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IRIS Assessment Plan
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IRIS Assessment Plan for Inorganic Mercury Salts (Scoping and Problem Formulation Materials)

(Mercuric Chloride [7487-94-7], Mercuric Sulfide [1344-48-5], Mercurous Chloride [10112-91-1])

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Integrated Risk Information System
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ABBREVIATIONS

ADME	absorption, distribution, metabolism, and excretion
ATSDR	Agency for Toxic Substances and Disease Registry
CA	California
CASRN	Chemical Abstracts Service registry number
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CICAD	Concise International Chemical Assessment Documents
DNT	developmental neurotoxicity
DWEL	drinking water equivalent level
EPA	Environmental Protection Agency
EPCRA	Emergency Planning and Community Right-to-Know Act
GI	gastrointestinal
HA	health advisory
HERO	Health and Environmental Research Online
Hg	mercury
$HgCl_2$	mercuric chloride
Hg_2Cl_2	mercurous chloride
HgS	mercuric sulfide
IAP	IRIS Assessment Plan
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
MCL	maximum contaminant level
MEG-N	military exposure guideline
MRL	minimal risk level
NCEA	National Center for Environmental Assessment
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
OLEM	Office of Land and Emergency Management
ORD	Office of Research and Development
OW	Office of Water
PBPK	physiologically based pharmacokinetic
PECO	populations, exposures, comparators, and outcomes
PHG	public health goals
RCRA	Resource Conservation Recovery Act
REL	reference exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RIVM	Dutch National Institute for Public Health and the Environment
TDI	tolerable daily intake
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_H	intraspecies uncertainty factor
WHO	World Health Organization
WOS	Web of Science

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1. INTRODUCTION

The Integrated Risk Information System (IRIS) Program is undertaking a [re]assessment of the health effects of inorganic mercury salts (mercuric chloride, mercuric sulfide, mercurous chloride). Among these three salts, only one, mercuric chloride, has a previously developed IRIS reference dose (RfD) [https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=692 (U.S. EPA, 1995)]. During fiscal year 2018, Environmental Protection Agency (EPA) prioritized its IRIS assessments to meet the highest needs of EPA programs and regions and to bring greater focus to assessments under development further described in the December 2018 IRIS Program Outlook (https://www.epa.gov/sites/production/files/2018-12/documents/iris_program_outlook_december_2018.pdf). IRIS assessments provide high-quality, publicly available information on the toxicity of chemicals to which the public might be exposed. These assessments are not regulations but provide a critical part of the scientific foundation for decisions made in EPA program and regional offices to protect public health.

As part of the assessment development, the IRIS Program undertakes scoping and 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 and summary of the underlying data may also be conducted to help identify the extent of the evidence and health effects that have been studied for the chemical of interest. Based on 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 efforts and conclusions are contained in the **IRIS Assessment Plan (IAP)**.

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

Figure 1 displays the context of the IAP and Systematic Review Protocol in the systematic review process.

This document presents the draft IAP for oral exposures of the three most commonly occuring inorganic mercury salts—mercuric chloride, mercuric sulfide, and mercurous chloride—deemed important to EPA's program offices. It describes the Agency's need for the assessment; objectives and specific aims of the assessment; draft populations, exposures, comparators, and outcomes (PECO) criteria that outline the evidence considered most pertinent to address the

specific aims of the assessment; and identification of key areas of scientific complexity. Brief background information on uses and the potential for human exposure to inorganic mercury salts is provided for context.

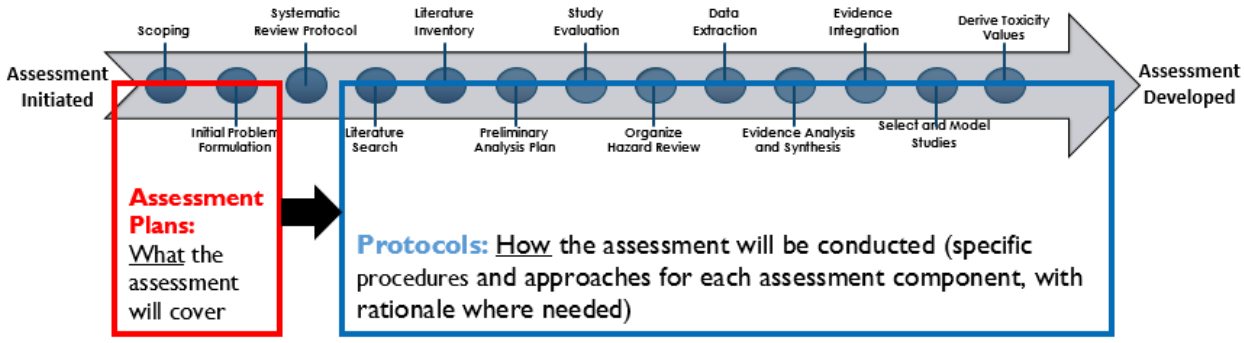


Figure 1. Integrated Risk Information System (IRIS) systematic review problem formulation and method documents.

2. SCOPING AND INITIAL PROBLEM FORMULATION

2.1. BACKGROUND

Mercury occurs naturally in the environment and can exist as elemental, organic, or inorganic mercury. This IRIS assessment will evaluate the potential human health effects of the three most commonly occurring inorganic mercury salts: mercuric chloride ($HgCl_2$), mercuric sulfide (HgS, cinnabar), and mercurous chloride (Hg_2Cl_2, calomel) (WHO, 2003). Elemental mercury and methylmercury are not included in this assessment. EPA is currently evaluating the developmental neurotoxicity (DNT) effects following methylmercury exposure in humans to update the oral RfD. There are no ongoing efforts to update the inhalation reference concentration (RfC) for elemental mercury based on prioritization efforts described in the December 2018 IRIS Program Outlook. Further details on the elemental and methylmercury assessments can be found at https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=370 and https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=343693, respectively.

Mercury occurs naturally in geologic materials in the environment and can exist in inorganic form as salts. It also can exist in elemental form as a liquid or gas or in its highly toxic organic form (methylmercury). In its inorganic form, mercury occurs abundantly in the environment, primarily as the minerals cinnabar (HgS) and metacinnabar and as impurities in other minerals (USGS, 1970). Its geologic associations are with volcanic rocks and hydrothermal systems, where it can readily combine with chlorine, sulfur, and other elements and subsequently weather to form inorganic salts.

Inorganic mercury salts can be transported in water and occur in soil. Dust containing these salts can enter the air from mining deposits of ores that contain mercury. Emissions of both elemental or inorganic mercury can occur from coal-fired power plants, burning of municipal and medical waste, and from factories that use mercury. Inorganic mercury can also enter water or soil from the weathering of rocks that contain inorganic mercury salts, and from factories or water treatment facilities that release water contaminated with mercury (ATSDR, 1999).

Although the use of mercury salts in consumer products, such as medicinal products, are phased out, inorganic mercury compounds are still being widely used in skin lightening soaps and creams. Mercuric chloride is used in photography and as a topical antiseptic and disinfectant, wood preservative, and fungicide. In the past, mercurous chloride was widely used in medicinal products, including laxatives, worming medications, and teething powders. It has since been replaced by safer and more effective agents (ATSDR, 1999). Mercuric sulfide is used to color paints and is one of the red coloring agents used in tattoo dyes (ATSDR, 1999). Details of the physical and chemical properties of each of the compounds is provided in Supplemental Material, Appendix A, Table A-1.

Human exposure to inorganic mercury salts can occur both in occupational and environmental settings (ATSDR, 1999). Occupations with higher risk of exposure to mercury and its salts include mining, electrical equipment manufacturing, and chemical and metal processing in which mercury is used. In the general population, exposure to mercuric chloride can occur through the dermal route from the use of soaps and creams or topical antiseptics and disinfectants (Mckelvey et al., 2011). Another, less well-documented, source of exposure to inorganic mercury salts among the general population is from their use in ethnic religious, magical, and ritualistic practices and in herbal remedies (WHO, 2003).

Although inorganic mercury salts can enter the body through ingestion, inhalation, or through the dermal exposure route, there is limited scientific data on both the inhalation and dermal routes of exposure (ATSDR, 1999). Oral exposures have been well studied based on the understanding that ingestion is the primary route through which most inorganic mercury salts are absorbed in the body. When inorganic mercury salts are ingested, up to 40% can enter through the stomach and intestines; however, less than 10% is generally absorbed through the intestinal tract (ATSDR, 1999). The extent of transport across the intestinal tract depends on the compound's solubility (Friberg and Nordberg, 1973) and how easily it dissociates in the intestinal lumen to become available for absorption (Endo et al., 1990). Absorption of mercurous forms[1] is less likely than absorption of mercuric forms due to the former's poor solubility (Friberg and Nordberg, 1973). In animal studies, using whole-body retention data to indicate absorption, it is estimated that 20–25% absorption occurs when mercuric chloride is given via the oral route of exposure (Nielsen and Andersen, 1990). This oral absorption has been shown to vary depending on the intestinal pH (Endo et al., 1990), age, and diet (Kostial et al., 1978). Nutritional status might also contribute to the intestinal absorption of Hg^{2+} because of competition with nutritionally essential divalent cations such as Cu^{2+} or Zn^{2+} for membrane-embedded transporters. Although mercurous chloride is insoluble and not readily absorbed, small amounts may be converted into the mercuric ion and then absorbed in the lumen of the intestine, causing the toxicity. Evidence of dermal absorption in individuals following dermal application of ointments that contained inorganic mercury salts (Kang-Yum and Oransky, 1992; Bourgeois et al., 1986; De Bont et al., 1986) and in urine samples from women using skin lightening creams containing inorganic mercury salts (Mckelvey et al., 2011; Barr et al., 1973) have been reported. Although small amounts of inorganic mercury salts can enter through skin (WHO, 2003), inhalation and dermal penetration are generally not considered to be significant routes of exposure for inorganic mercury salts because of their physical and chemical properties.

[1]Mercury with a valence state of +1 is referred to as mercurous mercury (e.g., mercurous chloride), and mercury with a valence state of +2 is referred to as mercuric mercury (e.g., mercuric chloride, mercuric sulfide). Once absorbed into the system, inorganic mercury enters an oxidation-reduction cycle. Absorbed divalent cations from exposure to mercuric compounds can, in turn, be reduced to the metallic or monovalent form and released as exhaled metallic mercury vapor (ATSDR, 1999).

Once absorbed into the body, inorganic mercury salts are systemically distributed and readily accumulate in the kidneys and liver (Nielsen and Andersen, 1990; Yeoh et al., 1989). For instance, Sin et al. (1983) found the kidney to have the highest mercury levels following repeated oral exposure of mice to mercury chloride over a period of 2–8 weeks. The amount of inorganic divalent mercury that crosses the blood-brain and placental barriers is very low because of its poor solubility (Inouye and Kajiwara, 1990; Clarkson, 1989). However, occasionally some methylmercury can be converted to inorganic mercury in the brain, and if this happens, it can remain in the brain for a long time (ATSDR, 1999). Inorganic mercury salts are mainly excreted through urine or feces over a period of several weeks or months (ATSDR, 1999). The elimination half-life for inorganic salts is about 40 days (Goyer, 1991). Other minor routes of excretion from the human body include exhalation through the lungs and by secretion in saliva, bile, and sweat (Clarkson et al., 1988).

An assessment for mercuric chloride is currently available on the IRIS Program website [https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=692 (U.S. EPA, 1995)]. In 1995, IRIS derived an oral RfD value of 3×10^{-4} mg/kg-day for mercuric chloride based on autoimmune effects (autoimmune glomerulonephritis) in brown Norway rats in subchronic-duration feeding and subcutaneous studies (Andres, 1984; Bernaudin et al., 1981; Druet et al., 1978). An RfD for mercuric sulfide or mercurous chloride is not available on IRIS at this time. No inhalation toxicity values (RfC) have been derived for any of the inorganic mercury salts (mercuric chloride, mercuric sulfide, or mercurous chloride). A cancer assessment for mercuric chloride was conducted by EPA in 1995. Based on the qualitative weight-of-evidence characterization, mercuric chloride was classified as a possible human carcinogen. However, no quantitative cancer values were derived for either oral or inhalation exposures because of lack of human data and limited animal carcinogenicity data. [https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=692 (U.S. EPA, 1995)].

2.2. SCOPING SUMMARY

During scoping, the IRIS Program met with EPA program and regional offices that had interest in an IRIS assessment for inorganic mercury salts to discuss specific assessment needs. Table 1 provides a summary of input from this outreach.

Table 1. Environmental Protection Agency (EPA) program and regional office interest in an assessment of inorganic mercury salts

EPA program or regional office	Oral	Inhalation	Statutes/regulations	Anticipated uses/interest
OLEM	✓	✓[a]	CERCLA; EPCRA; RCRA Subtitle I (underground storage tanks)	Toxicological information from inorganic mercury salts may be used to make risk determinations for response actions (e.g., short-term removals, long-term remedial response actions) under CERCLA and RCRA including Subtitle I. For example, CERCLA authorizes EPA to conduct short- or long-term cleanups at Superfund sites and later recover cleanup costs from potentially responsible parties under Section 107.

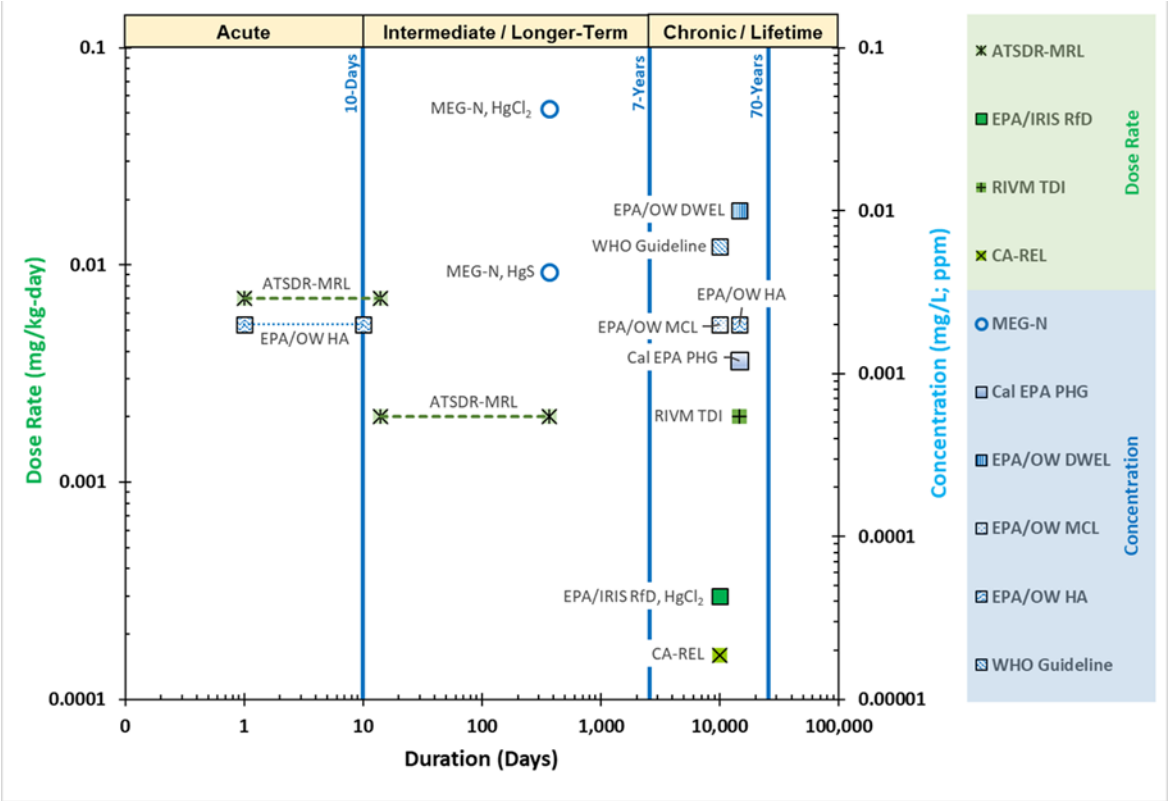
CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; EPCRA = Emergency Planning and Community Right-to-Know Act; OLEM = Office of Land and Emergency Management; RCRA = Resource Conservation Recovery Act.

[a]Additional discussions with OLEM indicated a primary need for oral exposure values and no anticipated need for inhalation values. In addition, dermal exposure was not indicated as a need.

2.3. PROBLEM FORMULATION

EPA has identified the Agency for Toxic Substances and Disease Registry (ATSDR) *Toxicological Profile for Mercury* (ATSDR, 1999) as the most recent health agency assessment to help identify the health effects most likely to require critical evaluation, although all potential health effects will be considered in this assessment. The ATSDR toxicological profile includes information on different forms of mercury including metallic mercury (also known as elemental mercury), inorganic mercury, and organic mercury. However, this assessment will focus on three inorganic mercury salts (i.e., mercuric chloride, mercurous chloride, and mercuric sulfide) and only for the oral route of exposure. Figure 2 provides an overview of current (July 2019) oral values and standards (including toxicity values, health advisories, and regulations) from different state and federal agencies and international bodies for inorganic mercury salts, while Table 2 specifically provides the endpoints and the basis for derivation of the oral toxicity values from federal and international bodies. Unlike the toxicity values presented in Table 2, it must be noted that not all of the information presented in the Figure 2 is directly comparable. Specifically, in addition to toxicity values that may inform regulatory decisions, Figure 2 also provides dose levels (mg/kg/day) and exposure concentrations (mg/L) that are based on toxicity values (or similar estimates) combined with other information and considerations (e.g., human exposure information). These other values and standards include non-enforceable public health goals (e.g., EPA HA, WHO guideline, Cal EPA PHG) as well as an EPA MCL, which is enforceable. ATSDR (1999) has derived oral minimal risk levels (MRLs) for acute (0.007 mg/kg-day) and intermediate (0.002 mg/kg-day) durations of

exposure to individual inorganic mercury salts based on kidney effects reported in a 1993 National Toxicology Program (NTP) study of mercuric chloride (NTP, 1993). Most of the supporting studies of oral exposure to inorganic mercury salts were on mercuric chloride. The findings reported in ATSDR (1999) are consistent with other assessments (WHO, 2003; U.S. EPA, 1995). The World Health Organization (WHO) derived a toxicity value of 0.002 mg/kg-day based on renal effects in rats (WHO, 2003). EPA-IRIS derived an oral RfD in 1995 for mercuric chloride based on autoimmune effects (autoimmune glomerulonephritis) of 3×10^{-4} mg/kg-day. EPA (Office of Water) derived a chronic maximum contaminant level (MCL) value of 0.002 mg/L for mercury salts using drinking water equivalent level (DWEL) values based on autoimmune glomerulonephritis in rats (U.S. EPA, 2018, 1988). The International Agency for Research (IARC) concluded that there is limited evidence in experimental animals for the carcinogenicity for mercuric chloride and it is not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 1993).



ATSDR = Agency for Toxic substances and Disease Registry; CalEPA = California Environmental Protection Agency; DWEL = Drinking Water Equivalent Level; EPA = Environmental Protection Agency; HA = health advisory; IRIS = Integrated Risk Information System; MCL = Maximum Contaminant Level; MEG-N = Military Exposure Guideline; MRL = Minimal Risk Level; OW = Office of Water; PHG = public health goals; REL = reference exposure level; RfD = Reference Dose; RIVM = Dutch National Institute for Public Health and the Environment; TDI = tolerable daily intake; WHO = World Health Organization.

Figure 2. Current oral values and standards for inorganic mercury salts. Line segments indicate relevant durations for individual values.

Table 2. Inorganic mercury salts oral toxicity values (mg/kg-day) from U.S. federal and international bodies

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

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

In this IAP, systematic review methods were used to identify initial literature for all three inorganic mercury salts. These methods were implemented in accordance with the IRIS Quality Assurance Project Plan. The literature search focused on studies published after the release of the ATSDR Toxicological Profile in 1999. Searches included studies from 1997 through February 2019 to overlap at least 2 years to ensure no studies were missed. PubMed, Toxline, and Web of Science (WOS) databases were searched. A PECO (see Table 5) was used to focus the research question(s), search terms, and inclusion/exclusion criteria in the evidence map. Detailed literature search strategies (see Appendix B), literature search methods and initial results (see Appendix C), and initial literature inventory summaries (see Appendix D, Figure D-1 to Figure D-6) are described in the supplemental materials/appendices at the end of this document. The results obtained from the systematic review process for both oral and inhalation studies, helped inform the specific aims and anticipated analysis.

Abstracts and full text were screened for oral studies (see Figure D-1 to Figure D-3) for all three inorganic mercury salts. Studies that did not meet the PECO criteria were either excluded or tagged as supplemental material. Mercuric chloride had 131 (2 human and 129 animal) studies

that warranted further evaluation. Over 700 studies (mechanistic and absorption, distribution, metabolism, and excretion (ADME) studies) were tagged as supplemental. Similarly, 30 animal studies were considered for further evaluation for mercuric sulfide. Table 3 and Table 4 provide the summaries of mercuric chloride and mercuric sulfide oral studies, respectively, organized by evidence type, study design, and health systems assessed. No oral studies met the PECO criteria for mercurous chloride.

Similarly, abstract and full-text screening was conducted for inhalation studies (see Figure D-4 to Figure D-6) for all three inorganic mercury salts. One epidemiology study that was identified for mercuric chloride will be further evaluated for its suitability in the assessment. No inhalation studies were identified during literature screening for mercuric sulfide and mercurous chloride. Therefore, this assessment will focus on deriving reference values for oral exposures based on the following considerations: (1) the failure to identify inhalation studies after abstract and full-text level screening for any of the three inorganic mercury salts, and (2) further discussion and clarification from the interested EPA office that exposure to inorganic mercury salts via inhalation is unlikely, it was determined this assessment will focus on the oral route of exposure.

Table 3. Summary of mercuric chloride oral studies by evidence type, study design, and health systems assessed

Health outcome	Animal						Human
	Mouse			Rat			
	Subchronic	Chronic	Repro/ dev	Subchronic	Chronic	Repro/ dev	General/ occupation
ADME/PBPK	8	2	1	12	1	3	
Cancer	0	0	0	1	0	0	
Cardiovascular	1	0	0	4	1	1	
Developmental	0	0	1	1	0	1	
Endocrine	2	1	1	7	1	0	
Gastrointestinal	1	0	0	3	0	2	
Hematologic	0	1	0	6	1	0	
Hepatic	4	0	0	6	1	2	
Immune	4	0	2	3	0	1	2
Lymphatic	0	0	0	0	0	1	
Nervous	2	1	2	11	1	4	
Other	4	1	1	12	3	4	
Renal	5	1	0	9	2	2	
Reproductive	5	1	1	8	1	1	
Respiratory	0	0	0	2	0	0	
Systemic/whole body	10	1	2	18	3	5	
Urinary	1	0	0	2	1	1	

PBPK = physiologically based pharmacokinetic.

Table 4. Summary of mercuric sulfide oral studies by evidence type, study design, and health systems assessed

Animal			
	Mouse		Rat
Health outcome	Subchronic	Repro/dev	Subchronic
ADME/PBPK	3	1	1
Cardiovascular	0	0	0
Developmental	0	1	0
Hematologic	1	1	0
Hepatic	2	0	0
Nervous	2	1	0
Renal	1	0	1
Systemic/whole body	0	1	1

PBPK = physiologically based pharmacokinetic.

Based on a preliminary literature survey, EPA anticipates conducting a further systematic review analysis for the following health effect categories based on the available data and sensitivity of the endpoints:

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

2.4. KEY SCIENCE ISSUES

Based on the preliminary literature survey, the following key scientific issues and potential mode-of-action hypotheses were identified that warrant evaluation in this assessment.

- **Key science issue #1: Consideration of the use of mercuric chloride information to inform the assessment of mercuric sulfide:** The systematic review efforts identified 30 animal oral studies for further study evaluation for determining suitable health outcomes for mercuric sulfide. Depending on the quality of the available evidence, relevant studies will be considered for deriving the toxicity reference value using traditional dose-response assessment methods. If this is not possible, alternative methods will be considered. These alternative methods may include the consideration of using mercuric chloride information to assess potential mercuric sulfide human health hazards. Both mercuric chloride and mercuric sulfide are divalent and have mercury in +2 oxidation state; however, the solubilities of the two salts differ by about four orders of magnitude. Thus, the bioavailability for mercuric sulfide is expected to be low compared with mercuric chloride. Therefore, an understanding of the toxicokinetic and toxicodynamic profiles of mercuric chloride versus those of mercuric sulfide will be informative in determining the human health hazards of these salts.

- **Key science issue #2: Consideration of the use of mercuric chloride information to inform the assessment of mercurous chloride:** The systematic review did not identify any animal or human studies for further study evaluation for any health outcomes for mercurous chloride. In the absence of data, alternative methods to assess the human health hazard of this chemical may be considered. These alternative methods may include the consideration of using mercuric chloride information to assess potential mercurous chloride human health hazards. These compounds have different oxidation states (mercuric chloride as Hg^{2+} and mercurous chloride as Hg^{1+}) and their solubilities differ significantly (the mercurous form is less soluble and, presumably, less bioavailable). Therefore, an understanding of the toxicokinetic and toxicodynamic profiles of mercuric chloride versus those of mercurous chloride will be informative in determining the human health hazards of these salts.

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

The overall objective of this assessment is to identify adverse health effects and characterize exposure-response relationships for these effects of inorganic mercury salts (i.e., mercuric chloride, mercuric sulfide, and mercurous chloride). This assessment will use systematic review methods to evaluate the epidemiological and toxicological literature for inorganic mercury salts, including consideration of relevant mechanistic evidence. The evaluation and analyses conducted in this assessment will be consistent with relevant EPA guidance.[2] The systematic review protocol will be disseminated after release of the draft assessment plan and will reflect changes made to the specific aims and PECO in response to public input.

3.1. ASSESSMENT APPROACH

A standard approach will be followed to derive toxicity values (RfDs) for these inorganic mercury salts, as appropriate based on the available evidence. When available evidence is lacking, alternative methods, including the potential use of toxicokinetic and/or toxicodynamic information for one salt to inform the assessment of another salt, will be considered to characterize the human health hazards of these salts.

3.2. SPECIFIC AIMS

For each of the three inorganic mercury salts, the assessment will:

- Prepare an initial literature inventory to identify epidemiology and toxicology studies reporting the effects of exposure to inorganic mercury salts as outlined in the PECO (see Section 3.3). Literature dated from 1997 onwards will be considered for evaluation. For information published prior to 1997, the ATSDR document, that undergoes rigorous interagency review and public comment, (ATSDR, 1999) will be used as a resource. In addition, studies cited in the Health Effects chapter of the ATSDR assessment will be screened against the PECO and all studies that meet the PECO criteria will be subject to subsequent systematic review steps, including study evaluation and considered as part of evidence integration and suitability for dose-response analysis. Furthermore, studies containing supplemental material that may be potentially relevant to an assessment will be tracked during the literature screening process. Supplemental material includes mechanistic evidence informative for the mode of action/adverse outcome pathway

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

analysis, ADME information, sensitization studies etc. (See table 6 for a full listing of types of supplemental material).

- Determine the extent to which a mechanistic analysis is warranted, based on factors such as scope, complexity, and confidence in the evidence in humans and animals, likelihood to impact evidence synthesis conclusions for human health, and directness or relevance of the model systems for understanding potential human health hazards.

- Conduct study quality evaluations (risk of bias and sensitivity) using validated criteria for individual epidemiology and toxicological studies and physiologically based pharmacokinetic (PBPK) models, if the data are available.

- Extract data on relevant health outcomes from epidemiological and toxicological studies.

- Synthesize the evidence across studies, assessing similar health outcomes using a narrative approach.

- For each health outcome, express strength of evidence conclusions from across studies (or subsets of studies) separately for studies in humans and animals, respectively. If studies informing mechanisms were synthesized, then mechanistic evidence from either human or animal studies will be integrated with the health effects evidence; will also consider life stage-specific differences in susceptibility, where data are available.

- For each health outcome under consideration for the derivation of toxicity values of inorganic mercury salts, integrate the strength of evidence conclusions across evidence streams (human and animal) to conclude whether a substance is hazardous to humans; identify and discuss issues concerning potentially susceptible populations and life stages.

- Derive toxicity values 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.

3.3. DRAFT POPULATIONS, EXPOSURES, COMPARATORS, AND OUTCOMES (PECO) CRITERIA

The PECO is used to identify the evidence that addresses the specific aims of the assessment, as well as to focus the search terms and inclusion/exclusion criteria in a systematic review. The draft PECO for inorganic mercury salts (see Table 5) was based on (1) nomination of the chemicals 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 inorganic mercury salts (primarily reviews and authoritative health assessment documents such as ATSDR and systematic review of literature) to

identify the major health hazards associated with exposure to inorganic mercury salts and key areas of scientific complexity.

Table 5. Draft populations, exposures, comparators, outcomes (PECO) criteria for the inorganic mercury salts assessment

PECO element	Evidence
Populations	**Human:** Any population and life stage (occupational or general population, including children and other sensitive populations). **Animal:** Nonhuman mammalian animal species (whole organism) of any life stage (including preconception, in utero, lactation, peripubertal, and adult stages). Nonmammalian models and in vitro studies will be tracked as supplemental.
Exposures	*Exposure based on administered dose or concentration, biomonitoring data (e.g., urine, blood, or other specimens), environmental or occupational-setting measures (e.g., air, water levels), or job title or residence. Relevant forms are listed below:* • Mercuric chloride (7487-94-7) and all synonyms including mercuric perchloride, mercury bichloride, mercury chloromercurate (II), mercury dichloride, mercury perchloride, mercury (II) chloride, $HgCl_2$, dichloromercury, calochlor, bichloride of mercury • Mercuric sulfide (1344-48-5) and synonyms including cinnabar, mercury (II) sulfide, mercury (II) sulfide black, mercury (II) sulfide red, mercury sulfide, mercury sulphide, vermilion, Chinese red, ethiops mineral, HgS • Mercurous chloride (10112-91-1) and synonyms including calomel, calogreen, chloromercury, dimercury dichloride, mercury (I) chloride, mercury chloride, mercury monochloride, mercury protochloride, mercury subchloride, mild mercury chloride, Hg_2Cl_2 **Human:** Any exposure to the relevant forms of inorganic mercury salts listed above, including occupational exposures via oral or inhalation route. Other exposure routes, including dermal exposure, will be tracked during screening as "potentially relevant supplemental information." **Animal:** Any exposure to inorganic mercury salts via the oral or inhalation route. Studies involving exposures to mixtures will be included only if they include exposure to inorganic mercury salts alone. Other exposure routes, including dermal or injection exposures, will be tracked during screening as "potentially relevant supplemental information."
Comparators	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of inorganic mercury salts, or exposure to inorganic mercury salts for shorter periods of time. Case reports and case series will be tracked as "potentially relevant supplemental information." **Animal:** A concurrent control group exposed to vehicle-only treatment or untreated control.

Table 5. Draft populations, exposures, comparators, outcomes (PECO) criteria for the inorganic mercury salts assessment (continued)

PECO element	Evidence
Outcomes	All health outcomes (both cancer and noncancer). In general, endpoints related to clinical diagnostic criteria, disease outcomes, histopathological examination, or other apical/phenotypic outcomes will be prioritized for evidence synthesis over outcomes such as biochemical measures. As discussed above, based on preliminary screening work, EPA anticipates that a systematic review for health effect categories other than those identified (i.e., renal, immunological, neurological, hepatic, hematological, and reproductive effects) will not be undertaken unless a significant amount of new evidence is found upon review of references during the comprehensive literature search.
PBPK models	Studies describing PBPK models for inorganic mercury salts. Toxicokinetic differences among life stages (including gestation and postnatal development) will be included where data are available.

Studies that meet the PECO criteria will be selected for further study quality evaluation and the utility of these studies for dose-response as part of the evidence synthesis. In addition to the PECO criteria, studies containing supplemental material that is also potentially relevant to the specific aims will be tracked during the literature screening process. Table 6 presents major categories of "potentially relevant supplemental material." This includes mechanistic information from both mammalian and nonmammalian model systems, as well as ADME and toxicokinetic information (including data informing bioavailability, such as solubility studies because solubility is known to affect the absorption of inorganic mercury salts). These potentially relevant studies will be "tagged" as such during screening to organize and prioritize evidence for consideration during assessment development. Inclusion of these studies in the evidence synthesis will depend on their likelihood to affect assessment conclusions for hazard identification or dose-response analysis and will be based on their utility for addressing the identified key science issues (see Section 2.4) or other important assessment uncertainties identified during review of the studies meeting the PECO criteria.

Table 6. Major categories of "Potentially Relevant Supplemental Material"

Category	Evidence
Mechanistic	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, ex vivo, and in silico studies.
ADME and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion, including toxicokinetic studies. This category includes studies of bioavailability and solubility because inorganic mercury salts are soluble or insoluble in differing media. Such information may be helpful in updating or revising the parameters used in existing PBPK models.
Exposure characteristics	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	Studies involving exposures to mixtures will be included if the exposure also includes exposure to mercuric chloride, mercuric sulfide, or mercurous chloride.
Routes of exposure not meeting PECO criteria	Studies other than for oral and inhalation routes of exposure, (e.g., dermal exposure).
Case reports or case series	Descriptive studies of individual patients or small groups of individuals presenting clinical symptoms or disease.
Reviews	Reviews and other summary documents (including other agency assessments).

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APPENDIX A. PHYSICAL AND CHEMICAL PROPERTIES OF INORGANIC MERCURY SALTS (COMPARISON OF MERCURIC CHLORIDE, MERCUROUS CHLORIDE, AND MERCURIC SULFIDE)

Table A-1. Physical and chemical properties of inorganic mercury salts (mercuric chloride, mercurous chloride, and mercuric sulfide)

Characteristics	Mercuric chloride	Mercurous chloride (calomel)	Mercuric sulfide (cinnabar)
CASRN	7487-94-7	10112-91-1	1344-48-5
Other names	$HgCl_2$, mercury (II) chloride, mercury perchloride	Hg_2Cl_2, Cl_2Hg_2, mercury (I) chloride, dimercury dichloride, mercury subchloride, mercury protochloride	HgS, mercury (II) sulfide, vermilion
Molecular weight	271.492 g/mol	472.084 g/mol	232.652 g/mol
Physical properties	Mercuric chloride is an odorless white crystalline solid. Density of 5.4 g/cm^3 with a melting point of 277°C. Slightly volatile at ordinary temperatures. Can be sublimed unchanged. Corrosive to the mucous membranes.	Mercurous chloride is an odorless white solid. Sinks in water. Density is 7.15 g/cm^3 with a melting point of 525°C.	Mercuric sulfide is an odorless red or black solid. Insoluble and sinks in water. Density is 8.1 g/cm^3 with a melting point of 580°C.
Chemical properties	Mercuric chloride volatizes slightly at ordinary temperature and appreciably at 100°C. It is corrosive to mucous membranes and used as a topical antiseptic and disinfectant.	Mercurous chloride is an irritant, cathartic, or purgative. Seldom causes systemic poisoning but may be fatal if retained to 30−40 mg/kg. Contact with eyes causes mild irritation.	Mercuric sulfide may cause allergic skin reaction.
Oxidation state	+2	+1	+2
Solubility in water	69 g/L at 20°C	2.0×10^{-3} g/L at 25°C	1.0×10^{-3} g/L at 20°C

Table A-1. Physical and chemical properties of inorganic mercury salts (mercuric chloride, mercurous chloride, and mercuric sulfide) (continued)

Characteristics	Mercuric chloride	Mercurous chloride (calomel)	Mercuric sulfide (cinnabar)
Absorption	GI tract: 7–15%		GI, <0.2%; oral administration
Distribution	Kidney, liver, spleen. Does not readily pass blood-brain barrier or placenta because of its poor lipid solubility.	Does not readily pass blood-brain barrier or placenta because of poor lipid solubility.	Kidney, spleen, liver. Does not readily pass blood-brain barrier or placenta.
Biotransformation	Hg^{2+} to Hg^0		HgS to Hg^{2+} and perhaps Hg^{2+} to Hg^0
Excretion	Urine and feces		Urine and feces
References	https://pubchem.ncbi.nlm.nih.gov/compound/mercuric_chloride#section=Top	https://pubchem.ncbi.nlm.nih.gov/compounds/24956#section=Top WHO (2003)	https://pubchem.ncbi.nlm.nih.gov/compound/62402#section=Top

GI = gastrointestinal.

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APPENDIX B. LITERATURE SEARCH STRATEGIES

Table B-1. Literature search strategies for inorganic mercury salts

Source	Search terms	Year
PubMed	**Mercuric chloride:** ((((("Bichloride of mercury" OR "Calochlor" OR "Corrosive sublimate" OR "Dichloromercury" OR "HgCl2" OR "Mercuric chloride" OR "Mercuric perchloride" OR "Mercury bichloride" OR "Mercury chloromercurate (II)" OR "Mercury dichloride" OR "Mercury perchloride" OR "Mercury (II) chloride"))) AND ("2018/01/01"[Date - Publication] : "2019/02/15"[Date - Publication]))	1997–Feb 2019 Search results: 1,997
	Mercuric sulfide: ((alpha-HgS OR Chinese red OR Cinnabar OR Ethiops mineral OR Aethiops mineral OR HgS OR Mercuric sulfide OR Mercury (II) sulfide OR Mercury (II) sulfide black OR Mercury (II) sulfide red OR Mercury sulfide OR Mercury sulphide OR Vermilion)) AND ("2018/01/01"[Date - Publication] : "2019/02/15"[Date - Publication])	1997–Feb 2019 Search results: 1,200
	Mercurous chloride: ((calogreen OR calomel OR chloromercuri OR Cl2Hg2 OR mercury dichloride OR Hg2Cl2 OR hydrochloric acid mercury salt OR mercurous chloride OR mercury (I) chloride OR mercury chloride OR mercury monochloride OR mercury protochloride OR mercury subchlorides OR mild mercury chloride)) AND ("2018/01/01"[Date - Publication] : "2019/02/15"[Date - Publication])	1997–Feb 2019 Search results: 2,612
WOS	**Mercuric chloride:** TS=("Bichloride of mercury" OR "Calochlor" OR "Corrosive sublimate" OR "Dichloromercury" OR "HgCl2" OR "Mercuric chloride" OR "Mercuric perchloride" OR "Mercury bichloride" OR "Mercury chloromercurate (II)" OR "Mercury dichloride" OR "Mercury perchloride" OR "Mercury (II) chloride" OR "7487-94-7") AND PY=2018-2019	1997–Feb 2019 Search results: 3,888
	Mercuric sulfide: TS=("alpha-HgS" OR "Chinese red" OR "Cinnabar" OR "Ethiops mineral" OR "HgS" OR "Mercuric sulfide" OR "Mercury (II) sulfide" OR "Mercury (II) sulfide black" OR "Mercury (II) sulfide red" OR "Mercury sulfide" OR "Mercury sulphide" OR "Vermilion") AND PY=2018-2019	1997–Feb 2019 Search results: 3,862
	Mercurous chloride: TS=("Calogreen" OR "Calomel" OR "Chloromercuri" OR "Cl2Hg2" OR "Dimercury dichloride" OR "Hg2Cl2" OR "Hydrochloric acid mercury salt OR Mercurous chloride" OR "Mercury (I) Chloride" OR "Mercury chloride" OR "Mercury monochloride" OR "Mercury protochloride" OR "Mercury subchloride" OR "Mild mercury chloride") AND PY=2018-2019	1997–Feb 2019 Search results: 2,150

Table B-1. Literature search strategies for inorganic mercury salts (continued)

Source	Search terms	Year
Toxline	**Mercuric chloride:** @OR+("Bichloride+of+mercury"+Calochlor+"Corrosive+sublimate"+Dichloromercury+HgCl2+"Mercuric+chloride"+"Mercuric+perchloride"+"Mercury+bichloride"+"Mercury+chloromercurate+(II)"+"Mercury+dichloride"+"Mercury+perchloride"+"Mercury+(II)+chloride"+@TERM+@rn+7487-94-7)+@NOT+@org+pubmed+pubdart+@AND+@RANGE+yr+2018+2019	1997–Feb 2019 Search results: 359
	Mercuric sulfide: @OR+("alpha-HgS"+"Chinese+red"+"Cinnabar"+"Ethiops+mineral"+"HgS"+"Mercuric+sulfide"+"Mercury+(II)+sulfide"+"Mercury+(II)+sulfide+black"+"Mercury+(II)+sulfide+red"+"Mercury+sulfide"+"Mercury+sulphide"+"Vermilion"+@TERM+@rn+1344-48- 5)+@NOT+@org+pubmed+pubdart+@AND+@RANGE+yr+2018+2019	1997–Feb 2019 Search results: 72
	Mercurous chloride: (@OR+("Calogreen"+"Calomel"+"Chloromercuri"+"Cl2Hg2"+"Dimercury+dichloride"+"Hg2Cl2" +"Hydrochloric+acid+mercury+salt"+"Mercurous+chloride"+"Mercury+(I)+Chloride"+"Mercury+chloride"+"Mercury+monochloride"+"Mercury+protochloride"+"Mercury+subchloride"+"Mild+mercury+chloride"+@TERM+@rn+10112-91- 1)+@AND+@RANGE+yr+1999+2018)+@NOT+@org+pubmed+pubdart	1997–Feb 2019 Search results: 61

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APPENDIX C. LITERATURE SEARCH METHODS AND INITIAL RESULTS

The current assessment focuses on literature searches from 1997 (after publication of 1999 ATSDR toxicological profile but covering 2 previous years). This literature survey consisted of a broad search from 1997 through February 2019 using chemical names (mercuric chloride, mercurous chloride, and mercuric sulfide), Chemical Abstracts Service registry number (CASRN), and synonyms. Three different databases including PubMed, Toxline, and Web of Science were searched. The results of this literature search are documented and can be found on the Health and Environmental Research Online (HERO) website on mercury salts project page (https://heronet.epa.gov/heronet/index.cfm/project/page/project_id/2697).

Following the literature search from three different databases (PubMed, Toxline, and WOS), preliminary screening was performed to remove the duplicates for each chemical. The studies were then uploaded and sorted in SWIFT Review (Sciome Inc), a text-mining work bench for systematic review, using a predetermined list of health outcomes and evidence streams. The SWIFT Review filters that were applied focused on lines of evidence (human, animal, in vitro) and health outcomes (cancer, 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). Following SWIFT review, screening, studies were manually screened using Distiller (Distiller SR), another systematic review tool. The studies were screened by title/abstract for relevance against the PECO criteria as described in Section 3. Reviewed studies were placed into one of three categories: (1) PECO relevant (oral and inhalation studies), (2) not PECO relevant, or (3) supplemental information including various categories such as dermal and other routes of exposure, case-reports, mechanistic studies, ADME/PBPK, mixture studies, reviews, bioavailability, nonmammalian, and other studies. Mechanistic data can be informative to linking biomarkers to apical effects. The initial results of the binning are shown in Figures in supplemental materials/Appendix (mercuric chloride, Figure D-1, Figure D-4; mercuric sulfide, Figure D-2, Figure D-5; and mercurous chloride, Figure D-3, Figure D-6), for oral and inhalation exposures, respectively. Many studies reported more than one health effect/outcome category; therefore, there is not a one-to-one correspondence between the total number of studies across the endpoints and the total number of studies identified in the screening process. Following the title/abstract screening, PECO-relevant studies were tagged for full-text screening. Remaining studies were either excluded as non-PECO-relevant or tagged as supplemental. Once the studies were screened for full text, appropriate studies were categorized for further evaluation to determine the dose-response relationships. Remaining studies were again

tagged as non-PECO-relevant or supplemental. When necessary, the supplemental studies will be evaluated further as supporting data for the assessment.

APPENDIX D. INITIAL LITERATURE INVENTORY SUMMARIES

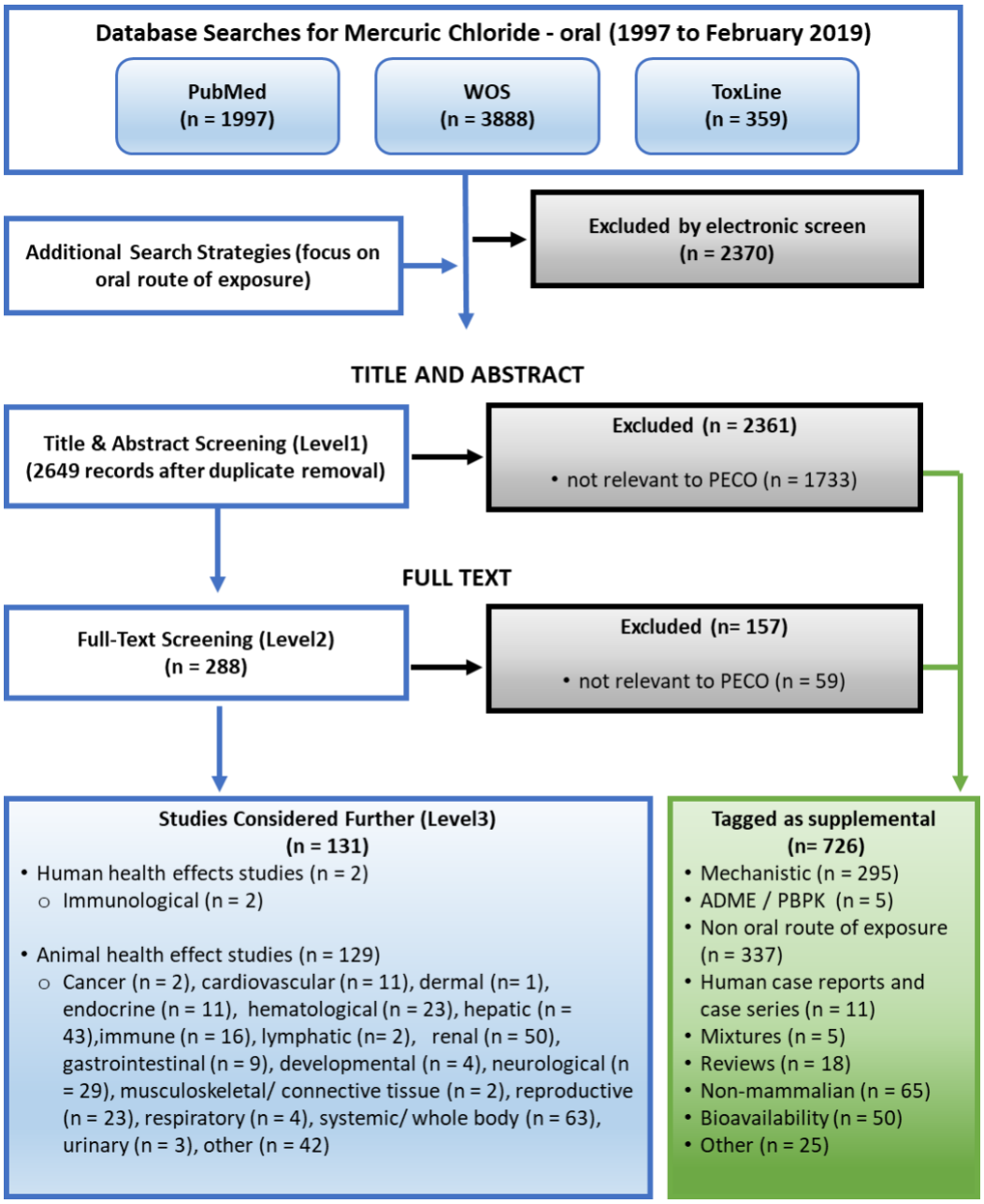

Figure D-1. Results of initial literature survey—database searches for mercuric chloride for oral exposures.

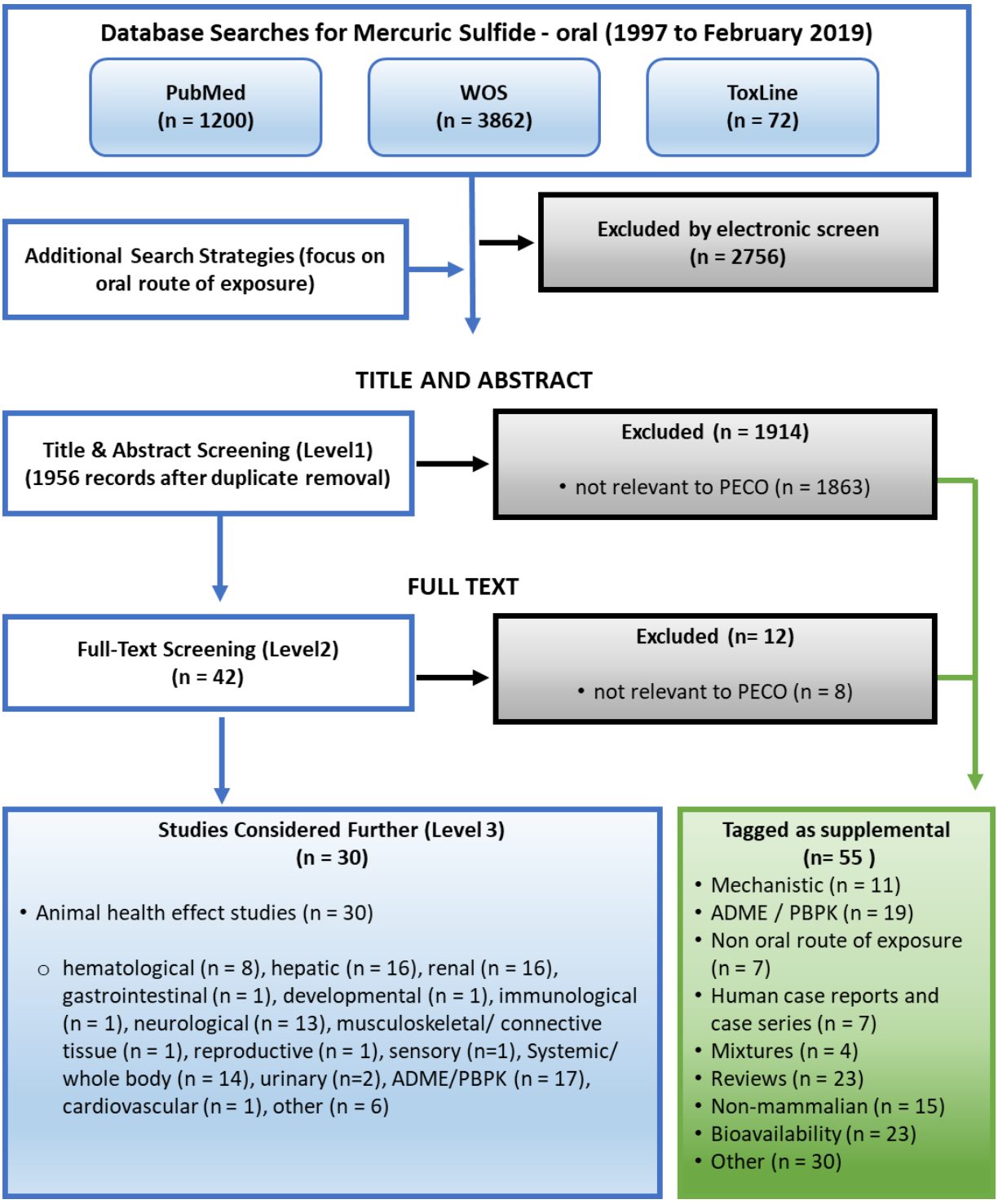

Figure D-2. Results of initial literature survey—database searches for mercuric sulfide for oral exposures.

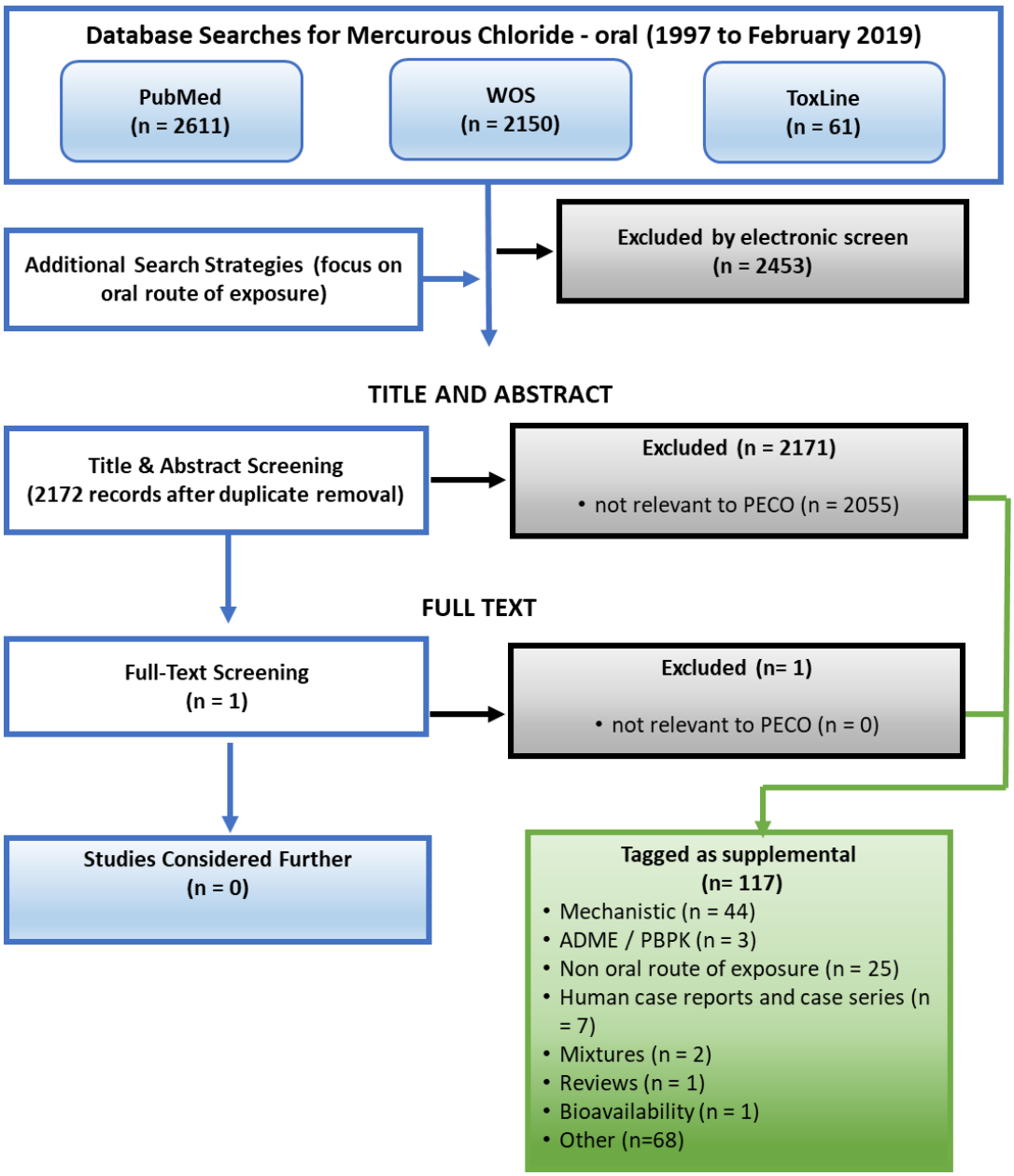

Figure D-3. Results of initial literature survey—database searches for mercurous chloride for oral exposures.

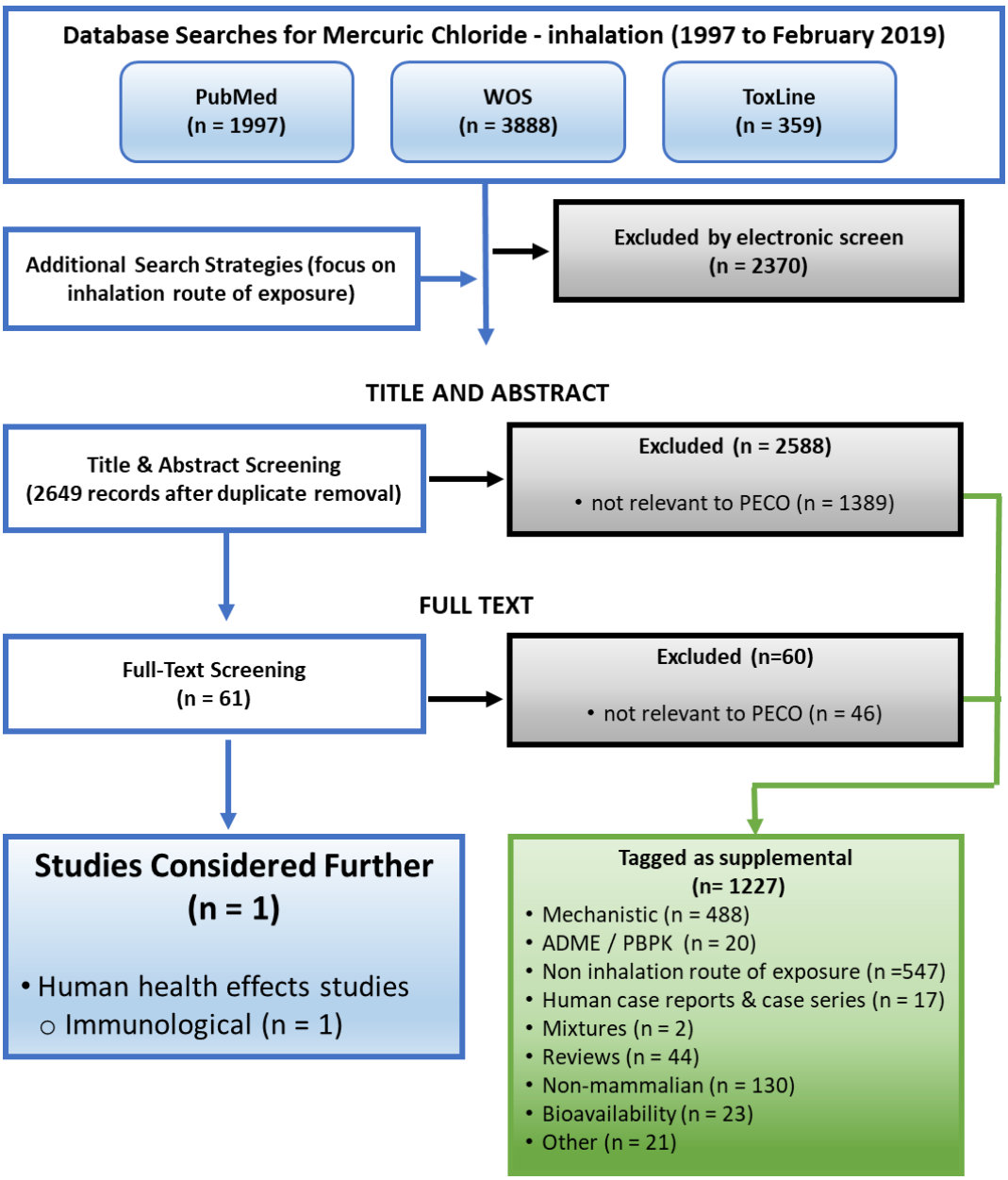

Figure D-4. Results of initial literature survey—database searches for mercuric chloride for inhalation exposures.

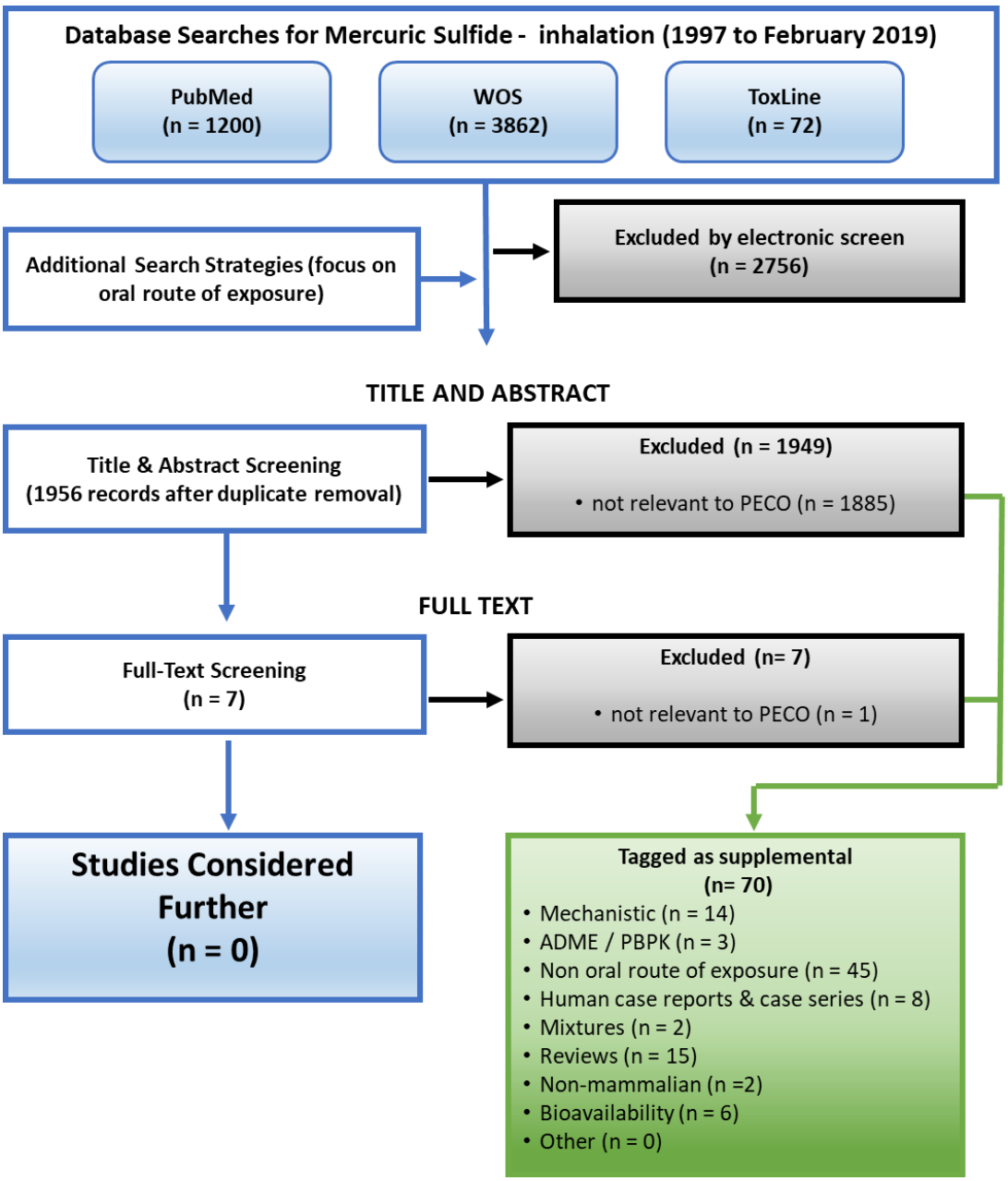

Figure D-5. Results of initial literature survey—database searches for mercuric sulfide for inhalation exposures.

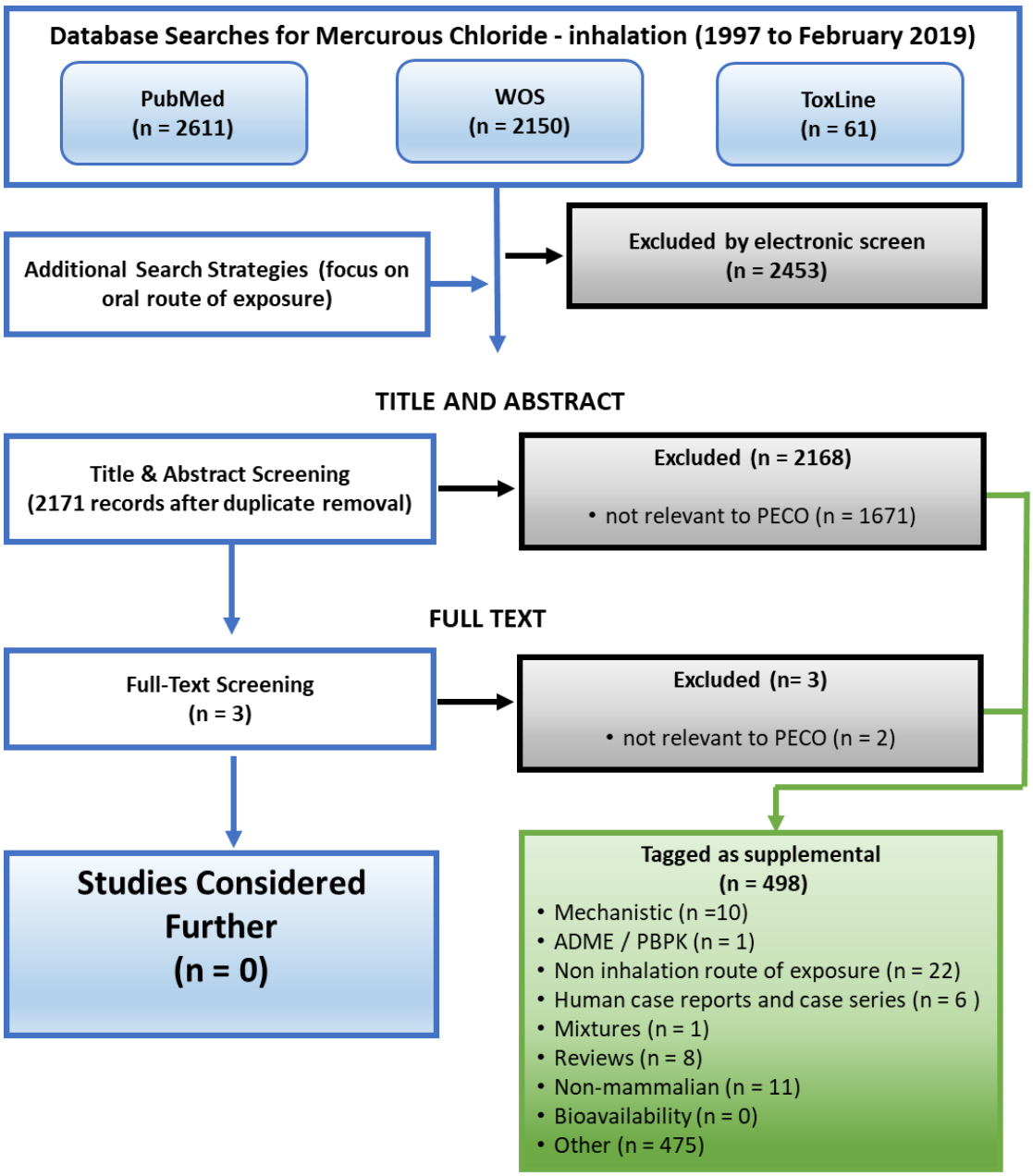

Figure D-6. Results of initial literature survey—database searches for mercurous chloride for inhalation exposures.