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IRIS Assessment Plan for Oral Exposure to Vanadium and Compounds (Scoping and Problem Formulation Materials)

July 2020

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

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ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
EPA	Environmental Protection Agency
HERO	Health and Environmental Research Online
IAP	IRIS Assessment Plan
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
CPAD	Chemical and Pollutant Assessment Division
CPHEA	Center for Public Health and Environmental Assessment
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PECO	populations, exposures, comparators, and outcomes
RfC	reference concentration
RfD	reference dose

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1. INTRODUCTION

The Integrated Risk Information System (IRIS) Program is undertaking a reassessment of the health effects of vanadium and compounds. An assessment of oral exposure to vanadium and compounds was identified as an Agency priority in December 2018 (https://www.epa.gov/iris/iris-program-outlook). The IRIS Program announced the initiation of a vanadium and compounds inhalation assessment in December 2019, which will be performed separately from the assessment of oral exposure.

IRIS assessments provide high quality, publicly available information on the toxicity of chemicals to which the public might be exposed. These assessments are not regulations but are influential scientific information and provide a critical part of the scientific foundation for decisions made in the Environmental Protection Agency (EPA) program and regional offices to protect public health. IRIS assessments are also used by states and local health agencies, other federal agencies, international health organizations, and other external stakeholders.

As part of the initial steps in assessment development, the IRIS Program undertakes scoping and initial problem formulation activities. During scoping activities, the IRIS Program consults with the EPA program and/or regional offices requesting the IRIS assessment to identify the nature of the hazard characterization needed, the most important exposure pathways, and the level of detail required to inform Agency decisions. A broad, preliminary literature survey may also be conducted to assist in identifying the extent of the evidence and health effects that have been studied for the chemical of interest. Based on the preliminary literature survey and the scope defined by the EPA, the IRIS Program undertakes problem formulation activities to frame the scientific questions that will be the focus of the assessment. A summary of the IRIS Program's scoping and problem formulation conclusions are contained in the **IRIS Assessment Plan (IAP)**.

The IAP is followed by development of a **Systematic Review Protocol**, which presents detailed methods for conducting the full systematic review and dose-response analysis, including any adjustments made to the IAP in response to public input. The IAP describes *what* will be assessed, and the chemical-specific protocol describes *how* the assessment will be conducted. Figure 1 displays the context of the IAP and Systematic Review Protocol in the systematic review process.

This document presents the IAP for vanadium and compounds—a summary of the IRIS Program's scoping and initial problem formulation conclusions. It describes the Agency need for the assessment; objectives and specific aims of the assessment; draft Populations, Exposures, Comparators, and Outcomes (PECO) criteria that outline the evidence considered most pertinent to address the specific aims of the assessment; and identification of key areas of scientific complexity.

Brief background information on the uses and occurrence of vanadium and compounds, and the potential for human exposure, is provided for context.

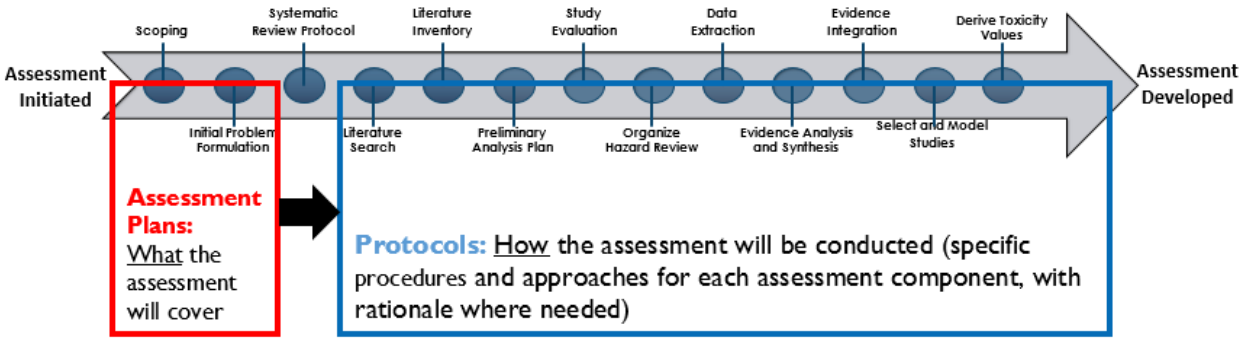


Figure 1. IRIS systematic review problem formulation and method documents.

2. SCOPING AND INITIAL PROBLEM FORMULATION

2.1. BACKGROUND

Vanadium is a naturally occurring metal that is the 22nd most abundant element in the earth's crust and is found in a variety of minerals and nearly all coal and petroleum crude oils. The focus of this document is on oral exposure to vanadium and compounds and potential impacts on human health. Although vanadium is not classified as an essential nutrient in mammals, it is included in some multivitamins and dietary supplements (ATSDR, 2012; IOM, 2001). Likely due to its natural abundance, vanadium is present in human breast milk, although at relatively low levels compared to other trace elements (Krachler et al., 2000). It is also present at low concentrations in the majority of foods, which serve as the major source of background vanadium exposure in the general population (ATSDR, 2012). The Institute of Medicine (IOM) Panel on Micronutrients found that the risk of adverse effects resulting from intake of vanadium from food was unlikely, whereas increased risk was likely to result from chronic intake of supplements containing larger doses of vanadium (IOM, 2001). Inorganic vanadium compounds and organic vanadium-containing compounds have also been studied as anti-diabetics (Treviño et al., 2019; Smith et al., 2008) and for anticancer properties (Bishayee et al., 2010), although these potential therapeutic applications remain investigational at this time. Organic anthropogenic vanadium compounds synthesized to treat diabetes and cancer are likely to have different toxicokinetic properties from inorganic vanadium (ATSDR, 2012). The primary source of environmental exposure to vanadium is from inorganic vanadium compounds (see additional information below), and thus these are the primary focus of this assessment (Section 3.2 describes that studies of exposure to organic anthropogenic vanadium compounds will be tracked as potentially relevant supplemental material to reflect this focus).

Natural releases of vanadium into water and soil occur due to weathering of rocks and atmospheric deposition (Schlesinger et al., 2017; ATSDR, 2012). Fossil fuel combustion is the biggest anthropogenic source of vanadium to the atmosphere (Schlesinger et al., 2017; ATSDR, 2012), and leachates from ores, slags, sewage sludge, fertilizers, and ash ponds and coal preparation wastes contribute to anthropogenic release of vanadium into water and soil (ATSDR, 2012). Increasing use of fossil fuels from unconventional sources (heavy oils, bitumen from tar sands) that are richer in vanadium than conventional oil, as well as the increased mining of vanadium to meet the demand for industrial applications such as steel production and vanadium redox-flow batteries, could lead to an overall increase in vanadium releases (Watt et al., 2018; Schlesinger et al., 2017).

Vanadium has a complex chemistry, existing in the environment with a possible four oxidation states (+2, +3, +4, +5), 23 species, and nine charges that include both anions and cations (Kelsall et al., 1993). Although it forms complexes with organic matter, vanadium is typically not incorporated into organic compounds, and therefore transformation generally occurs between various inorganic compounds during its transport through the environment (ATSDR, 2012). Speciation of inorganic vanadium compounds occurs as a complex function of factors including pH, redox potential, and concentration. In water, vanadium occurs as oxygen-containing ions, with vanadate species (+5) predominating under oxic conditions and high pH, vanadyl (+4) occuring under suboxic conditions and low pH, and vanadium (+3) occuring under anoxic conditions (Gustafsson, 2019; Huang et al., 2015). Vanadium (+2) is readily oxidized and unstable. As expected, based on those conditions, vanadate (+5) and vanadyl (+4) are the prevailing vanadium species in most natural waters (Gustafsson, 2019). In the body, vanadium undergoes redox cycling and speciation driven by factors such as pH, local availability of reducing equivalents (e.g., glutathione-SH, NADH), and complexation with biomolecules (NTP, 2008; Byczkowski and Kulkarni, 1996; Nielsen, 1995). Although ingested vanadium is likely reduced to vanadyl (+4) in the acidic conditions of the stomach, it has been found that vanadate (+5) is absorbed more effectively than vanadyl (+4) in the gastrointestinal tract. The absorption of vanadium following oral exposure is therefore expected to be influenced by the form of ingested vanadium as well as residence time, conditions in the gastrointestinal tract, and speed of conversion (Treviño et al., 2019; Nielsen, 1995). It is generally reported that pentavalent vanadium is more toxic than tetravalent vanadium (ATSDR, 2012; NTP, 2008). In laboratory studies, vanadyl sulfate ($VOSO_4$) is a commonly studied tetravalent vanadium compound, and vanadium pentoxide (V_2O_5), sodium metavanadate ($NaVO_3$), sodium orthovanadate (Na_3VO_4), and ammonium vanadate (NH_4VO_3) are commonly studied pentavalent vanadium compounds (Table 1).

In 2016, the U.S. Environmental Protection Agency (EPA) included vanadium on the drinking water Fourth Contaminant Candidate List (CCL 4), which is a list of contaminants that are not currently subject to national primary drinking water regulations but are known or anticipated to occur in public water systems. Contaminants listed on the CCL may require regulation under the Safe Drinking Water Act (SDWA) if the Agency determines that the contaminant may have an adverse effect on the health of persons; the contaminant is known to occur or there is substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and in the sole judgment of the Administrator, regulation of the contaminant presents a meaningful opportunity for health risk reductions for persons served by public water systems (Safe Drinking Water Act, 2019). Vanadium was monitored under EPA's Third Unregulated Contaminant Monitoring Rule (UCMR 3) from 2013 to 2015 and 3,625 out of 4,922 public water systems (73.6%) detected vanadium at or above the minimum reporting level (2 µg/L). The data show that 163 of these public water systems (3.3%) had results above the reference concentration

used in the UCMR 3 (21 µg/L)[1] (https://www.epa.gov/sites/production/files/2017-02/documents/ucmr3-data-summary-january-2017.pdf). In December 2018, an Integrated Risk Information System (IRIS) assessment of oral exposure to vanadium was identified by the EPA Office of Water as a priority for an IRIS assessment(https://www.epa.gov/iris/iris-program-outlook)).

Existing human health reference values for vanadium and compounds from federal, state, and international agencies are depicted in Figure 2 (see Table 2 for a tabular summary, including derivation details of the displayed values; current as of May 2020). IRIS published a health effects assessment of vanadium and compounds in 1987, which includes a reference dose (RfD) for lifetime oral exposure to vanadium pentoxide (U.S. EPA, 1987). The RfD was based on an unpublished study by Stokinger et al. (1953) described in Patty's Industrial Hygiene and Toxicology (1981) in which an unspecified strain of rats were fed vanadium pentoxide over a lifetime at levels of 10 and 100 ppm vanadium. An RfD of 0.009 mg/kg-day for vanadium pentoxide was derived based on the no-observed-adverse-effect level (NOAEL) of 10 ppm vanadium (approximately 17.9 ppm vanadium pentoxide) for decreased hair cystine content. The RfD was calculated by assuming that rats eat food equivalent to 5% of their body weight and by applying an uncertainty factor (UF) of 100 (a factor of 10 for interspecies extrapolation and a factor of 10 to provide added protection for unusually sensitive individuals). IRIS also reviewed the carcinogenicity data available for vanadium and compounds and concluded that the weight of evidence classification for vanadium under the 1986 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986) is Group D, not classifiable.

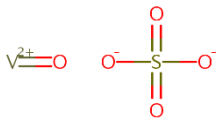
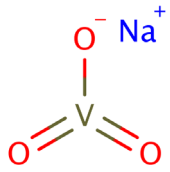
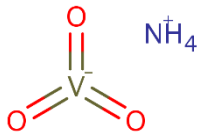
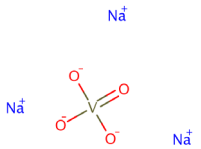
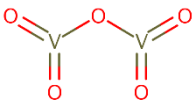
EPA also developed provisional peer-reviewed toxicity values (PPRTVs) for vanadium and its soluble inorganic compounds other than vanadium pentoxide in 2009, including a chronic provisional RfD (p-RfD) and subchronic p-RfD for vanadium. These values were based on kidney histopathology in a 6-month study by Boscolo et al. (1994), in which rats were given sodium metavanadate in drinking water at levels of 1, 10, or 40 µg/mL vanadium; EPA estimated that this corresponded to doses of 0.12, 1.2, or 4.7 mg/kg-day based on default drinking water and body weight estimates. A subchronic p-RfD of 0.0007 mg/kg-day for vanadium was derived based on the NOAEL of 0.12 mg/kg-day by adjusting upward by 0.1 mg/kg-day to account for likely background exposure to vanadium in diet and by applying a UF of 300 (a factor of 10 for interspecies extrapolation, a factor of 10 to protect unusually sensitive individuals, and a factor of 3 to account for database deficiencies). A chronic p-RfD of 0.00007 mg/kg-day for vanadium was derived from this same study by applying an additional UF of 10 to account for extrapolation to chronic exposure duration. This assessment also concluded that there was "Inadequate Information to Assess [the]

[1] The reference concentration for vanadium in drinking water used in the UCMR 3 was based on the ATSDR 1992 minimal risk level (MRL) of 0.003 mg/kg-day. The ATSDR 1992 Toxicological Profile for Vanadium is no longer publicly available and has been replaced by ATSDR (2012). The UCMR 3 reference concentration provides context around the detection of a particular contaminant above the minimum reporting level and does not constitute an "action level".

Carcinogenic Potential" of vanadium based on the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005).

Since the publication of these prior assessments by EPA, new information on the health effects of vanadium and compounds has become available. The Agency for Toxic Substances and Disease Registry (ATSDR) 2012 Toxicological Profile of Vanadium concluded that increased blood pressure, hematological alterations, alterations in neurobehavioral tests, and developmental toxicity were the most sensitive outcomes in laboratory animal studies following intermediate duration (15–364 day) oral exposure to vanadium compounds, but noted that increased blood pressure and hematological effects were not consistently observed across animal studies at higher dose levels or in a 12-week controlled human trial (ATSDR, 2012). More recently, NTP has undertaken a series of studies in rats and mice on the health effects of oral (drinking water) exposure to vanadyl sulfate and sodium metavanadate, which include evaluation of a range of health outcomes and will provide additional information on the comparative toxicity of two common vanadium oxidation states. These include 14-day studies in rats and mice (Roberts et al., 2016), a 13-week study in mice, and an extended developmental toxicity study in rats in which F1 offspring are exposed from gestation day (GD) 6 through 13 weeks post-weaning. NTP's developmental and 13-week drinking water studies are expected to be posted by 2020, and interim results are currently available (https://ntp.niehs.nih.gov/ntp/results/pubs/posters/roberts_sot20190300.pdf).

Table 1. Chemical identity and physiochemical properties of selected vanadium compounds as curated by EPA's CompTox Chemicals Dashboard

Name	Elemental vanadium	Vanadyl sulfate	Sodium metavanadate	Ammonium metavanadate	Sodium orthovanadate	Vanadium pentoxide
CASRN	7440-62-2	27774-13-6	13718-26-8	7803-55-6	13721-39-6	1314-62-1
DTXSID[a]	2040282	4021428	3044336	1052533	2037269	2023806
Structure						
Molecular weight (g/mol)	50.942	163	121.928	116.978	183.907	181.878
Molecular formula	V	$VOSO_4$	$NaVO_3$	NH_4VO_3	Na_3VO_4	V_2O_5
Selected Synonym(s)	Vanadium	(Oxido)vanadium(2^+) sulfate; oxo(sulfato)vanadium; oxovanadium(IV) sulfate; vanadium oxide sulfate; vanadium oxosulfate; vanadium oxysulfate; vanadium sulfate; vanadic sulfate; vanadyl monosulfate; vanadin(IV) oxide sulfate	Sodium vanadate; sodium trioxidovanadate(1^-); sodium vanadium oxide; sodium vanadium trioxide; vanadic acid, monosodium salt; sodium vanadate(V)	Ammonium trioxovanadate(1^-); ammonium tris(oxido)vanadate(1^-); ammonium monovanadate; ammonium vanadate(V); vanadic acid, ammonium salt; ammonium vanadium oxide; ammonium vanadium trioxide	Trisodium tetraoxidovanadate (3^-); sodium vanadium oxide, trisodium vanadate, sodium vanadate(V), vanadic acid, trisodium salt	Vanadium oxide; mu-oxido[tetrakis(oxido)]divanadium; divanadium pentoxide; vanadic anhydride; vanadin(V) oxide; vanadium(V) oxide
Water solubility (mol/L)[b]	--	--	--	--	--	--

Name	Elemental vanadium	Vanadyl sulfate	Sodium metavanadate	Ammonium metavanadate	Sodium orthovanadate	Vanadium pentoxide
LogP: Octanol-Water[b]	--	--	–	--	--	--
Melting Point (°C)[b]	1.90e+3	--	630	--	858	690
Boiling Point (°C)[b]	3.00e+3	--		--	--	1.75e+3
Vapor Pressure (mmHg)[b]	--	--	--	--	--	--
Bioconcentration Factor[b]	4.36e+3	4.5	5.54	26.4	--	15.4

[a]DTXSIDs are unique substance identifiers used for curation by the EPA's Distributed Structure-Searchable Toxicity (DSSTox) project.

[b]Experimental average values for physiochemical properties are shown here. Median values and ranges for physiochemical properties are also provided on the Chemicals Dashboard at https://comptox.epa.gov/dashboard/. If no experimental values were available on the Chemicals Dashboard, "--" is shown.

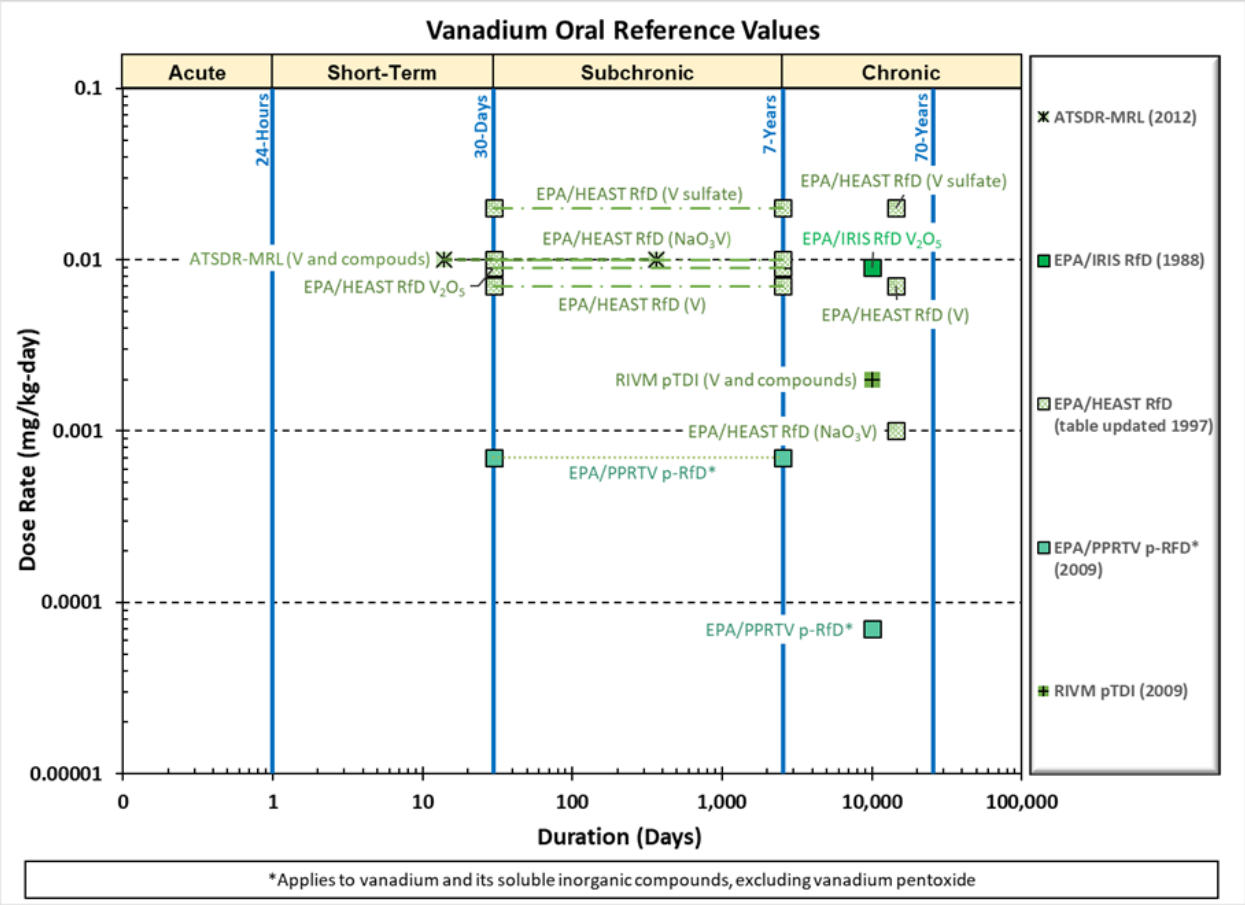


Figure 2. Available health effect reference values for oral exposure to vanadium compounds (current as of May 2020).

Table 2. Details on derivation of the available health effect reference values for oral exposure to vanadium compounds[a] (current as of May 2020; please consult citation source entities and other entities in Appendix Table A-1 for current values)

Reference value name[b]	Duration	Compound	Reference value (mg/kg-day)	Health effect	Point of departure	Qualifier	Source	Uncertainty factors[c]	Notes on derivation	Review status
EPA RfD (IRIS)[d]	Lifetime (chronic)	Vanadium pentoxide	0.009	Decreased cystine in hair of rats	0.89 mg/kg-day	NOAEL	Stokinger et al. (1953)	Total UF = 100 UF_A = 10 UF_H = 10	NOAEL Estimated[e]	Final (U.S. EPA, 1987)
EPA p-RFD (PPRTV)[f]	Subchronic	Vanadium and soluble inorganic compounds (excluding vanadium pentoxide)	0.0007	Kidney lesions in male rats exposed for 6 mos.	0.12 mg/kg-day $NOAEL_{ADJ}$ 0.22 mg/kg-day	NOAEL	Boscolo et al. (1994)	Total UF = 300 UF_A = 10 UF_H = 10 UF_{DB} = 3	NOAEL Adjusted[g]	Provisional (U.S. EPA, 2009)
	Chronic		0.00007					Total UF = 3,000 UF_A = 10 UF_H = 10 UF_S = 10 UF_{DB} = 3		
EPA RfD (HEAST)[h]	Subchronic Chronic	Vanadium	0.007 0.007	Minor serum cholesterol changes in rats	0.7 mg/kg-day	NOAEL	Schroeder et al. (1970)	Total UF = 100 UF_A = 10 UF_H = 10	NOAEL Estimated[i]	Provisional (U.S. EPA, 1997)
	Subchronic Chronic	Vanadium sulfate	0.02 0.02		2.24 mg/kg-day	NOAEL				
	Subchronic	Vanadium pentoxide	0.009	Adopted IRIS chronic RfD	--	--	--	--	Adopted IRIS chronic RfD	

Reference value name[b]	Duration	Compound	Reference value (mg/kg-day)	Health effect	Point of departure	Qualifier	Source	Uncertainty factors[c]	Notes on derivation	Review status
	Subchronic	Sodium meta-vanadate	0.01	Impaired kidney function in rats exposed for 3 mos.	1.3 mg/kg-day	NOAEL	Domingo et al. (1985)	Total UF = 100 UF_A = 10 UF_H = 10	NOAEL Conversion [j]	Provisional (U.S. EPA)
	Chronic		0.001					Total UF = 1,000 UF_A = 10 UF_H = 10 UF_S = 10		
ATSDR-MRL	Intermediate (15–365 days)	Vanadium and compounds	0.01	No change in blood pressure, body wt., or hematological or clinical chemistry parameters at highest dose in a 12-wk. study	0.5 mg/kg-day 0.12 mg/kg-day	NOAEL H_6O_8SV NOAEL V	Fawcett et al. (1997)	Total UF = 10 UF_H = 10	NOAEL V Calculated[k]	Final (ATSDR, 2012)
RIVM pTDI	Chronic	Vanadium and compounds	0.002	Develop-mental effects in rats	5 mg/kg-day 2.1 mg/kg-day	LOAEL NaO_3V LOAEL V	Domingo et al. (1986)	Total UF = 1,000 UF_A = 10 UF_H = 10 UF_L = 10	LOAEL V Calculated[l]	Provisional (Tiesjema and Baars, 2009)

[a]Health effect reference values listed in Table 2 are shown in Figure 2.
[b]ATSDR = Agency for Toxic Substances and Disease Registry; HEAST = Health Effects Assessment Summary Tables; MRL = Minimal Risk Level; PPRTV = Provisional Peer-Reviewed Toxicity Value; RfD = Reference Dose; RIVM = *Rijksinstituut voor Volksgezondheid en Milieu,* The Netherlands Institute for Public Health and the Environment; TDI = Tolerable Daily Intake.

[c]UF = uncertainty factor; subscripts indicate the type of UF that was applied. UF_H – inter-human variability; UF_A – animal to human variability; UF_L – LOAEL to NOAEL adjustment; UF_S – subchronic to chronic adjustment; UF_{DB} – database uncertainty.
[d]This RfD has been adopted as a state value by the Nevada Division of Environmental Protection.
[e]The NOAEL was estimated based on the assumption that rats exposed to 10 ppm vanadium (17.85 ppm vanadium pentoxide) in food were consuming 5% of their body weight in food per day.
[f]The chronic p-RfD has been adopted as a state value by the Michigan Department of Environment, Great Lakes & Energy.
[g]The NOAEL was adjusted upwards to account for possible additional vanadium exposure from the rats' basal diet.
[h]The chronic RfD for sodium metavanadate has been adopted by the Nevada Division of Environmental Protection.
[i]The NOAEL was estimated for rats exposed to 5 ppm vanadium in the form of vanadyl sulfate in drinking water.
[j]Rats were exposed to 10 ppm sodium metavanadate in their drinking water. Support documentation indicates that this exposure is equivalent to a dose rate of 0.55 mg vanadium/kg-day. While this is not explicitly stated anywhere in the text, 0.55 mg vanadium/kg-day equals 1.3 mg/kg-day sodium metavanadate, as per the following molecular weight conversion. Thus, 1.3 mg/kg-day was likely used as the point of departure:
NOAEL $NaVO_3$ = NOAEL V × $NaVO_3$ M.W./V molar mass = 0.55 mg V/kg-day × 121.928 g $NaVO_3$/mol/50.942 g V/mol = 1.3 mg $NaVO_3$/kg-day.
[k]NOAEL V = NOAEL $VOSO_4 \cdot 3H_2O$ × V molar mass/$VOSO_4 \cdot 3H_2O$ M.W. = 0.5 mg $VOSO_4 \cdot 3H_2O$/kg-day × 50.942 g V/mol/217.041 g $VOSO_4 \cdot 3H_2O$/mol = 0.12 mg V/kg-day.
[l]LOAEL V = LOAEL $NaVO_3$ × V molar mass/$NaVO_3$ M.W. = 5 mg NAO_3V/kg-day × 50.942 g V/mol/121.928 g $NaVO_3$/mol = 2.1 mg V/kg-day.

Table 3. Details on additional oral reference values lacking derivation descriptions[a]

Reference value name[b]	Duration	Compound	Reference value (mg/kg-day)	Health effect	Point of departure	Qualifier	Source	Uncertainty factors	Notes on derivation	Review status
TCEQ RfD	Chronic	Vanadium	0.0018	NR	NR	NR		NR	RfD developed with TCEQ's protocol (TCEQ, 2012)	Final (TCEQ, 2018)

[a]Health effect reference values listed in Table 3 are not shown in Figure 2 because they did not provide descriptions of how the value was derived.
[b]TCEQ = Texas Commission on Environmental Quality

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2.2. SCOPING SUMMARY

During scoping, the IRIS Program met with EPA program and regional offices that had interest in an IRIS assessment for vanadium and compounds to discuss specific assessment needs. Table 4 provides a summary of input from this outreach.

Table 4. EPA program and regional office interest in a reassessment of vanadium compounds

EPA program or regional office	Oral	Inhalation[a]	Statutes/regulations	Anticipated uses/interest
Office of Water	✓		Safe Drinking Water Act (SDWA) and Clean Water Act (CWA)	The SDWA requires EPA to list[b] contaminants that are currently not subject to any proposed or promulgated National Primary Drinking Water Regulation (NPDWR) but are known or anticipated to occur in public water systems, including vanadium. Contaminants listed on the CCL may require future regulation under SDWA. Under Section 304(a) of the CWA, EPA derives recommended ambient water quality criteria for the protection of human health. States and tribes may use these values or other values in their water quality standards to protect designated uses. Vanadium and compounds (oral) toxicological information may be used to address risk under the CWA and SDWA.

[a]The IRIS Program announced the initiation of a vanadium and compounds (inhalation) assessment in December 2019. A separate IAP will be released regarding the inhalation assessment.
[b]EPA's Final Contaminant Candidate List (CCL) 4 lists vanadium.

2.3. PROBLEM FORMULATION

Systematic review methods were used to identify a preliminary literature inventory for vanadium and compounds. The ATSDR Toxicological Profile for Vanadium (ATSDR, 2012) was selected as the starting point for the literature search because it is the most recent and comprehensive review of health effects of vanadium and compounds published by a U.S. federal government agency. All references from the 2012 ATSDR Toxicological Profile for Vanadium were extracted by an EPA information specialist and stored in the Health and Environmental Research Online (HERO) database (https://hero.epa.gov/hero/index.cfm/project/page/project_id/2357).[2] Database searches were then conducted on March 28, 2019 by an EPA information specialist in three online databases (PubMed, Web of Science, Toxline)[3] and repeated on March 9, 2020 to identify records that had been published since the release of the 2012 ATSDR Toxicological Profile for Vanadium. The year 2010 was selected as the start date for the literature search as a precaution to capture records published near the last literature search date for the citations in the ATSDR document.[4] This literature search strategy is designed to be broad, but like any search strategy, studies may be missed (e.g., studies published before 2010 that were not included in the ATSDR document; cases where the specific chemical is not mentioned in title, abstract, or keyword content; "grey" literature that is not indexed in the databases listed above). Thus, when additional references that appeared to meet PECO criteria were identified through curation of references cited in reviews or assessments, these references were annotated with respect to the source of the record and screened using the same methods applied to the rest of the literature inventory. IRIS encourages the identification of any additional missing studies by the public. All records were stored in the HERO database. Draft PECO criteria (Populations, Exposures, Comparators, Outcomes; see Table 6) were used to focus the research questions and guide screening to identify relevant literature.

Studies that met PECO criteria were briefly summarized using DistillerSR[5], and studies which did not meet PECO criteria but contained potentially relevant supplemental material were inventoried. For animal studies, the following information was captured: chemical form, study type [acute (<24 hours), short term (1–30 days), subchronic (30–90 days), chronic (>90 days), reproductive, developmental], duration of treatment, route, species, strain, sex, dose or concentration levels tested, dose or concentration units, health system and specific endpoints assessed, and a brief summary of findings at the health system level (null, no-observed-effect level

[2]EPA's HERO database provides access to the scientific literature behind EPA science assessments. The database includes more than 600,000 scientific references and data from the peer-reviewed literature used by EPA to develop its health assessment documents.
[3]The Toxline database was taken down and migrated to PubMed prior to the March 2020 literature search update, so the Toxline search was only conducted in March 2019.
[4]Personal correspondence with ATSDR indicated that the final literature update for the 2012 Toxicological Profile for Vanadium was conducted in August 2011.
[5]DistillerSR is a web-based systematic review software used to screen studies available at https://www.evidencepartners.com/products/distillersr-systematic-review-software.

[NOEL], or lowest-observed-effect level [LOEL] based on author-reported statistical significance with an indication of which specific endpoints were affected). For human studies, the following information was summarized: chemical form, population type (e.g., general population-adult, occupational, pregnant women, infants and children), study type (e.g., controlled trial, cross-sectional, cohort, case-control), short free text description of study population, sex, major route of exposure (if known), description of how exposure was assessed, health system and specific outcome assessed, and a summary of findings at the health system level based on author-reported statistical significance (null or an indication of any associations found and a description of how the exposure was quantified in the analysis). Studies were extracted into DistillerSR by one team member and checked by at least one other team member. These study summaries are referred to as literature surveys and are presented using Tableau visualization software (https://www.tableau.com/).

These methods were implemented in accordance with EPA Quality Assurance policies and procedures (Quality Policy Procedures[6] and CIO 2105.0 (formerly 5360.1 A2)[7]). Detailed literature search strategies (Appendix B), literature search and screening methods (Appendix C), and a literature survey study flow selection diagram (Appendix D) are provided in the appendices at the end of this document, and the preliminary literature survey results are described in the following section. The results obtained from this systematic compilation of the evidence helped inform the specific aims and key science issues that will be the focus of the assessment.

2.4. PRELIMINARY LITERATURE SURVEY RESULTS

The literature search and screening process identified 142 studies that met PECO criteria (n = 48 human studies, n = 94 animal studies), and a total of 1,064 studies were tagged as potentially relevant supplemental material. No PBPK models for vanadium or vanadium compounds were identified.

Human studies: A preliminary survey of study designs and health systems assessed in the human studies that met PECO criteria is provided in Figure 3 and a tabular summary is provided in Figure 4. Human studies identified in the literature search included nine controlled trials that administered vanadyl sulfate or sodium metavanadate directly to study participants. Of the controlled human trials, seven were conducted in diabetic patients for the purpose of evaluating the therapeutic effects of vanadium supplementation, with treatment durations of 2–6 weeks (Afkhami-Arekani et al., 2008; Cusi et al., 2001; Goldfine et al., 2000; Boden et al., 1996; Halberstam et al., 1996; Cohen et al., 1995; Goldfine et al., 1995); one evaluated effects of vanadium supplementation on insulin sensitivity in healthy adults, with a treatment duration of 7 days; and one evaluated effects of vanadium supplementation in weight training athletes, with a treatment duration of

[6]U.S Environmental Protection Agency Procedures for Quality Policy: https://www.epa.gov/sites/production/files/2015-10/documents/21060.pdf
[7]Policy and Program Requirements for the Mandatory Agency -Wide Quality System: https://www.epa.gov/sites/production/files/2015-09/documents/epa_order_cio_21050.pdf

12 weeks (Fawcett et al., 1997). The literature search also identified 39 observational epidemiology studies, which evaluated the association of health outcomes with total vanadium but the specific form of vanadium was not determined. This included 37 studies (n = 13 case-control, 14 cross-sectional, and 10 cohort) in which vanadium exposure was evaluated using biomonitoring of blood (whole blood, plasma, or serum), urine, hair, seminal plasma, cerebrospinal fluid, saliva, or nails, but in which the route of exposure was unclear; and two ecological studies that evaluated the association of human health outcomes with vanadium levels in soil, drinking water, or food.

Health System	controlled trial	case-control	cross-sectional	cohort	ecological	Grand Total
Cancer		4				4
Cardiovascular	7		3	1		11
Dermal		1				1
Developmental		1	1	5	1	8
Endocrine			1	1		2
Gastrointestinal	7					7
Hematologic	3		1			4
Hepatic	1					1
Immune	1		1	1		3
Metabolic	8	2		1		11
Nervous		5	3		1	9
Other			1			1
Renal	1			1		2
Reproductive			3	1		4
Systemic/Whole Body	3			1		4
Grand Total	9	13	14	10	2	48

Figure 3. Survey of human studies that met PECO criteria by study design and health systems assessed.

Click here to view interactive version, which includes a more detailed description of study design and results. The numbers indicate the number of studies that investigated a particular health system, not the number of studies that observed an association with vanadium exposure. If a study evaluated multiple health outcomes, it is shown here multiple times.

Figure 4. Tabular summary of study designs and exposure measurements used in human studies that met PECO criteria (continued on following page). Click here to view interactive version, which includes a more detailed description of study design and results.

Health System	Chemical Name	Population	Study Design	Sex	Reference	Exposure Measurement / Biomonitoring Matrix: direct administration (oral)	blood	cerebrospinal fluid	hair	semen	urine	saliva	soil
Hematologic	Vanadium	children	cross-sectional	both	Lopez-Rodriguez et al., 2017		■						
	Vanadyl sulfate	general population	controlled trial	both	Cohen et al., 1995	■							
					Fawcett et al., 1997	■							
					Halberstam et al., 1996	■							
Hepatic	Vanadyl sulfate	general population	controlled trial	both	Fawcett et al., 1997	■							
Immune	Vanadium	general population	cross-sectional	both	Pedro et al., 2019								■
		infants	cohort	both	Zhou et al., 2019		■						
	Vanadyl sulfate	general population	controlled trial	both	Fawcett et al., 1997	■							
Metabolic	Sodium metavanadate	general population	controlled trial	both	Afkhami-Ardekani et al., 2008	■							
					Goldfine et al., 1995	■							
	Vanadium	general population	case-control	both	Li et al., 2017		■						
					Wang et al., 2014		■						
		pregnant women	cohort	female	Wang et al., 2020						■		
	Vanadyl sulfate	general population	controlled trial	both	Boden et al., 1996	■							
					Cohen et al., 1995	■							
					Cusi et al., 2001	■							
					Goldfine et al., 2000	■							
					Halberstam et al., 1996	■							
					Jentjens and Jeukendrup, 2002	■							
Nervous	Vanadium	general population	case-control	both	Roos et al., 2013			■					
					Squadrone et al., 2018		■						
				female	Naylor et al., 1984				■				
			cross-sectional	both	Kihira et al., 2015				■				
		children	case-control	both	Alqhazo and Rashaid, 2018				■				
					Skalny et al., 2017				■				
			cross-sectional	both	Blaurock-Busch et al., 2012				■				
				male	Tinkov et al., 2019		■		■				
			ecological	both	Zahran et al., 2012								■
Other	Vanadium	general population	cross-sectional	both	Inonu et al., 2019							■	
Renal	Vanadium	general population	cohort	both	Liu et al., 2020		■						
	Vanadyl sulfate	general population	controlled trial	both	Fawcett et al., 1997	■							
Reproductive	Vanadium	general population	cross-sectional	female	Zheng et al., 2015		■						
				male	Skalnaya et al., 2015					■			
					Wang et al., 2018					■	■		
		pregnant women	cohort	female	Jin et al., 2018						■		
Systemic/Whole Body	Sodium metavanadate	general population	controlled trial	both	Goldfine et al., 1995	■							
	Vanadium	pregnant women	cohort	female	Skalny et al., 2020				■				
	Vanadyl sulfate	general population	controlled trial	both	Cohen et al., 1995	■							
					Goldfine et al., 2000	■							

Exposure Measurement:
■ biomonitoring
■ direct administration (oral)
■ soil

Figure 4 continued.

Animal studies: A preliminary survey of the types of vanadium compounds evaluated in animal studies that met PECO criteria is shown in Figure 5, and a preliminary survey of study designs, species, and health effects evaluated in the animal studies is provided in Figure 6. The animal studies evaluated exposure to ammonium metavanadate, sodium metavanadate, sodium orthovanadate, vanadyl sulfate, vanadium pentoxide, calcium orthovanadate, or calcium pyrovanadate. Of these, vanadyl sulfate and sodium metavanadate were the most frequently studied compounds. Two studies reported that animals were exposed to "ammonium vanadate" (Susić and Kentera, 1986) and "sodium vanadate" (Sun et al., 2014), which were inferred to be ammonium metavanadate and sodium metavanadate (respectively) based on the synonyms reported in Table 1 and are referred to accordingly here. Four studies reported that animals were exposed to "vanadium" or "vanadate" but the specific chemical form was unclear. The majority of studies were conducted in rats and mice, but data were also available in rabbits, cattle, goats, and sheep. Among the 94 available animal studies, 23 included experiments in animal models of diabetes that evaluated the therapeutic effects of vanadium compounds on diabetic symptoms.

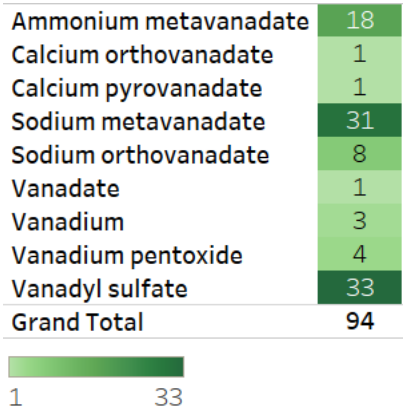

Figure 5. Survey of the vanadium compounds evaluated in the available animal studies, showing the number of studies that evaluated each vanadium compound. Click here to view interactive version, which includes a more detailed description of study design and results. If study evaluated multiple types of vanadium compounds, it is shown here multiple times.

Tabular summaries of the study designs and health effects evaluated in chronic, subchronic, and reproductive or developmental studies that tested multiple dose levels are provided in Figures 7, 8, and 9, respectively.[8] In general, these study designs are preferred for toxicity value derivation over acute/short-term studies or studies that test a single dose level (U.S. EPA, 2002), although there may be circumstances where other study designs are more suitable. Figures are organized by health outcomes evaluated. Diabetic animal models are not shown in Figures 7–9 but are included in Figures 5 and 6 and in the interactive figures in Tableau.

[8]Dose levels shown in tabular summaries are those reported by the authors. For the assessment, doses reported as concentrations in food or drinking water (e.g., ppm, µg/mL) will be converted to mg/kg-day.

Health System	acute		short-term			subchronic				chronic					reproductive		developmental		Grand Total
	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		16
Cancer						1				2	2								5
Cardiovascular			2	1		9	1	1	1	10		1	1				2		28
Dermal										1									1
Developmental				1													6	1	8
Endocrine								1		2			1				1		5
Gastrointestinal				1		1													2
Hematologic			6			8		1		5									20
Hepatic	1		6	3		4	3	1		1					2	1	4		22
Immune			6	2		7	3	1		2							2		21
Lymphatic						1													1
Metabolic			8	1		16	1	1	1	4			1		3		1		37
Musculoskeletal			1	1		1							1						4
Nervous			2	1		7				1							2		13
Ocular						1													1
Renal			3	3		5	2	1		5					3	1	3		24
Reproductive				1			1			1				1	8	2	2		14
Respiratory			1	2		2				1							2		7
Systemic/Whole Body	2	1	15	3	1	26	2	1	1	9	3		1	1	4	1		1	68
Urinary										1									1
Grand Total	2	1	17	3	1	34	4	1	1	15	3	1	1	1	9	2	9	2	94

1 26

Figure 6. Survey of animal studies that met PECO criteria by study design and species and health systems assessed. Click here to view interactive version, which includes a more detailed description of study design and results. The numbers indicate the number of studies that investigated a particular health system, not the number of studies that observed an association with vanadium exposure. If a study evaluated multiple species, study designs, or health outcomes, it is shown here multiple times.

Health System	Chemical Name	Species	Sex	Dosing Duration	All dose levels	Dose units	Reference	
Cancer	Ammonium metavanadate	mouse	male	30 wk	0, 10, 20	ppm V	Kingsnorth et al., 1986	
	Vanadyl sulfate	rat	female	180 d (28 d with 15 ppm, then with 25 ppm till 180 d)	0, 15/25	ppm V	Thompson et al., 1984	
Cardiovascular	Sodium metavanadate	rat	male	6 or 7 mon	0, 1, 10, 40	ug V/mL	Boscolo et al., 1994	
				7 mon	0, 10, 40	ug V/mL	Carmignani et al., 1992	
				24 wk	0, 300, 3000	ppm	Susic and Kentera, 1988	
		cattle	not reported	150 d	0, 3, 6, 9	ppm V	Pal et al., 2018	
	Sodium orthovanadate	rat	male	56 wk	0, 100, 200	ppm V	Steffen et al., 1981	
	Vanadyl sulfate	rat	not reported	24 wk	0, 0.25, 1.2	mg/kg-d	Shah et al., 2016	
Dermal	Vanadium pentoxide	rat	male	75 d	0, 500, 1000	ppm V	Mountain et al., 1953	
				103 d	0, 100, 150	ppm V	Mountain et al., 1953	
Endocrine	Sodium metavanadate	cattle	not reported	150 d	0, 3, 6, 9	ppm V	Pal et al., 2018	
	Sodium orthovanadate	rat	male	56 wk	0, 100, 200	ppm V	Steffen et al., 1981	
Hematologic	Sodium metavanadate	rat	male	24 wk	0, 300, 3000	ppm	Susic and Kentera, 1988	
	Vanadium pentoxide	rat	male	103 d	0, 100, 150	ppm V	Mountain et al., 1953	
	Vanadyl sulfate	rat	female	180 d (28 d with 15 ppm, then with 25 ppm till 180 d)	0, 15/25	ppm V	Thompson et al., 1984	
Immune	Vanadium pentoxide	rat	both	6 mon	0, 1, 100	mg V/L	Mravcova et al., 1993	
Metabolic	Sodium metavanadate	cattle	not reported	150 d	0, 3, 6, 9	ppm V	Pal et al., 2018	
	Vanadyl sulfate	rat	not reported	24 wk	0, 0.25, 1.2	mg/kg-d	Shah et al., 2016	
Musculoskeletal	Sodium metavanadate	cattle	not reported	150 d	0, 3, 6, 9	ppm V	Pal et al., 2018	
Renal	Sodium metavanadate	rat	male	6 or 7 mon	0, 1, 10, 40	ug V/mL	Boscolo et al., 1994	
				24 wk	0, 300, 3000	ppm	Susic and Kentera, 1988	

Route of Exposure:
- oral (diet)
- oral (gavage)
- oral (water)

Figure 7. Preliminary summary of multidose chronic animal studies (continued on following page). Click here to view interactive version, which includes a more detailed description of study design and results.

Health System	Chemical Name	Species	Sex	Dosing Duration	All dose levels	Dose units	Reference	
Reproductive	Sodium metavanadate	goat	female	130 d	0, 2, 4, 6	ppm V	Tripathi et al., 2018	
Systemic/Whole Body	Ammonium metavanadate	mouse	male	30 wk	0, 10, 20	ppm V	Kingsnorth et al., 1986	
	Sodium metavanadate	rat	male	24 wk	0, 300, 3000	ppm	Susic and Kentera, 1988	
		cattle	not reported	150 d	0, 3, 6, 9	ppm V	Pal et al., 2018	
		goat	female	130 d	0, 2, 4, 6	ppm V	Tripathi et al., 2018	
	Sodium orthovanadate	rat	male	56 wk	0, 100, 200	ppm V	Steffen et al., 1981	
	Vanadium pentoxide	rat	male	75 d	0, 500, 1000	ppm V	Mountain et al., 1953	
				103 d	0, 100, 150	ppm V	Mountain et al., 1953	
	Vanadyl sulfate	rat	female	180 d (28 d with 15 ppm, then with 25 ppm till 180 d)	0, 15/25	ppm V	Thompson et al., 1984	
Urinary	Sodium metavanadate	rat	male	7 mon	0, 10, 40	ug V/mL	Carmignani et al., 1992	

Route of Exposure:
oral (diet)
oral (water)

Figure 7 continued.

Health System	Chemical Name	Species	Sex	Dosing Duration	All dose levels	Dose units	Reference	
Cardiovascular	Ammonium metavanadate	rat	female	35 d	0, 3, 15, 30	mg V/kg	Wang et al., 2019	
	Sodium metavanadate	rat	male	3 mon	0, 5, 10, 50	ppm	Domingo et al., 1985	
		cattle	female	90 d	0, 2.5, 5	ppm V	Gupta et al., 2020	
	Vanadyl sulfate	goat	not reported	84 d	0, 1, 2, 3	mg V/d	Zarqami et al., 2017	
Endocrine	Sodium metavanadate	cattle	female	90 d	0, 2.5, 5	ppm V	Gupta et al., 2020	
Hematologic	Sodium metavanadate	rat	female	10 wk	0, 50, 100	ppm V	Adachi et al., 2000	
		cattle	female	90 d	0, 2.5, 5	ppm V	Gupta et al., 2020	
Hepatic	Ammonium metavanadate	rat	female	5 wk	0, 3, 15, 30	mg V/kg	Wang et al., 2016	
				35 d	0, 3, 15, 30	mg V/kg	Wang et al., 2019	
	Sodium metavanadate	rat	female	10 wk	0, 50, 100	ppm V	Adachi et al., 2000	
			male	3 mon	0, 5, 10, 50	ppm	Domingo et al., 1985	
		cattle	female	90 d	0, 2.5, 5	ppm V	Gupta et al., 2020	
	Sodium orthovanadate	mouse	male	13 wk	0, 1, 10, 50	mg V/L	Sharma et al., 1981	
	Vanadyl sulfate	mouse	male	5 wk	0, 2, 10	mg/L	Villani et al., 2007	
					0, 10, 100, 50..	mg/L	Villani et al., 2007	

Route of Exposure:
oral (diet)
oral (water)

Figure 8. Preliminary summary of multidose subchronic animal studies (continued on following pages). Click here to view interactive version, which includes a more detailed description of study design and results.

Health System	Chemical Name	Species	Sex	Dosing Duration	All dose levels	Dose units	Reference	
Immune	Sodium metavanadate	rat	female	10 wk	0, 50, 100	ppm V	Adachi et al., 2000	
			male	3 mon	0, 5, 10, 50	ppm	Domingo et al., 1985	
		cattle	female	90 d	0, 2.5, 5	ppm V	Gupta et al., 2020	
	Sodium orthovanadate	mouse	male	13 wk	0, 1, 10, 50	mg V/L	Sharma et al., 1981	
	Vanadyl sulfate	mouse	male	5 wk	0, 2, 10	mg/L	Villani et al., 2007	
					0, 10, 100, 500, 1000	mg/L	Villani et al., 2007	
Lymphatic	Ammonium metavanadate	rat	female	35 d	0, 3, 15, 30	mg V/kg	Wang et al., 2019	
Metabolic	Sodium metavanadate	rat	male	3 mon	0, 5, 10, 50	ppm	Domingo et al., 1985	
		cattle	female	90 d	0, 2.5, 5	ppm V	Gupta et al., 2020	
	Vanadyl sulfate	goat	not reported	84 d	0, 1, 2, 3	mg V/d	Zarqami et al., 2017	
Nervous	Sodium metavanadate	rat	female	10 wk	0, 50, 100	ppm V	Adachi et al., 2000	
			male	8 wk	0, 4.1, 8.2, 16.4	mg/kg-d	Sanchez et al., 1998	
				12 wk	0, 0.5, 1.0, 2.0	g/L	Sun et al., 2017	
Renal	Ammonium metavanadate	rat	female	5 weeks	0, 3, 15, 30	mg V/kg	Wang et al., 2016	
				35 d	0, 3, 15, 30	mg V/kg	Wang et al., 2019	
	Sodium metavanadate	rat	male	3 mon	0, 5, 10, 50	ppm	Domingo et al., 1985	
		cattle	female	90 d	0, 2.5, 5	ppm V	Gupta et al., 2020	
	Sodium orthovanadate	mouse	male	13 wk	0, 1, 10, 50	mg V/L	Sharma et al., 1981	
	Vanadyl sulfate	mouse	male	5 wk	0, 2, 10	mg/L	Villani et al., 2007	
					0, 10, 100, 500, 1000	mg/L	Villani et al., 2007	

Route of Exposure:
oral (diet)
oral (gavage)
oral (water)

Figure 8 continued.

Health System	Chemical Name	Species	Sex	Dosing Duration	All dose levels	Dose units	Reference	
Reproductive	Vanadyl sulfate	mouse	male	5 wk	0, 2, 10	mg/L	Villani et al., 2007	
					0, 10, 100, 500, 1000	mg/L	Villani et al., 2007	
Respiratory	Ammonium metavanadate	rat	female	35 d	0, 3, 15, 30	mg V/kg	Wang et al., 2019	
	Sodium metavanadate	rat	male	3 mon	0, 5, 10, 50	ppm	Domingo et al., 1985	
Systemic/ Whole Body	Ammonium metavanadate	rat	female	35 d	0, 3, 15, 30	mg V/kg	Wang et al., 2019	
	Sodium metavanadate	rat	female	10 wk	0, 50, 100	ppm V	Adachi et al., 2000	
			male	3 mon	0, 5, 10, 50	ppm	Domingo et al., 1985	
				8 wk	0, 4.1, 8.2, 16.4	mg/kg-d	Sanchez et al., 1998	
		cattle	female	90 d	0, 2.5, 5	ppm V	Gupta et al., 2020	
	Sodium orthovanadate	mouse	male	13 wk	0, 1, 10, 50	mg V/L	Sharma et al., 1981	
	Vanadium	rat	male	60 d	0, 20, 40	mg/kg	Tubafard et al., 2010	
	Vanadyl sulfate	mouse	male	5 wk	0, 2, 10	mg/L	Villani et al., 2007	
					0, 10, 100, 500, 1000	mg/L	Villani et al., 2007	
		goat	not reported	84 d	0, 1, 2, 3	mg V/d	Zarqami et al., 2017	

Route of Exposure:
- oral (diet)
- oral (gavage)
- oral (water)

Figure 8 continued.

Health System	Chemical Name	Species	Sex	Dosing Duration	All dose levels	Dose units	Reference	
Cardiovascular	Sodium metavanadate	rat	both	60 d (F0 male); 14 d premating + gestation + lactation (F0 female)	0, 5, 10, 20	mg/kg-d	Domingo et al., 1986	■
Developmental	Sodium metavanadate	rat	both	60 d (F0 male); 14 d premating + gestation + lactation (F0 female)	0, 5, 10, 20	mg/kg-d	Domingo et al., 1986	■
				GD6-GD14	0, 5, 10, 20	mg/kg	Paternain et al., 1987	■
	Vanadyl sulfate	mouse	both	GD6-15	0, 37.5, 75, 150	mg/kg-d	Paternain et al., 1990	■
Hepatic	Sodium metavanadate	rat	both	60 d (F0 male); 14 d premating + gestation + lactation (F0 female)	0, 5, 10, 20	mg/kg-d	Domingo et al., 1986	■
	Vanadyl sulfate	mouse	female (dam)	GD6-15	0, 37.5, 75, 150	mg/kg-d	Paternain et al., 1990	■
Immune	Sodium metavanadate	rat	both	60 d (F0 male); 14 d premating + gestation + lactation (F0 female)	0, 5, 10, 20	mg/kg-d	Domingo et al., 1986	■
Renal	Sodium metavanadate	rat	both	60 d (F0 male); 14 d premating + gestation + lactation (F0 female)	0, 5, 10, 20	mg/kg-d	Domingo et al., 1986	■
	Vanadyl sulfate	mouse	female (dam)	GD6-15	0, 37.5, 75, 150	mg/kg-d	Paternain et al., 1990	■
Reproductive	Sodium metavanadate	rat	both	60 d (F0 male); 14 d premating + gestation + lactation (F0 female)	0, 5, 10, 20	mg/kg-d	Domingo et al., 1986	■
			female (dam)	GD6-GD14	0, 5, 10, 20	mg/kg	Paternain et al., 1987	■
		mouse	male	64 d	0, 20, 40, 60, 80	mg/kg-d	Llobet et al., 1993	■
	Sodium orthovanadate	rat	female (dam)	mating-PND1	0, 0.25, 0.50	mg/mL	Ganguli et al., 1994a	■
	Vanadyl sulfate	mouse	female (dam)	GD6-15	0, 37.5, 75, 150	mg/kg-d	Paternain et al., 1990	■
Respiratory	Sodium metavanadate	rat	both	60 d (F0 male); 14 d premating + gestation + lactation (F0 female)	0, 5, 10, 20	mg/kg-d	Domingo et al., 1986	■
Systemic/ Whole Body	Sodium metavanadate	mouse	male	64 d	0, 20, 40, 60, 80	mg/kg-d	Llobet et al., 1993	■

Route of Exposure:
■ oral (gavage)
■ oral (water)

Figure 9. Preliminary summary of multidose reproductive and developmental animal studies. Click here to view interactive version, which includes a more detailed description of study design and results.

Studies in progress by the National Toxicology Program: The interim results of NTP's extended developmental study in rats and 13-week study in mice (currently available as a poster,[9] with complete results expected to be published in 2020) were also considered for problem formulation, as these studies were conducted by NTP following nomination by the EPA and National Institute of Environmental Health Sciences and are intended to address data gaps related to the oral toxicity of pentavalent and tetravalent vanadium compounds.[10]

In the developmental study, rat F1 offspring were initially exposed in utero and via breast milk, and then continued to receive the same dose levels as their mothers via drinking water for 13 weeks following weaning. Moribundity of F0 dams was observed during parturition and lactation in the 250 and 500 mg/L sodium metavanadate dose groups, with decreased maternal body weights in proportion to dose. F1 pups exposed to sodium metavanadate had decreased survival from postnatal days 1-10 in the 500 mg/L dose group, and F1 body weights at the end of the study were found to be decreased in males at doses ≥125 mg/L and in females in the 500 mg/L dose group. Conversely, no impacts on F0 or F1 survival or body weight were observed in rats exposed to vanadyl sulfate. Analysis of total vanadium concentrations in plasma and urine of a subset of F1 rats at the end of the exposure period in the developmental study indicated higher absorption of sodium metavanadate compared to vanadyl sulfate when consuming similar levels of vanadium, which may explain the differential toxicity between these two compounds. The analysis of clinical pathology, organ weight, and histopathology data from the developmental study is still ongoing. Similarly, NTP's 13-week study in mice observed toxicity following exposure to sodium metavanadate but not vanadyl sulfate. Mice exposed to sodium metavanadate had decreased body weights (observed at doses of 500 mg/L in males and at 250 and 500 mg/L in females), decreased thymus weights (observed at doses of 250 mg/L in males and 500 mg/L in females), increased erythrocytes and reticulocytes (observed at 500 mg/L in males and females), and small decreases in hematocrit and hemoglobin.

Comparison with studies used in the 1987 IRIS assessment: As described earlier in this document, the 1987 IRIS RfD for vanadium pentoxide was based on a chronic (lifetime) NOAEL of 10 ppm vanadium for decreased hair cystine levels from the study in rats by Stokinger et al. (1953). Decreased hair cystine content is a biomarker that has been associated with certain pathological conditions in rodents and humans (Mountain et al., 1953) but has limited interpretation with respect to adversity and biological significance. For comparative purposes to provide an overview of chronic health effects data that has become available since the 1987 IRIS vanadium health effects assessment, Table 5 summarizes the study designs and NOELs/LOELs (reflecting only author-reported statistical significance) in the chronic animal studies from the current literature inventory that tested multiple dose levels of vanadium and which were not included in the 1987 IRIS

[9] https://ntp.niehs.nih.gov/ntp/results/pubs/posters/roberts_sot20190300.pdf.
[10] https://ntp.niehs.nih.gov/getinvolved/nominate/summary/nm-n20806.html?utm_source=direct&utm_medium=prod&utm_campaign=ntpgolinks&utm_term=nm-n20806.

assessment. Dose levels in this table are expressed as elemental vanadium to allow for comparison across compounds. The author-reported NOELs in these studies ranged from 1 to 100 ppm vanadium in drinking water and 3 to 6 ppm in diet. The author-reported LOELs ranged from 1 to 200 ppm vanadium in drinking water, 6 to 125.3 ppm vanadium in diet, and 0.078 mg/kg-day via oral gavage.

Summary: The literature inventory includes a range of study designs and outcomes that are potentially useful for hazard identification and/or dose-response analysis for vanadium and compounds. Based on this preliminary literature survey, EPA anticipates conducting a systematic review for any health effects associated with oral exposure to vanadium and compounds.

Table 5. Summary of NOELs and LOELs from all multidose chronic animal studies that were not included in the 1987 IRIS health effects assessment of vanadium, with doses expressed as to (A) parts-per-million (ppm) vanadium or (B) mg/kg-day vanadium. NOELs and LOELs are based on author-reported statistical significance. Results (bolded) from Stokinger et al. 1953 (used to derive the 1987 IRIS RfD) are shown for reference. Studies are ordered from lowest to highest LOEL, followed by lowest to highest NOEL for studies that observed no effects within the tested dose range.

A.

Reference[a]	Chemical name	Route	Species (Strain)	NOEL (ppm vanadium)[b]	LOEL (ppm vanadium)[b]	Effects summary at LOEL
Boscolo et al. (1994)[c]	Sodium metavanadate	Drinking water	Rat (Sprague-Dawley)	--	1	Increased systolic and diastolic blood pressure, decreased plasma aldosterone, decreased urinary kallikrein, decreased urinary calcium. (Increased plasma renin activity and increased urinary kininase I and II observed at 10 ppm vanadium.)
Pal et al. (2018) [c]	Sodium metavanadate	Diet	Cattle (Karan Fries [Tharparkar x Holstein Friesian] crossbred calves)	3	6	Increased insulin-like growth factor, increased total triiodothyronine (T3), increased total thyroxin (T4), increased bone alkaline phosphatase, decreased bone protein tyrosine phosphatase
Carmignani et al. (1992) [c]	Sodium metavanadate	Drinking water	Rat (Sprague-Dawley)	--	10	Increased plasma renin activity, plasma aldosterone, aortic blood pressure; urine parameters (increased kallikrein levels, kininase I and II levels, enkephalinase levels)
Mravcová et al. (1993) [c]	Vanadium pentoxide	Drinking water	Rat (Wistar)	1	10	Increased spleen weight, decreased phagocytosis
Stokinger et al. (1953) [c]	***Vanadium pentoxide***	***Diet***	***Rat***	***10***	***100***	***Decreased hair cystine***
Susić and Kentera (1988) [d]	Sodium metavanadate	Diet	Rat (Long-Evans)	--	125.3	Decreased body weight, decreased cardiac output, increased total peripheral resistance. (Increased hematocrit and decreased plasma,

Reference[a]	Chemical name	Route	Species (Strain)	NOEL (ppm vanadium)[b]	LOEL (ppm vanadium)[b]	Effects summary at LOEL
						blood and extracellular fluid volume observed at 1253 ppm vanadium.)
Steffen et al. (1981) [c]	Sodium orthovanadate	Drinking water	Rat (Sprague-Dawley)	--	100	Increased systolic blood pressure, increased relative heart weight. (Decreased body weight gain at 200 ppm vanadium.)
Tripathi et al. (2018) [c]	Sodium metavanadate	Diet	Goat (Alpine × Beetal and Saanen × Beetal)	6	--	No change in final body weight, food intake, milk yield, or milk composition
Kingsnorth et al. (1986) [c]	Ammonium metavanadate	Drinking water	Mouse (CD-1)	20	--	No change in or survival or body weight gain

[a]Carmignani et al. (1992) was published in a book containing proceedings of the 31st Congress of the EUROTOX. All other studies were published in peer-reviewed journals.

[b]1 ppm = 1 mg/kg diet or 1 mg/L drinking water.

[c]Studies by Boscolo et al. (1994), Pal et al. (2018), Carmignani et al. (1992), Mravcová et al. (1993), Stokinger et al. (1953), Steffen et al. (1981), Tripathi et al. (2018), and Kingsnorth et al. (1986) were interpreted as reporting dose levels for vanadium compounds in terms of elemental vanadium. Doses shown in this table are those reported by the authors.

[d]Susić and Kentera (1988) reported a LOEL of 300 ppm $NaVO_3$. This was converted to elemental vanadium using the following molecular weight conversion: LOEL V = LOEL $NaVO_3$ × V molar mass/$NaVO_3$ M.W. = 300 ppm $NaVO_3$ × 50.942 g V/mol/121.928 g $NaVO_3$/mol = 125.3 ppm V

B.

Reference[a]	Chemical name	Route	Species (Strain)	NOEL (mg/kg-day vanadium)	LOEL (mg/kg-day vanadium)	Effects summary at LOEL
Shah et al. (2016)[e]	Vanadyl sulfate	Gavage	Rat	--	0.078	Increased serum triglycerides, increased total cholesterol, increased LDL-c, increased VLDL-c, decreased HDL-c, decreased plasma glucose, decreased serum insulin

[e]Shah et al. (2016) reported a LOEL of 0.25 mg $VOSO_4$/kg-day. This was converted to elemental vanadium using the following molecular weight conversion: LOEL V = LOEL $VOSO_4$ × V molar mass/$VOSO_4$ M.W. = 0.25 mg $VOSO_4$/kg-day × 50.942 g V/mol/163 g $VOSO_4$/mol = 0.078 mg V/kg-day

2.5. KEY SCIENCE ISSUES

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

- **Key science issue #1: <u>Consideration of potential toxicity and toxicokinetic differences across vanadium compounds.</u>** Differential absorption has been observed across inorganic vanadium compounds. For instance, as described earlier in this document, studies in progress by NTP preliminarily report that drinking water exposure to sodium metavanadate (+5) in rats led to higher levels of vanadium in plasma and urine as compared to vanadyl sulfate (+4) at similar vanadium exposure levels. This is consistent with reports that vanadate (+5) is absorbed more readily in the gastrointestinal tract compared to vanadyl (+4) (Treviño et al., 2019; Nielsen, 1995). Absorption may be correlated with toxicity, as the effects observed by NTP were more pronounced following exposure to sodium metavanadate compared to vanadyl sulfate. To address these apparent differences, in addition to more fully characterizing the toxicokinetic differences across compounds (including potential interconversion within the body), EPA plans to conduct separate toxicity evaluations for different vanadium compounds where the evidence supports such an analysis.

- **Key science issue #2: <u>Consideration of vanadium speciation</u>.** Available information indicates that vanadium in solution can readily interconvert between oxidation states and will form different spectrums of species as a function of factors including pH, concentration, and redox potential. For instance, tetravalent vanadium in drinking water is stable at acidic pH but can convert to pentavalent species at neutral or basic pH (Mutlu et al., 2017). Given the apparent toxicokinetic (and, likely, toxicity) differences across vanadium compounds (see Key Science Issue #1), study evaluations will, to the extent possible, consider factors that could affect vanadium oxidation state and speciation in the available toxicity studies. Speciation of vanadium at low environmental concentrations will also be of particular interest.

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

The overall objectives of this assessment are to identify adverse human health effects of exposure to vanadium and compounds and characterize exposure-response relationships for these effects to support development of toxicity values. The evaluation conducted in this assessment will utilize EPA guidance.[11] The systematic review protocol will be disseminated after review of the draft assessment plan and will reflect changes made to the specific aims, key science issues, and PECO in response to public input. The systematic review protocol will also provide specific details on the methods that will be used to carry out the specific aims outlined below.

3.1. SPECIFIC AIMS

- Identify epidemiological (i.e., human) and toxicological (i.e., experimental animal) literature reporting effects of exposure to vanadium compounds as outlined in the PECO, and inventory literature that is potentially relevant to the specific aims (e.g. toxicokinetic, mechanistic). The ATSDR Toxicological Profile for Vanadium (ATSDR, 2012) will serve as the starting point for the literature search because it is the most recent and comprehensive review of health effects of vanadium and compounds published by a US federal government agency. Database searches will be conducted to identify records that had been published since the literature was last searched for the 2012 ATSDR Toxicological Profile for Vanadium.

- Conduct study evaluations (risk of bias and sensitivity) for individual epidemiological and toxicological studies and (if identified in future literature searches) PBPK models.

- Extract data on relevant health outcomes from epidemiological and toxicological studies included based on the study evaluation (full data extraction of *low* confidence studies may not be performed for poorly studied health effects or for health effects on which extensive *medium* and *high* confidence studies exist in the evidence base).

- Review and incorporate the available toxicokinetic and mechanistic information, as warranted to support assessment decisions. The toxicokinetic analyses will focus primarily

[11]The EPA guidelines have been developed over time and address the state of the science at the time they were developed. Thus, evaluation methods may be updated as new science emerges, or when existing guidelines are updated. EPA guidance documents can be found at: http://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance/

on the key science issues identified in Section 2.5. The scope of the analysis of mechanistic information will be determined by the complexity and confidence in the phenotypic evidence in humans and animals, the likelihood of the analyses to affect evidence synthesis conclusions for human health, and the directness or relevance of the available model systems for understanding potential human health hazards.

- For each evidence stream (i.e., studies in humans, animal studies, and mechanistic or other supplemental studies, as appropriate and depending on data availability), synthesize the evidence across studies, assessing similar health outcomes using a narrative approach.

- For each health outcome, determine the strength of the evidence within and across evidence streams to draw evidence integration judgments about the potential for vanadium and compounds exposure to be hazardous to humans. Identify and discuss issues concerning potentially susceptible populations and life stages.

- Derive oral toxicity values (e.g., reference doses [RfDs], cancer risk estimates for oral exposure) as supported by the available data.

- Characterize uncertainties and identify key data gaps and research needs, such as limitations of the evidence base, limitations of the systematic review, and consideration of dose relevance and pharmacokinetic differences when extrapolating findings from higher dose animal studies to lower levels of human exposure.

3.2. DRAFT PECO CRITERIA

The PECO is used to identify the evidence that addresses the specific aims of the assessment as well as to focus the search terms and inclusion/exclusion criteria in a systematic review. The draft PECO for vanadium and compounds (Table 6) was based on (1) nomination of the chemicals for assessment, (2) discussions with scientists in the Office of Water to determine the scope of the assessment that will best meet Agency needs, and (3) preliminary review of the health effects literature for vanadium and compounds to identify the health hazards potentially associated with oral exposure to vanadium and compounds and key areas of scientific complexity.

Table 6. Draft populations, exposures, comparators, outcomes (PECO) criteria for the vanadium compounds assessment

PECO element	Evidence
Populations	**Human:** Any population and lifestage (occupational or general population, including children, women of childbearing age, and other sensitive populations). **Animal:** Nonhuman mammalian animal species (whole organism) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages).
Exposures	**Relevant forms:** Any form of vanadium. The focus will be on soluble inorganic vanadium compounds that are relevant for environmental exposures, including the vanadium compounds shown in Table 1 (e.g.,vanadyl sulfate, sodium metavanadate, sodium orthovanadate, ammonium metavanadate, vanadium pentoxide). Studies of organic anthropogenic vanadium compounds that are synthesized for pharmacologic uses [e.g., bis(maltolato)oxyvanadium (VI)],

PECO element	Evidence
	vanadium nanomaterials, and vanadium alloys that otherwise meet PECO criteria will be tracked through full text screening for evidence mapping purposes and tagged as "potentially relevant supplemental information," but a full systematic review will not be performed for these compounds and they will not be considered for reference value derivation. **Human:** Any exposure to vanadium compound(s) via the oral route, including exposure via breastmilk. 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. Other exposure routes, including inhalation, will be tagged as "potentially relevant supplemental information." **Animal:** Any exposure to vanadium compound(s) via the oral route, including exposure via breastmilk. Studies involving exposures to mixtures will be included only if they include an arm with exposure to vanadium compound(s) alone; otherwise, they will be tagged as potentially relevant supplemental material. Other exposure routes, including inhalation, dermal, or injection, will be tagged as "potentially relevant supplemental information."
Comparators	**Human:** 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. However, worker surveillance studies are considered to meet PECO criteria even if no referent group is presented. Case reports describing findings in 1- 3 people in non-occupational or occupational settings will be tagged 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).
PK/PBPK models	Studies describing pharmacokinetic (PK) or physiologically based pharmacokinetic (PBPK) models for any form of vanadium will be included. **Classical Pharmacokinetic (PK) or Dosimetry Model Studies:** Classical PK or dosimetry modeling usually divides the body into just one or two compartments, which are not specified by physiology, where movement of a chemical into, between, and out of the compartments is quantified empirically by fitting model parameters to ADME data. This category is for papers that provide detailed descriptions of PK models, that are not a PBPK model. Note: ADME studies often report classical PK parameters, such as bioavailability (fraction of an oral dose absorbed), volume of distribution, clearance rate, and/or half-life or half-lives. If a paper only provides such results in tables with minimal description of the underlying model or software (i.e., uses standard PK software without elaboration), including "non-compartmental analysis," it should only be listed as a supplemental material ADME study. **Physiologically-based Pharmacokinetic (PBPK) or Mechanistic Dosimetry Model Studies:** PBPK models represent the body as various compartments (e.g., liver, lung, slowly perfused tissue, richly perfused tissue) in order to quantify the movement of chemicals or particles into and out of the body (compartments) by defined routes of exposure, metabolism and elimination, and thereby estimate concentrations in blood or target tissues.

In addition to the PECO criteria, studies containing supplemental material that are also potentially relevant to the specific aims will be tracked during the literature screening process. Table 7 presents major categories of supplemental material. The criteria are utilized to tag studies during screening and to prioritize studies for consideration in the assessment based on likelihood to impact assessment conclusions.

It is important to emphasize that being tagged as supplemental material does not mean the study is excluded from consideration in the assessment. The initial screening level distinctions between a study meeting the PECO criteria and a supplemental study are often made for practical reasons and the tagging structure in Table 7 is designed to ensure the supplemental studies are categorized for easy retrieval during the course of developing the assessment. Studies that meet the PECO criteria are those that are most likely to be used to derive toxicity values and will thus undergo individual level study evaluation and data extraction, as described in the protocol. For evidence-rich topics this is most likely to be animal and epidemiological evidence. For most IRIS assessments, identifying all available pharmacokinetic models is also considered critical and thus those are generally included in the PECO criteria. In contrast, the impact on the assessment conclusions of individual studies tagged as supporting material is often difficult to assess during the screening phase of the assessment. Studies tagged as supplemental may (1) become critical to the interpretation of other evidence at the level of needing individual level study evaluation (e.g., genotoxicity studies when conducting a cancer MOA analysis is needed); (2) may be a single study that contributes to a well-accepted scientific conclusion and does not need to be evaluated and summarized at the individual study level (e.g., dioxin as an aromatic hydrocarbon receptor (AhR) agonist); (3) provide key references for preparing certain sections in an IRIS assessment (e.g., background information on sources, production, or use; overview of toxicokinetics); or (4) provide context for the decision to conduct the assessment or for the assessment conclusions (e.g., information on pathways and levels of exposure).

Table 7. Major categories of "Potentially Relevant Supplemental Material"

Category	Evidence
Mechanistic studies	Studies reporting measurements related to a health outcome that inform the biological or chemical events associated with phenotypic effects, in both mammalian and non-mammalian model systems, including in vitro, in vivo (by various routes of exposure), ex vivo, and in silico studies.
Non-mammalian model systems	Studies in non-mammalian model systems, e.g., fish, birds, *C. elegans*.
Non-oral route of administration	Studies in which humans or animals (whole organism) were exposed via a non-oral route (e.g., inhalation, injection, dermal exposure).

Category	Evidence
ADME and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion, including toxicokinetic studies. These are primarily controlled experiments, where defined exposures usually occur by intravenous, oral, inhalation, or dermal routes, and the concentration of particles, a chemical, or its metabolites in blood or serum, other body tissues, or excreta are then measured. Such information may be helpful in deriving chemical-specific factors for animal-to-human extrapolation and for updating or revising the parameters used in existing PBPK models. *Studies describing environmental fate and transport or metabolism in bacteria or model systems not applicable to humans or animals should not be tagged.
Exposure characteristics (no health outcome assessment)	Exposure characteristic studies include data that are unrelated to toxicological endpoints, but which provide information on exposure sources or measurement properties of the environmental agent (e.g., demonstrate a biomarker of exposure).
Mixture studies	Mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest.
Case reports	Case reports describing health outcomes after exposure will be tracked as potentially relevant supplemental information when the number of subjects is ≤3.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts/abstract only	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Organic anthropogenic vanadium compounds, nanomaterials, and alloys	Studies of organic anthropogenic vanadium compounds, nanomaterials, and alloys that otherwise meet PECO criteria. These studies were tracked through full text screening for evidence mapping purposes, but a full systematic review will not be performed for these compounds and they will not be considered for reference value derivation.

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APPENDIX A. SURVEY OF EXISTING VANADIUM TOXICITY VALUES

Table A-1 lists websites which were searched for relevant human health reference values for vanadium and compounds, along with indications of the results of the search. In addition to these sources, the ToxVal database on the Chemicals Dashboard (https://comptox.epa.gov/dashboard/chemical_lists/TOXVAL_V5) was also searched for both reference values and potential points of departure (PODs) for development of values. When values were identified for vanadium, they are shown in Figure 2 and described in Table 2 if details were provided on how the values were derived. When values were identified from sources that did not provide derivation details, they are described in Table 3. The values in these tables are current as of May 2020.

Table A-1. Sources searched for human health reference values for vanadium

Source[a]	Search results	Query and/or link
ATSDR	See Table 2	http://www.atsdr.cdc.gov/toxprofiles/index.asp
		https://www.atsdr.cdc.gov/mrls/mrllist.asp
CalEPA	No values found	http://www.oehha.ca.gov/tcdb/index.asp
		https://www.arb.ca.gov/toxics/healthval/healthval.htm
DWSHA	No values found	https://www.epa.gov/sites/production/files/2018-03/documents/dwtable2018.pdf
Health Canada	No values found	https://www.canada.ca/en/services/health/publications/healthy-living.html
		http://publications.gc.ca/site/archivee-archived.html?url=http://publications.gc.ca/collections/collection_2012/sc-hc/H128-1-11-638-eng.pdf
		http://publications.gc.ca/site/archivee-archived.html?url=http://publications.gc.ca/collections/Collection/H46-2-96-194E.pdf
HEAST	See Table 2	http://epa-heast.ornl.gov/heast.php
		https://nepis.epa.gov/Exe/ZyPDF.cgi/2000O0GZ.PDF?Dockey=2000O0GZ.PDF
IRIS	See Table 2	http://www.epa.gov/iris/
ITER	2 records found; no unique values	https://toxnet.nlm.nih.gov/newtoxnet/iter.htm

Source[a]	Search results	Query and/or link
MI EGLE	PPRTV value was adopted as state value (see Table 2)	https://www.michigan.gov/documents/deq/deq-rrd-chem-CleanupCriteriaTSD_527410_7.pdf
MDH	No values found	https://www.health.state.mn.us/communities/environment/risk/guidance/gw/table.html
NHMRC	No values found	https://www.nhmrc.gov.au/about-us/publications/australian-drinking-water-guidelines
NY DEC	No values found	https://www.dec.ny.gov/docs/remediation_hudson_pdf/techsuppdoc.pdf
OPP	No search results found	https://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1
PPRTV	See Table 2	https://www.epa.gov/pprtv/provisional-peer-reviewed-toxicity-values-pprtvs-assessments
RIVM	See Table 2	https://www.rivm.nl/bibliotheek/rapporten/711701092.pdf
	No values found	https://www.rivm.nl/bibliotheek/rapporten/711701025.pdf
TCEQ	See Table 3	https://www.tceq.texas.gov/remediation/trrp/trrppcls.html
WHO	Environmental Health Criteria document available; no reference values found	http://www.who.int/ipcs/publications/ehc/en/

[a]ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IRIS = Integrated Risk Information System; ITER = International Toxicity Estimates for Risk; MDH = Minnesota Department of Health; MI EGLE = Michigan Department of Environment, Great Lakes & Energy; NHMRC = National Health and Medical Research Council; NY DEC = New York State Department of Environmental Conservation; OPP = Office of Pesticide Programs; PPRTV = Provisional Peer-Reviewed Toxicity Values; RIVM = *Rijksinstituut voor Volksgezondheid en Milieu,* The Netherlands Institute for Public Health and the Environment; TCEQ = Texas Commission on Environmental Quality; WHO = World Health Organization.

APPENDIX B. LITERATURE SEARCH STRATEGIES

Table B-1. Literature search strategies for vanadium compounds

Source	Search strategy	Number of records
ATSDR Toxicological Profile for Vanadium (2012)	References pulled from ATSDR document	363
WOS 3/28/2019 3/9/2020	((TS="Ammonium metavanadate" OR TS="Ammonium monovanadate" OR TS="Ammonium trioxovanadate" OR TS="Monosodium trioxovanadate" OR TS="Oxosulfatovanadium pentahydrate" OR TS="Sodium metavanadate" OR TS="Sodium o-vanadate" OR TS="Sodium orthovanadate" OR TS="Sodium pervanadate" OR TS="Sodium tetraoxovanadate" OR TS="Sodium trioxovanadate" OR TS="Sodium vanadate" OR TS="Trisodium orthovanadate" OR TS="Trisodium tetraoxovanadate" OR TS="Trisodium vanadate" OR TS="Vanadic sulfate" OR TS="vanadium" OR TS="Vanadyl sulfate" OR TS="Vanadic" OR TS="Vanadin" OR TS="sodium peroxyvanadate" OR TS="Vanadyl sulfate pentahydrate" OR TS="Ammonium vanadate" OR TS="Divanadium trioxide" OR TS="Sodium hexavanadate") AND PY=(2010-2019)) ((TS="Sodium tetravanadate" OR TS="Sodium vanadite" OR TS="Sulfovanadic acid" OR TS="vanadium salt" OR TS="Tetrachlorovanadium" OR TS="Trichlorooxo vanadium" OR TS="Trichlorooxovanadium" OR TS="Trichlorooxovanadium oxide" OR TS="Vanadic acid" OR TS="Vanadic oxide" OR TS="Vanadious" OR TS="Vanadosulfuric acid" OR TS="Vanadyl chloride" OR TS="Vanadyl trichloride" OR TS="Divanadium pentaoxide" OR TS="Divanadium pentoxide" OR TS="Vanadic acid anhydride" OR TS="Vanadic anhydride" OR TS="Vanadin(V) oxide" OR TS="Vanadium dust" OR TS="Vanadium fume" OR TS="Vanadium oxide" OR TS="Vanadium pentaoxide" OR TS="Vanadium pentoxide") AND PY=(2010-2019)) ((TS="Vanadium" AND (TS="chloride" OR TS="dichloride" OR TS="oxide" OR TS="oxychloride" OR TS="oxytrichloride" OR TS="sesquioxide" OR TS="sulfate" OR TS="sulphate" OR TS="tetrachloride" OR TS="trichloride" OR TS="trioxide")) AND PY=2010-2019)	24,878
PUBMED 3/28/2019 3/9/2020	(((7440-62-2[rn] OR 00J9J9XKDE[rn] OR 27774-13-6[rn] OR 6DU9Y533FA[rn] OR 13718-26-8[rn] OR 13721-39-6[rn] OR 7803-55-6[rn] OR FL85PX638G[rn] OR 12439-96-2[rn] OR "Ammonium metavanadate"[tw] OR "Ammonium monovanadate"[tw] OR "Ammonium trioxovanadate"[tw] OR "Monosodium trioxovanadate"[tw] OR "Oxosulfatovanadium pentahydrate"[tw] OR "Sodium metavanadate"[tw] OR "Sodium o-vanadate"[tw] OR "Sodium orthovanadate"[tw] OR "Sodium pervanadate"[tw] OR "Sodium tetraoxovanadate"[tw] OR "Sodium trioxovanadate"[tw] OR "Sodium	4,888

Source	Search strategy	Number of records
	vanadate"[tw] OR "Trisodium orthovanadate"[tw] OR "Trisodium tetraoxovanadate"[tw] OR "Trisodium vanadate"[tw] OR "Vanadic sulfate"[tw] OR vanadium[tw] OR "Vanadyl sulfate"[tw] OR Vanadic[tw] OR Vanadin[tw] OR "sodium peroxyvanadate"[tw] OR "Vanadyl sulfate pentahydrate"[tw] OR 16785-81-2[rn] OR 12436-28-1[rn] OR 12058-74-1[rn] OR 64082-34-4[rn] OR 10580-52-6[rn] OR 7718-98-1[rn] OR 1314-34-7[rn] OR 7632-51-1[rn] OR 11115-67-6[rn] OR 7727-18-6[rn] OR "Ammonium vanadate"[tw] OR "Divanadium trioxide"[tw] OR "Sodium hexavanadate"[tw] OR "Sodium tetravanadate"[tw] OR "Sodium vanadite"[tw] OR "Sulfovanadic acid"[tw] OR "vanadium salt"[tw] OR Tetrachlorovanadium[tw] OR "Trichlorooxo vanadium"[tw] OR Trichlorooxovanadium[tw] OR "Trichlorooxovanadium oxide"[tw] OR "Vanadic acid"[tw] OR "Vanadic oxide"[tw] OR Vanadious[tw] OR "Vanadosulfuric acid"[tw] OR "Vanadyl chloride"[tw] OR "Vanadyl trichloride"[tw] OR 1314-62-1[rn] OR "Divanadium pentaoxide"[tw] OR "Divanadium pentoxide"[tw] OR "Vanadic acid anhydride"[tw] OR "Vanadic anhydride"[tw] OR "Vanadin(V) oxide"[tw] OR "Vanadium dust"[tw] OR "Vanadium fume"[tw] OR "Vanadium oxide"[tw] OR "Vanadium pentaoxide"[tw] OR "Vanadium pentoxide"[tw]) OR (Vanadium[tw] AND (chloride[tw] OR dichloride[tw] OR oxide[tw] OR oxychloride[tw] OR oxytrichloride[tw] OR sesquioxide[tw] OR sulfate[tw] OR sulphate[tw] OR tetrachloride[tw] OR trichloride[tw] OR trioxide[tw]))) AND ("2010"[PDAT] : "3000"[PDAT]))	
TOXLINE 3/28/2019	@SYN0+@AND+@OR+(@TERM+@rn+7440-62-2+@TERM+@rn+27774-13-6+@TERM+@rn+13718-26-8+@TERM+@rn+13721-39-6+@TERM+@rn+7803-55-6+@TERM+@rn+12439-96-2+@TERM+@rn+16785-81-2+@TERM+@rn+12436-28-1+@TERM+@rn+12058-74-1+@TERM+@rn+64082-34-4+@TERM+@rn+10580-52-6+@TERM+@rn+7718-98-1+@TERM+@rn+1314-34-7+@TERM+@rn+7632-51-1+@TERM+@rn+11115-67-6+@TERM+@rn+7727-18-6+@TERM+@rn+1314-62-1)+@RANGE+yr+2010+2019+@NOT+@org+pubmed+pubdart+nih @SYN0+@AND+@OR+(FL85PX638G+6DU9Y533FA+00J9J9XKDE+"Ammonium+metavanadate"+"Ammonium+monovanadate"+"Ammonium+trioxovanadate"+"Monosodium+trioxovanadate"+"Oxosulfatovanadium+pentahydrate"+"Sodium+metavanadate"+"Sodium+o-vanadate"+"Sodium+orthovanadate"+"Sodium+pervanadate"+"Sodium+tetraoxovanadate"+"Sodium+trioxovanadate"+"Sodium+vanadate"+"Trisodium+orthovanadate"+"Trisodium+tetraoxovanadate"+"Trisodium+vanadate"+"Vanadic+sulfate"+vanadium+"Vanadyl+sulfate"+Vanadic+Vanadin+"sodium+peroxyvanadate"+"Vanadyl+sulfate+pentahydrate"+"Ammonium+vanadate"+"Divanadium+trioxide"+"Sodium+hexavanadate"+"Sodium+tetravanadate"+"Sodium+vanadite"+"Sulfovanadic+acid"+"vanadium+salt"+"Trichlorooxo+vanadium"+Tetrachlorovanadium+Trichlorooxovanadium+"Trichlorooxovanadium+oxide"+"Vanadic+acid"+"Vanadium+dust"+"Vanadium+fume"+"Vanadium+oxide"+"Vanadium+pentaoxide"+"Vanadium+pentoxide"+"Vanadic+oxide"+Vanadious+"Vanadosulfuric+acid"+"Vanadyl+chloride"+"Vanadyl+trichloride"+"Divanadium+pentaoxide"+"Divanadium+pentoxide"+"Vanadic+acid+an	15

Source	Search strategy	Number of records
	hydride"+"Vanadic+anhydride"+"Vanadin+V+oxide")+@RANGE+yr+2010+2019+@NOT+@org+pubmed+pubdart+nih @SYN0+@AND+vanadium+@OR+(chloride+dichloride+oxide+oxychloride+oxytrichloride+sesquioxide+sulfate+sulphate+tetrachloride+trichloride+trioxide)+@RANGE+yr+2010+2019+@NOT+@org+pubmed+pubdart+nih	
TOTAL	25,988 unique items were discovered using this search strategy.	25,988

APPENDIX C. LITERATURE SEARCH AND SCREENING METHODS

All references were pulled from the 2012 ATSDR Toxicological Profile for Vanadium, and database searches were conducted to identify records that had been published since the release of the ATSDR document. The databases listed below were searched for records published between 2010–2020. 2010 was selected as the start date as a precaution to capture records published near the last literature search date for the citations in the ATSDR document.

- PubMed (National Library of Medicine)
- Web of Science (Thomson Reuters)
- ToxLine (National Library of Medicine)

The literature search was conducted by an EPA information specialist on March 28, 2019, and an update to the database searches was performed on March 9, 2020. All records were stored in the HERO database. Because the number of records retrieved was large, records were imported into SWIFT Review software (https://www.sciome.com/swift-review/; see also (Howard et al., 2016)) to identify those most likely applicable to human health. In brief, SWIFT Review has pre-set literature search filters that were developed by information specialists that can be applied to separate studies that may present a health outcome from those that likely do not (e.g., exposure only, analytical methods). The filters function like a typical search strategy, where studies are tagged as belonging to a certain category based on terms appearing in title, abstract, keyword or medical subject headings (MeSH) fields content. The records identified in the literature search for vanadium were filtered using tags in SWIFT Review for lines of evidence (human, animal, in vitro). The details of the search strategies that underlie the filters are available at https://hawcprd.epa.gov/media/attachment/SWIFT-Review_Search_Strategies.pdf. Studies not retrieved using these filters were not considered further. Studies that included one or more of the search terms in the title, abstract, keyword, or MeSH fields were exported as a RIS file for screening in DistillerSR as described below.

The subset of studies identified using the SWIFT Review filters was imported into DistillerSR for title/abstract and full-text screening. Four additional records that appeared to meet PECO criteria were identified through curation of references cited in the review article by Bishayee et al. (2010); these additional records were also uploaded into DistillerSR, annotated with respect to source of the record, and screened using the same methods described below. Both title/abstract and full-text screening were conducted by two independent reviewers. Records that met PECO

criteria (Table 6) during title and abstract screening were considered for full-text screening. At both the DistillerSR title/abstract and full-text review levels, screening conflicts were resolved by discussion between the primary screeners with consultation by a third reviewer (if needed) to resolve any remaining disagreements. For citations with no abstract, the articles were initially screened based on all or some of the following: title relevance (title should indicate clear relevance), and page numbers (articles two pages in length or less were assumed to be conference reports, editorials, or letters). During title/abstract or full-text level screening in DistillerSR, studies that did not meet the PECO criteria, but which could provide supporting information were categorized (or "tagged") as supplemental information according to the categories listed in Table 7.

APPENDIX D. PRELIMINARY LITERATURE SURVEY SUMMARY

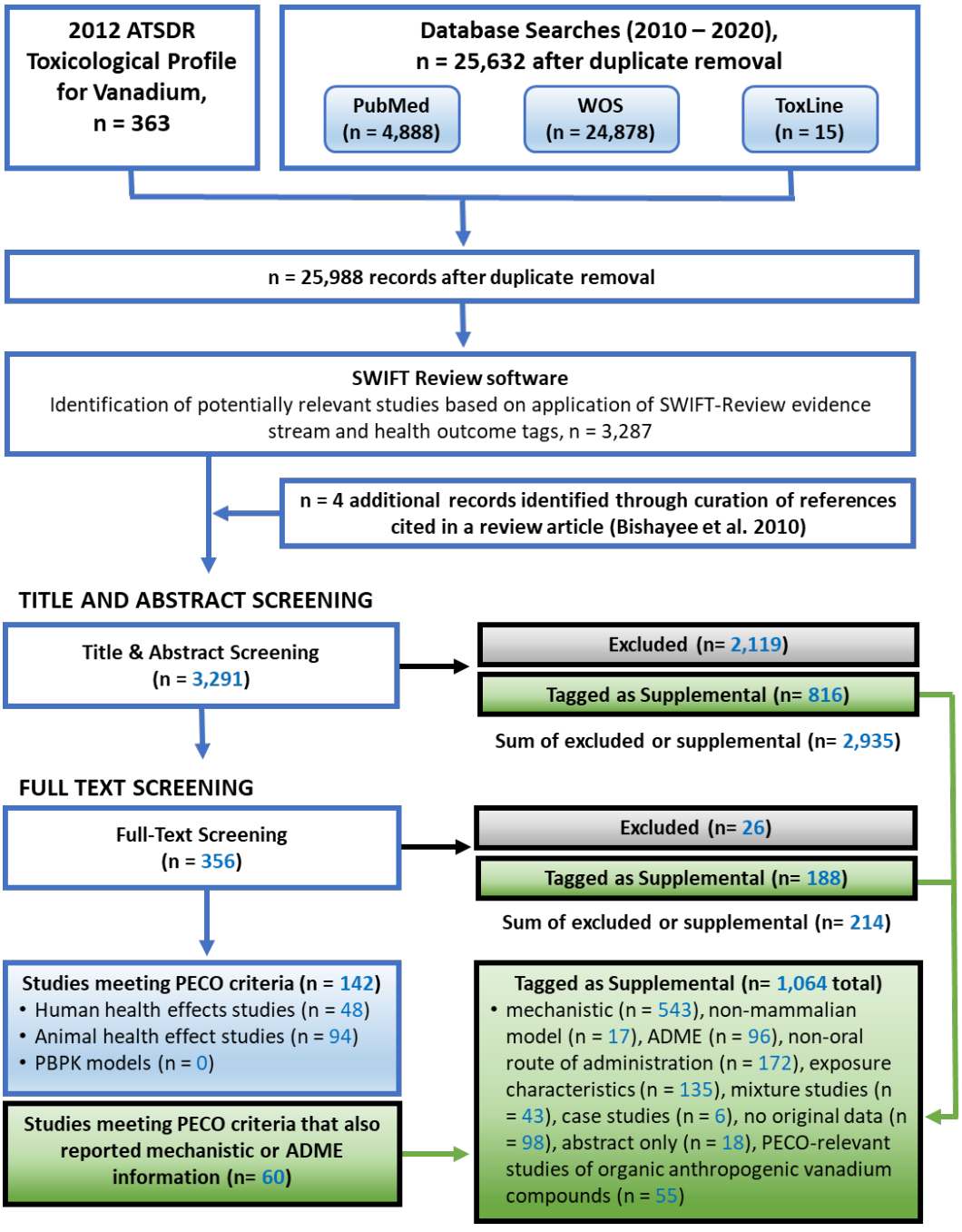

Figure D-1. Literature survey study flow selection diagram. Click here to view interactive visualization of results of the title/abstract and full text screening.