar"+"Ethiops+mineral"+"HgS"+"Mercuric+sulfide"+"Mercury+(II)+sulfide"+"Mercury+(II)+sulfide+black"+"Mercury+(II)+sulfide+red"+"Mercury+sulfide"+"Mercury+sulphide"+"Vermilion"+@TERM+@rn+1344-48- 5)+@NOT+@org+pubmed+pubdart+@AND+@RANGE+yr+2018+2019 Mercurous chloride: (@OR+("Caloreen"+"Calomel"+"Chloromercuri"+"Cl2Hg2"+"Dimercury+dichloride"+"Hg2Cl2" +"Hydrochloric+acid+mercury+salt"+"Mercurous+chloride"+"Mercury+(I)+Chloride"+"Mercury+chloride"+"Mercury+monochloride"+"Mercury+protochloride"+"Mercury+subchloride"+"Mild+mercury+chloride"+@TERM+@rn+10112-91- 1)+@AND+@RANGE+yr+1999+2018)+@NOT+@org+pubmed+pubdart	1997–Feb 2019 Search results: 359 1997–Feb 2019 Search results: 72 1997–Feb 2019 Search results: 61

Draft PECO Statement

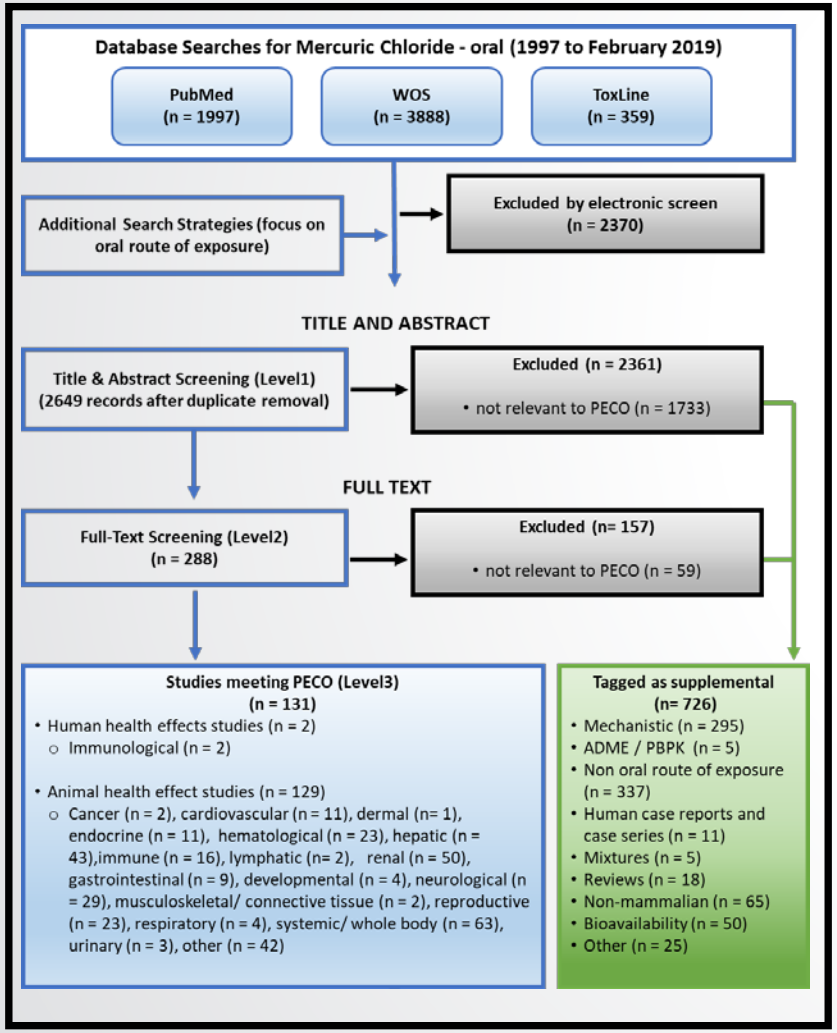
PECO element	Evidence
Populations	**Human:** Any population and life stage (occupational or general population, including children and other sensitive populations). **Animal:** Nonhuman mammalian animal species (whole organism) of any life stage (including preconception, in utero, lactation, peripubertal, and adult stages). Nonmammalian models and in vitro studies will be tracked as supplemental.
Exposures	*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. Relevant forms are listed below:* • Mercuric chloride (7487-94-7) and all synonyms including mercuric perchloride, mercury bichloride, mercury chloromercurate (II), mercury dichloride, mercury perchloride, mercury (II) chloride, $HgCl_2$, dichloromercury, calochlor, bichloride of mercury • Mercuric sulfide (1344-48-5) and synonyms including cinnabar, mercury (II) sulfide, mercury (II) sulfide black, mercury (II) sulfide red, mercury sulfide, mercury sulphide, vermilion, Chinese red, ethiops mineral, HgS • Mercurous chloride (10112-91-1) and synonyms including calomel, calogreen, chloromercury, dimercury dichloride, mercury (I) chloride, mercury chloride, mercury monochloride, mercury protochloride, mercury subchloride, mild mercury chloride, Hg_2Cl_2 **Human:** Any exposure to the relevant forms of inorganic mercury salts listed above, including occupational exposures via oral or inhalation route. Other exposure routes, including dermal exposure, will be tracked during screening as "potentially relevant supplemental information." **Animal:** Any exposure to inorganic mercury salts via the oral or inhalation route. Studies involving exposures to mixtures will be included only if they include exposure to inorganic mercury salts alone. Other exposure routes, including dermal or injection exposures, will be tracked during screening as "potentially relevant supplemental information."

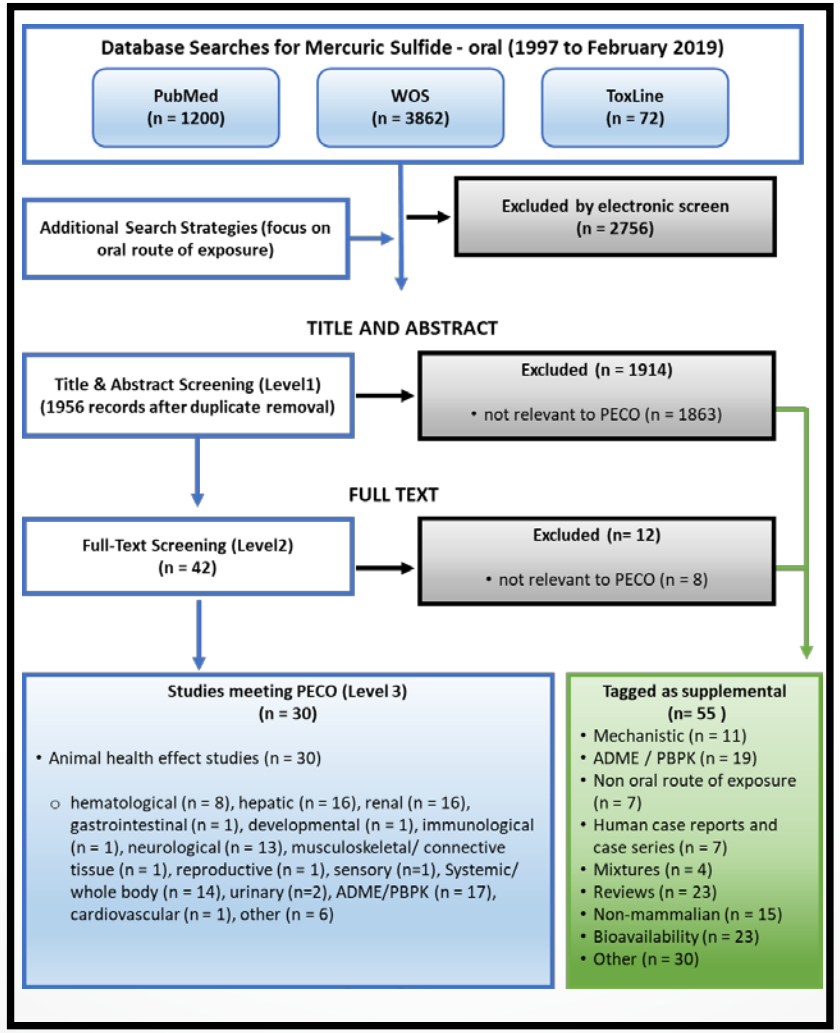
Draft PECO Statement - cont'd

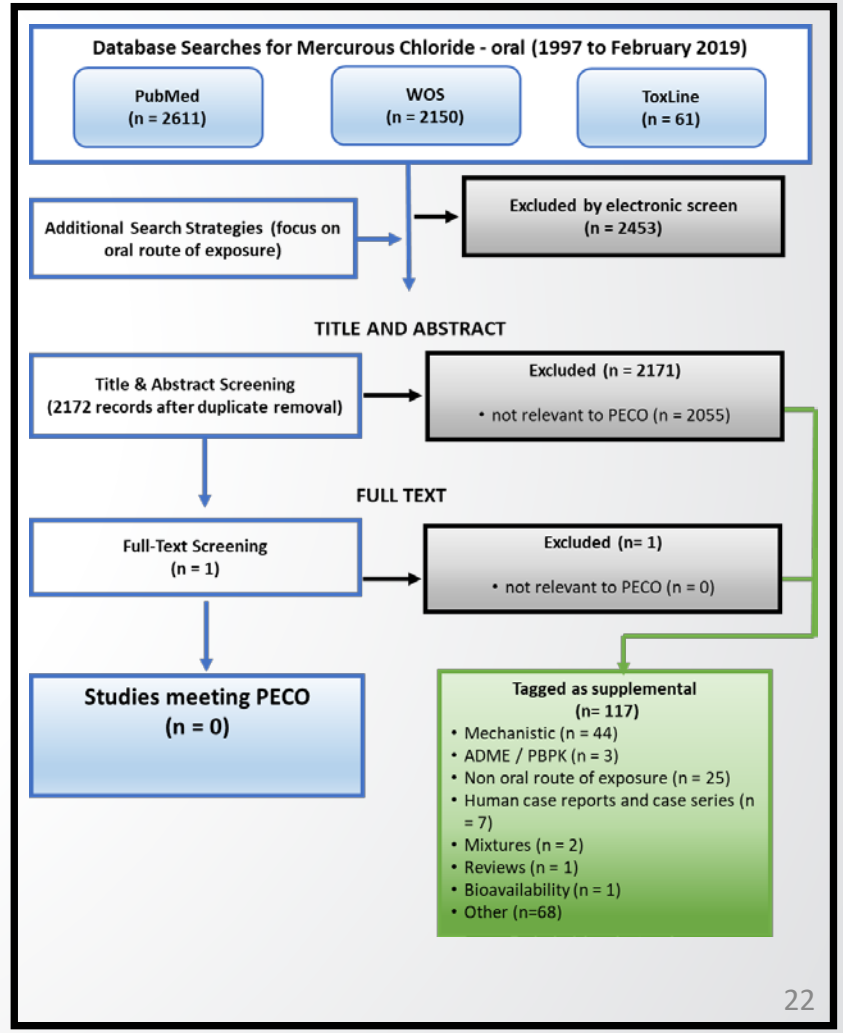
PECO element	Evidence
Comparators	Human: A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of inorganic mercury salts, or exposure to inorganic mercury salts for shorter periods of time. Case reports and case series will be tracked as "potentially relevant supplemental information." Animal: A concurrent control group exposed to vehicle-only treatment or untreated control.
Outcomes	All health outcomes (both cancer and noncancer). 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. As discussed above, based on preliminary screening work, EPA anticipates that a systematic review for health effect categories other than those identified (i.e., renal, immunological, neurological, hepatic, hematological, and reproductive effects) will not be undertaken unless a significant amount of new evidence is found upon review of references during the comprehensive literature search.
PBPK models	Studies describing PBPK models for inorganic mercury salts. Toxicokinetic differences among life stages (including gestation and postnatal development) will be included where data are available.

Preliminary Literature Survey

Oral studies

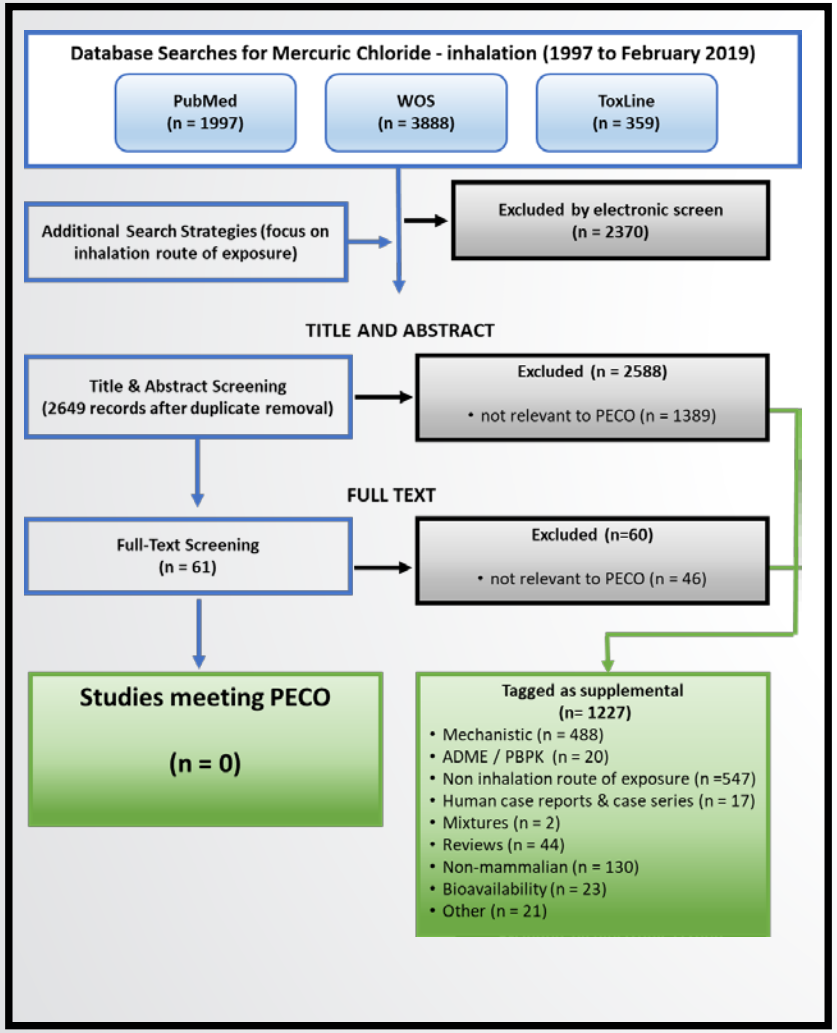


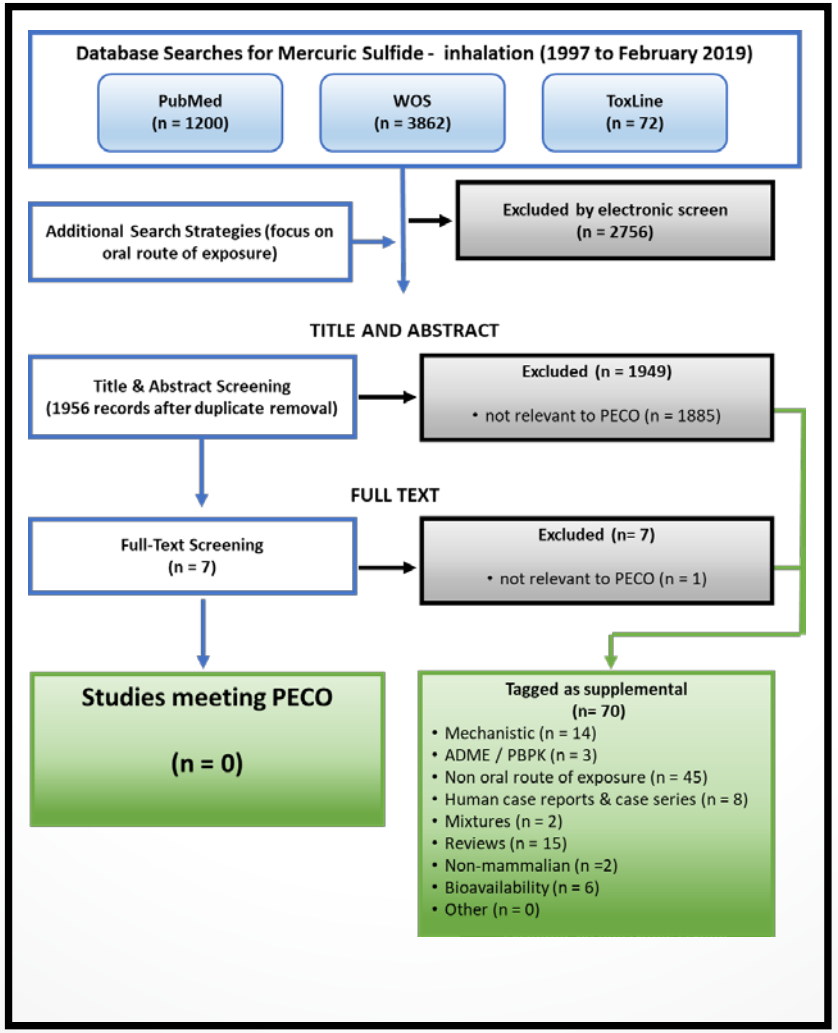


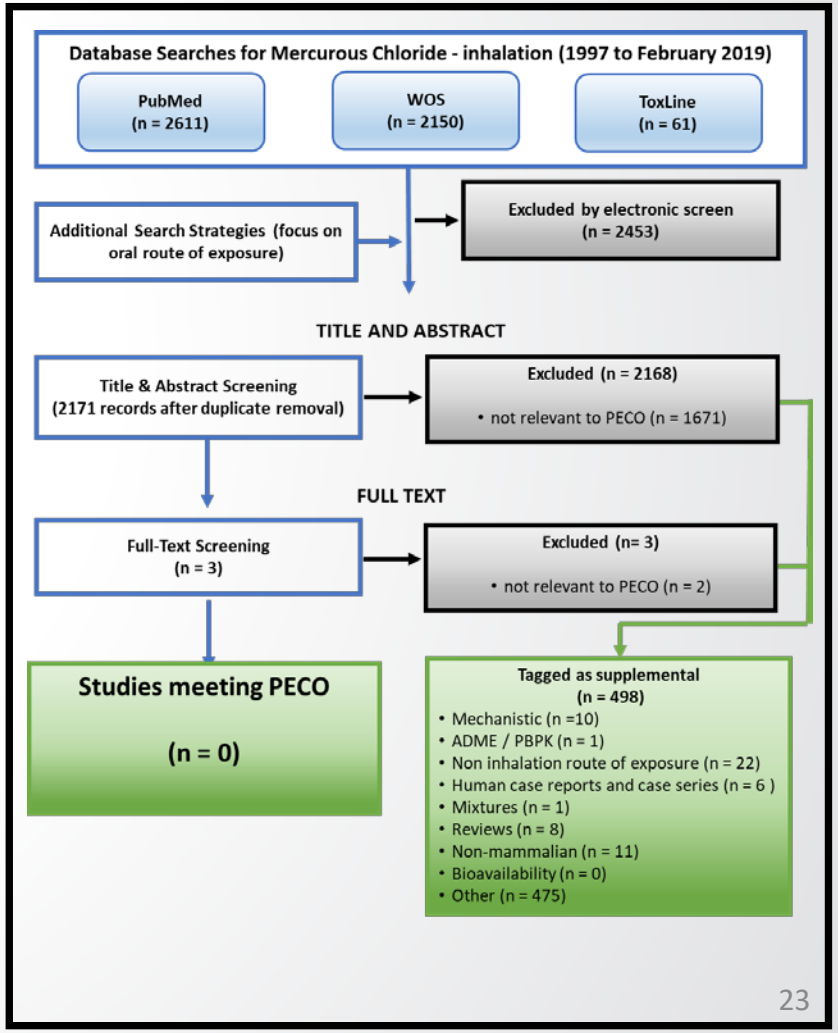


Preliminary Literature Survey- cont'd

Inhalation studies







Scoping decision to focus on oral exposure only

- At the time of the initial nomination by OLEM there was an indication of possible inhalation exposure to inorganic mercury salts in Superfund sites; however, upon further examination the inhalation exposure was determined to pertain to elemental mercury and exposure concerns to inorganic mercury salts via inhalation were deemed unlikely.

- Further, our preliminary literature survey of the available data for inorganic mercury salts did not identify any inhalation studies for mercuric chloride, mercuric sulfide, or mercurous chloride.

Health Outcomes to be Evaluated

Based on the preliminary literature survey, EPA anticipates conducting a further systematic review analysis for the following health effect categories:

- Renal effects
- Immunological effects
- Nervous system effects
- Hepatic effects
- Reproductive effects
- Hematologic effects

Science Topic #1

- **Toxicokinetic characteristics of various mercury forms including solubility, bioavailability, distribution, conversion (oxidation state).** Inorganic mercury salts are present in different oxidation states. For example, both mercuric chloride and mercuric sulfide are divalent and have mercury in a +2 oxidation state whereas mercurous chloride has a +1 oxidation state (which may change in different biological systems). In addition, the solubilities of the three salts differ by several orders of magnitude. These characteristics are expected to influence the toxicokinetics of the different salts. An understanding of these characteristics or other information on the bioavailability, tissue distribution and toxicokinetic profiles of the different salts is expected to be informative in evaluating potential human health hazards.

Science Topic #2

- **Key molecular interactions and sequelae of mercuric ion on potential target tissues (e.g., kidney, immune system).** Mercuric ion has been identified in the literature as a presumed toxic moiety in potential target tissues through its binding to sulfhydryl groups. Further understanding of the conversion of mercurous to mercuric ion following exposure to mercurous chloride and its key molecular interactions with biological targets may be important to consider in the assessment.

Science Topic #3

- **Alternative methods or new approaches to inform data poor mercury salts (i.e., mercurous chloride and mercuric sulfide).** Both mercuric sulfide and mercurous chloride lack or have minimal *in vivo* toxicity data. Information relevant to the potential application of alternative approaches to derive toxicity values for these salts (e.g., read-across) may be useful to assessment development.