IRIS Public Science Meeting

April 24, 2019

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.
- **To report technical difficulties or webinar issues to the meeting host,** use the “chat” pod of the Adobe Connect Webinar.

INTRODUCTION AND ROLE OF PROTOCOLS IN THE IRIS PROCESS

Kris Thayer

Director, Integrated Risk Information System (IRIS)

National Center for Environmental Assessment

Office of Research and Development

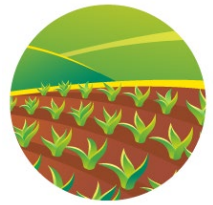
U.S. Environmental Protection Agency

- **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)

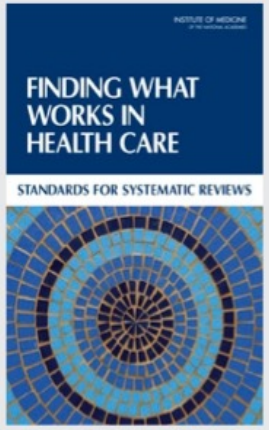


Broad Input to Support

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

Systematic Review

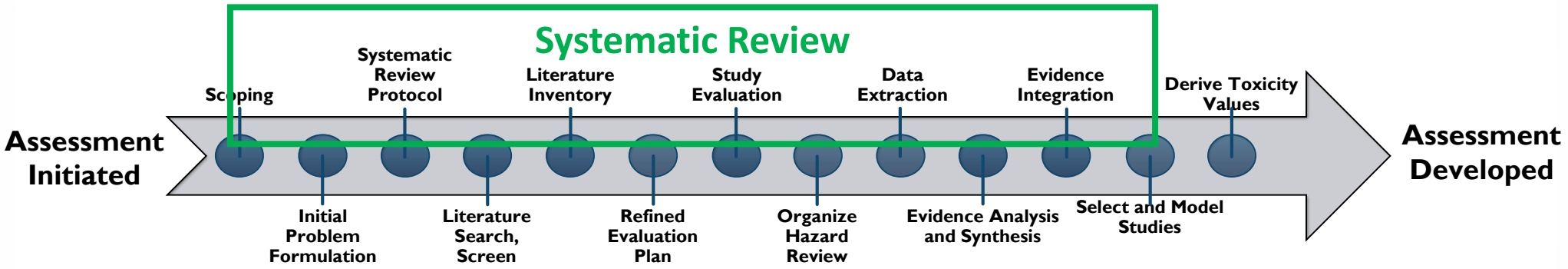
A structured and documented process for transparent literature review



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."

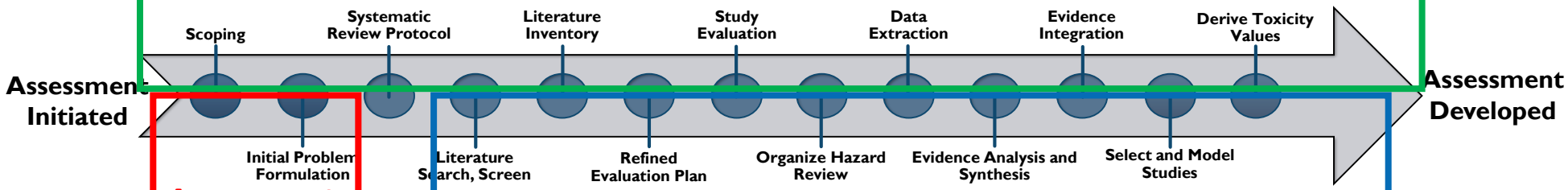
[1] Institute of Medicine. Finding What works in Health Care: Standards for Systematic Reviews. p.13-34. The National Academies Press. Washington, D.C. 2011

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)

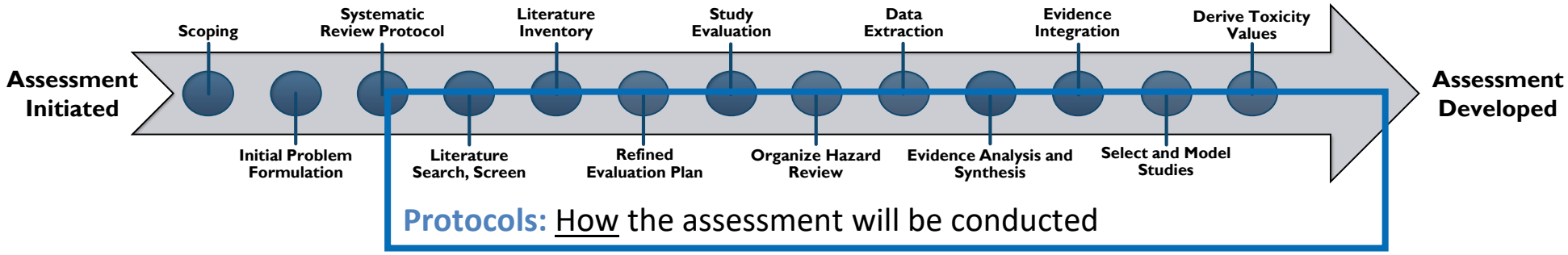
Assessment plans replace previous "Scoping and Problem Formulation" Documents

What we are presenting today

IAPs Represent Continuous Refinement of Scoping and Problem Formulation Materials

Scoping & Problem Formulation Document (Released for Cr(VI) in Apr. and Oct. 2014)	Assessment Plan Document use for new starts after 2017
Introduction and background	Introduction and background
Production and use, human exposure pathways, environmental fate	Concise discussion to extent this information provides necessary context
Scoping (“Scope of the Assessment”)	Scoping (“Scoping Summary”)
[Not explicitly discussed]	Table of Agency Interest
Problem Formulation	Problem Formulation
Preliminary Literature Survey (conducted by manual review of studies retrieved)	Preliminary Literature Survey (conducted using various approaches, e.g. machine-learning, prior assessments)
Systematic Review Elements	Systematic Review Elements
[Not explicitly discussed]	Specific Aims
Hazard Questions for Systematic Review	Draft Populations, Exposures, Comparators, Outcomes (PECO)
[Not explicitly discussed]	Assessment Approach
Key Issues	Key Science Issues

IRIS Protocol



- Previous Cr(VI) problem formulation content has been presented in IAP format in the protocol
- List of included, excluded, and studies tagged as supplemental are disseminated through protocols (either during initial release or as an update)

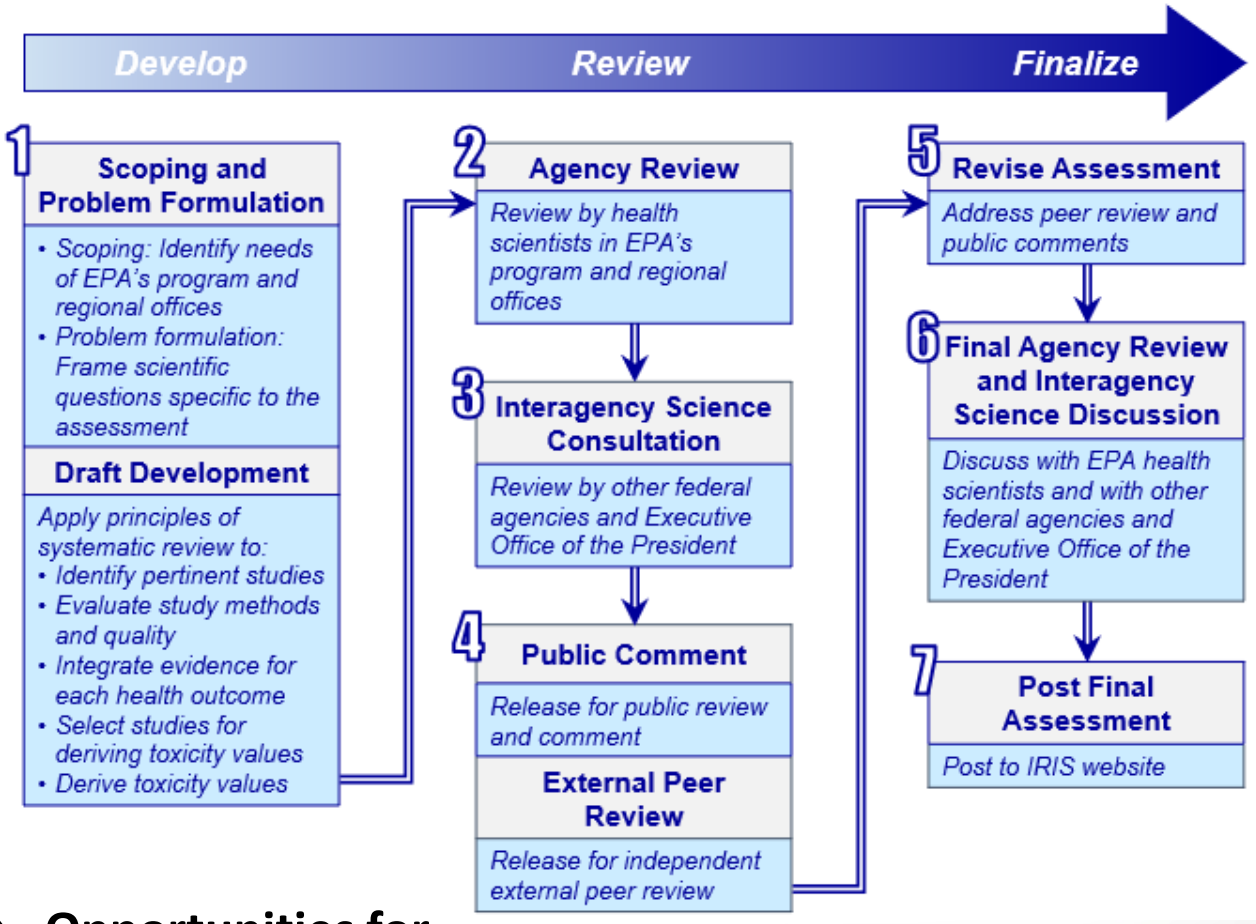
IRIS Assessment Plans, Protocols, and 7-Step IRIS Process

Early Step 1: IRIS Assessment Plans

- <u>What</u> the assessment covers
- 30 day public comment period + public science meeting

Mid-Step 1: Protocols

- <u>How</u> the assessment will be conducted
- 30-45 day public comment



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

IRIS Protocol Content

3. ASSESSMENT APPROACH, SPECIFIC AIMS, AND DRAFT POPULATIONS, EXPOSURES, COMPARATORS, AND OUTCOMES (PECO) CRITERIA

3.1. ASSESSMEN

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input received during
government health ag
consideration of the pl
materials released in 2
include evaluations of
systems: respiratory, g
developmental. As dis
the systematic review
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3.1.1. Evaluation of

EPA's 1998 IRI
inhalation route of exp
Cr(VI) and increased i
reached by other feder

4. LITERATURE SEARCH AND SCREENING STRATEGIES

4.1. LITERATURE SEARCH STRATEGIES

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retrieved in the
strategy was tai

APPENDIX A. ELECTRONIC DATABASE SEARCH STRATEGIES

Table A-1. Literature search query strings for computerized databases

	Hits

5. REFINED EVALUATION PLAN

The purpose of the refined evaluation pla
studies that met PECO criteria and are to be carri
determine which studies tagged as "potentially re
considered in the assessment. Refinements of PE
comments on the preliminary materials released
4440628}; (2) literature screening and creation c
potentially relevant supplemental material by EP
inventories by subject-matter experts. The refine
grouped by outcomes, that will be the primary fo
specifications will aid implementation of the end
evaluation is outcome and analysis-specific.

5.1. AIRBORNE CHARACTERIZATIO

Studies that met PECO criteria include th
of physical and chemical forms. Airborne Cr(VI)
respiratory tract deposition (e.g., particulates, du
compounds containing Cr(VI) meeting PECO crite
of Cr(VI) meeting PECO criteria will be evaluated
properties or airborne characteristics. It will be t
mixtures (such as Cr[VI] in extremely acidic or al
the toxicity or introduce uncertainties. In additio
airborne Cr(VI) will be taken into consideration
dose-response analysis.

5.1.1. Toxicokinetics

Information on the toxicokinetics of Cr(VI) is provided elsewhere in this document (see Sections 3.1 and 6.4). Of the PBPK models available that met PECO criteria, evaluations will be limited to those accounting for Cr(VI) reduction in the stomach compartment and interspecies differences in gastric pH and physiology. Models must also include parameterization for mice, rats, and humans. This narrows the evaluation to models that may be suitable for the dose-response assessment. Furthermore, based on the issues related to toxicokinetics outlined in Sections 3.1 and 6.4, and discussions and comments from public meetings {EPA, 2014, 4440628; EPA, 2013, 4440626}, route-to-route extrapolations will not be considered.

5.1.2. Toxicogenomics

Twenty-five toxicogenomic studies were identified during screening as "potentially relevant supplemental material." Due to the complex nature of these studies, the animal bioassays that generated available microarray data will be assessed for risk of bias using criteria described in Section 6.3. Microarray data reporting quality will be evaluated using the proposed Minimum Information About a Microarray Experiment (MIAME) {Brazma, 2001, 4449307} and the quality of microarray data will be assessed based on standard practices in the field {Bourdon-Lacombe, 2015, 4449305}. For expression microarray data, the assessment of data quality reflects specificities of microarray platforms, but it often includes evaluation of multivariate similarities between microarrays using unsupervised multivariate projection methods and clustering, as well as other diagnostic plots, such as boxplots of log-intensities. The quality of microarray data will also be

6. STUDY EVALUATION (REPORTING, RISK OF BIAS, AND SENSITIVITY) STRATEGY

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9.2).

6.1. STUD

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below can be
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6.4. PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODEL DESCRIPTIVE SUMMARY AND EVALUATION

PBPK (or classical pharmacokinetic [PK]) models should be used in an assessment when an applicable one exists and no equal or better alternative for dosimetric extrapolation is available. Any models used should represent current scientific knowledge and accurately translate the science into computational code in a reproducible, transparent manner. For a specific target
organ/tissu
model or ar
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ex vivo and
below in Fi

6.5. MECHANISTIC STUDY EVALUATION

Sections 9 and 10 outline an approach for considering information from mechanistic studies (including in vitro, in vivo, ex vivo, and in silico studies) where the specific analytical approach is targeted to the assessment needs depending on the extent and nature of the human and animal evidence. In this way, the mechanistic synthesis might range from a high-level summary of potential mechanisms of action to specific, focused questions needed to fill data gaps identified from the human and animal syntheses and integration (e.g., shape of the dose-response curve in the low-dose region, applicability of the animal evidence to humans, addressing susceptible populations). Individual study-level evaluation of mechanistic endpoints will typically be pursued only when the interpretation of studies is likely to significantly impact hazard conclusions or assumptions about dose-response, and the issues that need resolution have not been sufficiently addressed in prior assessments or reviews published in peer-reviewed journals. Assessing potential bias in in vitro studies is an active area of method development in the field of systematic review. Historically, most tools used to assess these studies have focused on reporting quality, though current trends are to expand the assessment to include methodological quality with consideration of potential bias, for example, Science in Risk Assessment and Policy (SciRAP) evaluation of reliability for in vitro studies {Molander, 2015, 2825938;Beronius, 2014, 2826339;Agerstrand, 2011, 2127810}. Toxicogenomic studies will be evaluated for risk of bias and sensitivity using the criteria identified in the refined evaluation plan (see Section 5). If other mechanistic endpoints require study-level evaluation, the criteria will be described in the assessment.

From Cr(VI) protocol (2019)

IRIS Protocol Content

7. ORGANIZING THE HAZARD REVIEW

The organization and scope of the hazard evaluation is determined by the available evidence for the chemical regarding routes of exposure, metabolism and distribution, outcomes evaluated, and number of studies pertaining to each outcome, as well as the results of the evaluation of sources of bias and sensitivity. The hazard evaluations will be organized around organ systems (e.g., respi… hepatic system) informed by one or multiple related outcomes, and a decision will be made a… system) to organize the s…

Table 13 lists son…

These questions extend f… evaluation plan to includ… as the direction and mag…

8. DATA EXTRACTION OF STUDY METHODS AND RESULTS

Data extraction and content management will be carried out using Health Assessment Workspace Collaborative (HAWC). Data extraction elements that may be collected from …ontent of

9. SYNTHESIS WITHIN LIN…

For the purposes of this assessment, evi… distinct, but related processes. The syntheses o… mechanistic evidence) described in this section … of evidence to draw overall conclusions for each… Section 10). The phrase "evidence integration" … evidence" used in some other assessment proce… 86237;NRC, 2014, 2345577;U.S. EPA, 2017, 444…

For each potential health hazard or smal… synthesize the available human and animal heal… considered, although the specific analytical appr… depending on the extent and nature of the huma… Each synthesis will be written to provide a sum… addresses considerations that may suggest caus… introduced by Austin Bradford Hill {Hill, 1965, 7… relationship, strength of the association, tempor… and "natural experiments" in humans [{U.S. EPA… Importantly, the evidence synthesis process exp… from the individual study evaluations (see Secti…

Table 14. Information most relevant to describing primary considerations informing causality during evidence syntheses

Consideration	Description and synthesis methods
Consistency	• Examines the similarity of results (e.g., direction; magnitude) across studies. When inconsistencies exist, the synthesis considers whether results were "conflicting" (i.e., unexplained positive and negative results in similarly exposed human populations or in similar animal models) or "differing" [i.e., mixed results explained by differences between human populations, animal models, exposure conditions, or study methods; (U.S. EPA, 2005, 86237)] based on analyses of potentially important explanatory factors such as: ○ Confidence in the studies' results, including study sensitivity (e.g., some study results that appear to be inconsistent may be explained by potential biases or other attributes that affect sensitivity, resulting in variations in the degree of confidence accorded to the study results). ○ Exposure, including route (if applicable), levels, duration, etc. ○ Populations or species, including consideration of potential susceptible groups or differences across life stage at exposure or endpoint assessment. ○ Toxicokinetic information as an explanation for any observed differences in responses across route of exposure, other aspects of exposure, species, or life stages. The interpretation of the consistency of the evidence and the magnitude of the reported effects will emphasize biological significance as more relevant to the assessment than statistical significance. Statistical significance (as reported by *p*-values, etc.) provides no evidence about effect size or biological significance, and a lack of statistical significance will not be automatically interpreted as evidence of no effect.
Strength (effect magnitude) and precision	• Examines the effect magnitude or relative risk, based on what is known about the assessed endpoint(s), and considers the precision of the reported results based on analyses of variability (e.g., confidence intervals; standard error). In some cases, this may include consideration of the rarity or severity of the findings (in the context of the health effect being examined). Syntheses will analyze results both within and across studies, and may consider the utility of combined analyses (e.g., meta-analysis). While larger effect magnitudes and precision (e.g., $p < 0.05$) help reduce concerns about chance, bias, or other factors as explanatory, syntheses should also consider the biological or population-level significance of small effect sizes. Thus, a lack of statistical significance should not be automatically interpreted as evidence of no effect.

10. INTEGRATION ACROSS LINES OF EVIDENCE

For the analysis of human health outcomes that might… assessments draw integrated conclusions across human, anim… Section 9). During evidence integration, a two-step, sequentia… depicted in Figure 4):

- First, judgments regarding the strength of the evidenc… animal studies are made in parallel. These judgments … MOA understanding) in exposed humans and animals, … biological plausibility and coherence of the available h… Note that at this stage, the animal evidence judgment … relevance of that evidence.
- Second, the animal and human evidence judgments ar… conclusion(s) that incorporates inferences drawn base… relevance of the animal evidence (i.e., based on default… coherence…

STEP 1: INT… EFFECT AN… IN HUMANS

HUMAN EV…

The synthesis … effects and m… studies is co… make a judgme… hu…

ANIMAL EV…

The synthesis … effects and m… studies is co… make a judgme…

Figure 4.

Table 16. Evidence profile table template

Studies and interpretation	Factors that increase strength	Factors that decrease strength	Summary of findings	Human and animal evidence judgments	Inference across lines of evidence	Overall evidence integration conclusion
[Health effect or outcome grouping]						
Evidence from human studies [route]					• Human relevance of findings in animals • Coherence across lines of evidence (i.e., for both health effect-specific and mechanistic data) • Other inferences • Information on susceptibility ○ MOA analysis inferences (e.g., cross-species inferences of toxicokinetics, or quantitative implications) ○ Relevant information from other sources (e.g., read across; other potentially related health hazards)	Describe conclusion(s) and primary basis for the integration of all available evidence (across human, animal, and mechanistic): • ⊕⊕⊕ • ⊕⊕⊙ • ⊕⊙⊙ • ⊙⊙⊙ • − − − Summarize the models and range of dose levels upon which the conclusions were primarily reliant
• References • Study confidence (based on evaluation of risk of bias and sensitivity) • Study design description	• Consistency or replication • Dose-response gradient • Coherence of observed effects (apical studies) • Effect size (magnitude, severity) • Mechanistic evidence providing plausibility • Medium or high-confidence studies*	• Unexplained inconsistency • Imprecision • Low-confidence studies* or other concerns about methods or design across studies • Other (e.g., single/few studies) • Evidence demonstrating implausibility	• Results information (general endpoints affected/unaffected) across studies • Human mechanistic evidence informing biological plausibility: discuss how data influenced the human evidence judgment (e.g., evidence of precursors in exposed humans) Could be multiple rows (e.g., grouped by study confidence or population) if this informs heterogeneity of results	Describe the strength of the evidence from human studies, and primary basis for judgment: • ⊕⊕⊕ Robust • ⊕⊕⊙ Moderate • ⊕⊙⊙ Slight • ⊙⊙⊙ Indeterminate • − − − Compelling evidence of no effect		

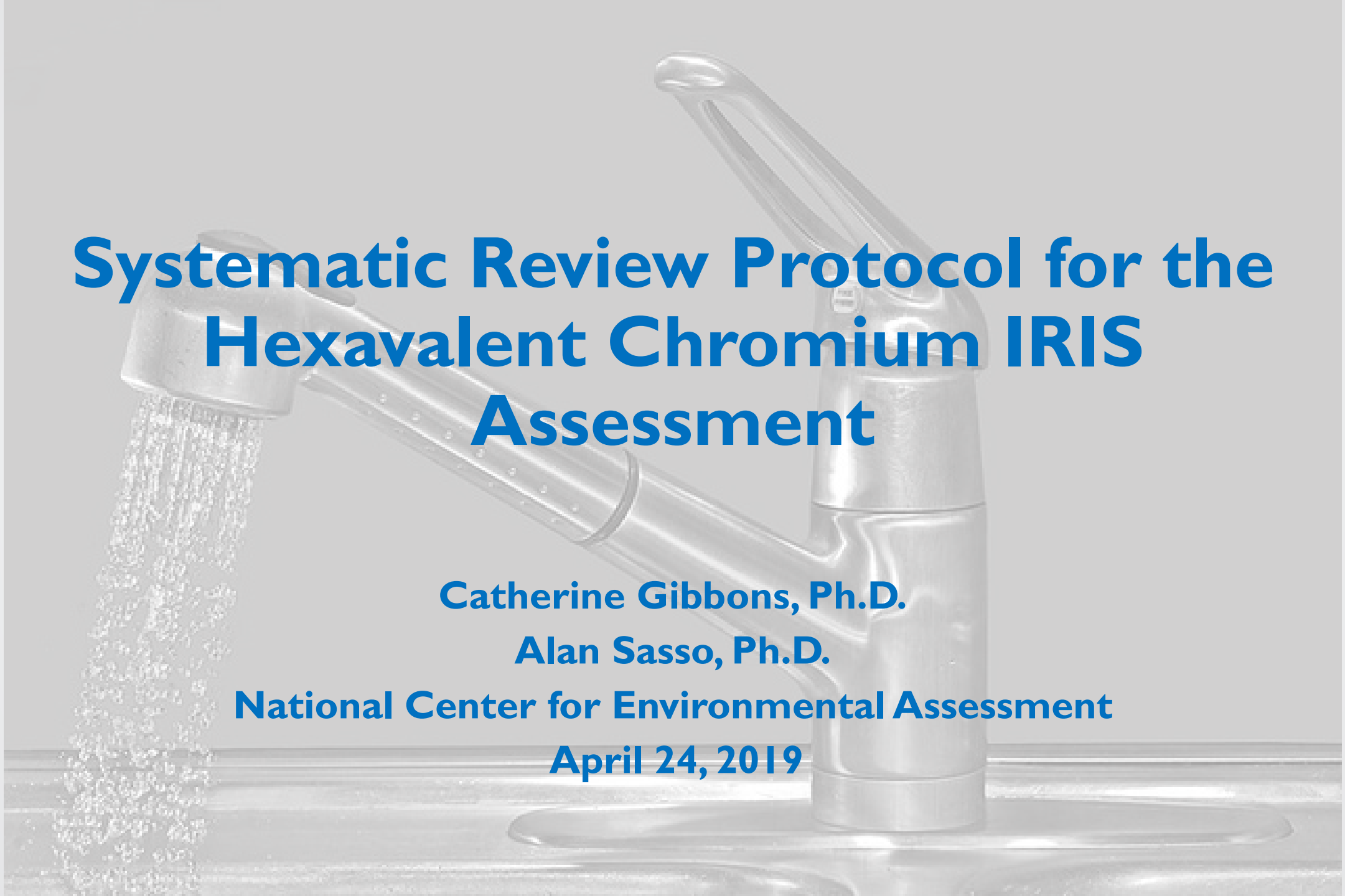
11. DOSE-RESPONSE ASSESSMENT: SELECTING STUDIES AND QUANTITATIVE ANALYSIS

The previous sections of this protocol describe how systematic review principles are applied to evaluate study quality (potential bias and sensitivity) and reach evidence synthesis and integration conclusions on health outcomes (or hazard identification) associated with exposure to the chemical of interest. Selection of specific data sets for dose-response assessment and performance of the dose-response assessment is conducted after hazard identification is complete and involves database and chemical-specific biological judgments. A number of EPA guidance and support documents detail data requirements and other considerations for dose-response modeling, …ew of the …05, …al …5, …g the … analysis …sede …g …re …ler of … is likely …2, …onlinear …ot occur …ence …her or

chemicals with direct mutagenic activity or those for which the data indicate a linear component below the POD, an oral slope factor (OSF) and/or an inhalation unit risk (IUR) facilitates estimation

[10]Dose-response assessments may also be conducted for shorter durations, particularly if the evidence base for a chemical indicates risks associated with shorter exposures to the chemical {U.S. EPA, 2002, 88824}.

From Cr(VI) protocol (2019)



Systematic Review Protocol for the Hexavalent Chromium IRIS Assessment

Catherine Gibbons, Ph.D.
Alan Sasso, Ph.D.
National Center for Environmental Assessment
April 24, 2019

Hexavalent Chromium [Cr(VI)]

- Elemental chromium is a metal that exists naturally in the form of oxide minerals
  - Predominant oxidation states are trivalent [Cr(III)] and hexavalent [Cr(VI)]
  - Industrial uses for Cr(VI): chrome plating, stainless steel production, pigments, corrosion inhibition
- Cr(VI) is a known human carcinogen by the inhalation route of exposure
- No evidence of carcinogenicity of Cr(VI) via the oral route until 2008
  - National Toxicology Program 2-year drinking water study in rats and mice
- The revised Cr(VI) IRIS assessment was identified as a priority need by EPA programs and regions

Today's Webinar

- Cr(VI) Protocol Highlights
  - New implementation of systematic review methodologies
  - New toxicological studies in rodents to improve oral assessment
  - New epidemiological studies in humans to improve inhalation assessment
  - New toxicokinetics and mode of action studies to improve hazard and dose-response assessments
- Public input on systematic review methods and emerging science
  - Reminder: 45-day public comment period closes April 29th

Cr(VI) in Water

- EPA data indicate widespread occurrence in US drinking water
  - Third Unregulated Contaminant Monitoring Rule (UCMR3)
  - Cr(VI) detected in ~90% of public water systems at or above 0.03 µg/L
  - Maximum contaminant level (MCL) is 100 µg/L (total chromium)
- Toxic effects from oral exposures in current IRIS assessment (1998) & what's new:

Cancer

- No data were available to determine carcinogenicity
- NTP (2008) drinking water study in rodents reported tumors and other effects
  - "Clear evidence of carcinogenic activity" in male and female rats and mice

Noncancer

- Oral reference dose (RfD) based on animal study published in 1958
  - High uncertainty because no effects were observed
  - New evidence will reduce uncertainty when calculating this value

➢ Hundreds of mode of action and toxicokinetics studies published since 1998

Cr(VI) in Air

- EPA classifies chromium compounds as hazardous air pollutants (HAPs)
  - Sources: chrome plating, stainless steel production and welding, chrome ore refining, coal/oil combustion, and colored glass production
  - Residential air levels downwind of industrial facilities have been correlated with emissions
- Toxic effects from inhalation exposures in current IRIS assessment (1998) & what's new:

Cancer

- *Human carcinogen* by the inhalation route of exposure
- Inhalation Unit Risk was based on data for total chromium
  - New science is available from Cr(VI)-specific exposures and updated occupational cohorts

Noncancer

- Two noncancer inhalation reference concentrations (RfCs)
  - Acid mists and particulates RfCs differ by ~50-fold
  - New science can clarify dose-response and reduce uncertainty

Scoping/Problem Formulation: Health Effects

Hazard identification and dose-response assessments include:

- Cancer
- Noncancer effects
  - Respiratory
  - Gastrointestinal
  - Hepatic
  - Hematological
  - Immunological
  - Reproductive
  - Developmental

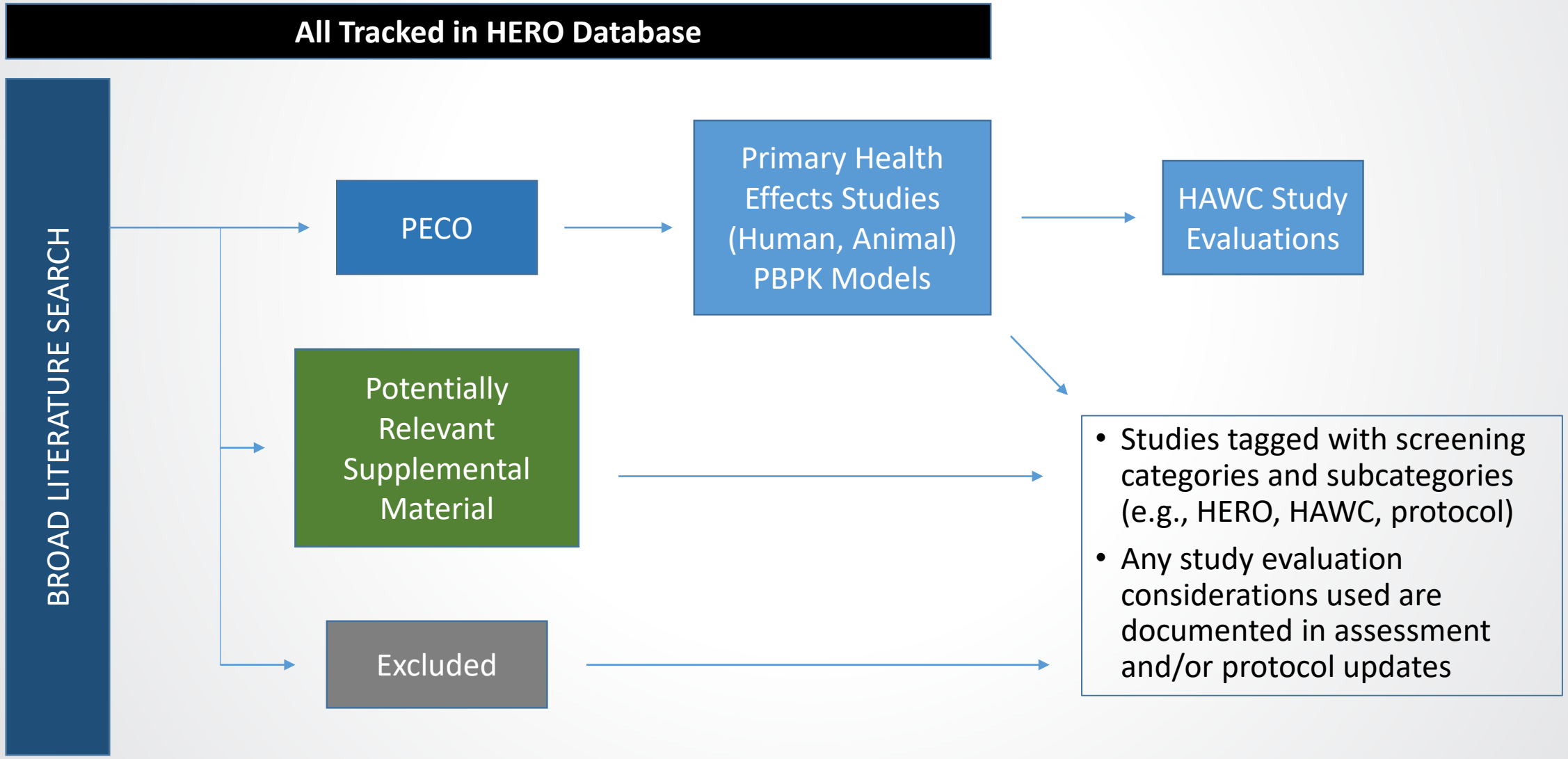
Hazard identification will not be revisited for lung cancer and nasal lesions

- Classifications of lung cancer (*human carcinogen*) and nasal lesions (*evidence demonstrates* Cr(VI) causes nasal lesions in humans) will be adopted
- Focus review of evidence on identifying studies that have the potential to:
  - improve quantitative dose-response analyses
  - influence the dose-response (e.g., MOA, identification of susceptible subpopulations)

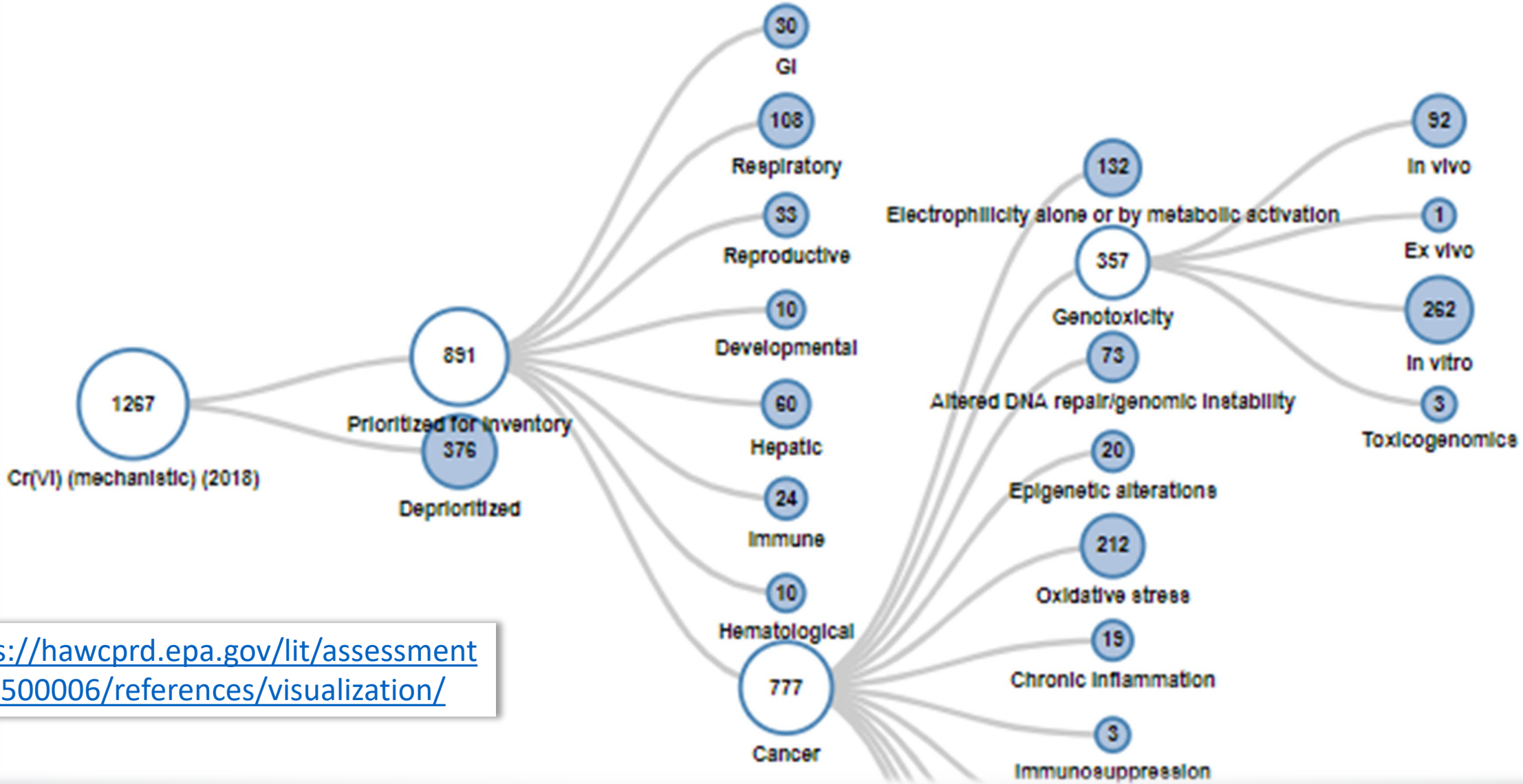
Health effects and routes *not* included:

- Nephrotoxicity—acute effect only
- Neurotoxicity, endocrine effects—no evidence identified
- Dermal route—scoping did not indicate need

Transparent Documentation of Literature Search and Screening Steps



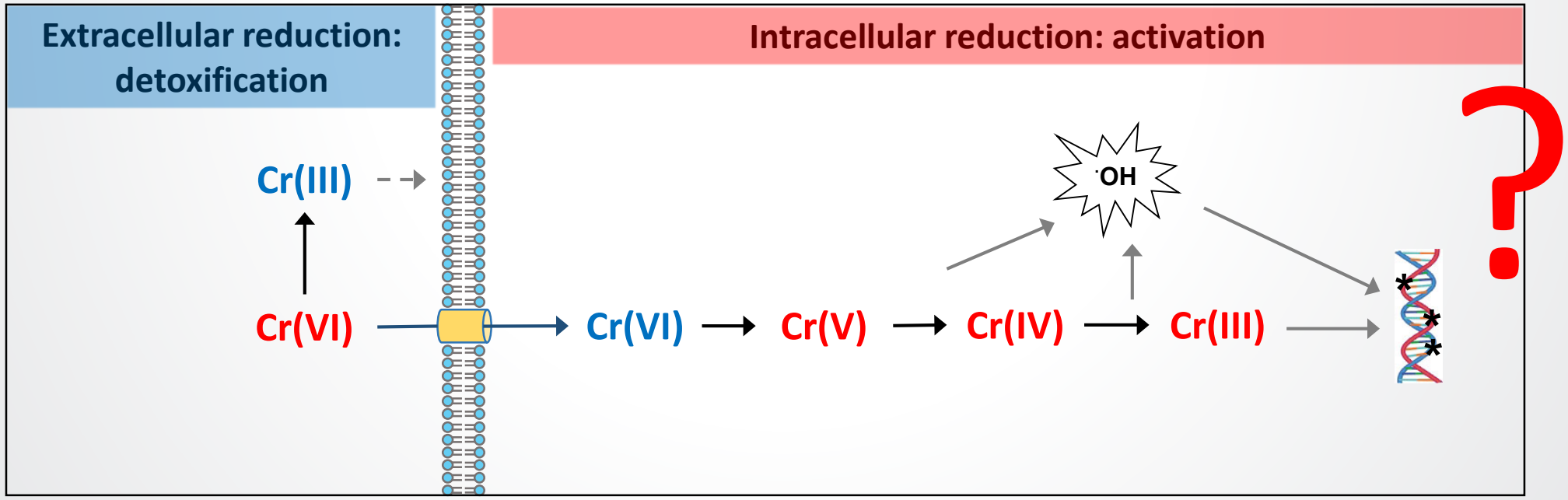
Example of Subcategorization and Screening: Mechanistic Studies in HAWC



https://hawcprd.epa.gov/lit/assessment/100500006/references/visualization/

Key Consideration: Toxicokinetics of Cr(VI)

- Cr(VI) reduces to trivalent chromium [Cr(III)] in biological fluids
  - Cr(III) is poorly absorbed by cells, has limited toxicity, and is considered to be a micronutrient
  - Humans might detoxify Cr(VI) more effectively than rodents, particularly in the stomach due to higher acid content



Adapted from *Zhitkovich, Chem Res Toxicol 24: 1617-1629 (2011)*

Key Consideration: Cancer Mode of Action (MOA)

- A thorough and transparent systematic review of the mutagenic potential of ingested and inhaled Cr(VI) will be conducted
  - Conflicting scientific evidence is available regarding a mutagenic MOA for cancer from drinking water exposures to Cr(VI)
  - A large volume of studies relevant to cancer MOA have been published
    - Over 1,200 studies have been identified
    - These studies include in vivo, in vitro, and in silico model systems
  - Database includes new toxicogenomic analyses that will be fully considered
- Both linear and non-linear quantitative approaches will be presented to provide insights into uncertainties of model choice and mechanisms

Summary and Next Steps

- IRIS has moved toward full implementation of systematic review
  - Consistent with systematic review practice, a protocol for Cr(VI) has been drafted for public release
  - The updated Cr(VI) IRIS assessment will be the **first use** of systematic review methods for the evaluation, analysis, and integration of epidemiological, toxicological, and mechanistic evidence for the identified health effects associated with Cr(VI) exposure
  - Our goals: transparently described and accessible, consistently applied, scientifically supported