



# IRIS Public Science Meeting

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August 19, 2020



# 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.



## Important Note

- EPA has extended the public comment to **COB Wednesday, September 23, 2020**. For more information regarding the public comment period, visit the IRIS website, the Federal Register, and/or Regulations.gov (Docket ID: EPA-HQ-ORD-2020-0183).



# INTRODUCTION AND ROLE OF ASSESSMENT PLANS IN THE IRIS PROCESS

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- **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.

## Integrated Risk Information System

CONTACT US SHARE

### IRIS Assessments in Development

- [Vanadium and Compounds \(Oral\) - IRIS Assessment Plan \(IAP\)](#) **NEW**
- [Update to the Systematic Review Protocol for the PFAS IRIS Assessments](#)
- [PBPBK Modeling for Chloroprene and a Supplemental Analysis of Metabolite Clearance \(Draft Report\)](#)

[See the Full List of Assessments in Development](#)

### Staying Connected

- [How IRIS connects with you](#)
- [How you can connect with IRIS](#)

Get email alerts

[sign up](#)

EPA's mission is to protect human health and the environment. EPA's IRIS Program supports this mission by identifying and characterizing the health hazards of chemicals found in the environment. Each IRIS assessment can cover a chemical, a group of related chemicals, or a complex mixture.

### Basic Information

- [Learn About IRIS](#)
- [Guidance & Tools](#)
- [IRIS Process](#)
- [History of IRIS](#)

### IRIS Assessments

- [Browse A to Z List of Chemicals](#)
- [Browse by Organ/System](#)
- [Assessments in Development](#)

### Program Materials

- [Developments in the IRIS Program](#)
- [IRIS Program Outlook](#)
- [IRIS Agenda](#)
- [IRIS Dockets](#)
- [Other Program Materials](#)

### Recent Additions

- 08/19: [IRIS Public Science Meeting \(Webinar\) for Vanadium \(Oral\)](#)
- 07/28: [Update to the Systematic Review Protocol for the PFAS IRIS Assessments](#)
- 07/24: [IRIS Assessment Plan for Vanadium and Compounds \(Oral\)](#)

#### Search IRIS

By Chemical, CASRN, or Keyword

Search the IRIS database of final assessr

[Search](#)

#### IRIS Calendar

- [Public meetings & workshops - list view](#)
- [Public meetings & workshops - month view](#)
- [Stakeholder requested meetings - list view](#)

## IRIS Program Outlook

Program Outlook

Agendas

**UPDATE: EPA released an update to the Program Outlook Document in June 2020.**

To maintain transparency, the IRIS Program is providing an updated outlook of program activities. The following document describes assessments that are in development and projected public milestone dates. Updates to the IRIS Outlook document will occur at least three times a year (February, June, October).

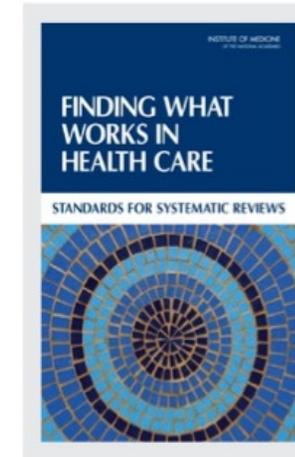
See the current [list of assessments in development](#).

Table 1. IRIS Program Outlook – June 2020

Current Status	Assessment	Next Anticipated Public Step(s)	Projected Fiscal Year Quarter
Post-Peer Review	Ethyl tertiary butyl ether (ETBE) <sup>1</sup>	Step 7: Final	FY20 – Q4
	tert-Butyl Alcohol <sup>1</sup>	Step 7: Final	FY20 – Q4
Draft Development	Arsenic, Inorganic	Step 1: Systematic Review Protocol	<a href="#">Released May 28, 2019, NAS review meeting July 16, 2019.</a>
		Step 4: Public Comment Draft	FY22 – Q2
		Step 4: External Peer Review	FY22 – Q4
	Chromium VI	Step 1: Systematic Review Protocol	<a href="#">Released March 15, 2019, Public Science Meeting April 24, 2019.</a>
		Step 4: Public Comment Draft	FY21 – Q4
		Step 4: External Peer Review	FY22 – Q1
Chloroform (Inhalation)		Step 1: IRIS Assessment Plan	<a href="#">Released September 18, 2017, Public Meeting on September 27, 2017.</a>
		Step 1: Systematic Review Protocol	<a href="#">Released January 31, 2018.</a>
		Step 4: Public Comment Draft	FY21 – Q3
		Step 4: External Peer Review	FY21 – Q4
Methylmercury		Step 1: IRIS Assessment Plan	<a href="#">Released April 4, 2019, Public Science Meeting May 15, 2019.</a>
		Step 1: Systematic Review Protocol	<a href="#">Released May 26, 2020</a>
		Step 4: Public Comment Draft	FY23 – Q3
		Step 4: External Peer Review	FY24 – Q1

<https://www.epa.gov/iris>

### **A structured and documented process for transparent literature review**

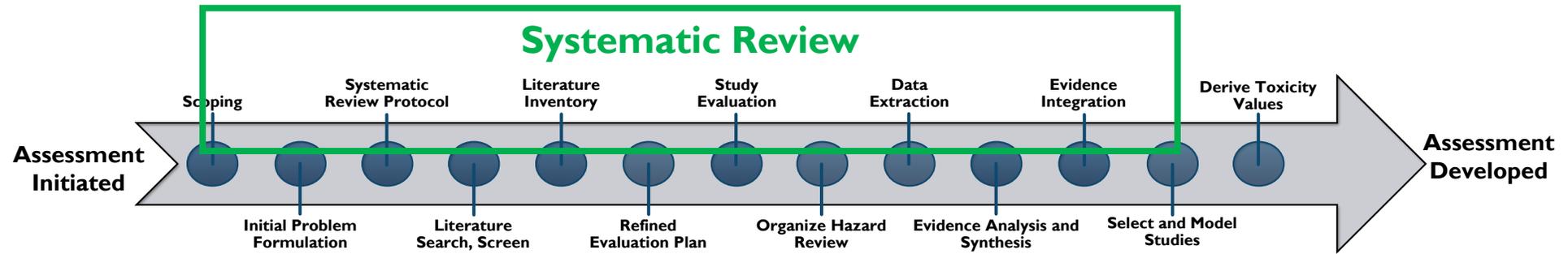


*“As defined by IOM [Institute of Medicine]<sup>1</sup>, systematic review ‘is a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies.’”*

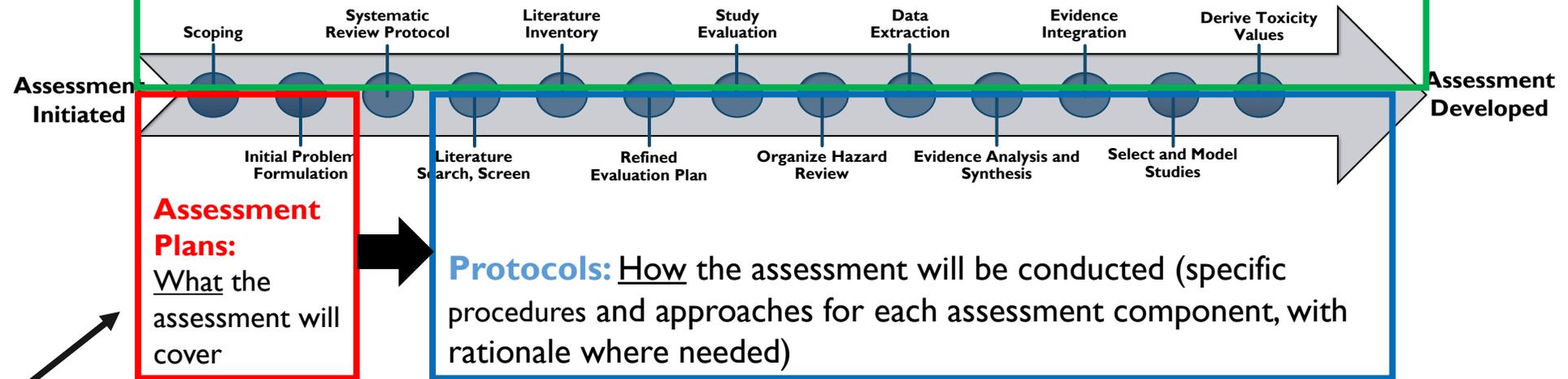
<sup>1</sup> Institute of Medicine. Finding What works in Health Care: Standards for Systematic Reviews. p.13-34. The National Academies Press. Washington, D.C. 2011



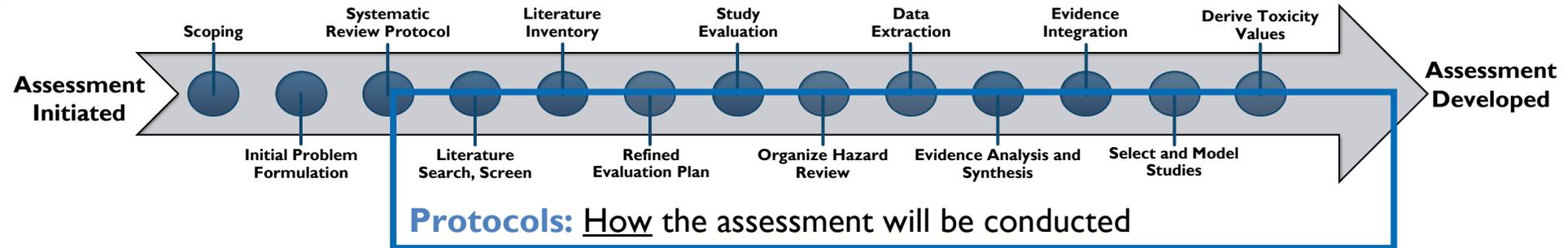
# Systematic Review in IRIS Assessments



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



What we are presenting today



- 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

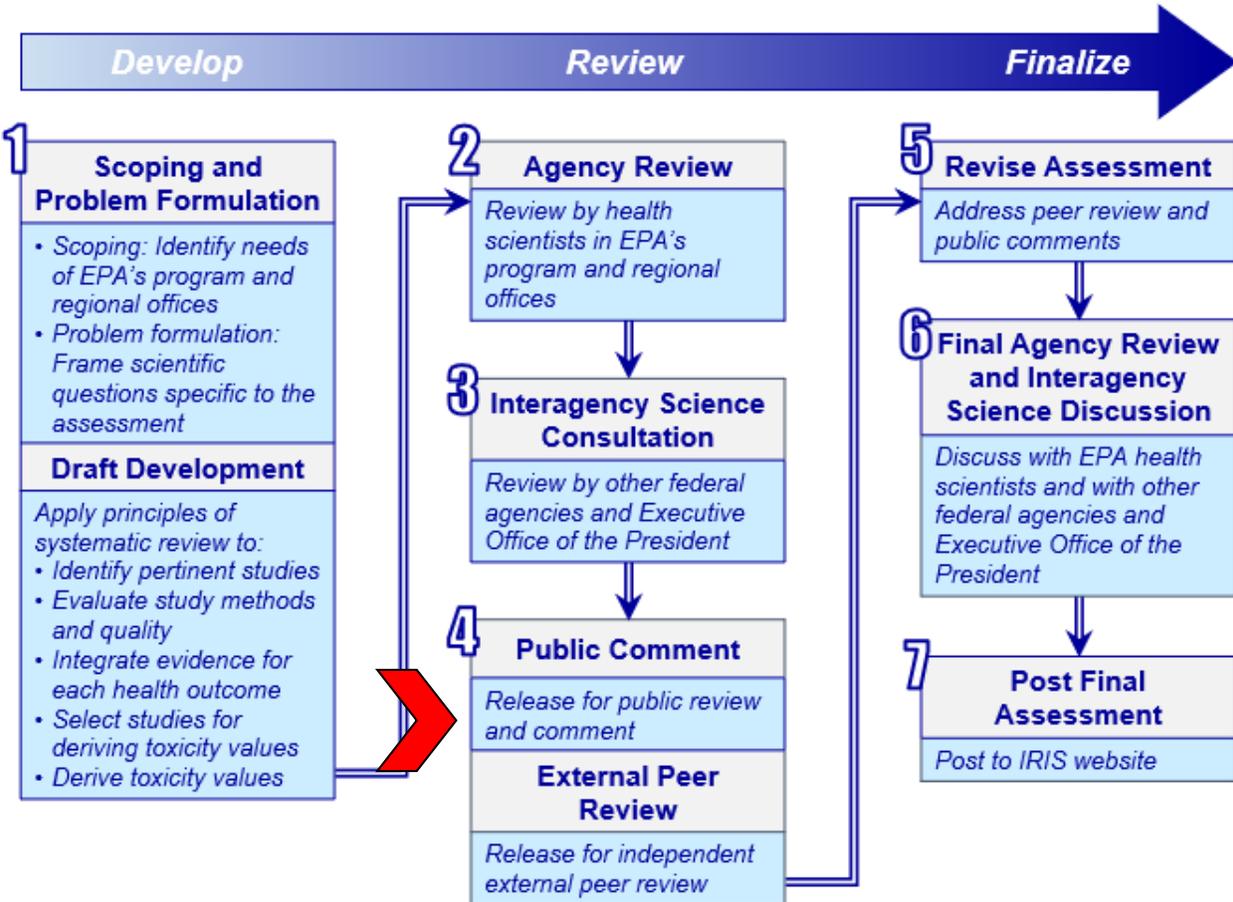
## Early Step I: IRIS Assessment Plans

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

## Mid-Step I: Protocols

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

 **Opportunities for Public Comment**





# IRIS Assessment Plan for Vanadium and Compounds (Oral Exposure)

Presentation for the IRIS Public Science Meeting  
August 19, 2020

**Erin Yost (Assessment Manager)**

Center for Public Health and Environmental Assessment  
Office of Research and Development  
U.S. Environmental Protection Agency

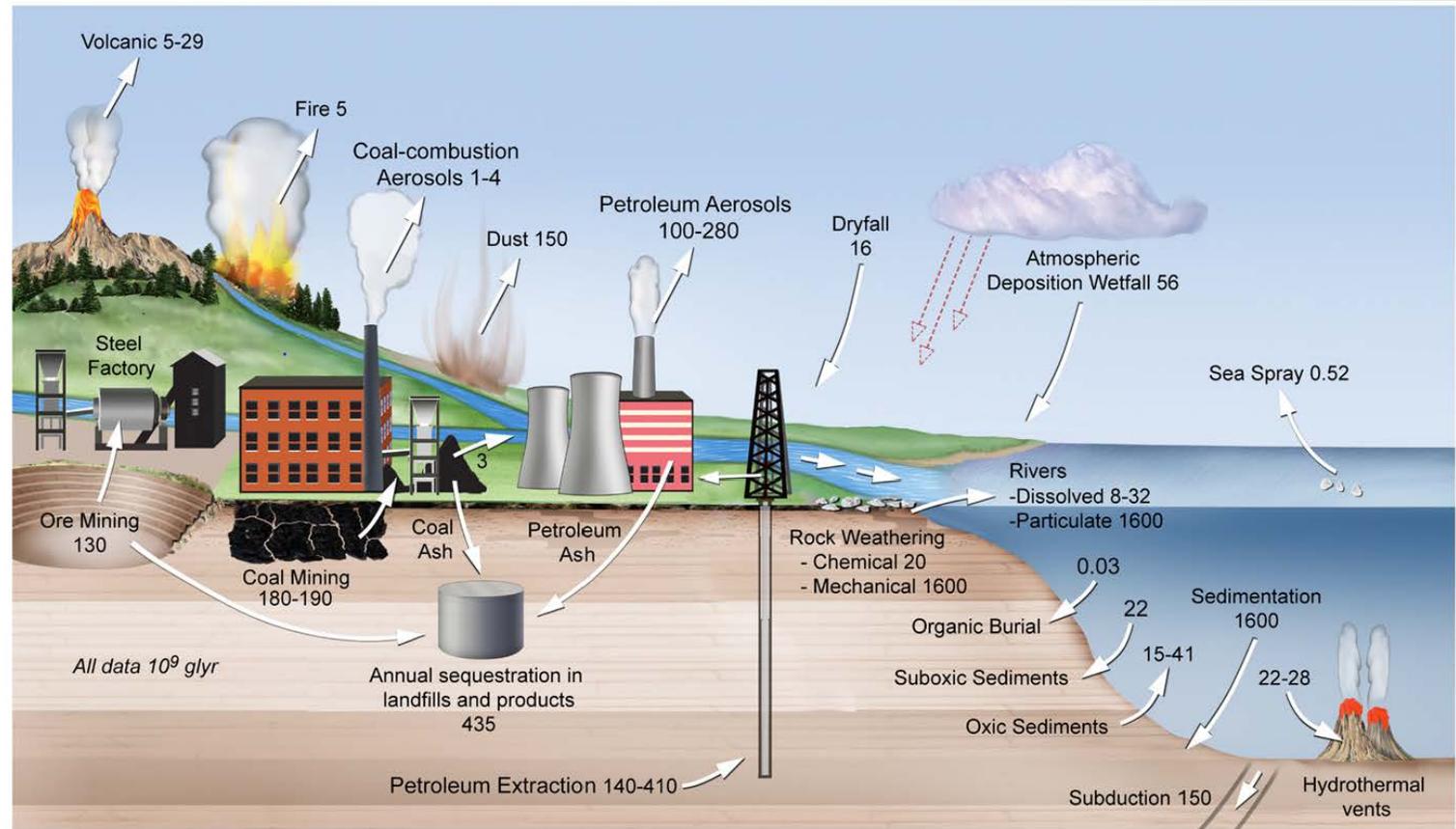


# Outline of the Presentation

- Background
- Scoping Summary
- Literature Search Strategy and Draft PECO
- Overall Objectives and Specific Aims
- Preliminary Literature Inventory
- Key Science Issues

## • Vanadium occurrence

- 22<sup>nd</sup> most abundant element in earth's crust
- Found in a variety of minerals and nearly all coal and petroleum crude oils
- Used in steel production and in vanadium redox-flow batteries



Source: Schlesinger et al. (2017). Global biogeochemical cycle of vanadium. *PNAS* 114 (52), p. E11094

[www.pnas.org/cgi/doi/10.1073/pnas.1715500114](http://www.pnas.org/cgi/doi/10.1073/pnas.1715500114)

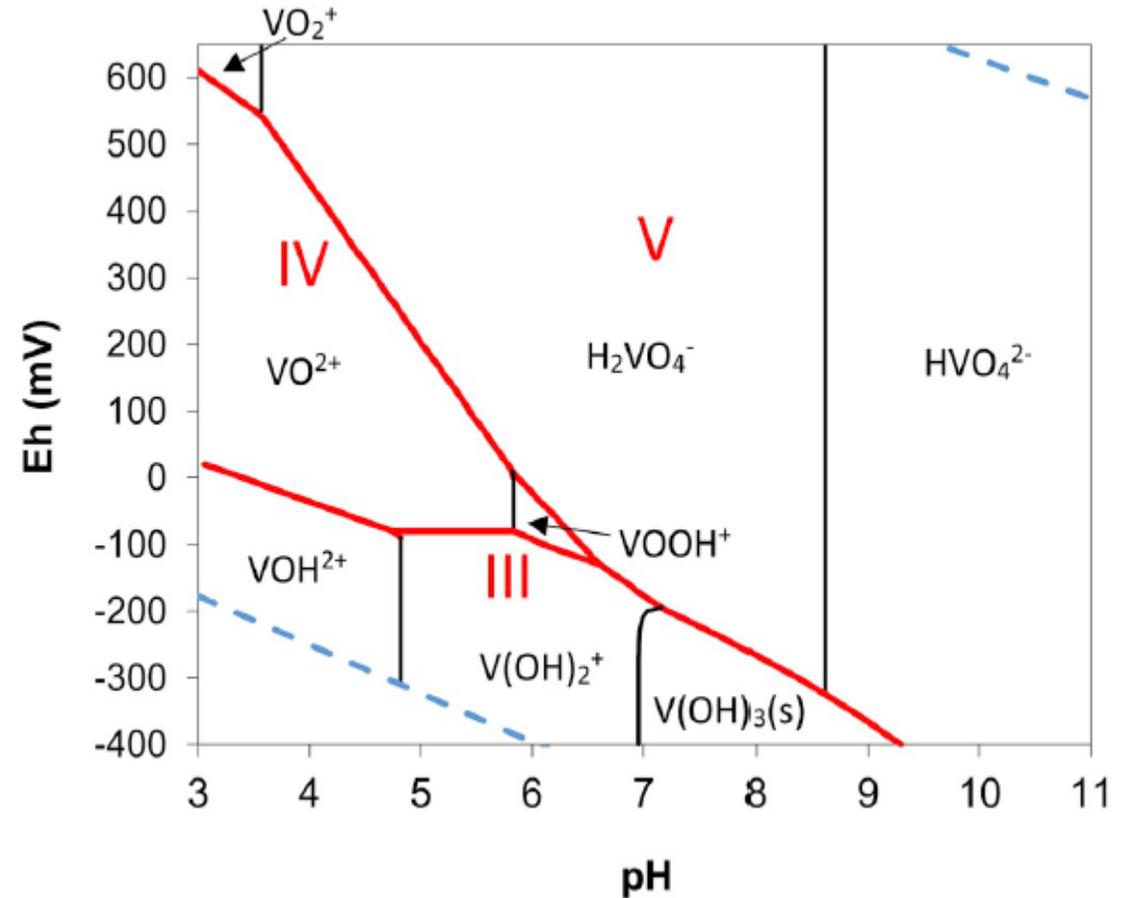
- **Vanadium oral exposure**

- Present in majority of foods
- Used in some vitamins and dietary supplements
- Medicinal applications (insulin mimetic)
- Monitoring under EPA's Third Unregulated Contaminant Monitoring Rule (UCMR 3) from 2013 to 2015:
  - 3,625 out of 4,922 public water systems measured vanadium in at least one sample at or above the minimum reporting level (2  $\mu\text{g}/\text{L}$ )
  - 163 out of 4,922 public water systems (3.3%) had results at or above the reference concentration used in the UCMR 3 (21  $\mu\text{g}/\text{L}$ ).



## • Vanadium speciation

- +5, +4, +3 are the most common oxidation states
- Speciation depends on multiple factors including pH, concentration, and redox potential
- Toxicokinetics and toxicity appear to vary across vanadium species
  - +5 absorbed more readily in the GI tract compared to +4
  - +5 generally considered to be more toxic than +4



Source: Gustafsson (2019). Vanadium geochemistry in the biogeosphere –speciation, solid-solution interactions, and ecotoxicity. *J. Appl.* 102, p. 6. <https://doi.org/10.1016/j.apgeochem.2018.12.027>

- **Current EPA oral toxicity values for vanadium and compounds**
  - 1987: IRIS assessment of vanadium and compounds.
    - RfD was derived for vanadium pentoxide.
    - Weight of evidence for cancer was found to be Group D, not classifiable.
  - 2009: PPRTV assessment of soluble inorganic vanadium compounds other than vanadium pentoxide.
    - Chronic and subchronic p-RfD were derived for vanadium.
    - Weight of evidence for cancer was found to be “Inadequate Information to Assess [the] Carcinogenic Potential”.
  - 1997: Health Effects Summary Table (HEAST)
    - Subchronic and chronic RfDs were derived for vanadium and vanadium sulfate, and subchronic RfDs were derived for vanadium pentoxide (adopted from IRIS value) and sodium metavanadate.



# Scoping Summary

- During scoping, the IRIS Program met with EPA program and regional offices that had interest in an IRIS assessment for vanadium compounds to discuss specific assessment needs.

EPA Program or Regional Office	Oral	Inhalation*	Statues/ Regulations	Anticipated Uses / Interest
Office of Water	✓		Safe Drinking Water Act (SDWA) and Clean Water Act (CWA)	<ul style="list-style-type: none"><li>• Vanadium is listed on EPA’s Final Contaminant Candidate List (CCL) 4. Contaminants listed on the CCL may require regulation under the SDWA.</li><li>• Under the CWA, EPA derives 304(a) recommended ambient water quality criteria for the protection of human health.</li><li>• Vanadium and compounds (oral) toxicological information may be used to inform risk determinations associated under the CWA and SDWA.</li></ul>

\*The IRIS program announced the initiation of a vanadium compounds assessment (inhalation) in December 2019.

A separate IAP will be released regarding the inhalation assessment.



# Literature Search Strategy

- ATSDR Toxicological Profile for Vanadium (2012) used as the starting point for the literature search
  - All citations retrieved from document
- Database searches were conducted on March 28, 2019 and March 9, 2020 to identify studies published since 2010 (intended to capture studies since the development of the ATSDR Toxicological Profile for Vanadium)
  - Web of Science
  - PubMed
  - Toxline



# PECO Criteria

PECO element	Evidence
<u>Populations</u>	<p><b>Human:</b> Any population and lifestage</p> <p><b>Animal:</b> Nonhuman mammalian animal species (whole organism) of any lifestage</p>
<u>Exposures</u>	<p><b>Relevant forms:</b> Any form of vanadium. Focus on inorganic vanadium compounds; organic anthropogenic vanadium compounds, nanomaterials, and alloys are tracked as supplemental information.</p> <p><b>Human:</b> Any exposure to vanadium compound(s) via the oral route. Studies will also be included if biomarkers of vanadium exposure are evaluated (e.g., measured vanadium levels in tissues or bodily fluids) but the exposure route is unclear.</p> <p><b>Animal:</b> Any exposure to vanadium compound(s) via the oral route.</p>
<u>Comparators</u>	<p><b>Human:</b> A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits), or exposure for shorter periods of time, or cases versus controls.</p> <p><b>Animal:</b> A concurrent control group exposed to vehicle-only treatment or untreated control.</p>
<u>Outcomes</u>	All health outcomes (both cancer and noncancer).
<u>PBPK models</u>	Studies describing physiologically based pharmacokinetic (PBPK) models for any form of vanadium will be included.



# Overall Objectives and Specific Aims

- Identify literature as outlined in the PECO.
- Conduct study evaluations for individual studies that meet PECO criteria, and evaluate and validate PBPK models.
- Review and incorporate the available toxicokinetic and mechanistic information, as warranted to inform assessment decisions.
- Synthesize the evidence across studies, assessing similar health outcomes using a narrative approach.
- Develop evidence integration conclusions across evidence streams.
- Derive toxicity values as supported by the available data. Characterize uncertainties and identify key data gaps and research needs.



# Preliminary Literature Inventory

## Literature flow diagram:

25,988 total records identified

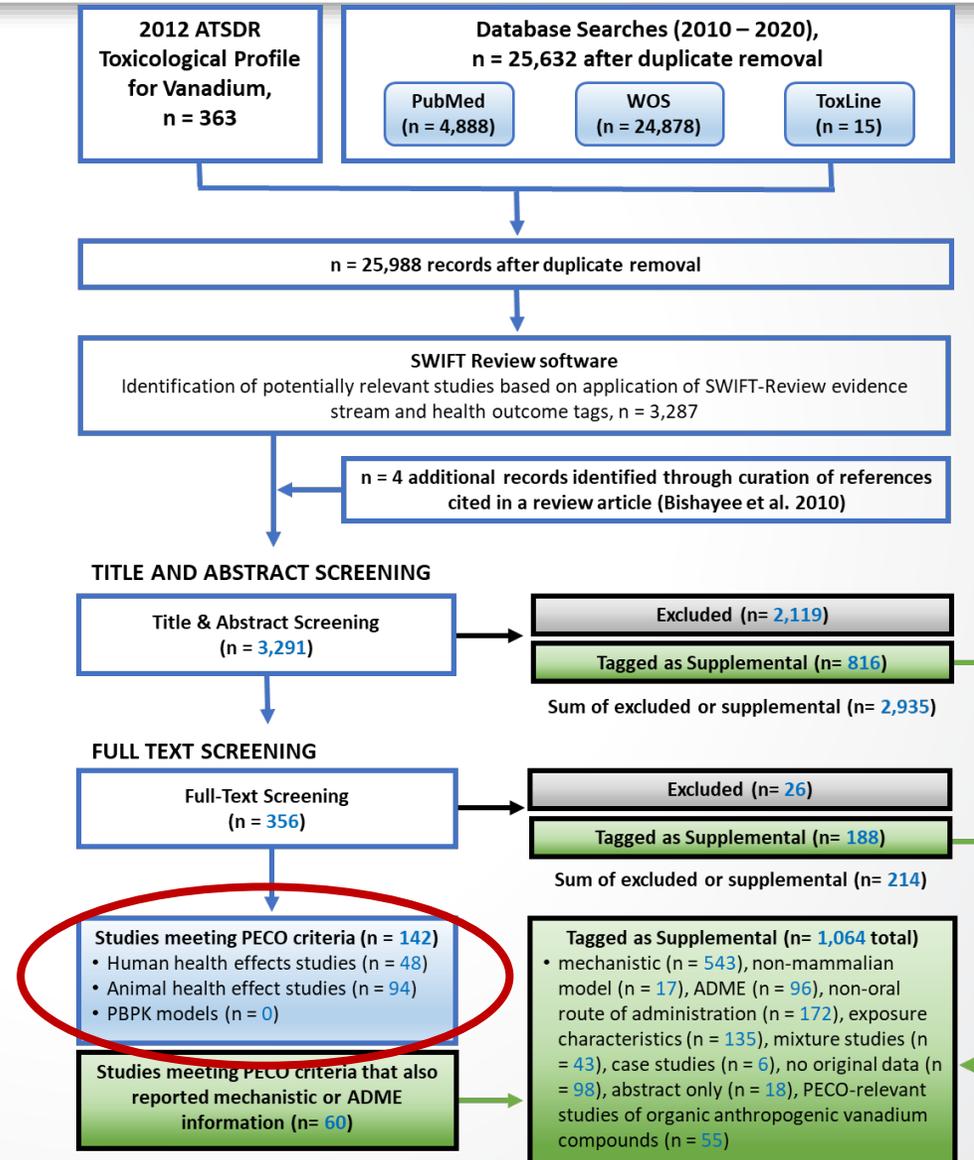


3,291 screened manually



142 met PECO criteria

(1,064 tagged as supplemental)

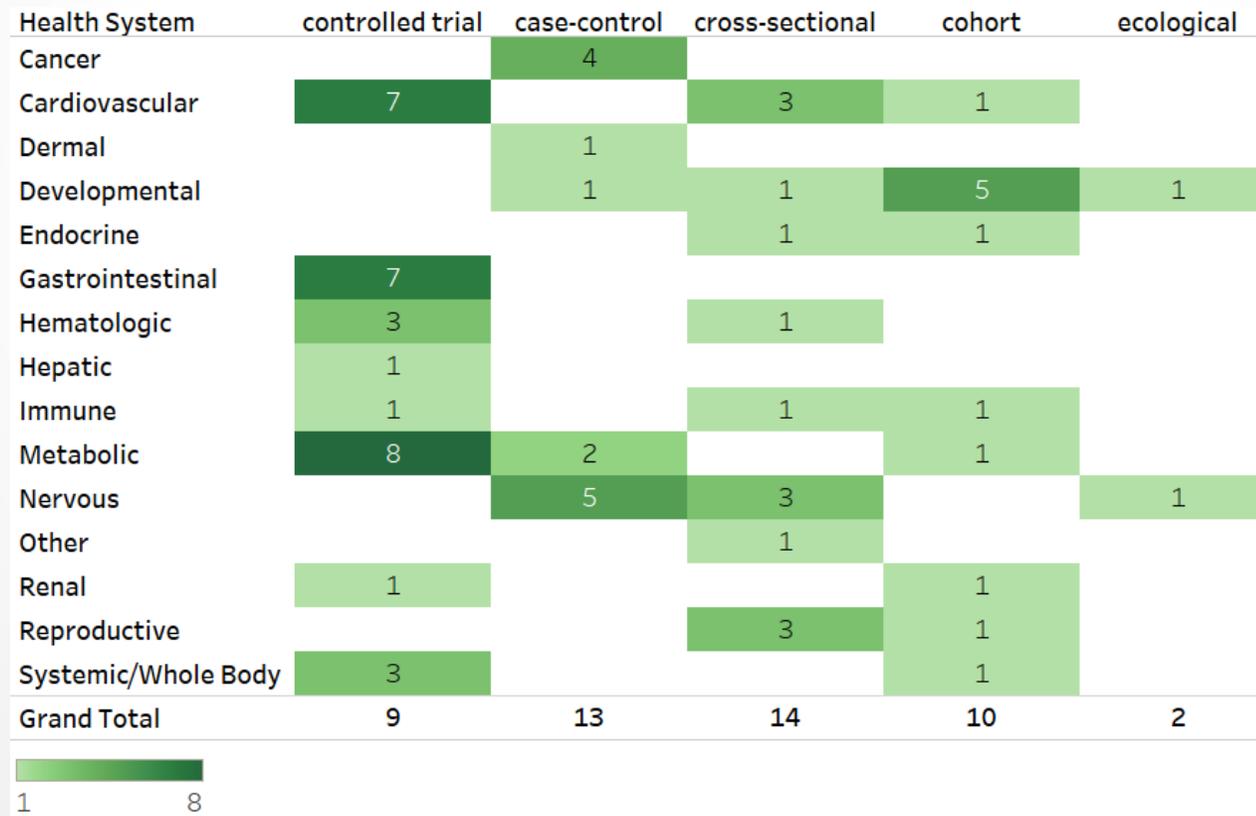




# Preliminary Literature Inventory Results

## Human evidence:

- 9 controlled human trials (vanadyl sulfate or sodium metavanadate)
- 39 epidemiology studies





# Preliminary Literature Inventory Results

**Animal evidence:** 94 studies (includes 23 studies in diabetic animal models)

Health System	acute		short-term			subchronic				chronic					reproductive		developmental	
	rat	mouse	rat	mouse	sheep	rat	mouse	cattle	goat	rat	mouse	rabbit	cattle	goat	rat	mouse	rat	mouse
ADME					1	8	1			1	1		1		3		2	
Cancer						1				2	2							
Cardiovascular			2	1		9	1	1	1	10		1	1				2	
Dermal										1								
Developmental				1													6	1
Endocrine								1		2			1				1	
Gastrointestinal				1		1												
Hematologic			6			8		1		5								
Hepatic	1		6	3		4	3	1		1					2	1	4	
Immune			6	2		7	3	1		2							2	
Lymphatic						1												
Metabolic			8	1		16	1	1	1	4			1		3		1	
Musculoskeletal			1	1		1							1					
Nervous			2	1		7				1							2	
Ocular						1												
Renal			3	3		5	2	1		5					3	1	3	
Reproductive				1			1			1				1	8	2	2	
Respiratory			1	2		2				1							2	
Systemic/Whole Body	2	1	15	3	1	26	2	1	1	9	3		1	1	4	1		1
Urinary										1								
<b>Grand Total</b>	<b>2</b>	<b>1</b>	<b>17</b>	<b>3</b>	<b>1</b>	<b>34</b>	<b>4</b>	<b>1</b>	<b>1</b>	<b>15</b>	<b>3</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>9</b>	<b>2</b>	<b>9</b>	<b>2</b>





# Preliminary Literature Inventory Results

## Vanadium compounds evaluated in the available animal studies:

Vanadyl sulfate	33
Sodium metavanadate	31
Ammonium metavanadate	18
Sodium orthovanadate	8
Vanadium pentoxide	4
Vanadium	3
Vanadate	1
Calcium orthovanadate	1
Calcium pyrovanadate	1





## Studies in progress by NTP

- **13-week developmental exposure study in rats and 13-week adult exposure study in mice**
- Exposure to sodium metavanadate (+5) or vanadyl sulfate (+4) in drinking water
- Complete results expected to be published in 2020

- **Consideration of potential toxicity and toxicokinetic differences across vanadium compounds.** Differential absorption has been observed across inorganic vanadium compounds and may be correlated with toxicity. To address these apparent differences, in addition to more fully characterizing the toxicokinetic differences across compounds, the EPA plans to conduct separate toxicity evaluations for different vanadium compounds where the evidence supports such an analysis.

- **Consideration of vanadium speciation.** Available information indicates that vanadium in solution can readily interconvert between oxidation states and will form different species as a function of factors including pH, concentration, and redox potential (e.g., +4 in drinking water is stable at low pH but oxidized to +5 as pH is increased). Study evaluations will, to the extent possible, consider factors that could affect vanadium oxidation state and speciation in the available toxicity studies.



**Thank you!**