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

May 2021

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

ADME	absorption, distribution, metabolism, and excretion
ATSDR	Agency for Toxic Substances and Disease Registry
CPAD	Chemical and Pollutant Assessment Division
CPHEA	Center for Public Health and Environmental Assessment
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
MeSH	Medical Subject Headings
MOA	mode of action
NTP	National Toxicology Program
OAR	Office of Air and Radiation
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PECO	populations, exposures, comparators, and outcomes
PK	pharmacokinetic
POD	point of departure
RfC	reference concentration
RfD	reference dose

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1. INTRODUCTION

The Integrated Risk Information System (IRIS) Program is undertaking an assessment of the health effects from inhalation exposure to vanadium and compounds. The IRIS Program announced the initiation of this assessment in December 2019. An assessment of oral exposure to vanadium and compounds was identified as an Environmental Protection Agency (EPA) priority in December 2018 (https://www.epa.gov/iris/iris-program-outlook) and will be performed separately from the assessment of inhalation exposure (https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=348792).

IRIS assessments provide high quality, publicly available information on the toxicity of chemicals to which the public might be exposed. These assessments are a critical part of the scientific foundation for decisions made in EPA program and regional offices to protect public health. IRIS assessments also are 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 EPA program and regional offices 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 might 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 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 is the draft IAP for inhalation exposure to 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 identifies key areas

of scientific complexity. Brief background information on uses and potential for human exposure is provided for context.

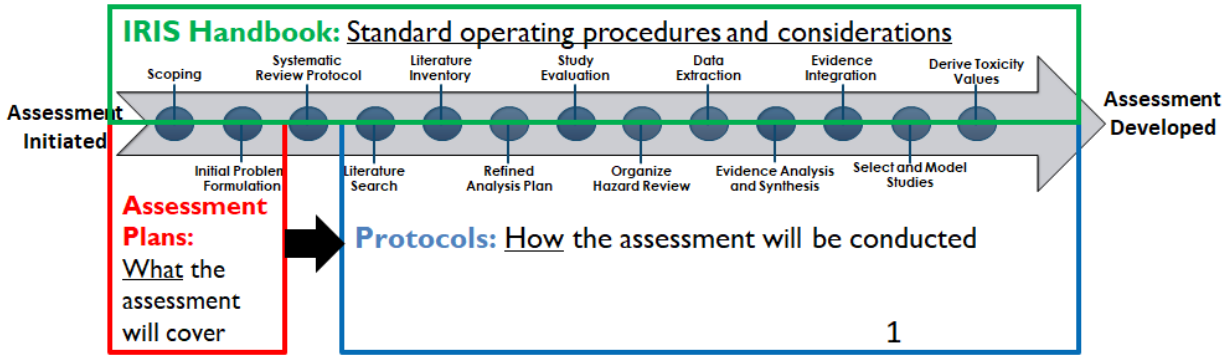


Figure 1. IRIS systematic review problem formulation and method documents.

2. SCOPING AND INITIAL PROBLEM FORMULATION

2.1. BACKGROUND

The focus of this document is on inhalation exposure to vanadium and compounds and its potential impacts on human health. Oral exposure to vanadium compounds is currently under evaluation in a separate assessment (https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=348792).

Vanadium is a transition metal that occurs naturally in Earth's crust and is a component of various minerals and most ores, tars, coal, and petroleum crude oils (WHO, 1988). Natural sources of vanadium in the air include continental dust, marine aerosol, and volcanic emissions (ATSDR, 2012). Vanadium has been reported to have natural background concentrations in the air ranging from tenths of a nanogram to a few nanograms (WHO, 2000). The use of heavy oils and bitumen from tar sands (which are richer in vanadium than conventional oil) and the use of vanadium in industrial applications (e.g., steel production, vanadium redox-flow batteries, and catalytic converters) could contribute to the release of vanadium into the environment (Schlesinger et al., 2017; ATSDR, 2012). Fossil fuel combustion is thought to be the major anthropogenic source of vanadium to the atmosphere (Schlesinger et al., 2017; ATSDR, 2012), with vanadium pentoxide found adsorbed onto particulate matter (PM) as a result (Fortoul et al., 2014). In addition, occupational exposure to vanadium occurs through the inhalation of dust generated during vanadium processing and residual oil fly ash during cleaning of oil-burning boilers and furnaces. Residual oil fly ash is a mixture of different vanadium compounds and other metals and components of PM (Hauser et al., 1995).

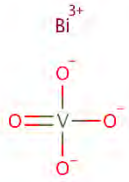
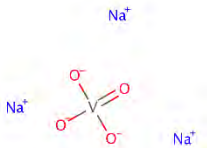
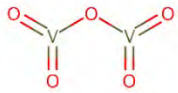
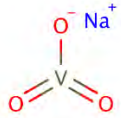
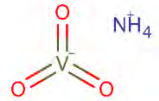
Vanadium has a complex chemistry, existing in the environment with three common oxidation states (+3, +4, +5) (Gustafsson, 2019). Among them, vanadium pentoxide (V_2O_5), a +5 vanadium species, is the most common form of vanadium used for industrial applications such as metal alloy production and catalytic processes. Evidence from one study suggests that pentavalent vanadium, in particular vanadium pentoxide, also can be among the vanadium compounds present in PM emitted from diesel engines and in PM in urban atmospheric aerosols (Shafer et al., 2012). In crude oils, vanadium is present as an organometallic complex, and upon burning in boilers or furnaces, vanadium is left behind as vanadium pentoxide in the fly ash (IPCS, 2001). Other than vanadium pentoxide, specific vanadium compounds relevant to environmental inhalation have not been well characterized.

Following inhalation, at least some vanadium appears to be absorbed in the lungs, as seen by an increase in blood and urine vanadium levels in experimentally or occupationally exposed subjects (ATSDR, 2012). Most occupational exposure studies, however, do not identify the form of

vanadium compounds to which workers were exposed. Important to note is that vanadium speciation is a complex function of factors such as pH, redox potential, and vanadium concentration, which could presumably shift upon inhalation and subsequent absorption. In the aqueous phase, vanadate species (+5) predominate under oxic conditions and high pH, while vanadyl (+4) occurs under suboxic conditions and low pH and trivalent vanadium (+3) occurs under anoxic conditions (Gustafsson, 2019; Huang et al., 2015). Factors such as pH, local availability of reducing equivalents [e.g., glutathione-sulfhydryl (SH), nicotinamide adenine dinucleotide (NADH)], and complexation with biomolecules might cause speciation of vanadium and also might cause it to undergo redox cycling in the body (NTP, 2008; Byczkowski and Kulkarni, 1996; Nielsen, 1995).

Existing human health reference values for inhalation of vanadium from federal, state, and international agencies are depicted, respectively, for vanadium pentoxide and vanadium compounds (excluding vanadium pentoxide), in Figure 2 and Figure 3 (see Table A-2 and Table A-3, for a tabular summary, including derivation details; current as of May 2020). No inhalation reference concentration (RfC) exists in IRIS. An IRIS assessment addressing inhaled vanadium pentoxide was developed (U.S. EPA, 2011) but not finalized (see: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=125). The IRIS Program published a health effects assessment of vanadium and compounds in 1987 that included a reference dose (RfD) but not an RfC. EPA's Provisional Peer-Reviewed Toxicity Values (PPRTV) program developed two assessments of vanadium and compounds: one on vanadium pentoxide alone (U.S. EPA, 2008) and one on vanadium and its soluble inorganic compounds other than vanadium pentoxide (U.S. EPA, 2009). The 2008 PPRTV assessment identified inflammation of the bronchoalveolar region (respiratory effects) as the most sensitive endpoint for inhaled vanadium pentoxide on the basis of a 16-day exposure study in female rats conducted by the National Toxicology Program (NTP, 2002); a subchronic provisional (p)-RfC of 0.0001 mg/m^3 also was derived. A chronic p-RfC of 0.000007 mg/m^3 or 7E−06 mg/m^3 was derived on the basis of nonneoplastic lesions of the respiratory tract in female rats from the 2002 NTP 2-year vanadium pentoxide exposure study (U.S. EPA, 2008). The 2008 PPRTV assessment of vanadium pentoxide (U.S. EPA, 2008) also concluded that the available evidence for vanadium pentoxide inhalation exposure is *suggestive of carcinogenic potential* under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) and derived an inhalation unit risk of 8.3 $(mg/m^3)^{-1}$ on the basis of the dose-response relationship for alveolar/bronchiolar neoplasms (adenoma and carcinoma) in mice in the 2-year NTP carcinogenicity study (NTP, 2002). The evidence for the mode of action (MOA) for vanadium pentoxide tumorigenicity is insufficient, but data provide some support for a mutagenic MOA and an MOA dependent on cellular cytotoxicity and reparative regeneration (U.S. EPA, 2008). The 2009 PPRTV assessment (U.S. EPA, 2009) found no human or animal inhalation studies were available to derive subchronic and chronic p-RfCs or evaluate potential carcinogenicity for soluble inorganic vanadium compounds other than vanadium pentoxide.

Table 1. Chemical identity and physiochemical properties of vanadium compounds potentially relevant to inhalation exposure

Name	Elemental vanadium	Bismuth orthovanadate	Sodium orthovanadate	Vanadium pentoxide	Sodium metavanadate	Ammonium metavanadate	Vanadium dioxide[a]
CASRN	7440-62-2	14059-33-7	13721-39-6	1314-62-1	13718-26-8	7803-55-6	12036-21-4
DTXSID[b]	2040282	20893971	2037269	2023806	3044336	1052533	5065194
Structure	V						
Oxidation state	0	+5	+5	+5	+5	+5	+4
Molecular weight (g/mol)	50.942	323.918	183.907	181.878	121.928	116.978	82.94
Molecular formula	V	BiO_4V	Na_3VO_4	V_2O_5	$NaVO_3$	NH_4VO_3	VO_2
Selected Synonym(s)	Vanadium	Bismuth vanadate(V) ($BiVO_4$); bismuth($^{3+}$) tetraoxidovana-date($^{3-}$); bismuth vanadium oxide; vanadic acid; bismuth vanadate ($BiVO_4$); bismuth vanadate yellow; C.I. Pigment Yellow 184; Hostaperm Oxide	Trisodium tetraoxidovana-date($^{3-}$); 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	Sodium vanadate; sodium trioxidovanadate($^{1-}$); sodium vanadium oxide; sodium vanadium trioxide; vanadic acid, monosodium salt; sodium vanadate(V)	Ammonium trioxovanadate($^{1-}$); ammonium trisoxidovanadate($^{1-}$); ammonium monovanadate; ammonium vanadate(V); vanadic acid, ammonium salt; ammonium vanadium oxide; ammonium vanadium trioxide	Bisoxidovanadium; dioxido de vanadio; dioxyde de vanadium; divanadium tetraoxide; divanadium tetroxide; vanadium (IV) oxide; vanadium dioxide; vanadium(IV) oxide

Name	Elemental vanadium	Bismuth orthovanadate	Sodium orthovanadate	Vanadium pentoxide	Sodium metavanadate	Ammonium metavanadate	Vanadium dioxide[a]
		Yellow BV 01; Irgacolor Yellow 2GTM					
Water solubility (mol/L)[b]	–	–	–	–	–	–	1.94×10^2
Melting Point (°C)[c,d]	1.90×10^3	500[c]	858	690	630	–	243
Boiling Point (°C)[c]	3.00×10^3	–	–	1.75×10^3	–	–	564
Vapor Pressure (mmHg)[c]	–	–	–	–	–	–	–

[a]For vanadium dioxide, the values are predicted values from EPA's CompTox Chemicals Dashboard.
[b]DTXSIDs are unique substance identifiers used for curation by the EPA's Distributed Structure-Searchable Toxicity (DSSTox) project.
[c]Experimental average values for physiochemical properties are shown here. Median values and ranges for physiochemical properties are also provided on EPA's CompTox Chemicals Dashboard at https://comptox.epa.gov/dashboard/. If no experimental values were available on EPA's CompTox Chemicals Dashboard, "–" is shown.
[d]Melting point data available from this site: https://www.chemicalbook.com/ChemicalProductProperty_EN_CB2331380.htm.

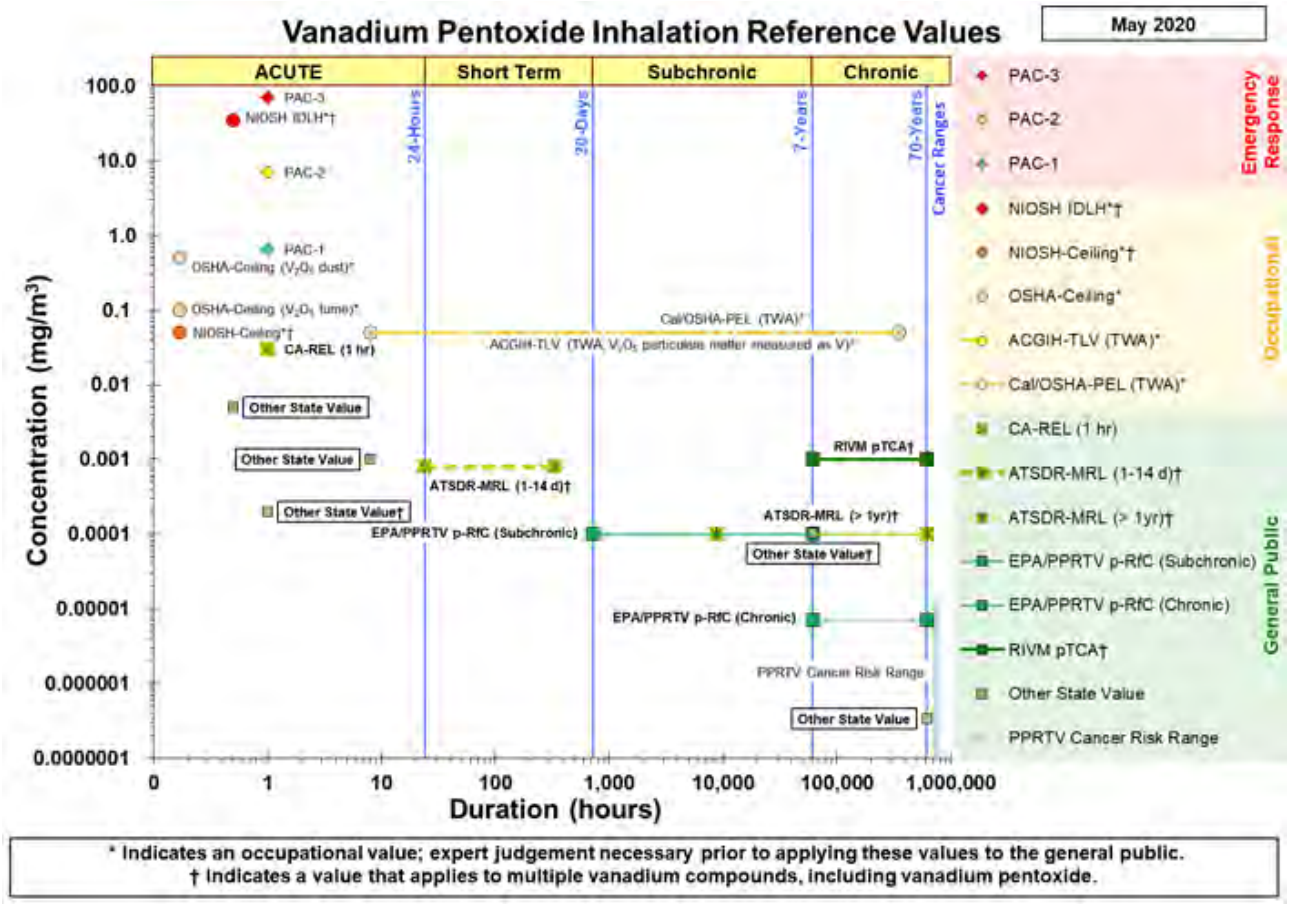


Figure 2. Available health effect reference values for inhalation exposure to vanadium pentoxide.

This includes values applying to vanadium pentoxide; for details, see Table A-2 and Table A-3.
Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CA-REL = California reference exposure level; EPA = Environmental Protection Agency; IDLH = immediately dangerous to life or health; MRL = minimal risk level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure level; PPRTV = Provisional Peer-Reviewed Toxicity Value; pTCA = provisional tolerable concentration; REL = recommended exposure limit; p-RfC = provisional reference concentration; RIVM =

; TLV = threshold limit value; V_2O_5 = vanadium pentoxide.

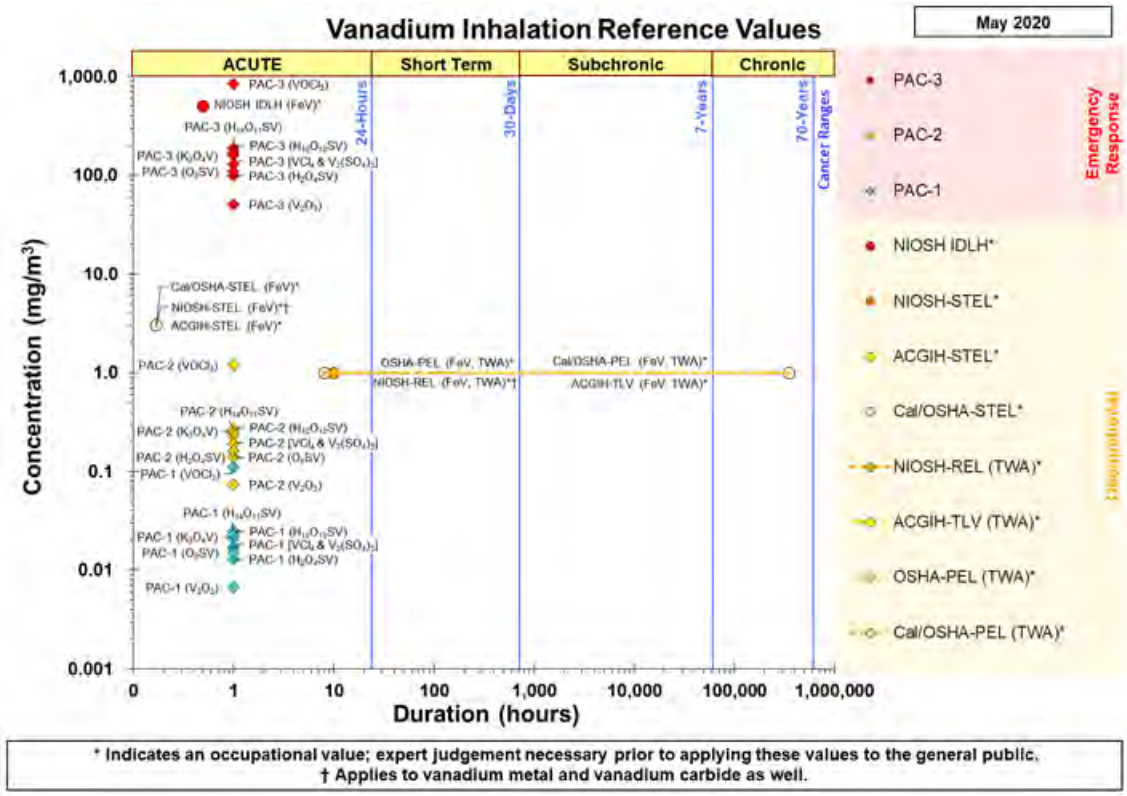


Figure 3. Available health effect reference values for inhalation exposure to vanadium compounds, excluding vanadium pentoxide.

This includes values applying to vanadium compounds excluding vanadium pentoxide; for details, see Table A-2 and Table A-3.

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; Cal/OSHA = California Division of Occupational Safety and Health ; FeV = ferrovanadium; H_2O_4SV = vanadium sulfate; $H_{14}O_{11}SV$ = vanadium (II) sulfate heptahydrate; $H_{10}O_{10}SV$ = vanadyl sulfate pentahydrate; IDLH = immediately dangerous to life or health; K_3O_4V = potassium orthovanadate; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; O_5SV = vanadyl sulfate; PAC = Protective Action Criteria; PEL = permissible exposure level; REL = recommended exposure limit; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average; VCl_4 = vanadium tetrachloride; V_2O_3 = vanadium trioxide; $VOCl_3$ = trichlorooxovanadium; $V_2(SO_4)_3$ = vanadium (III) sulfate.

2.2. SCOPING SUMMARY

During scoping, the IRIS Program met with EPA program and regional offices that had interest in an IRIS assessment for inhalation exposure to vanadium and compounds to discuss specific assessment needs. Table 2 summarizes input from this outreach. EPA's Office of Transportation and Air Quality within the Office of Air and Radiation (OAR) nominated vanadium compounds (including vanadium pentoxide) for an inhalation exposure assessment under the IRIS Program. Vanadium has been used as a metal catalyst to control emissions from diesel engines employed in mobile sources such as on-highway heavy-duty trucks, nonroad equipment, or marine vessels. Under certain conditions, the use of vanadium in diesel engine emission control devices can result in the potential for exposures to vanadium compounds, such as vanadium pentoxide. A vanadium (inhalation) assessment could therefore help inform decisions about potential health risks from the use of vanadium in these emission control devices.

Table 2. EPA program and regional office interest in the assessment of inhalation exposure to vanadium and compounds

EPA program or regional office	Oral	Inhalation	Statute/Regulation	Anticipated uses/Interest
Office of Air and Radiation		✓	Clean Air Act	Vanadium and compounds are mobile source air toxics. Toxicological information developed for this assessment may be used to inform risk management decisions.

2.3. INITIAL 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 review of health effects of vanadium and compounds published by a U.S. federal agency. Database searches were initially conducted on March 28, 2019, by an EPA information specialist using three online databases (PubMed, Web of Science, Toxline)[1] and then repeated on March 9, 2020, to identify records that had been published since the release of the 2012 ATSDR *Toxicological Profile for Vanadium*. The start date for the literature search was selected as 2010 to ensure records published near the last literature search date for the citations in the ATSDR document were

[1]The Toxline database was migrated to PubMed prior to the March 2020 literature search update, so the Toxline search was conducted only in March 2019.

captured.[2] This literature search strategy is designed to be broad, but like any search strategy, studies might 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 the title, abstract, or keyword content; or "gray" literature 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 other assessments, these references were annotated with the source of the record and screened using the same methods applied to the rest of the literature inventory. The IRIS Program also encourages the public to identify any additional missing studies. References should be submitted to the docket in the form of a public comment. For more information, visit regulations.gov or the IRIS website (https://www.epa.gov/iris). All references from the 2012 ATSDR *Toxicological Profile for Vanadium*, literature searches, and other relevant assessments 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).[3] Draft PECO criteria (see Table 5) were used to guide screening to identify relevant literature.

Studies that met PECO criteria were summarized briefly using DistillerSR,[4] and studies that 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, short term, subchronic, chronic, reproductive, developmental), duration and timing 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 (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) and characteristics (e.g., sex ratios) with a short free text description of study population; study type (e.g., controlled trial, cross-sectional, cohort, case-control); major route of exposure (if known) and a description of how exposure was assessed; health system and specific outcome(s) 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). These study summaries are referred to as preliminary literature surveys and are presented using Tableau visualization software (https://www.tableau.com/) in this IAP.

[2]Personal correspondence with ATSDR indicated the final literature update for the 2012 *Toxicological Profile for Vanadium* was conducted in August 2011.
[3]EPA's HERO database provides access to the scientific literature behind EPA science assessments. The database includes scientific references and data from the peer-reviewed literature used by EPA to develop its health assessment documents.
[4]DistillerSR is a web-based systematic review software used to screen studies available at https://www.evidencepartners.com/products/distillersr-systematic-review-software.

These methods were implemented in accordance with EPA Quality Assurance policies and procedures [Quality Policy Procedures[5] and CIO 2105.0 (formerly 5360.1 A2)[6]]. Detailed literature search strategies (Appendix B), literature search and screening methods (Appendix C), and a literature survey study flow 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.

2.3.1. PRELIMINARY LITERATURE SURVEY RESULTS

The preliminary literature search and screening process identified 97 studies that met PECO criteria (n = 67 human studies, n = 30 animal studies), and a total of 1,249 studies were tagged as potentially relevant supplemental material. No physiologically-based pharmacokinetic (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 4 with a more detailed summary provided in Figure 5. The literature search identified 67 human studies including 2 case reports/case series, 15 case-control studies, 23 cohort studies, 1 controlled trial study, 23 cross-sectional studies, and 3 ecological studies. Among the cohort studies, four studies involve pregnant women (Figure 4).

The populations evaluated in the available human studies were general population, occupational, children, infants, and pregnant women. The predominant health outcomes investigated included respiratory, cardiovascular, nervous system, and immune system effects. Fewer studies evaluated developmental, dermal, hematological, hepatic, reproductive, renal, and endocrine endpoints. Six human studies evaluated cancer, including a cohort study and five case-control studies.

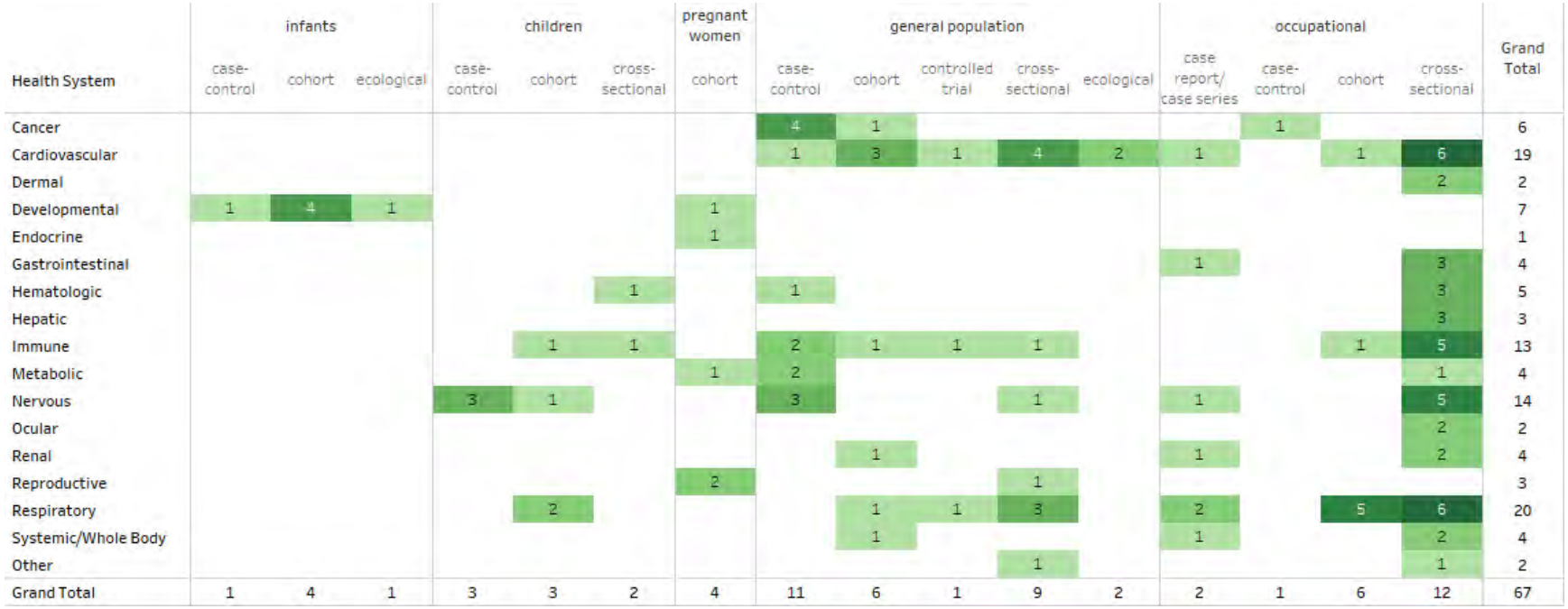
Regarding exposure classification, the epidemiological literature includes several studies with exposure to vanadium pentoxide or vanadium (form unknown) measured in the air or in workers with occupational exposure as boilermakers or in vanadium-containing steel production facilities (Figure 5). Seven studies reported air levels of vanadium pentoxide and 20 studies reported vanadium (form unknown) as vanadium dust (2 studies) or as part of PM (12 studies). In the occupational exposure category, seven studies reported on vanadium pentoxide while nine studies involved exposure to vanadium (unknown form).

In addition, the literature search identified 40 observational epidemiological studies, which evaluated the association of health outcomes with total vanadium from biomonitoring, in which the route of exposure and specific vanadium form were unknown. This included 35 studies (15 case-

[5]U.S. Environmental Protection Agency Environmental Information Quality Procedures (CIO 2105-P-01.1) : https://www.epa.gov/sites/production/files/2021-04/documents/environmental_information_quality_procedure.pdf.

[6]U.S. Environmental Protection Agency Environmental Information Quality Policy (CIO2105.1): https://www.epa.gov/sites/production/files/2021-04/documents/environmental_information_quality_policy.pdf.

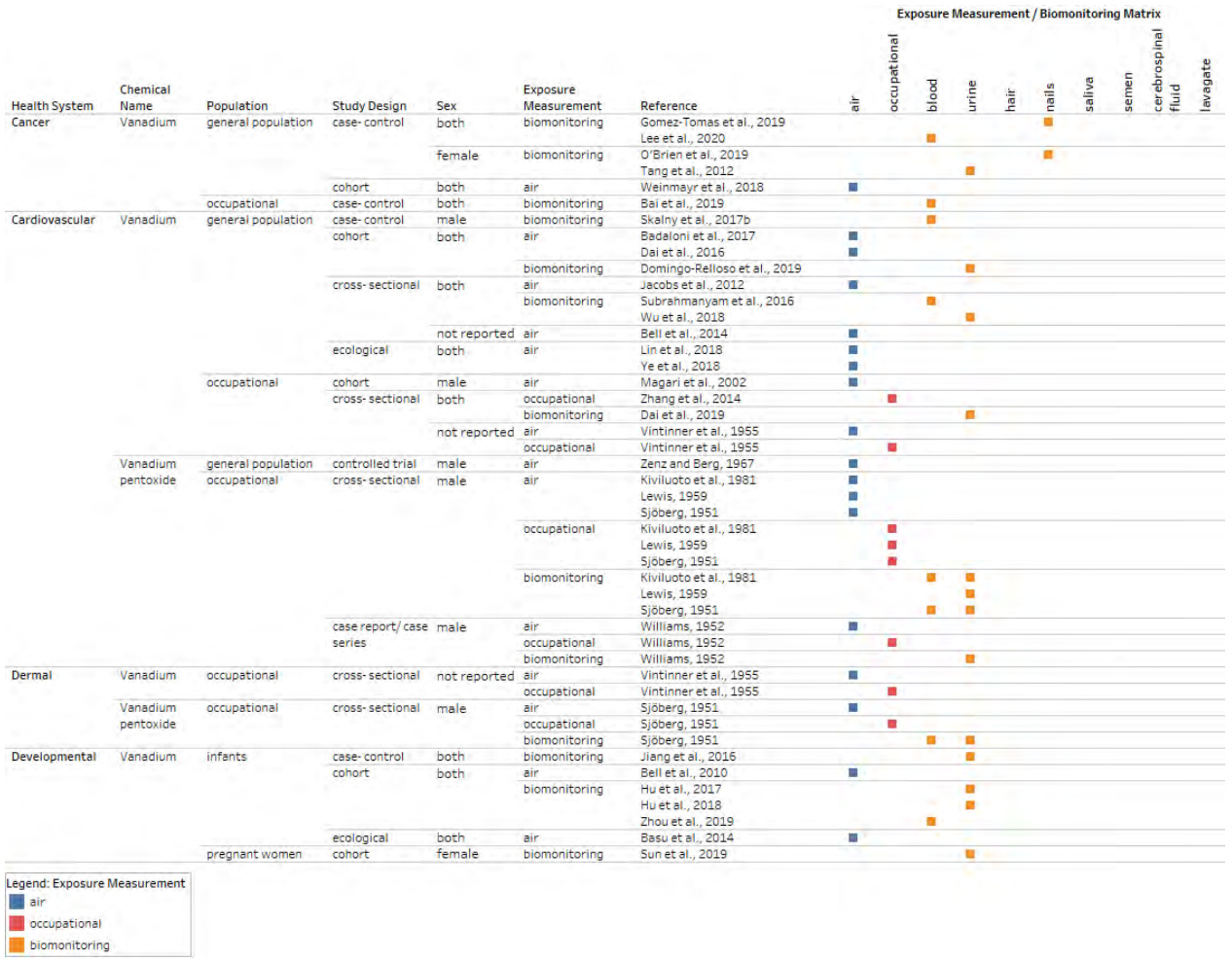
control, 9 cross-sectional, and 11 cohort) in which vanadium exposure was evaluated using biomonitoring of blood, urine, hair, semen, cerebrospinal fluid, saliva, nasal lavagate (lavage) or nails. Overall, of the 67 human studies identified, 9 reported presumed exposure to vanadium pentoxide and 58 reported exposure to vanadium (form unknown).



Health System	infants			children			pregnant women	general population					occupational				Grand Total
	case-control	cohort	ecological	case-control	cohort	cross-sectional	cohort	case-control	cohort	controlled trial	cross-sectional	ecological	case report/ case series	case-control	cohort	cross-sectional	
Cancer								4	1					1			6
Cardiovascular								1	3	1	4	2	1		1	6	19
Dermal																2	2
Developmental	1	4	1				1										7
Endocrine							1										1
Gastrointestinal													1			3	4
Hematologic						1		1								3	5
Hepatic																3	3
Immune					1	1		2	1	1	1				1	5	13
Metabolic							1	2								1	4
Nervous				3	1			3			1		1			5	14
Ocular																2	2
Renal									1				1			2	4
Reproductive							2				1						3
Respiratory					2				1	1	3		2		5	6	20
Systemic/Whole Body									1				1			2	4
Other											1					1	2
Grand Total	1	4	1	3	3	2	4	11	6	1	9	2	2	1	6	12	67

Figure 4. Survey of human studies that met PECO criteria by study design and health systems assessed.

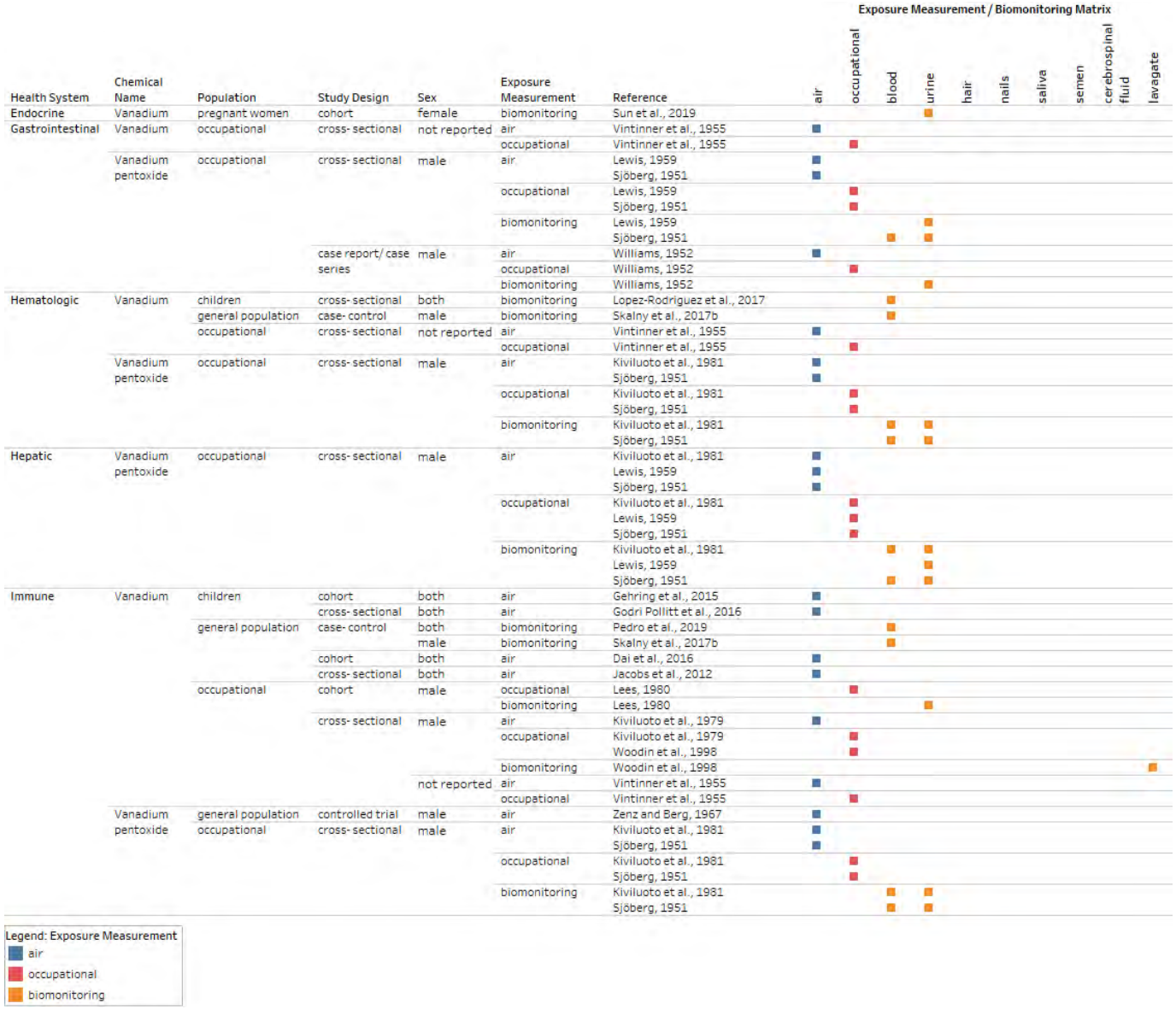
The numbers indicate the number of studies that investigated a particular health system, and not the number of studies that observed an association with vanadium exposure. If a study evaluated multiple health outcomes or multiple study designs, it is displayed multiple times. Hence, the totals do not necessarily indicate the number of individual studies for a given health outcome. The interactive version of the figure, including more details on the study designs and results, is available at the following URL: https://public.tableau.com/views/VanadiumInhalationIAPVisualizations/ReadMe?:language=en&:display_count=y&:origin=viz_share_link.



Health System	Chemical Name	Population	Study Design	Sex	Exposure Measurement	Reference
Cancer	Vanadium	general population	case- control	both	biomonitoring	Gomez-Tomas et al., 2019
						Lee et al., 2020
				female	biomonitoring	O'Brien et al., 2019
						Tang et al., 2012
			cohort	both	air	Weinmayr et al., 2018
		occupational	case- control	both	biomonitoring	Bai et al., 2019
Cardiovascular	Vanadium	general population	case- control	male	biomonitoring	Skalny et al., 2017b
			cohort	both	air	Badaloni et al., 2017
						Dai et al., 2016
					biomonitoring	Domingo-Relloso et al., 2019
			cross- sectional	both	air	Jacobs et al., 2012
					biomonitoring	Subrahmanyam et al., 2016
						Wu et al., 2018
				not reported	air	Bell et al., 2014
			ecological	both	air	Lin et al., 2018
						Ye et al., 2018
		occupational	cohort	male	air	Magari et al., 2002
			cross- sectional	both	occupational	Zhang et al., 2014
					biomonitoring	Dai et al., 2019
				not reported	air	Vintinner et al., 1955
					occupational	Vintinner et al., 1955
	Vanadium pentoxide	general population	controlled trial	male	air	Zenz and Berg, 1967
		occupational	cross- sectional	male	air	Kiviluoto et al., 1981
						Lewis, 1959
						Sjöberg, 1951
					occupational	Kiviluoto et al., 1981
						Lewis, 1959
						Sjöberg, 1951
					biomonitoring	Kiviluoto et al., 1981
						Lewis, 1959
						Sjöberg, 1951
			case report/ case series	male	air	Williams, 1952
					occupational	Williams, 1952
					biomonitoring	Williams, 1952
Dermal	Vanadium	occupational	cross- sectional	not reported	air	Vintinner et al., 1955
					occupational	Vintinner et al., 1955
	Vanadium pentoxide	occupational	cross- sectional	male	air	Sjöberg, 1951
					occupational	Sjöberg, 1951
					biomonitoring	Sjöberg, 1951
Developmental	Vanadium	infants	case- control	both	biomonitoring	Jiang et al., 2016
			cohort	both	air	Bell et al., 2010
					biomonitoring	Hu et al., 2017
						Hu et al., 2018
						Zhou et al., 2019
			ecological	both	air	Basu et al., 2014
		pregnant women	cohort	female	biomonitoring	Sun et al., 2019

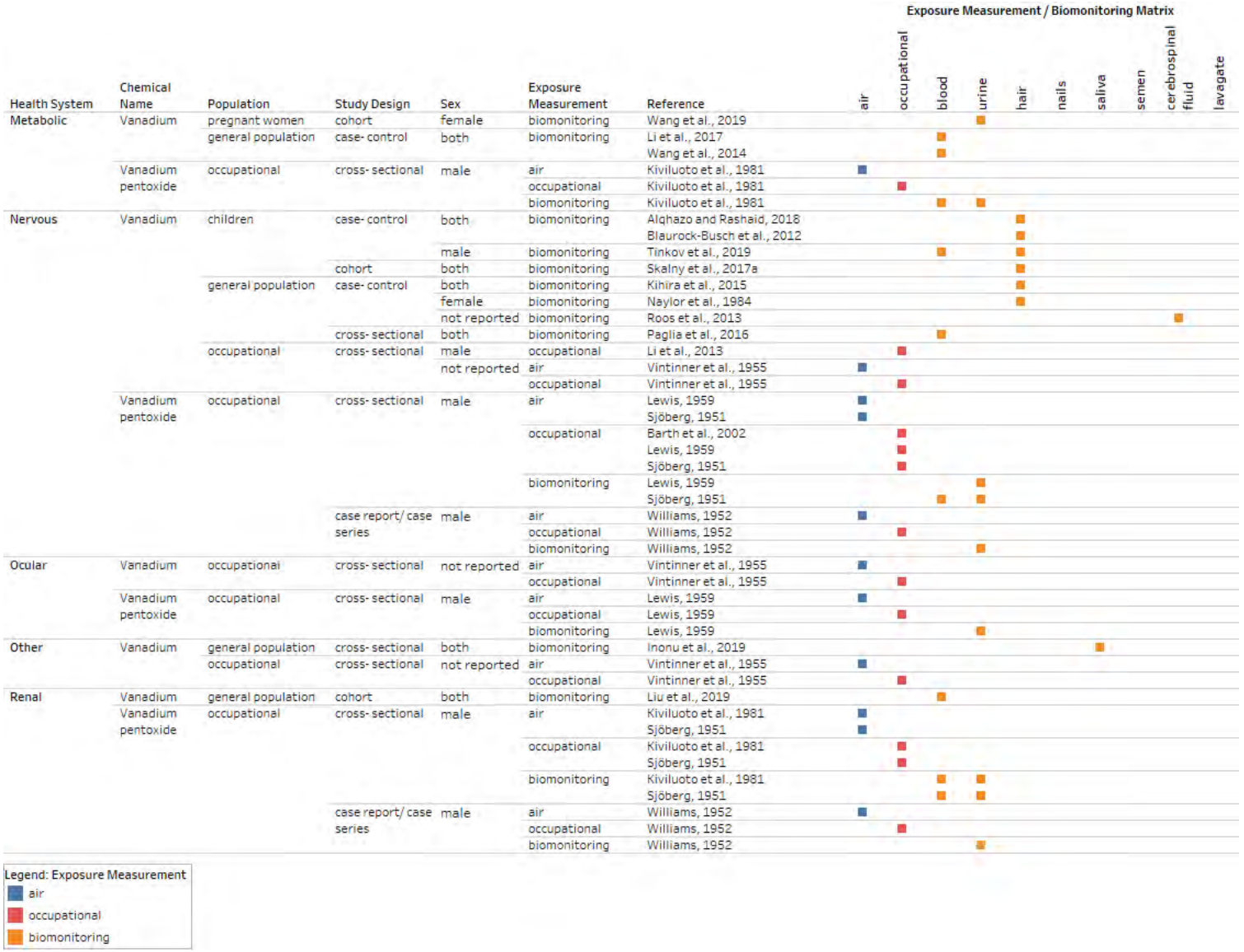
Figure 5. Tabular summary of study designs and exposure measurements used in human studies that met PECO criteria.

In the figure, for studies where vanadium is indicated, the actual form is unknown. The interactive version of the figure, including more details on the study designs and results, is available at the following URL: https://public.tableau.com/views/VanadiumInhalationIAPVisualizations/ReadMe?:language=en&:display_count=y&:origin=viz_share_link.



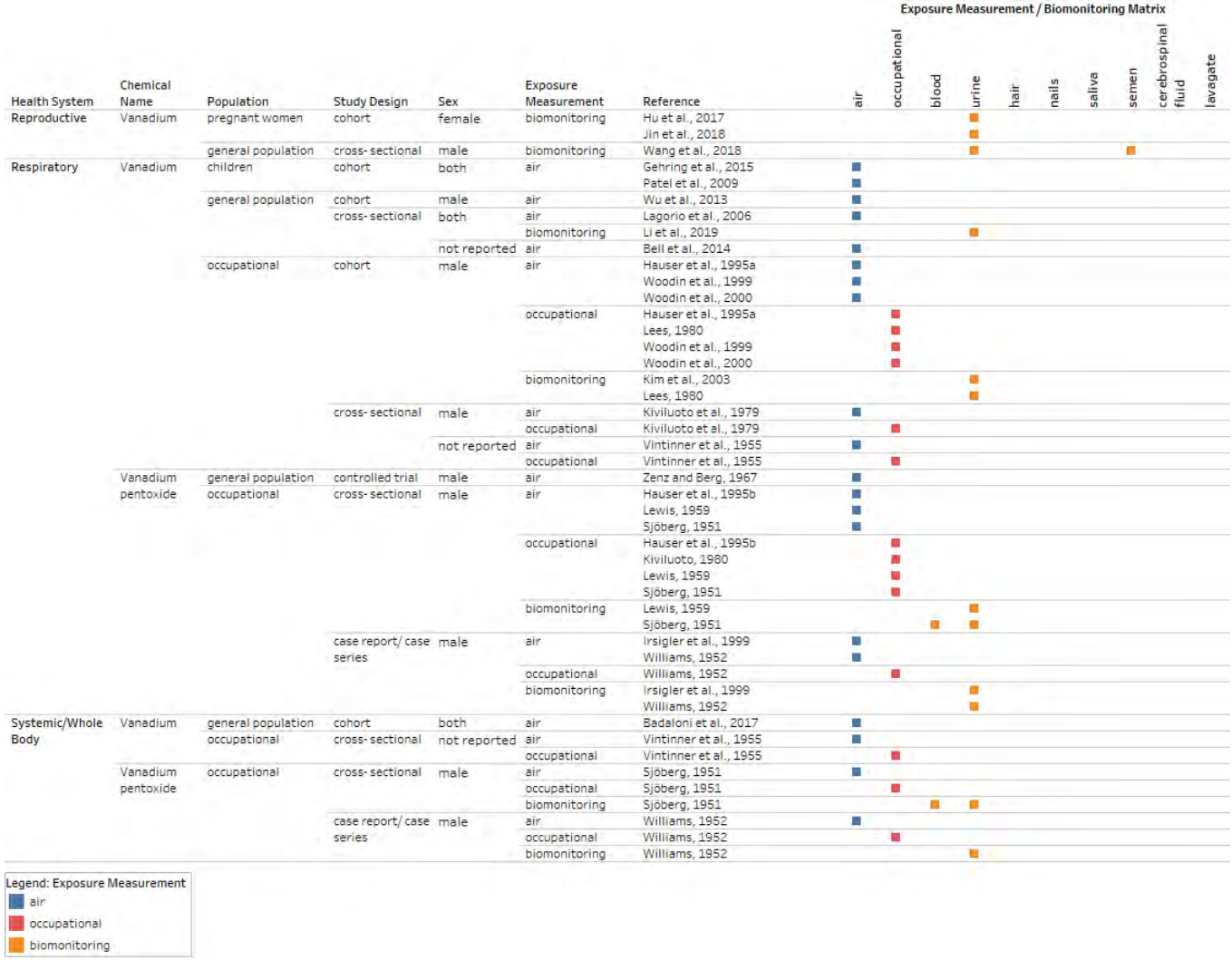
Health System	Chemical Name	Population	Study Design	Sex	Exposure Measurement	Reference
Endocrine	Vanadium	pregnant women	cohort	female	biomonitoring	Sun et al., 2019
Gastrointestinal	Vanadium	occupational	cross-sectional	not reported	air	Vintinner et al., 1955
					occupational	Vintinner et al., 1955
	Vanadium pentoxide	occupational	cross-sectional	male	air	Lewis, 1959
						Sjöberg, 1951
					occupational	Lewis, 1959
						Sjöberg, 1951
					biomonitoring	Lewis, 1959
						Sjöberg, 1951
			case report/ case series	male	air	Williams, 1952
					occupational	Williams, 1952
					biomonitoring	Williams, 1952
Hematologic	Vanadium	children	cross-sectional	both	biomonitoring	Lopez-Rodriguez et al., 2017
		general population	case-control	male	biomonitoring	Skalny et al., 2017b
		occupational	cross-sectional	not reported	air	Vintinner et al., 1955
					occupational	Vintinner et al., 1955
	Vanadium pentoxide	occupational	cross-sectional	male	air	Kiviluoto et al., 1981
						Sjöberg, 1951
					occupational	Kiviluoto et al., 1981
						Sjöberg, 1951
					biomonitoring	Kiviluoto et al., 1981
						Sjöberg, 1951
Hepatic	Vanadium pentoxide	occupational	cross-sectional	male	air	Kiviluoto et al., 1981
						Lewis, 1959
						Sjöberg, 1951
					occupational	Kiviluoto et al., 1981
						Lewis, 1959
						Sjöberg, 1951
					biomonitoring	Kiviluoto et al., 1981
						Lewis, 1959
						Sjöberg, 1951
Immune	Vanadium	children	cohort	both	air	Gehring et al., 2015
			cross-sectional	both	air	Godri Pollitt et al., 2016
		general population	case-control	both	biomonitoring	Pedro et al., 2019
				male	biomonitoring	Skalny et al., 2017b
			cohort	both	air	Dai et al., 2016
			cross-sectional	both	air	Jacobs et al., 2012
		occupational	cohort	male	occupational	Lees, 1980
					biomonitoring	Lees, 1980
			cross-sectional	male	air	Kiviluoto et al., 1979
					occupational	Kiviluoto et al., 1979
						Woodin et al., 1998
					biomonitoring	Woodin et al., 1998
				not reported	air	Vintinner et al., 1955
					occupational	Vintinner et al., 1955
	Vanadium pentoxide	general population	controlled trial	male	air	Zenz and Berg, 1967
		occupational	cross-sectional	male	air	Kiviluoto et al., 1981
						Sjöberg, 1951
					occupational	Kiviluoto et al., 1981
						Sjöberg, 1951
					biomonitoring	Kiviluoto et al., 1981
						Sjöberg, 1951

Figure 5. continued.



Health System	Chemical Name	Population	Study Design	Sex	Exposure Measurement	Reference
Metabolic	Vanadium	pregnant women	cohort	female	biomonitoring	Wang et al., 2019
		general population	case- control	both	biomonitoring	Li et al., 2017
						Wang et al., 2014
	Vanadium pentoxide	occupational	cross- sectional	male	air	Kiviluoto et al., 1981
					occupational	Kiviluoto et al., 1981
					biomonitoring	Kiviluoto et al., 1981
Nervous	Vanadium	children	case- control	both	biomonitoring	Alqhazo and Rashaid, 2018
						Blaurock-Busch et al., 2012
				male	biomonitoring	Tinkov et al., 2019
			cohort	both	biomonitoring	Skalny et al., 2017a
		general population	case- control	both	biomonitoring	Kihira et al., 2015
				female	biomonitoring	Naylor et al., 1984
				not reported	biomonitoring	Roos et al., 2013
			cross- sectional	both	biomonitoring	Paglia et al., 2016
		occupational	cross- sectional	male	occupational	Li et al., 2013
				not reported	air	Vintinner et al., 1955
					occupational	Vintinner et al., 1955
	Vanadium pentoxide	occupational	cross- sectional	male	air	Lewis, 1959
						Sjöberg, 1951
					occupational	Barth et al., 2002
						Lewis, 1959
						Sjöberg, 1951
					biomonitoring	Lewis, 1959
						Sjöberg, 1951
			case report/ case series	male	air	Williams, 1952
					occupational	Williams, 1952
					biomonitoring	Williams, 1952
Ocular	Vanadium	occupational	cross- sectional	not reported	air	Vintinner et al., 1955
					occupational	Vintinner et al., 1955
	Vanadium pentoxide	occupational	cross- sectional	male	air	Lewis, 1959
					occupational	Lewis, 1959
					biomonitoring	Lewis, 1959
Other	Vanadium	general population	cross- sectional	both	biomonitoring	Inonu et al., 2019
		occupational	cross- sectional	not reported	air	Vintinner et al., 1955
					occupational	Vintinner et al., 1955
Renal	Vanadium	general population	cohort	both	biomonitoring	Liu et al., 2019
	Vanadium pentoxide	occupational	cross- sectional	male	air	Kiviluoto et al., 1981
						Sjöberg, 1951
					occupational	Kiviluoto et al., 1981
						Sjöberg, 1951
					biomonitoring	Kiviluoto et al., 1981
						Sjöberg, 1951
			case report/ case series	male	air	Williams, 1952
					occupational	Williams, 1952
					biomonitoring	Williams, 1952

Figure 5. continued.



Health System	Chemical Name	Population	Study Design	Sex	Exposure Measurement	Reference
Reproductive	Vanadium	pregnant women	cohort	female	biomonitoring	Hu et al., 2017
						Jin et al., 2018
		general population	cross-sectional	male	biomonitoring	Wang et al., 2018
Respiratory	Vanadium	children	cohort	both	air	Gehring et al., 2015
						Patel et al., 2009
		general population	cohort	male	air	Wu et al., 2013
			cross-sectional	both	air	Lagorio et al., 2006
					biomonitoring	Li et al., 2019
				not reported	air	Bell et al., 2014
		occupational	cohort	male	air	Hauser et al., 1995a
						Woodin et al., 1999
						Woodin et al., 2000
					occupational	Hauser et al., 1995a
						Lees, 1980
						Woodin et al., 1999
						Woodin et al., 2000
					biomonitoring	Kim et al., 2003
						Lees, 1980
			cross-sectional	male	air	Kiviluoto et al., 1979
					occupational	Kiviluoto et al., 1979
				not reported	air	Vintinner et al., 1955
					occupational	Vintinner et al., 1955
	Vanadium pentoxide	general population	controlled trial	male	air	Zenz and Berg, 1967
		occupational	cross-sectional	male	air	Hauser et al., 1995b
						Lewis, 1959
						Sjöberg, 1951
					occupational	Hauser et al., 1995b
						Kiviluoto, 1980
						Lewis, 1959
						Sjöberg, 1951
					biomonitoring	Lewis, 1959
						Sjöberg, 1951
			case report/ case series	male	air	Irsigler et al., 1999
						Williams, 1952
					occupational	Williams, 1952
					biomonitoring	Irsigler et al., 1999
						Williams, 1952
Systemic/Whole Body	Vanadium	general population	cohort	both	air	Badaloni et al., 2017
		occupational	cross-sectional	not reported	air	Vintinner et al., 1955
					occupational	Vintinner et al., 1955
	Vanadium pentoxide	occupational	cross-sectional	male	air	Sjöberg, 1951
					occupational	Sjöberg, 1951
					biomonitoring	Sjöberg, 1951
			case report/ case series	male	air	Williams, 1952
					occupational	Williams, 1952
					biomonitoring	Williams, 1952

Figure 5. continued.

Animal studies: A preliminary survey of study designs and health effects evaluated in the animal studies that met PECO criteria is provided in Figure 6.

Most of the available animal studies evaluated exposure to vanadium pentoxide. Only a few studies evaluated acute or short-term exposure to other vanadium compounds, such as sodium metavanadate, ammonium metavanadate, vanadium dioxide, sodium vanadate, and bismuth orthovanadate, of which ammonium metavanadate and sodium metavanadate included only single-concentration exposure studies (Figure 7). Most studies involved exposure to mice (n = 21), with several others exposing rats (n = 8), and only one study exposing rabbits and two exposing nonhuman primates. Of the 30 available animal studies, 10 are multiple exposure studies, 19 are single concentration studies, and 1 involved both single and multi-exposure experiments.

The study designs most relevant for RfC derivation are chronic, subchronic, reproductive, or developmental studies that tested multi-exposure concentrations. The designs and author-reported findings of the identified multi-exposure animal studies are summarized in Figure 8 (chronic studies) and Figure 9 (subchronic studies).

Health System	acute			short-term				subchronic		chronic				Grand Total
	non-human primate	rat	rabbit	non-human primate	mouse	rat	rabbit	mouse	rat	non-human primate	mouse	rat	rabbit	
Cancer											1	1		1
Cardiovascular					1	1		2	1		2	1		2
Dermal											1	1		1
Endocrine					1						1	1		2
Gastrointestinal							1				1	1		2
Hematologic								4	1		1	1		5
Hepatic					1	1	1	2	1		1	1	1	3
Immune		1			1	2		3	1		1	1		5
Metabolic								1						1
Nervous					4			2			1	1		7
Renal					1	1		2	1		1	1	1	3
Reproductive					2	1		1	1		3	1		4
Respiratory	1	1		1	2	5	1	2	1	1	1	1	1	11
Systemic/Whole Body			1		4	3		1	1		1	1		7
Other						1								1
Grand Total	1	2	1	1	8	6	1	11	1	1	4	1	1	30

Figure 6. Survey of animal studies that met PECO criteria by study design, species, and health systems assessed.

The numbers indicate the number of studies that investigated a particular health system, and 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 displayed multiple times. Hence, the totals do not necessarily indicate the number of individual studies for a given health outcome. The interactive version of the figure, including more details on the study designs and results, is available at the following URL: https://public.tableau.com/views/VanadiumInhalationIAPVisualizations/ReadMe?:language=en&:display_count=y&:origin=viz_share_link.

Chemical Name	acute	short-term	subchronic	chronic	Grand Total
Ammonium metavanadate	1	1			2
Bismuth orthovanadate		1			1
Sodium metavanadate		1			1
Sodium vanadate	1				1
Vanadium dioxide		1			1
Vanadium pentoxide	3	13	11	6	27
Grand Total	4	15	11	6	30

Figure 7. Summary of the vanadium compounds evaluated by study design in the available animal studies.

These include both single exposure as well as multi-exposure animal studies. The interactive version of the figure including more details on the study designs and results is available at the following URL: https://public.tableau.com/views/VanadiumInhalationIAPVisualizations/ReadMe?:language=en&:display_count=y&:origin=viz_share_link.

Chemical Name	Species	Reference	Sex	Health System	All concentration levels	Concentration units
Vanadium pentoxide	non-human primate	Knecht et al., 1992	male	Respiratory	0, 0.1, 0.5, 1.1	mg/m^3
	rat	NTP, 2002	both	Cancer	0, 0.5, 1, 2	mg/m^3
				Cardiovascular	0, 0.5, 1, 2	mg/m^3
				Dermal	0, 0.5, 1, 2	mg/m^3
				Endocrine	0, 0.5, 1, 2	mg/m^3
				Gastrointestinal	0, 0.5, 1, 2	mg/m^3
				Hematologic	0, 0.5, 1, 2	mg/m^3
				Hepatic	0, 0.5, 1, 2	mg/m^3
				Immune	0, 0.5, 1, 2	mg/m^3
				Nervous	0, 0.5, 1, 2	mg/m^3
				Renal	0, 0.5, 1, 2	mg/m^3
				Reproductive	0, 0.5, 1, 2	mg/m^3
				Respiratory	0, 0.5, 1, 2	mg/m^3
				Systemic/Whole Body	0, 0.5, 1, 2	mg/m^3
	mouse	NTP, 2002	both	Cancer	0, 1, 2, 4	mg/m^3
				Cardiovascular	0, 1, 2, 4	mg/m^3
				Dermal	0, 1, 2, 4	mg/m^3
				Endocrine	0, 1, 2, 4	mg/m^3
				Gastrointestinal	0, 1, 2, 4	mg/m^3
				Hematologic	0, 1, 2, 4	mg/m^3
				Hepatic	0, 1, 2, 4	mg/m^3
				Immune	0, 1, 2, 4	mg/m^3
				Nervous	0, 1, 2, 4	mg/m^3
				Renal	0, 1, 2, 4	mg/m^3
				Reproductive	0, 1, 2, 4	mg/m^3
				Respiratory	0, 1, 2, 4	mg/m^3
				Systemic/Whole Body	0, 1, 2, 4	mg/m^3

Figure 8. Preliminary summary of multi-exposure chronic animal studies.

The interactive version of the figure, including more details on the study designs and results, is available at the following URL: https://public.tableau.com/views/VanadiumInhalationIAPVisualizations/ReadMe?:language=en&:display_count=y&:origin=viz_share_link.

Chemical Name	Species	Reference	Sex	Health System	All concentration levels	Concentration units
Vanadium pentoxide	rat	NTP, 2002	both	Cardiovascular	0, 1, 2, 4, 8, 16	mg/m^3
					0, 4, 8, 16	mg/m^3
				Hematologic	0, 1, 2, 4, 8, 16	mg/m^3
				Hepatic	0, 1, 2, 4, 8, 16	mg/m^3
				Immune	0, 1, 2, 4, 8, 16	mg/m^3
					0, 4, 8, 16	mg/m^3
				Renal	0, 1, 2, 4, 8, 16	mg/m^3
				Reproductive	0, 1, 2, 4, 8, 16	mg/m^3
				Respiratory	0, 1, 2, 4, 8, 16	mg/m^3
					0, 4, 8, 16	mg/m^3
				Systemic/Whole Body	0, 1, 2, 4, 8, 16	mg/m^3
			female	Reproductive	0, 4, 8, 16	mg/m^3
			male	Reproductive	0, 2, 4, 8	mg/m^3
	mouse	Lopez-Valdez et al., 2019	male	Respiratory	0, 1.27, 2.56	mg/m^3
		NTP, 2002	both	Cardiovascular	0, 1, 2, 4, 8, 16	mg/m^3
				Hepatic	0, 1, 2, 4, 8, 16	mg/m^3
				Immune	0, 1, 2, 4, 8, 16	mg/m^3
				Renal	0, 1, 2, 4, 8, 16	mg/m^3
				Reproductive	0, 1, 2, 4, 8, 16	mg/m^3
				Respiratory	0, 1, 2, 4, 8, 16	mg/m^3
				Systemic/Whole Body	0, 1, 2, 4, 8, 16	mg/m^3
			female	Reproductive	0, 4, 8, 16	mg/m^3
			male	Reproductive	0, 4, 8, 16	mg/m^3

Figure 9. Preliminary summary of multi-exposure subchronic animal studies.

The interactive version of the figure, including more details on the study designs and results, is available at the following URL: https://public.tableau.com/views/VanadiumInhalationIAPVisualizations/ReadMe?:language=en&:display_count=y&:origin=viz_share_link.

2.4. KEY SCIENCE ISSUES

The following key science issues were identified on the basis of the preliminary literature survey results (see Section 2.3.1) and review of past assessments on inhalation exposure to vanadium and compounds (see Section 2.1). Key Science Issue #1 relates to issues surrounding chemical speciation of vanadium, Issues #2 and #3 pertain to consideration in interpreting nonneoplastic lesions in the upper and lower respiratory tract and alveolar/bronchiolar neoplasms in rodents, and Key Science Issue #4 pertains to evaluating the MOA information relevant to potential carcinogenicity.

- Key Science Issue #1: Consideration of vanadium speciation and oxidation state.

  Considering oxidation status could be important as preliminary examination of findings from oral exposure studies in rodents appears to indicate increased toxicity of vanadium in the +5 oxidation state compared to vanadium +4 (Roberts et al., 2016). As noted in Section 2, vanadium in solution can convert between oxidation states and will form different species as a function of factors including pH, concentration, and redox potential. Study evaluations for the available inhalation studies, to the extent possible, will consider factors that could affect vanadium oxidation state and speciation [e.g., study methods that involved aerosolizing vanadium pentoxide (or other vanadium compound) from solution, e.g., González-Villalva et al. (2011), rather than exposure to vanadium as a dust, e.g., NTP (2002)]. In addition, data to inform potential conversion between vanadium oxidation state in the body also will be evaluated and discussed in the assessment.

- Key Science Issue #2: Interpretation of data on noncancer respiratory responses to vanadium pentoxide.

  The 2-year NTP (2002) study reports increasing incidences of nonneoplastic lesions in the upper and lower respiratory tract of rats and mice (both sexes) with increasing vanadium pentoxide exposure. Responses in all vanadium pentoxide exposure groups were highly elevated compared to controls. Information on the biology underlying these findings will aid interpretation of their use for hazard identification. Depending on the hazard identification decisions, methods for low-dose extrapolation and the associated uncertainties with any such approaches also would need to be explored and justified.

- Key Science Issue #3: Interpretation of data on rodent tumor responses.

  The NTP (2002) study also reports that tumor responses (alveolar/bronchiolar neoplasms) in male and female mice were highly elevated at all concentrations of vanadium pentoxide exposure: 70–80% increased incidence at the lowest tested vanadium concentration; control incidence in male mice was high (44%), but background incidence in females was very low (2%). Tumor incidence in male rats was elevated slightly but not statistically significant compared to concurrent controls. Previous reviews analyzed this tumor incidence against historical controls, which will be useful in interpreting these data as they are considered in the assessment. In summary, aspects of the rodent tumor data noted above and the uncertainties will be considered in the assessment.

- Key Science Issue #4. Cancer MOA for alveolar/bronchiolar neoplasms.

  As summarized in Section 2.1, there is some support for both a mutagenic MOA and an MOA dependent on cellular cytotoxicity and reparative regeneration (and potentially other undetermined mechanisms) as suggested in the EPA PPRTV assessment (U.S. EPA, 2008). A similar lack of a clearly delineated MOA for alveolar/bronchiolar lung tumors with vanadium pentoxide exposure was proposed in the unfinalized draft IRIS Assessment of Vanadium Pentoxide (U.S. EPA, 2011). As reported in these reviews, mutagenicity data for vanadium pentoxide appears generally negative, and some data support a mechanism involving DNA damage and cell proliferation. Given the potential uncertainties in the available MOA information and the potential impact of this information on assessment conclusions, a focused evaluation of the available evidence regarding cancer MOA(s) for

alveolar/bronchiolar neoplasms, including judgments regarding human relevance, is expected to be a key component of the vanadium (inhalation) IRIS assessment.

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

On the basis of the preliminary literature survey (Section 2.3) and identified key science issues (Section 2.4), this section outlines the specific aims and draft PECO criteria that will be used in developing this IRIS assessment. The overall objective of this assessment is to identify adverse health effects and characterize exposure-response relationships for these effects of inhalation exposure to vanadium compounds to support development of toxicity values. This assessment will use systematic review methods to evaluate the epidemiological and toxicological literature for vanadium compounds, including consideration of relevant mechanistic evidence. The evaluation conducted in this assessment will be consistent with relevant EPA guidance.[7] The systematic review protocol will be disseminated after review of this draft IRIS Assessment Plan and will reflect changes made to the specific aims and PECO criteria in response to public comments.

3.1. SPECIFIC AIMS

- Identify epidemiological (i.e., human) and toxicological (i.e., experimental animal) literature reporting effects of exposure to vanadium and compounds as outlined in the PECO criteria, 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 U.S. federal agency. Database searches will be conducted to identify records that were published since the literature was last searched for the 2012 ATSDR *Toxicological Profile for Vanadium*.

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

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

[7]EPA guidance documents: http://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance/.

- Review and incorporate the available toxicokinetic and mechanistic information, as warranted, to support assessment decisions. The toxicokinetic and mechanistic analyses will focus primarily on the key science issues identified in Section 2.4. 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 inhalation toxicity values [e.g., reference concentrations (RfCs), cancer risk estimates for inhalation 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 criteria are used to identify the evidence that addresses the specific aims of the assessment and to focus the search terms and inclusion/exclusion criteria in a systematic review. The draft PECO criteria for vanadium compounds (Table 3) were based on (1) nomination of the chemical for assessment, (2) discussions with scientists in EPA program and regional offices to determine the scope of the assessment that will best meet Agency needs, and (3) preliminary review of the health effects literature for vanadium compounds (primarily reviews and authoritative health assessment documents) to identify the major health hazards potentially associated with inhalation exposure to vanadium and compounds and key science issues.

Table 3. Population, exposure, comparator, outcome (PECO) criteria for the inhalation exposure to vanadium and compounds assessment

PECO element	Evidence
Populations	**Human:** Any population and life stage (occupational or general population, including children and other potentially sensitive populations). **Animal:** Nonhuman mammalian animal species (whole organism) at any life stage (including preconception, in utero, lactation, peripubertal, and adult stages). Studies of transgenic animals will be tracked as mechanistic studies under "potentially relevant supplemental material."

PECO element	Evidence
Exposures	**Relevant forms:** Any forms of vanadium. **Human:** Any exposure to vanadium compound(s) via the inhalation route, either explicitly stated or considered plausible based on exposure assessment. Exposure can be based on administered concentration, biomonitoring data (e.g., urine, blood, or other specimens), environmental or occupational measurements (e.g., air concentration), or job title or residence. Studies will be included if biomarkers of vanadium exposure are evaluated but the exposure route is unclear. Other exposure routes including oral will be tagged as "potentially relevant supplemental information." **Animal:** Any exposure to vanadium compound(s) via the inhalation route. Studies involving exposures to mixtures will be included only if they include an arm with exposure to a singular vanadium compound alone, otherwise, they will be tagged as "potentially relevant supplemental information." Other exposure routes, including intratracheal instillation, intranasal or oropharyngeal administration, oral, 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) to vanadium compounds, 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 or case series of >3 people will be considered to meet PECO criteria, while case reports describing findings in 1–3 people in nonoccupational or occupational settings will be tagged as "potentially relevant supplemental information." **Animal:** A concurrent control group exposed to vehicle-only treatment, untreated control, or other treatment group with a different exposure duration time period.
Outcomes	All health outcomes (both cancer and noncancer). In general, endpoints related to clinical diagnostic criteria, disease outcomes, histopathological examination, or other apical/phenotypic outcomes are considered to meet PECO criteria and are prioritized for evidence synthesis over outcomes such as biochemical measures.
PK or 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 (absorption, distribution, metabolism, and excretion) 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 inhalation concentration absorbed), volume of distribution, clearance rate, 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 "noncompartmental analysis," it should be listed only 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) 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 also potentially are relevant to the specific aims will be tracked during the literature screening process. Table 4 presents major categories of supplemental material. The criteria are used to tag studies during screening and to prioritize studies for consideration in the assessment based on likelihood to impact evidence synthesis conclusions for human health. Important to emphasize is 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 3 is designed to ensure that supplemental studies are categorized for easy retrieval while conducting the assessment. Studies that meet the PECO criteria are those that are most likely to be used to develop hazard conclusions and 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 epidemiological and toxicological studies. 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 gauge 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 is needed); (2) 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 preparation of certain chapters in an IRIS assessment (e.g., background information on sources, production, or use; overview of toxicokinetics); or (4) provide context for the rationale for conducting the assessment or for assessment conclusions (e.g., information on pathways and levels of exposure). From a practical perspective, determining that all of these studies meet the PECO criteria during the title and abstract level screening means that the full-text needs to be obtained for full-text screening for all of them, which would be very time and resource intensive. Thus, the tagging strategy outlined below allows these studies to be identified at the title and abstract level so the full text can be retrieved only as needed during the course of conducting the assessment.

Table 4. 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 nonmammalian model systems, including in vitro, in vivo (by any routes of exposure, includes transgenic models), ex vivo, and in silico studies. Genotoxicity tests are considered "mechanistic." Studies in which the chemical is used as a laboratory reagent generally do not need to be tagged (e.g., as a chemical probe used to measure antibody response).

Category	Evidence
Nonmammalian model systems	Studies in nonmammalian model systems, e.g., zebrafish, birds, *C. elegans*.
Noninhalation route of administration	Studies in which humans or animals (whole organism) were exposed via a noninhalation route (e.g., oral, injection, or dermal) and intratracheal, intranasal, or oropharyngeal routes of exposure. This categorization generally does not apply to epidemiological studies in which the exposure route may be unclear; such studies are considered to meet PECO criteria when inhalation exposure is plausible (further review of these studies will include consideration of whether route attribution can be inferred). Studies evaluating oral exposure to vanadium compounds are also under evaluation in a separate IRIS assessment (https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=348792).
Toxicokinetic (ADME)	Toxicokinetic (ADME) studies 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. These data are used to estimate the amount absorbed (A), distributed (D), metabolized (M), or excreted/eliminated (E) through urine, breath, feces. • The most informative studies are by the inhalation route and involve measurements over time such that the initial increase and subsequent concentration decline is observed, preferably at multiple exposure levels. Data collected from multiple tissues or excreta at a single timepoint, however, also inform distribution. • ADME data also can be collected from human subjects who have had environmental or workplace exposures that are not quantified or fully defined. To be useful, however, such data must involve either repeated measurements over a period when exposure is known (e.g., is zero because previous exposure ended) ***or*** time- and subject-matched tissue or excreta concentrations (e.g., plasma and urine, or maternal and cord blood). • ADME data, especially metabolism and tissue partition-coefficient information, can be generated using in vitro model systems. Although in vitro data may not be as definitive as in vivo data, these studies should also be tracked as ADME. For large evidence bases, separately tracking the in vitro ADME studies may be appropriate. *Studies describing environmental fate and transport or metabolism in bacteria are not tagged as ADME.
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 to meet PECO criteria because they do not contain an exposure or treatment group assessing only the chemical of interest. This categorization generally does not apply to epidemiological studies.
Case reports	Case reports of fewer than three subjects that describe health outcomes after exposure.
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.

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APPENDIX A. SURVEY OF EXISTING VANADIUM TOXICITY VALUES

Table A-1 lists websites that were searched for relevant inhalation reference values for vanadium and vanadium compounds, along with indications of the results of the search. In addition to these sources, the ToxVal database on EPA's CompTox 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. Details on derivation of the available health-effect reference values for inhalation exposure to vanadium and compounds are presented in Table A-2 (reference values).

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

Source[a]	Search results	Query and/or Link
ACGIH	See Table A-2	ACGIH (2009). TLVs and BEIs: Based on documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists
AIHA	No results found	{AIHA, 2019, 6514361}. 2019 ERPG/WEEL Handbook. Fairfax, VA: American Industrial Hygiene Association.
ATSDR	See Table A-2	http://www.atsdr.cdc.gov/toxprofiles/index.asp
		https://www.atsdr.cdc.gov/mrls/mrllist.asp
CompTox	See Table A-2	https://comptox.epa.gov/dashboard
CT DEEP	See Table A-2	https://eregulations.ct.gov/eRegsPortal/Browse/getDocument?guid={00D6A654-0300-CC47-9B95-397D2AD21304}
DFG	No current reference values found	https://onlinelibrary.wiley.com/doi/book/10.1002/9783527818402
EPA/NRC AEGL	No results found	https://www.epa.gov/aegl/access-acute-exposure-guideline-levels-aegls-values#chemicals
European Commission	No results found	https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017L0164&from=EN
Health Canada	No reference 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

Source[a]	Search results	Query and/or Link
HSA	See Table A-2	https://www.hsa.ie/eng/Publications_and_Forms/Publications/Latest_Publications/chemical_agents_code_of_practice_2020.87509.shortcut.html
IDEM	No results found	https://www.in.gov/idem/toxic/2343.htm
ID DEQ	See Table A-2	https://adminrules.idaho.gov/rules/current/58/580101.pdf
IFA	See Table A-2	https://limitvalue.ifa.dguv.de/WebForm_gw2.aspx
IRIS	1988 RfD available, no inhalation values found	http://www.epa.gov/iris/
JSOH	No results found	https://www.sanei.or.jp/?mode=view&cid=328
MassDEP	See Table A-2	https://www.mass.gov/service-details/massdep-ambient-air-toxics-guidelines
MDH	See Table A-2	https://www.health.state.mn.us/communities/environment/risk/guidance/air/table.html
MI EGLE	See Table A-2	https://www.michigan.gov/documents/deq/deq-rrd-chem-CleanupCriteriaTSD_527410_7.pdf
NATICH	See Table A-2	https://nepis.epa.gov/Exe/ZyPDF.cgi/2000NS7S.PDF?Dockey=2000NS7S.PDF
NC DEQ	No results found	https://files.nc.gov/ncdeq/Air%20Quality/rules/rules/D1104.pdf
NDEP	See Table A-2	https://ndep.nv.gov/resources/risk-assessment-and-toxicology-basic-comparison-levels
NIOSH	See Table A-2	http://www.cdc.gov/niosh/npg/npgdcas.html
		https://www.cdc.gov/niosh/docs/81-123/
NJ DEP	See Table A-2	https://www.state.nj.us/dep/aqpp/downloads/risk/ToxAll2020.pdf
NYS DEC	No reference values found	https://www.dec.ny.gov/docs/remediation_hudson_pdf/techsuppdoc.pdf
OAQPS	No results found	https://www.epa.gov/fera/dose-response-assessment-assessing-health-risks-associated-exposure-hazardous-air-pollutants
OEHHA	See Table A-2	http://www.oehha.ca.gov/tcdb/index.asp
Ontario Ministry of Labour	See Table A-2	https://www.labour.gov.on.ca/english/hs/pubs/oel_table.php
OR DEQ	No results found	https://www.oregon.gov/deq/FilterDocs/airtox-abc.pdf
OSHA	See Table A-2	https://www.osha.gov/chemicaldata/
PAC Database	See Table A-2	https://edms.energy.gov/pac/Search
PPRTV	See Table A-2	https://www.epa.gov/pprtv/provisional-peer-reviewed-toxicity-values-pprtvs-assessments
Publications Quebec	See Table A-2	http://legisquebec.gouv.qc.ca/en/showdoc/cr/S-2.1,%20r.%2013?csi_scan_9222d36c6a354dc6=BO9xyrMZ+270UP3j0MGuOD0kZjgFAAAAXrM3HA==&bcsi_scan_filename=S-2.1,%20r.%2013&bcsi_scan_9222d36c6a354dc6=KXzmpPueuN0L1AjnJOB1Zerr85YMAAAAyhrPTg==&bcsi_scan_filename=S-2.1,%20r.%2013
RI DEM	See Table A-2	http://www.dem.ri.gov/programs/benviron/air/pdf/airtoxgl.pdf

Source[a]	Search results	Query and/or Link
RIVM	See Table A-2	https://www.rivm.nl/bibliotheek/rapporten/711701092.pdf
	No results found	https://www.rivm.nl/bibliotheek/rapporten/609021044.pdf
		https://www.rivm.nl/bibliotheek/rapporten/711701025.pdf
Safe Work Australia	See Table A-2	https://www.safeworkaustralia.gov.au/exposure-standards#exposure-standards-in-australia
SWCAA	See Table A-2	http://www.swcleanair.org
TCEQ	No results found	https://www.tceq.texas.gov/toxicology/dsd/final
	See Table A-2	https://www.tceq.texas.gov/remediation/trrp/trrppcls.html
USAPHC	See Table A-2	https://phc.amedd.army.mil/topics/envirohealth/hrasm/Pages/TG230.aspx
VT DEC	See Table A-2	https://dec.vermont.gov/sites/dec/files/aqc/laws-regs/documents/AQCD%20Regulations%20ADOPTED_Dec132018.pdf#page=127
WAC	See Table A-2	https://apps.leg.wa.gov/WAC/default.aspx?cite=173-460-150
Worksafe	See Table A-2	https://worksafe.govt.nz/topic-and-industry/work-related-health/monitoring/exposure-standards-and-biological-exposure-indices/

[a]ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = Acute Exposure Guideline Levels; AIHA = American Industrial Hygiene Association; ATSDR = Agency for Toxic Substances and Disease Registry; CT DEEP = Connecticut Department of Energy & Environmental Protection; DFG = *Deutsche Forschungsgemeinschaft*, German Research Foundation; EPA = U.S. Environmental Protection Agency; HSA = Health and Safety Authority; IDEM = Indiana Department of Environmental Management; ID DEQ = Idaho Department of Environmental Quality; IFA = *Institut für Arbeitsschutz,* The Institute for Occupational Safety and Health; IRIS = Integrated Risk Information System; JSOH = Japan Society for Occupational Health; MassDEP = Massachusetts Department of Environmental Protection; MDH = Minnesota Department of Health; MI EGLE = Michigan Environment, Great Lakes & Energy; NATICH = National Air Toxics Information Clearinghouse; NC DEQ = North Carolina Department of Environmental Quality; NDEP = Nevada Division of Environmental Protection; NIOSH = National Institute for Occupational Safety and Health; NJ DEP = New Jersey Department of Environmental Protection; NRC = National Research Council; NYS DEC = New York State Department of Environmental Conservation; OAQPS = Office of Air Quality Planning and Standards; OEHHA = California Office of Environmental Health Hazard Assessment; OR DEQ = Oregon Department of Environmental Quality; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PPRTV = Provisional Peer-Reviewed Toxicity Value; RI DEM = Rhode Island Department of Environmental Management; RIVM = *Rijksinstituut voor Volksgezondheid en Milieu,* The Netherlands Institute for Public Health and the Environment; SWCAA = Southwest Clean Air Association; TCEQ = Texas Commission on Environmental Quality; USAPHC = United States Army Public Health Center; VT DEC = Vermont Department of Environmental Conservation; WAC = Washington Administrative Code.

Table A-2. Details on derivation of the available health effect reference values for inhalation exposure to vanadium and compounds (current as of May 2020; please consult citation source entities and other entities in Appendix A, Tables A-2 and A-3

	Reference value name	Duration	Vanadium form	Reference value (mg/m^3)	Health effect	Point of departure	Qualifier	Source	Uncertainty factors	Notes on derivation	Review status
Emergency Response	**PAC-3**	1 h	Ammonium metavanadate	80	Based on vanadium IDLH	–	–	–	–	Based on vanadium IDLH[a]	Final (DOE, 2018)
			Potassium orthovanadate	160	Based on vanadium IDLH	–	–	–	–	Based on vanadium IDLH[b]	
			Trichlorooxovanadium	120	Based on vanadium IDLH	–	–	–	–	Based on vanadium IDLH[c]	
			Sodium metavanadate	84	Based on vanadium IDLH	–	–	–	–	Based on vanadium IDLH[d]	
			Sodium orthovanadate	130	Based on vanadium IDLH	–	–	–	–	Based on vanadium IDLH[e]	
			Vanadium pentoxide	70	Adopted 1990 IDLH	–	–	(NIOSH, 1994a)	–	Adopted 1990 IDLH	
			Vanadium sulfate	100	Based on vanadium IDLH	–	–	–	–	Based on vanadium IDLH[f]	
			Vanadium tetrachloride	130	Based on vanadium IDLH	–	–	–	–	Based on vanadium IDLH[g]	
			Vanadium (III) sulfate								
			Vanadium trioxide	51	Based on vanadium IDLH	–	–	–	–	Based on vanadium IDLH[h]	
			Vanadium (II) sulfate heptahydrate	190	Based on vanadium IDLH	–	–	–	–	Based on vanadium IDLH[i]	
			Vanadyl sulfate	110	Based on vanadium IDLH	–	–	–	–	Based on vanadium IDLH[j]	
			Vanadyl sulfate pentahydrate	170	Based on vanadium IDLH	–	–	–	–	Based on vanadium IDLH[k]	
			Vanadium	35	Adopted IDLH	–	–	–	–	Adopted IDLH	

	Reference value name	Duration	Vanadium form	Reference value (mg/m^3)	Health effect	Point of departure	Qualifier	Source	Uncertainty factors	Notes on derivation	Review status
	PAC-2	1 h	Ammonium metavanadate	0.11	Based on vanadium compounds REL-Ceiling	–	–	–	–	Based on vanadium compounds REL-Ceiling[l]	
			Potassium orthovanadate	0.23	Based on vanadium compounds REL-Ceiling	–	–	–	–	Based on vanadium compounds REL-Ceiling[m]	
			Trichlorooxovanadium	0.17	Based on vanadium compounds REL-Ceiling	–	–	–	–	Based on vanadium compounds REL-Ceiling[n]	
			Sodium metavanadate	0.12	Based on vanadium compounds REL-Ceiling	–	–	–	–	Based on vanadium compounds REL-Ceiling[o]	
			Sodium orthovanadate	0.18	Based on vanadium compounds REL-Ceiling	–	–	–	–	Based on vanadium compounds REL-Ceiling[p]	
			Vanadium pentoxide	7	LOC	NR	NR		NR		
			Vanadium sulfate	0.14	Based on vanadium compounds REL-Ceiling	–	–	–	–	Based on vanadium compounds REL-Ceiling[q]	
			Vanadium tetrachloride	0.19	Based on vanadium compounds REL-Ceiling	–	–	–	–	Based on vanadium compounds REL-Ceiling[r]	
			Vanadium (III) sulfate								
			Vanadium trioxide	0.074	Based on vanadium compounds REL-Ceiling	–	–	–	–	Based on vanadium compounds REL-Ceiling[s]	

	Reference value name	Duration	Vanadium form	Reference value (mg/m^3)	Health effect	Point of departure	Qualifier	Source	Uncertainty factors	Notes on derivation	Review status
			Vanadium (II) sulfate heptahydrate	0.27	Based on vanadium compounds REL-Ceiling	–	–	–	–	Based on vanadium compounds REL-Ceiling[t]	
			Vanadyl sulfate	0.16	Based on vanadium compounds REL-Ceiling	–	–	–	–	Based on vanadium compounds REL-Ceiling[u]	
			Vanadyl sulfate pentahydrate	0.25	Based on vanadium compounds REL-Ceiling	–	–	–	–	Based on vanadium compounds REL-Ceiling[v]	
			Vanadium	5.8	Based on PAC-3	–	–	–	–	Based on PAC-3[w]	
	PAC-1	1 h	Ammonium metavanadate	0.01	Based on PAC-2	–	–	–	–	Based on PAC-2[x]	
			Potassium orthovanadate	0.021	Based on PAC-2	–	–	–	–	Based on PAC-2[y]	
			Trichlorooxovanadium	0.015	Based on PAC-2	–	–	–	–	Based on PAC-2[z]	
			Sodium metavanadate	0.011	Based on PAC-2	–	–	–	–	Based on PAC-2[aa]	
			Sodium orthovanadate	0.016	Based on PAC-2	–	–	–	–	Based on PAC-2[bb]	
			Vanadium pentoxide	0.64	Based on PAC-2	–	–	–	–	Based on PAC-2[cc]	
			Vanadium sulfate	0.013	Based on PAC-2	–	–	–	–	Based on PAC-2[dd]	
			Vanadium tetrachloride	0.017	Based on PAC-2	–	–	–	–	Based on PAC-2[ee]	
			Vanadium (III) sulfate								
			Vanadium trioxide	0.0067	Based on PAC-2	–	–	–	–	Based on PAC-2[ff]	
			Vanadium (II) sulfate heptahydrate	0.025	Based on PAC-2	–	–	–	–	Based on PAC-2[gg]	
			Vanadyl sulfate	0.015	Based on PAC-2	–	–	–	–	Based on PAC-2[hh]	

	Reference value name	Duration	Vanadium form	Reference value (mg/m^3)	Health effect	Point of departure	Qualifier	Source	Uncertainty factors	Notes on derivation	Review status
			Vanadyl sulfate pentahydrate	0.023	Based on PAC-2	–	–	–	–	Based on PAC-2[ii]	
			Vanadium	3	Adopted ferrovanadium NIOSH REL-STEL	–	–	–	–	Adopted ferrovanadium NIOSH REL-STEL	
Occupational	**NIOSH REL-Ceiling**[jj]	<15 min	Vanadium compounds, excludes vanadium metal and vanadium carbide	0.05	Skin, eye, and respiratory tract irritation	NA	NA		NA		Final (NIOSH, 1977)
	NIOSH REL-STEL	15 min	Ferrovanadium, vanadium metal, and vanadium carbide	3							
	NIOSH REL (TWA)	10-h TWA		1	Adopted OSHA PEL as a 10-h TWA	–	–	–	–	Adopted OSHA PEL as a 10-h TWA	
	NIOSH IDLH	30 min	Vanadium dust and fume, as V	35	Rhinorrhea, sneezing, lacrimation, and sore throat in workers	NR	NR	(Mcturk et al., 1956; Sjöberg, 1955; Vintinner et al., 1955; Williams, 1952)	NR		Final (NIOSH, 1994a, b)
			Ferrovanadium	500	Based on NIOSH REL (TWA)	–	–	–	–	Based on NIOSH REL (TWA)[kk]	Final (NIOSH / ILO, 1994)
	ACGIH TLV (TWA)[ll]	8-h TWA	Vanadium pentoxide, inhalable PM as V	0.05	Bronchitis, bronchospasm, cough, rhinorrhea, conjunctivitis, nasal hemorrhage, wheezing, rales, rhonchi, and pulmonary disease	NR	NR	(Zenz and Berg, 1967; Zenz et al., 1962; Wyers, 1946)	NR		Final (ACGIH, 2009)

	Reference value name	Duration	Vanadium form	Reference value (mg/m^3)	Health effect	Point of departure	Qualifier	Source	Uncertainty factors	Notes on derivation	Review status
			Ferrovanadium	1	Bronchitis, interstitial sclerosis, and perivascular edema in rats exposed for 2 mon; irritation of eyes and respiratory tract in workers	NR	NR	(OSHA, 1989; Stokinger, 1981; Roshchin et al., 1966; Roshchin, 1952)	NR	Value suggested by Roshchin (1952)	Final (ACGIH, 2001)
	ACGIH TLV-STEL[mm]	15 min		3							
	OSHA PEL-Ceiling	<15 min	Vanadium pentoxide fume	0.1	Adopted 1968 ACGIH TLV	–	–	(NIOSH, 1977)	–	Adopted 1968 ACGIH TLV	Final (OSHA, 2019b)
			Vanadium pentoxide dust	0.5							
	OSHA PEL (TWA)[nn]	8-h TWA	Ferrovanadium	1							Final (OSHA, 2019a)
	Cal/OSHA PEL (TWA)	8-h TWA	Vanadium pentoxide	0.05	NR	NR	NR		NR		Final (OSHA, 2019b)
			Ferrovanadium	1							Final (OSHA, 2019a)
	Cal/OSHA PEL-STEL	15 min		3							

	Reference value name	Duration	Vanadium form	Reference value (mg/m^3)	Health effect	Point of departure	Qualifier	Source	Uncertainty factors	Notes on derivation	Review status
General Public	**CA-REL**[oo]	Acute (1 h)	Vanadium pentoxide	0.03	Coughing and increased mucus production in male volunteers exposed for 8 h	0.1 mg/m^3 0.3 mg/m^3	NOAEL $NOAEL_{ADJ}$	(Zenz and Berg, 1967)	Total UF = 10 UF_A = 1 UF_H = 10	Duration adjustment: $C^n \times t = k$, where n = 2	Final (OEHHA, 2008)
	EPA p-RfC (PPRTV)[pp]	Sub-chronic	Vanadium pentoxide	0.0001	Bronchoalveolar inflammation in female rats exposed for 16 d	1 mg/m^3 0.18 mg/m^3 0.11 mg/m^3	LOAEL $LOAEL_{ADJ}$ $LOAEL_{HEC}$	(NTP, 2002)	Total UF = 1,000 UF_A = 3 UF_H = 10 UF_L = 3 UF_D = 10	Duration adjusted: (6-h/24-h) × (5-d/7-d) HEC Adjusted[qq]	Provisional (U.S. EPA, 2008)
		Chronic		0.000007	Chronic inflammation of the larynx and epithelial hyperplasia of the epiglottis in female rats	0.5 mg/m^3 0.09 mg/m^3 0.016 mg/m^3 0.0022 mg/m^3	LOAEL $LOAEL_{ADJ}$ $LOAEL_{HEC}$ $BMDL_{10}$		Total UF = 300 UF_A = 3 UF_H = 10 UF_D = 10	Duration adjusted: (6-h/24-h) × (5-d/7-d) HEC Adjusted[rr]	
	RIVM pTCA	Chronic	Vanadium compounds	0.001	Toxicity in laboratory animals	0.5 mg V_2O_5/m^3 1 mg V_2O_5/m^3	$LOAEL_{rats}$ $LOAEL_{mice}$	(NTP, 2002)	Total UF = 1,000 UF_A = 10 UF_H = 10 UF_L = 10	Adopted previous WHO guideline: (WHO, 1987)[ss]	Provisional (Tiesjema and Baars, 2009)
	ATSDR MRL[tt]	Acute (1–14 d)	Vanadium compounds	0.0008	Lung inflammation in female rats exposed to vanadium pentoxide	0.56 mg V/m^3 0.1 mg V/m^3 0.073 mg V/m^3	LOAEL $LOAEL_{ADJ}$ $LOAEL_{HEC}$	(NTP, 2002)	Total UF = 100 UF_A = 3 UF_H = 10 UF_L = 3	Duration adjusted: (6-h/24-h) × (5-d/7-d) HEC Adjusted[uu]	Final (ATSDR, 2012)

	Reference value name	Duration	Vanadium form	Reference value (mg/m^3)	Health effect	Point of departure	Qualifier	Source	Uncertainty factors	Notes on derivation	Review status
		Chronic (>1 y)		0.0001	Degeneration of respiratory epithelium of the epiglottis in male rats exposed to vanadium pentoxide	0.04 mg V/m^3 0.0071 mg V/m^3 0.003 mg V/m^3	$BMCL_{10}$ $BMCL_{ADJ}$ $BMCL_{HEC}$		Total UF = 30 UF_A = 3 UF_H = 10	Duration adjusted: (6-h/24-h) × (5-d/7-d) HEC Adjusted[vv]	
General Public (Other State Values)	**NDEP BCL**	6 y	Vanadium and compounds	0.000104	Based on chronic MRL	–	–	–	–	Based on chronic MRL[ww]	Final (NDEP, 2017)
		70 y	Vanadium pentoxide	0.000000338	Cancer	0.00830 $(\mu g/m^3)^{-1}$	PPRTV Cancer URF	(U.S. EPA, 2008)	NA	Calculated[xx]	
	CT DEEP HLV	30 min	Vanadium pentoxide	0.005	NR	NR	NR		NR		Final (CTDEP, 2015)
		8 h		0.001		0.05 mg/m^3	ACGIH TLV-TWA	(ACGIH, 2009)	Total UF = 50	Derivation details reported to NATICH: (U.S. EPA, 1993)	
	RI DEM AAL	1 h	Vanadium and compounds	0.0002	Adopted acute MRL	–	–	–	–	Adopted acute MRL[yy]	Final (RI DEM, 2008)

[a]PAC-3 = IDLH × (NH_4VO_3 MW ÷ V atomic mass) = 35 mg/m^3 × (116.98 g/mol ÷ 50.94 g/mol) = 80 mg/m^3.
[b]PAC-3 = IDLH × (K_3O_4V MW ÷ V atomic mass) = 35 mg/m^3 × (232.23 g/mol ÷ 50.94 g/mol) = 160 mg/m^3.
[c]PAC-3 = IDLH × ($VOCl_3$ MW ÷ V atomic mass) = 35 mg/m^3 × (173.29 g/mol ÷ 50.94 g/mol) = 120 mg/m^3.
The PAC tables state that this value is 120 ppm but following the documented derivation details gives a value of 120 mg/m^3; therefore, that the units in the PAC tables are erroneous is assumed.
[d]PAC-3 = IDLH × ($NaVO_3$ MW ÷ V atomic mass) = 35 mg/m^3 × (121.93 g/mol ÷ 50.94 g/mol) = 84 mg/m^3.
[e]PAC-3 = IDLH × (Na_3VO_4 MW ÷ V atomic mass) = 35 mg/m^3 × (183.91 g/mol ÷ 50.94 g/mol) = 130 mg/m^3.
[f]PAC-3 = IDLH × (H_2O_4SV MW ÷ V atomic mass) = 35 mg/m^3 × (149.01 g/mol ÷ 50.94 g/mol) = 100 mg/m^3.
[g]PAC-3 = IDLH × (VCl_4 MW ÷ V atomic mass) = 35 mg/m^3 × (192.74 g/mol ÷ 50.94 g/mol) = 130 mg/m^3.
PAC-3 = IDLH × [$V_2(SO_4)_3$ MW ÷ (2 × V atomic mass)] = 35 mg/m^3 × [390.05 g/mol ÷ (2 × 50.94 g/mol)] = 130 mg/m^3.
[h]PAC-3 = IDLH × [V_2O_3 MW ÷ (2 × V atomic mass)] = 35 mg/m^3 × [149.88 g/mol ÷ (2 × 50.94 g/mol)] = 51 mg/m^3.
[i]PAC-3 = IDLH × ($H_{14}O_{11}SV$ MW ÷ V atomic mass) = 35 mg/m^3 × (273.11 g/mol ÷ 50.94 g/mol) = 190 mg/m^3.

[j]PAC-3 = IDLH × (O_5SV MW ÷ V atomic mass) = 35 mg/m^3 × (163 g/mol ÷ 50.94 g/mol) = 110 mg/m^3.
[k]PAC-3 = IDLH × ($H_{10}O_{10}SV$ MW ÷ V atomic mass) = 35 mg/m^3 × (253.08 g/mol ÷ 50.94 g/mol) = 170 mg/m^3.
[l]PAC-2 = REL × (NH_4VO_3 MW ÷ V atomic mass) = 0.05 mg/m^3 × (116.98 g/mol ÷ 50.94 g/mol) = 0.11 mg/m^3.
[m]PAC-2 = REL × (K_3O_4V MW ÷ V atomic mass) = 0.05 mg/m^3 × (232.23 g/mol ÷ 50.94 g/mol) = 0.23 mg/m^3.
[n]PAC-2 = REL × ($VOCl_3$ MW ÷ V atomic mass) = 0.05 mg/m^3 × (173.29 g/mol ÷ 50.94 g/mol) = 0.17 mg/m^3.
[o]PAC-2 = REL × ($NaVO_3$ MW ÷ V atomic mass) = 0.05 mg/m^3 × (121.93 g/mol ÷ 50.94 g/mol) = 0.12 mg/m^3.
[p]PAC-2 = REL × (Na_3VO_4 MW ÷ V atomic mass) = 0.05 mg/m^3 × (183.91 g/mol ÷ 50.94 g/mol) = 0.18 mg/m^3.
[q]PAC-2 = REL × (H_2O_4SV MW ÷ V atomic mass) = 0.05 mg/m^3 × (149.01 g/mol ÷ 50.94 g/mol) = 0.14 mg/m^3.
[r]PAC-2 = REL × (VCl_4 MW ÷ V atomic mass) = 0.05 mg/m^3 × (192.74 g/mol ÷ 50.94 g/mol) = 0.19 mg/m^3.
PAC-2 = REL × [$V_2(SO_4)_3$ MW ÷ (2 × V atomic mass)] = 0.05 mg/m^3 × [390.05 g/mol ÷ (2 × 50.94 g/mol)] = 0.19 mg/m^3.
[s]PAC-2 = REL × [V_2O_3 MW ÷ (2 × V atomic mass)] = 0.05 mg/m^3 × [149.88 g/mol ÷ (2 × 50.94 g/mol)] = 0.074 mg/m^3.
[t]PAC-2 = REL × ($H_{14}O_{11}SV$ MW ÷ V atomic mass) = 0.05 mg/m^3 × (273.11 g/mol ÷ 50.94 g/mol) = 0.27 mg/m^3.
[u]PAC-2 = REL × (O_5SV MW ÷ V atomic mass) = 0.05 mg/m^3 × (163 g/mol ÷ 50.94 g/mol) = 0.16 mg/m^3.
[v]PAC-2 = REL × ($H_{10}O_{10}SV$ MW ÷ V atomic mass) = 0.05 mg/m^3 × (253.08 g/mol ÷ 50.94 g/mol) = 0.25 mg/m^3.
[w]PAC-2 = PAC-3 ÷ 6 = 35 mg/m^3 ÷ 6 = 5.8 mg/m^3.
[x]PAC-1 = PAC-2 ÷ 11 = 0.11 mg/m^3 ÷ 11 = 0.01 mg/m^3.
[y]PAC-1 = PAC-2 ÷ 11 = 0.23 mg/m^3 ÷ 11 = 0.021 mg/m^3.
[z]PAC-1 = PAC-2 ÷ 11 = 0.17 mg/m^3 ÷ 11 = 0.015 mg/m^3.
[aa]PAC-1 = PAC-2 ÷ 11 = 0.12 mg/m^3 ÷ 11 = 0.011 mg/m^3.
[bb]PAC-1 = PAC-2 ÷ 11 = 0.18 mg/m^3 ÷ 11 = 0.016 mg/m^3.
[cc]PAC-1 = PAC-2 ÷ 11 = 7 mg/m^3 ÷ 11 = 0.64 mg/m^3.
[dd]PAC-1 = PAC-2 ÷ 11 = 0.14 mg/m^3 ÷ 11 = 0.013 mg/m^3.
[ee]PAC-1 = PAC-2 ÷ 11 = 0.19 mg/m^3 ÷ 11 = 0.017 mg/m^3.
[ff]PAC-1 = PAC-2 ÷ 11 = 0.074 mg/m^3 ÷ 11 = 0.0067 mg/m^3.
[gg]PAC-1 = PAC-2 ÷ 11 = 0.27 mg/m^3 ÷ 11 = 0.025 mg/m^3.
[hh]PAC-1 = PAC-2 ÷ 11 = 0.16 mg/m^3 ÷ 11 = 0.015 mg/m^3.
[ii]PAC-1 = PAC-2 ÷ 11 = 0.25 mg/m^3 ÷ 11 = 0.023 mg/m^3.
[jj]Agencies of Sweden and Switzerland also report a short-term value of 0.05 mg/m^3 for vanadium pentoxide (IFA, 2019).
[kk]IDLH = REL × 500 = 1 mg/m^3 × 500 = 500 mg/m^3
NIOSH documentation states: "500 is an assigned protection factor for respirators and was used arbitrarily during the Standards Completion Program for deciding when the "most protective" respirators should be used for particulates."
[ll]Agencies of Australia, Ireland, New Zealand, Belgium, Japan, Poland, Singapore, South Korea, Spain, Switzerland, Ontario, and Quebec report the same values. The vanadium pentoxide value, furthermore, matches that of Austria, France, the United Kingdom, and Hungary (HSA, 2020; IFA, 2019; Gouvernement du Québec, 2019; Ontario Ministry of Labour, 2018; Safe Work Australia, 2018; Worksafe, 2018).
[mm]Agencies of Australia, Ireland, Belgium, Poland, South Korea, Spain, Ontario, and Quebec report the same values (HSA, 2020; IFA, 2019; Gouvernement du Québec, 2019; Ontario Ministry of Labour, 2018; Safe Work Australia, 2018).
[nn]Agencies of Denmark and China report the same value (IFA, 2019).

[oo]The Minnesota Department of Health's HRV, New Jersey Department of Environmental Protection's RfC, and Washington State's ASIL are identical to the CA-REL (MDH, 2019; NJ DEP, 2018; Washington State Legislature, 2009).

[pp]The chronic RfC has been adopted by the Nevada Division of Environmental Protection (NDEP, 2017).

[qq]$LOAEL_{HEC} = LOAEL_{ADJ} \times RDDR = 0.18\ mg/m^3 \times 0.616 = 0.11\ mg/m^3$.

[rr]$LOAEL_{HEC} = LOAEL_{ADJ} \times RDDR = 0.09\ mg/m^3 \times 0.182 = 0.016\ mg/m^3$.

[ss]Dividing each LOAEL by the uncertainty factor yields a value of 0.0005–0.001 mg V_2O_5/m^3. RIVM concluded that this was "only marginally different" from the World Health Organization's 1987 guideline based on human data. WHO's value—no longer in effect—of 0.001 mg V/m^3 was thus provisionally applied by RIVM to vanadium compounds.

[tt]Michigan Environment, Great Lakes and Energy; Nevada Division of Environmental Protection; Pennsylvania Department of Environmental Protection; and New Jersey Department of Environmental Protection have adopted the chronic MRL as an RfC. The New Jersey Department of Environmental Protection has also adopted the acute MRL as a short-term RfC with a 24-hour averaging time (U.S. EPA, 2020; NJ DEP, 2018; NDEP, 2017; DEQ, 2015).

[uu]$LOAEL_{HEC} = LOAEL_{ADJ} \times RDDR = 0.1\ mg\ V/m^3 \times 0.732 = 0.073\ mg\ V/m^3$.

[vv]$BMCL_{HEC} = BMCL_{ADJ} \times RDDR = 0.0071\ mg\ V/m^3 \times 0.423 = 0.003\ mg\ V/m^3$.

[ww]$BCL = AT \div [ET \times EF \times ED \times (1 \div MRL)] = (6\ yrs. \times 365\ days/yr. \times 24\ hrs./day) \div [24\ hrs./day \times 350\ days/yr. \times 6\ yrs. \times (1 \div 0.0001\ mg/m^3)] = 0.000104\ mg/m^3$.

[xx]$BCL = TR \times AT \div (ET \times EF \times ED \times URF) = (10^{-6} \times 70\ yrs. \times 365\ days/yr. \times 24\ hrs./day) \div [24\ hrs./day \times 350\ days/yr. \times 26\ yrs. \times 0.00830\ (\mu g/m^3)^{-1}] = 0.000338\ \mu g/m^3$.

[yy]The acute MRL listed by the Rhode Island Department of Environmental Management does not match the current value posted by ATSDR. The source for the Rhode Island Air Toxics Guideline was last updated in September 2008; thus, these values are assumed to be based on old MRLs that were in effect at that time.

AAL = acceptable ambient level; ACGIH = American Conference of Governmental Industrial Hygienists; ADJ = adjusted; ASIL = acceptable source impact level; AT = averaging time; ATSDR = Agency for Toxic Substances and Disease Registry; BCL = basic comparison level; BMCL = benchmark concentration level; BMDL = benchmark dose level; Cal/OSHA = California Division of Occupational Safety and Health; CA-REL = California reference exposure level; CT DEEP = Connecticut Department of Energy and Environmental Protection; DEQ = Department of Environmental Quality; DOE = Department of Energy; ED = exposure duration; EF = exposure frequency; EPA = Environmental Protection Agency; ET = exposure time; HEC = human equivalent concentration; HLV = hazard limiting value; H_2O_4SV = vanadium sulfate; $H_{14}O_{11}SV$ = vanadium (II) sulfate heptahydrate; $H_{10}O_{10}SV$ = vanadyl sulfate pentahydrate; HRV = health risk value; HSA = Health and Safety Authority; IFA = *Institut für Arbeitsschutz,* The Institute for Occupational Safety and Health; IDLH = immediately dangerous to life or health; K_3O_4V = potassium orthovanadate; LOAEL = lowest-observed-adverse-effect level; LOC = level of concern; MDH = Minnesota Department of Health; MRL = minimal risk level; MW = molecular weight; NA = not applicable; NATICH = National Air Toxics Information Clearinghouse; $NaVO_3$ = sodium metavanadate; Na_3VO_4 = sodium orthovanadate; NDEP = Nevada Division of Environmental Protection; NH_4VO_3 = ammonium metavanadate; NIOSH = National Institute for Occupational Safety and Health; NJ DEP = New Jersey Department of Environmental Protection; NOAEL = no-observed-adverse-effect level; NR = not reported; NTP = National Toxicology Program; OEHHA = Office of Environmental Health Hazard Assessment; OSHA = Occupational Safety and Health Administration; O_5SV = vanadyl sulfate; PAC = Protective Action Criteria; PEL = permissible exposure level; PPRTV = Provisional Peer-Reviewed Toxicity Value; pTCA = provisional tolerable concentration; RDDR = regional deposited dose ratio; REL = recommended exposure limit; RfC = reference concentration; RI DEM = Rhode Island Department of Environmental Management; RIVM = *Rijksinstituut voor Volksgezondheid en Milieu,* The Netherlands Institute for Public Health and the Environment; STEL = short-term exposure limit; TLV = threshold limit value; TR = target risk; TWA = time-weighted average; UF_A = animal-to-human variability; UF_D = database uncertainty; UF_H = interhuman variability; UF_L = LOAEL-to-NOAEL adjustment; URF = unit risk factor; V = vanadium; V_2O_5 = vanadium pentoxide; VCl_4 = vanadium tetrachloride; V_2O_3 = vanadium trioxide; $VOCl_3$ = trichlorooxovanadium; $V_2(SO_4)_3$ = vanadium (III) sulfate; WHO = World Health Organization.

Table A-3. Details on inhalation reference values from other agencies

	Reference value name	Duration	Vanadium form	Reference value (mg/m^3)	Health effect	Point of departure	Qualifier	Source	Uncertainty factors	Notes on derivation	Review status
Special Use	**USAPHC MEG – Critical**	1 h	Ammonium metavanadate	0.75	Adopted 2009 PACs	–	–	(DOE, 2009)	–	Adopted 2009 PACs (rounded to 2 significant figures)	Final (U.S. APHC, 2013)
			Sodium metavanadate	30							
			Sodium orthovanadate	130							
			Vanadium sulfate	310							
			Vanadium pentoxide	35							
			Vanadium tetrachloride	130							
			Vanadium (III) sulfate								
			Vanadium trioxide	52							
			Trichlorooxovanadium	750							
			Vanadyl sulfate	110							
			Vanadium	35							
	USAPHC MEG – Marginal	1 h	Ammonium metavanadate	0.32							
			Sodium metavanadate	1.2							
			Sodium orthovanadate	1.8							
			Vanadium sulfate	4.5							
			Vanadium pentoxide	7.0							
			Vanadium tetrachloride	0.19							
			Vanadium (III) sulfate								
			Vanadium trioxide	7.4							
			Trichlorooxovanadium	1.3							
			Vanadyl sulfate	1.6							
			Vanadium	0.50							

	Reference value name	Duration	Vanadium form	Reference value (mg/m^3)	Health effect	Point of departure	Qualifier	Source	Uncertainty factors	Notes on derivation	Review status
	USAPHC MEG – Negligible	1 h	Ammonium metavanadate	0.040							
			Sodium metavanadate	0.15							
			Sodium orthovanadate	0.25							
			Vanadium sulfate	0.60							
			Vanadium pentoxide	1.0							
			Vanadium tetrachloride	0.025							
			Vanadium (III) sulfate								
			Vanadium trioxide	1.0							
			Trichlorooxovanadium	0.15							
			Vanadyl sulfate	0.20							
			Vanadium	0.075							
		8 h	Ferrovanadium	1.0	Adopted ACGIH TLV-TWA	–	–	–	–	Adopted ACGIH TLV-TWA	
			Vanadium pentoxide	0.05	Adopted ACGIH TLV-TWA	–	–	–	–	Adopted ACGIH TLV-TWA	
		14 d	Ferrovanadium	0.34	Based on ACGIH TLV-TWA	–	–	–	–	Based on ACGIH TLV-TWA[a]	
			Vanadium pentoxide	0.00014	Based on acute MRL	–	–	–	–	Based on acute MRL[b]	
			Vanadium	0.00055	Based on acute MRL	–	–	–	–	Based on acute MRL[c]	
		1 y	Ferrovanadium	0.34	Based on ACGIH TLV-TWA	–	–	–	–	Based on ACGIH TLV-TWA[d]	
			Vanadium pentoxide	0.00014	Based on acute MRL	–	–	–	–	Based on acute MRL[e]	
			Vanadium	0.000068	Based on chronic MRL	–	–	–	–	Based on chronic MRL[f]	

	Reference value name	Duration	Vanadium form	Reference value (mg/m^3)	Health effect	Point of departure	Qualifier	Source	Uncertainty factors	Notes on derivation	Review status
General Public (Limited Details)	**MassDEP TEL**	24 h	Vanadium	0.00027	NR	NR	NR		NR	Values derived in accordance with this protocol: (MassDEP, 2011)	Final (MassDEP, 2019)
			Vanadium pentoxide	0.00014							
	MassDEP AAL	1 y	Vanadium	0.00027							
			Vanadium pentoxide	0.00003							
	WAC ASIL	24 h	Vanadium dust or fume	0.0001	NR	NR	NR		NR		Final (Washington State Legislature, 2009)
	SWCAA ASIL	24 h	Vanadium pentoxide	0.00017	NR	NR	NR		NR	Adopted 1998 Washington State ASIL	Final (SWCAA, 2020)
	ID DEQ AAC	24 h	Vanadium pentoxide, respirable dust, and fume	0.0025	NR	NR	NR		NR		Final (Idaho DEQ)
			Ferrovanadium	0.05							
	VT DEC HAAS	1 y	Vanadium pentoxide	0.00001	NR	NR	NR		NR		Final (VT ANR, 2018)
	TCEQ RfC	Chronic	Vanadium	0.00003	NR	NR	NR		NR		Final (TCEQ, 2018)
	ADEQ AQG	1 h	Vanadium	0.0015	Based on 24-hr AQG	–	–	–	–	Based on 24-hr AQG[g]	Final (U.S. EPA, 1993)[h]
		24 h		0.0004	Based on vanadium pentoxide ACGIH TLV	–	–	–	–	Based on vanadium pentoxide ACGIH TLV[i]	
	NDEP AAC	8 h	Vanadium	0.001	NR	0.05 mg/m^3	V_2O_5 ACGIH TLV-TWA	(ACGIH, 1991)	Total UF = 42		

	Reference value name	Duration	Vanadium form	Reference value (mg/m^3)	Health effect	Point of departure	Qualifier	Source	Uncertainty factors	Notes on derivation	Review status
	OK Dept. of Health AAC	24 h	Vanadium	0.0005	NR	0.05 mg/m^3	V_2O_5 ACGIH TLV-TWA	(ACGIH, 1991)	Total UF^j = 100		
	Pinellas County Air Pollution Control Board AAC	8 h	Vanadium pentoxide	0.00012	NR	NR	NR		NR		
		24 h		0.0005							
		1 y		0.02							
	NDDH ACG	8 h	Vanadium pentoxide	0.0005	NR	0.05 mg/m^3	ACGIH TLV-TWA	(ACGIH, 1991)	Total UF = 100		
	TX Air Control Board AAC	30 min	Vanadium pentoxide	0.0005	NR	NR	NR		NR	Based on occupational values	
		1 y		0.00005							
	VA Air Pollution Control AAC	24 h	Vanadium pentoxide	0.0008	NR	0.05 mg/m^3	ACGIH TLV-TWA	(ACGIH, 1991)	Total UF^k = 60		
Occupational (International)	**Latvia Limit Value**	8 h	Vanadium trioxide	0.5	NR	NR	NR		NR		Final (IFA, 2019)
			Vanadium and compounds	1							
			Vanadium pentoxide fume	0.1							
	China Limit Value	8 h	Vanadium	0.05	NR	NR	NR		NR		
	Finland OEL	8-h TWA	Ferrovanadium, as V	0.5	NR	NR	NR		NR		
			Vanadium pentoxide, as V	0.02							
	Austria Limit Value	Short-term	Vanadium pentoxide, respirable aerosol	0.25	NR	NR	NR		NR		
			Vanadium, inhalable aerosol, and vanadium carbide	1							
		8 h		0.5							

	Reference value name	Duration	Vanadium form	Reference value (mg/m^3)	Health effect	Point of departure	Qualifier	Source	Uncertainty factors	Notes on derivation	Review status
	HIOH Limit Value (Hungary)	Short-term	Vanadium pentoxide, respirable aerosol	0.2	NR	NR	NR		NR		
	Romania Limit Value	15 min	Ferrovanadium	1.5	NR	NR	NR		NR		
			Vanadium pentoxide	0.1							
		8-h TWA	Ferrovanadium	0.5							
			Vanadium pentoxide fume	0.05							
			Vanadium pentoxide dust	0.1							
	Denmark Limit Value	Short-term	Vanadium pentoxide, inhalable aerosol	0.06	NR	NR	NR		NR		
		8 h		0.03							
	Sweden Limit Value	8 h	Vanadium pentoxide, inhalable fraction	0.2	NR	NR	NR		NR		
	SER MAC (The Netherlands)	Short-term	Vanadium oxides	0.03	NR	NR	NR		NR		
		8 h		0.01							

[a]MEG = TLV × $IR_{occupational}$ ÷ $IR_{military}$ = 1 mg/m^3 × (10 m^3 ÷ 29.2 m^3) = 0.34 mg/m^3.

[b]MEG = MRL × ($IR_{general\ pop.}$ ÷ $IR_{military}$) = 0.0002 mg/m^3 × (20 m^3/day ÷ 29.2 m^3/day) = 0.00014 mg/m^3.
Based on the derivation details provided and information from Rhode Island Department of Environmental Management, it is assumed that an MRL of 0.0002 mg/m^3 was in effect when this value was derived.

[c]MEG = MRL × ($IR_{general\ pop.}$ ÷ $IR_{military}$) = 0.0008 mg/m^3 × (20 m^3/day ÷ 29.2 m^3/day) = 0.00055 mg/m^3.

[d]MEG = TLV × $IR_{occupational}$ ÷ $IR_{military}$ = 1 mg/m^3 × (10 m^3 ÷ 29.2 m^3) = 0.34 mg/m^3.

[e]MEG = MRL × ($IR_{general\ pop.}$ ÷ $IR_{military}$) = 0.0002 mg/m^3 × (20 m^3/day ÷ 29.2 m^3/day) = 0.00014 mg/m^3.
Based on the derivation details provided and information from Rhode Island Department of Environmental Management, it is assumed that an MRL of 0.0002 mg/m^3 was in effect when this value was derived.

[f]MEG = MRL × ($IR_{general\ pop.}$ ÷ $IR_{military}$) = 0.0001 mg/m^3 × (20 m^3/day ÷ 29.2 m^3/day) = 0.000068 mg/m^3.

[g]1-hr AQG = 24-hr AQG × 3.8 = 0.0004 mg/m^3 × 3.8 = 0.0015 mg/m^3.

[h]This document was compiled by the U.S. Environmental Protection Agency in 1993. Values from this document may have since been archived or updated by the state agencies that reported them.

[i]AQG = TLV ÷ 126 = 0.05 mg/m^3 ÷ 126 = 0.0004 mg/m^3.

[j]A factor of 100 is applied to category A substances.

[k]A factor of 60 is applied for noncarcinogens.

AAC = acceptable ambient concentration; AAL = allowable ambient limit, ACG = ambient concentration guideline; ACGIH = American Conference of Governmental Industrial Hygienists; ADEQ = Arizona Department of Environmental Quality; AQG = air quality guideline; ASIL = acceptable source impact level; DOE = Department of Energy; EPA = Environmental Protection Agency; HAAS = hazardous ambient air standard; HIOH = Hungarian Institute of Occupational Health; ID DEQ = Idaho Department of Environmental Quality; IFA = *Institut für Arbeitsschutz,* The Institute for Occupational Safety and Health; MAC = maximum admissible concentration; MassDEP = Massachusetts Department of Environmental Protection; MEG = military exposure guideline; MRL = minimal risk level; NDDH = North Dakota Department of Health; NDEP = Nevada Division of Environmental Protection; NR = not reported; OEL = occupational exposure limit; PAC = Protective Action Criteria; RfC = reference concentration; SER = Social and Economic Council of the Netherlands; SWCAA = Southwest Clean Air Agency; TCEQ = Texas Commission on Environmental Quality; TEL = toxic effects exposure limit; TLV = threshold limit value; TWA = time-weighted average; UF = uncertainty factor; USAPHC = United States Army Public Health Center; V = vanadium; V_2O_5 = vanadium pentoxide; VT DEC = Vermont Department of Environmental Conservation; WAC = Washington Administrative Code.

APPENDIX B. LITERATURE SEARCH STRATEGIES

Table B-1. Literature search strategies for vanadium compounds

Source	Search Strategy	Number of records
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)	24,887
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 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	4,888

Source	Search Strategy	Number of records
	"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+anhydride"+"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	15

Source	Search Strategy	Number of records
ATSDR Toxicological Profile for Vanadium (2012)	References pulled from ATSDR document	363
2008 & 2009 PPRTV Assessments	References pulled from PPRTV documents	75
2011 IRIS External Review Draft	References pulled from V_2O_5 IRIS document	49
2006 IARC Document	References pulled from IARC document	240
OAR	References provided by Office of Air and Radiation (OAR)	10
TOTAL	25,988 unique items were discovered using this search strategy.	25,988

APPENDIX C. PRELIMINARY LITERATURE SEARCH AND SCREENING METHODS

The Agency for Toxic Substances and Disease Registry (ATSDR) *Toxicological Profile for Vanadium* (ATSDR, 2012) was selected as the starting point for the literature search because it is the most recent review of health effects of vanadium compounds published by a U.S. federal agency. ATSDR assessments undergo public comment and external peer review. 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.[8]

Database searches were then conducted to identify records that had been published since development of the 2012 ATSDR *Toxicological Profile for Vanadium*. The databases listed below were searched for records published between 2010 and 2019. The start date of 2010 was selected to ensure records published near the time of release of the ATSDR document were captured.

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

Database searches were conducted by an EPA information specialist on March 28, 2019, and repeated on March 9, 2020,[9] and all records were stored in the HERO database. In total, 22,559 unique records were identified after duplicate removal. Because the number of records retrieved was large, records were imported into Sciome Workbench for Interactive computer-Facilitated Text-mining (SWIFT) Review software [see also Howard et al. (2016)] to identify those most likely applicable to human health. In brief, SWIFT Review has preset literature search filters, which were developed by information specialists, that can be applied to distinguish studies that might 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 Heading (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) and health outcomes (cancer,

[8]EPA's HERO database provides access to the scientific literature behind EPA science assessments. The database includes scientific references and data from the peer-reviewed literature used by EPA to develop its regulations.

[9]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.

cardiovascular, developmental, endocrine, gastrointestinal, hematological and immune, hepatic, mortality, musculoskeletal, neurological, nutrition and metabolic, ocular and sensory, renal, reproductive, respiratory, and skin and connective tissue). The details of the search strategies that underlie the filters are available at this link. 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,[10] as described below.

This literature search strategy is designed to be broad, but like any search strategy, studies might be missed (e.g., cases where the specific chemical is not mentioned in title, abstract, or keyword content; "gray" literature that is not indexed in the databases listed above). Thus, when additional references that were cited in prior assessments or shared by EPA program offices (e.g., Office of Air), 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. In this evidence map, additional references were provided by OAR and were identified by manual review of the following list of final or publicly available draft assessments:

- PPRTV assessment of vanadium pentoxide (U.S. EPA, 2008)
- PPRTV assessment of vanadium and its soluble compounds other than vanadium pentoxide (U.S. EPA, 2009)
- IRIS External Review Draft assessment of vanadium pentoxide (U.S. EPA, 2011)
- International Agency for Research on Cancer (IARC) document on vanadium pentoxide (IARC, 2006).

[10] DistillerSR is a web-based systematic review software used to screen studies available at https://www.evidencepartners.com/products/distillersr-systematic-review-software.

APPENDIX D. PRELIMINARY LITERATURE SURVEY SUMMARY

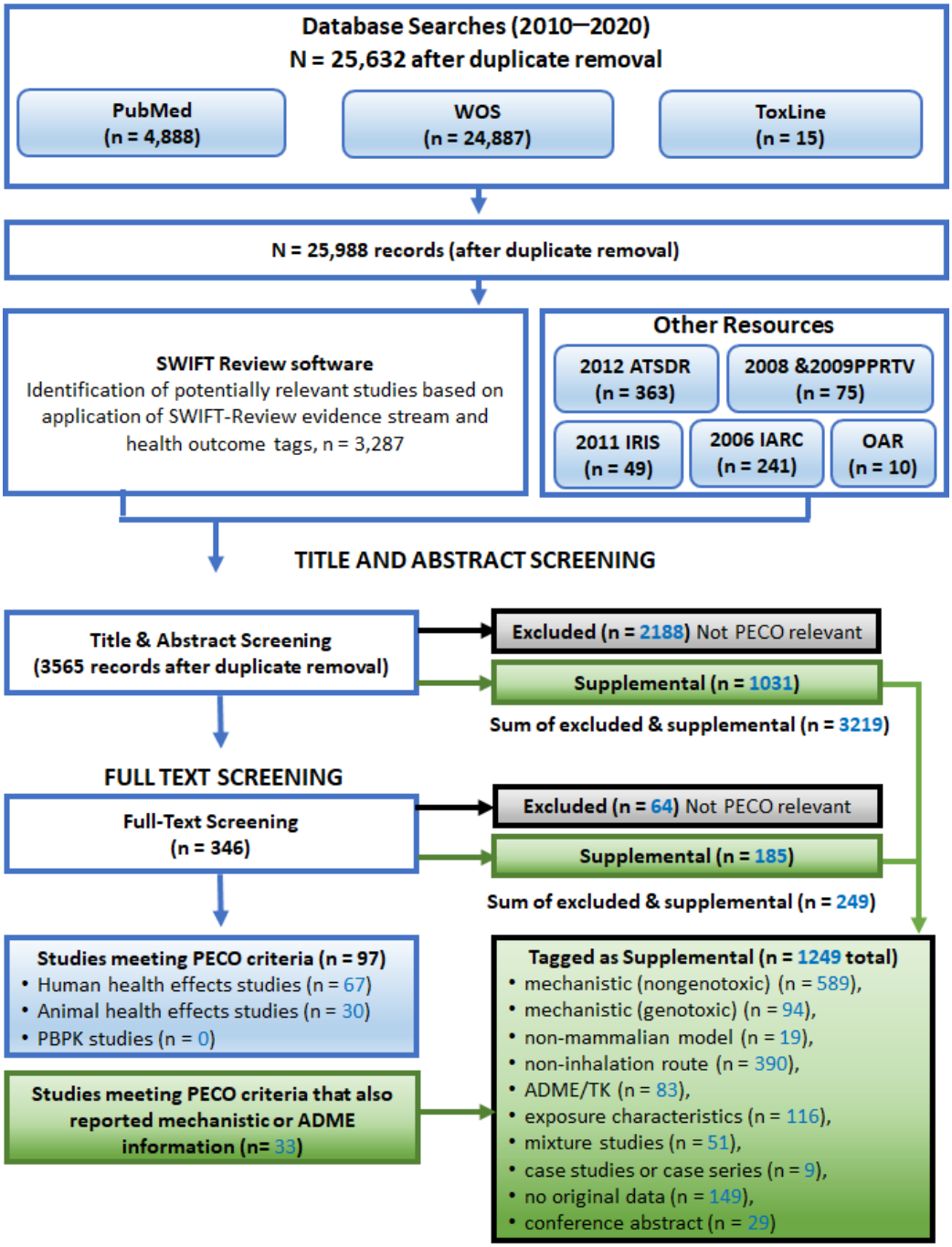

Figure D-1. Literature survey study flow selection diagram.