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Integrated Science Assessment for Lead

Appendix 12: Process for Developing the Pb Integrated Science Assessment

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Center for Public Health and Environmental Assessment
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DOCUMENT GUIDE

This Document Guide is intended to orient readers to the organization of the Lead (Pb) Integrated Science Assessment (ISA) in its entirety and to the sub-section of the ISA at hand (indicated in bold). The ISA consists of the Front Matter (list of authors, contributors, reviewers, and acronyms), Executive Summary, Integrated Synthesis, and 12 appendices, which can all be found at https://assessments.epa.gov/isa/document/&deid=359536.

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ACRONYMS AND ABBREVIATIONS

AQCD	Air Quality Criteria Document
BLL	blood lead level
CASAC	Clean Air Scientific Advisory Committee
CI	confidence interval
FRN	Federal Register Notice
GFR	glomerular filtration rate
HAWC	Health Assessment Workspace Collaborative
HERO	Health and Environmental Research Online
IQ	intelligence quotient
IRP	Integrated Review Plan
ISA	Integrated Science Assessment
LECES	Level of Biological Organization, Exposure, Comparison, Endpoint, and Study Design
LOD	limit of detection
NAAQS	National Ambient Air Quality Standards
NASGLP	North American Soil Geochemical Landscapes Project
NHANES	National Health and Nutrition Examination Survey
ORD	Office of Research and Development
Pb	lead
PbB	blood lead concentration
PECOS	Population, Exposure, Comparison, Outcome, and Study Design
PICOC	Population, Intervention, Comparison, Outcome, and Context
PM	particulate matter
PQAPP	Program Quality Assurance Project Plan
QA	quality assurance
QAPP	Quality Assurance Project Plan
QC	quality control
RBC	red blood cell
SWIFT-AS	SWIFT-Active Screener
U.S. EPA	United States Environmental Protection Agency

APPENDIX 12 PROCESS FOR DEVELOPING THE Pb INTEGRATED SCIENCE ASSESSMENT

Summary of Public Resources for the 2024 Pb ISA

This appendix describes the process for developing the Lead (Pb) Integrated Science Assessment (ISA), including literature search and screening methods; peer input and peer review; and public participation. This table summarizes the publicly available resources related to this ISA and its development. Readers looking for Federal Register Notices (FRNs) may search http://www.regulations.gov by either the document citation number (the reference number to the specific FRN) or the Docket ID number (reference number for the overall docket that may house multiple FRNs, as well as public comments in response to those FRNs).

2024 Pb ISA	https://assessments.epa.gov/isa/document/&deid=359536
Clean Air Scientific Advisory Committee	https://casac.epa.gov/ords/sab/f?p=113:1
Federal Register Notices	http://www.regulations.gov
Request for Information	Document Citation: 85 FR 40641 Docket ID: EPA-HQ-OAR-2020-0312-0001
Integrated Review Plan, Volume 2	Document Citation: 87 FR 13732 Docket ID: EPA-HQ-OAR-2020-0312-0010
Peer Input Workshop	Document Citation: 87 FR 27147 Docket ID: EPA-HQ-ORD-2020-0701-0001
Pb ISA External Review Draft	Document Citation: 88 FR 19302 Docket ID: EPA-HQ-ORD-2020-0701
Integrated Review Plan	https://www.epa.gov/naaqs/lead-pb-standards-planning-documents-current-review
ISA Preamble	https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310244
Literature	https://hero.epa.gov/hero/index.cfm/project/page/project_id/4081
Peer Input Workshop	https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=354420
Study Quality Evaluations	https://hawc.epa.gov/assessment/100500318/

12.1 Introduction

Integrated Science Assessments (ISAs) provide the scientific foundation for the review of the primary (health-based) and secondary (welfare[1]-based) National Ambient Air Quality Standards (NAAQS). ISAs contain a synthesis and evaluation of the most policy-relevant science using methods and approaches described in the Preamble to the Integrated Science Assessments (U.S. EPA, 2015b), hereafter "Preamble," which provides an overview of the ISA development process. The 2024 Pb ISA builds upon the conclusions and scientific evidence from the 2013 Pb ISA (U.S. EPA, 2013a) and prior Air Quality Criteria Documents (AQCDs) for Pb from 1977 (U.S. EPA, 1977), 1986 (U.S. EPA, 1986), and 2006 (U.S. EPA, 2006), and includes recent literature published since September 2011, the literature cutoff date of the 2013 Pb ISA. In March 2022, the United States Environmental Protection Agency (U.S. EPA) released the first two volumes of the Integrated Review Plan (IRP) for the Pb NAAQS review. Volume 2 of the IRP (U.S. EPA, 2022) identifies policy-relevant issues (i.e., those intended to frame the review and focus it on the critical scientific and policy questions related to the adequacy of the standards) and describes key considerations in the U.S. EPA's development of the Pb ISA. Volume 2 was made available for public comment and a consultation with the U.S. EPA's Clean Air Scientific Advisory Committee (CASAC) Pb Review Panel at a public meeting on April 8, 2022. The 2024 Pb ISA has been developed by U.S. EPA scientists in the Office of Research and Development (ORD), other U.S. EPA scientists with relevant experience, and external authors from ICF, a U.S. EPA contractor. The general ISA development steps are presented in Figure 12-1, though particular details can vary across assessments. This appendix supplements the 2015 ISA Preamble (U.S. EPA, 2015b) and Volume 2 of the IRP (U.S. EPA, 2022), and further describes the process of developing the 2024 Pb ISA, including methods for documentation, literature review, study quality evaluation, public engagement, and quality assurance (QA).

12.2 Documentation

12.2.1. Literature Database: Health and Environmental Research Online

To improve transparency, studies considered in the development of the ISAs are documented in the U.S. EPA Health and Environmental Research Online (HERO) database. The publicly accessible HERO project page for the 2024 Pb ISA contains the references that were considered for inclusion and provides bibliographic information and abstracts. Within HERO, each reference has a unique HERO ID

[1]Under The Clean Air Act section 302(h) (42 U.S.C. § 7602(h)), effects on welfare include "effects on soils, water, crops, vegetation, manmade materials, animals, wildlife, weather, visibility, and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being."

number. References can be viewed individually or filtered by appendix, discipline, or the draft in which they are referenced.

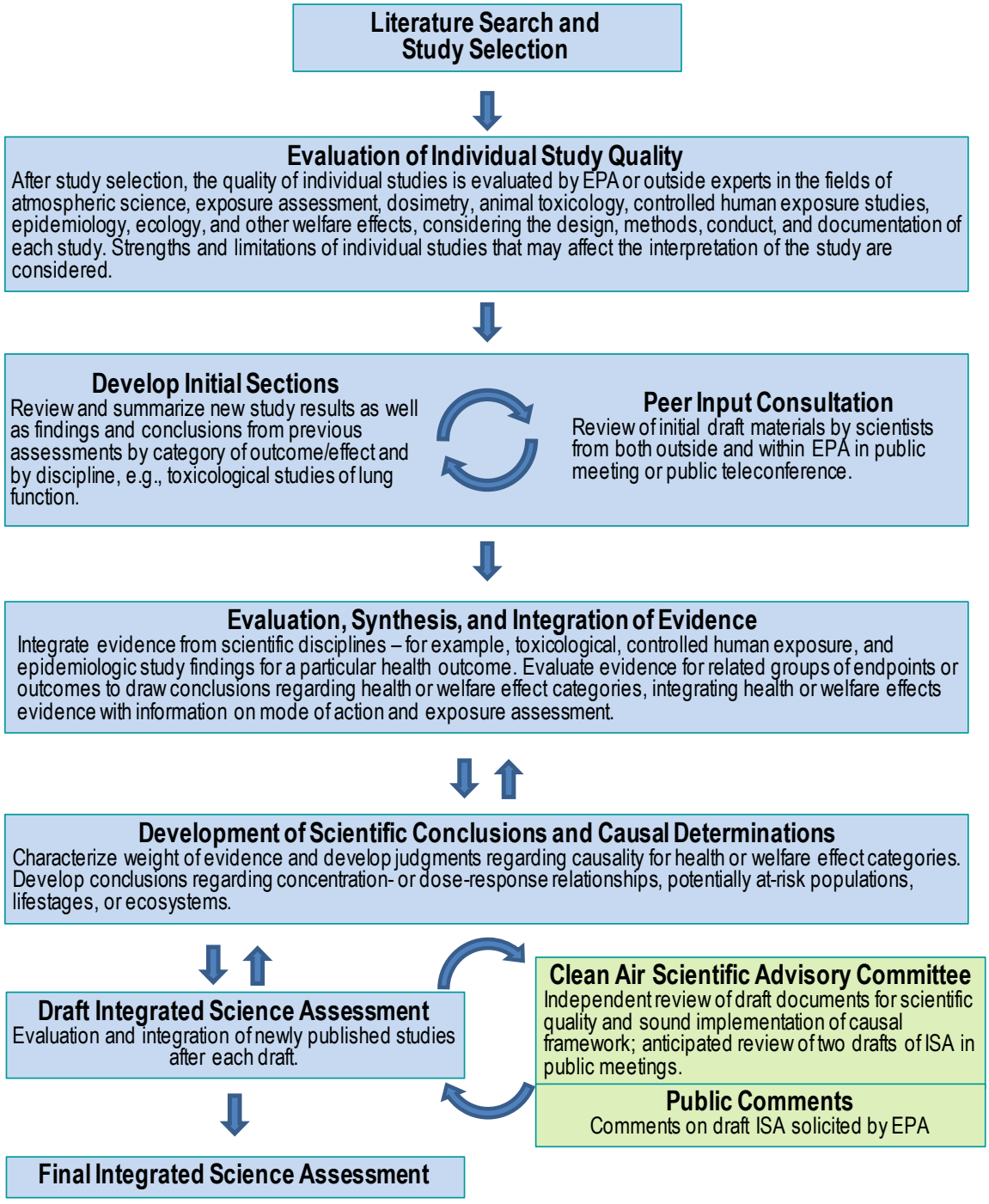
Inclusion and exclusion decisions for references at each stage of screening are recorded by a tagging system and are documented in the HERO database. A two-step screening process (title and abstract screening and full-text screening) was used for this ISA; subsequent sections of this appendix discuss the screening process in greater detail. References that passed through title and abstract screening are tagged in HERO as "Title-Abstract Screening Included." Inclusion and exclusion decisions from full-text screening of references passing through title and abstract screening are tagged in HERO as "Full-Text Screening Included." References identified from sources other than literature searches were also screened using the same discipline-specific criteria, and inclusion and exclusion decisions for these references are also documented in HERO. Specific data about concentrations, experimental design, and results are reported within the appendices.

12.2.2. Study Quality Documentation: Health Assessment Workspace Collaborative

Reference-specific information about study quality is documented in the U.S. EPA Health Assessment Workspace Collaborative (HAWC) for select health studies and can be accessed through the HAWC project page for this ISA. All decisions about full-text screening are additionally documented in the HERO database and on the publicly available HERO project page for this ISA. See Section 12.6 for a more detailed discussion about study quality.

12.3 Overview of the Process Steps for Developing Integrated Science Assessments

As described in the Preamble and shown in Figure 12-1, developing an ISA consists of the following steps: literature search and study selection; evaluating study quality; developing initial draft materials for peer-input consultation; evaluating, synthesizing, and integrating evidence; and developing scientific conclusions and causality determinations (U.S. EPA, 2015b).



Source: Modified from Figure II of the Preamble to the Integrated Science Assessment (U.S. EPA, 2015b).

Figure 12-1 General process for developing Integrated Science Assessments.

12.4 Relevance and Scope

As a synthesis and evaluation of the most policy-relevant science, the 2024 Pb ISA includes information on atmospheric science, exposure assessment, experimental health studies, epidemiologic health studies, and studies of effects on terrestrial and aquatic ecosystems. For the 2024 Pb ISA, "policy-relevant" science is described in Volume 2 of the IRP (U.S. EPA, 2022) as referring to "scientific information and analyses intended to address key questions related to the adequacy of the standards." Those "key questions" are also laid out in Volume 2 of the IRP. As stated in the Preamble (U.S. EPA, 2015b), "The key policy-relevant questions included in the IRP serve to clarify and focus the NAAQS review on the critical scientific and policy issues, including addressing uncertainties discussed during the previous review and newly emerging literature." The sections below describe the approaches and scoping statements used to identify relevant studies in each discipline. The use of scoping statements to define study relevance is consistent with recommendations by the National Academies of Sciences, Engineering, and Medicine for improving the design of risk assessment through planning, scoping, and problem formulation to better meet the needs of decision makers (NASEM, 2018).

12.4.1. Atmospheric Sciences

Studies were considered relevant for inclusion in the 2024 Pb ISA if they were judged to provide original data and to substantially advance the understanding of Pb emission sources; atmospheric and environmental processes (including chemistry and transport); measurement and estimation methods; or recent concentrations and trends. This approach to determining study relevance required judgments about whether a subject area of the research had the potential to inform policy specific to the NAAQS, and whether a study published in the area provided sufficiently original results to add to the existing body of knowledge.

Table 12-1 shows the relevance criteria used for broadly identifying recent environmental research advances and knowledge gaps. These criteria are based on the approach described by Mengist et al. (2020), who formulated a Population, Intervention, Comparison, Outcome, and Context (PICOC) statement that designated the population as the population of scientific research work itself and the outcome as the assessment of its knowledge and gaps.

Table 12-1 Population, Intervention, Comparison, Outcome, and Context statement to define the parameters and provide a framework for identifying relevant atmospheric science studies

Concept	Application
Population	Include policy-relevant scientific research on Pb source emissions, environmental processes (including chemistry and transport), measurement and estimation methods, and concentration and trends.
Intervention	Assess policy-relevant scientific advances and knowledge gaps.
Comparison	Evaluate emissions, concentrations, and their rates of change across sources, atmospheric and environmental processes, measurement and estimation methods, long-term temporal scales, seasons, diurnal cycles, geographic regions, and urban and neighborhood spatial scales.
Outcome	Identify policy-relevant scientific advances and knowledge gaps.
Context	Focus on policy-relevant research performed in the United States or Canada; for some topics, research performed outside of the United States or Canada can be excluded if sources or concentrations are not relevant to the United States or if the body of research is very large; for other topics, if source and concentration differences are not relevant to the topic or the number of publications is very small, non-U.S. research can be included.

Pb = lead.

12.4.2. Exposure, Toxicokinetics, and Biomarkers

The following guidelines were used to judge the relevance of studies examining Pb exposures, toxicokinetics, and biomarkers. Studies were included if they provided original data and substantially advanced understanding of Pb exposure through environmental media and other pathways; Pb toxicokinetics including uptake, distribution, metabolism, and elimination from the body; Pb biomarker measurement techniques; Pb biomarker concentration trends; and the relationships between Pb in environmental media and Pb biomarker concentrations, including biokinetic and empirical modeling of those relationships.

Exposure studies pertaining to the U.S. population and U.S.-based Pb sources were preferred. Studies were included from outside the United States if these studies were judged to have important findings, with a focus on studies from Canada, western Europe, and Australia (i.e., areas with study populations and air quality characteristics most similar to the United States). If it was deemed that studies from the United States, Canada, western Europe, or Australia were not adequate (i.e., little to no information that advanced understanding of a particular topic was found), then it was necessary to consider all studies regardless of geographic location. For Pb toxicokinetics and biomarker measurement techniques, studies, regardless of geographic location, were considered since the physical location in which a study took place may have less bearing on results. Finally, although exposures in relation to Pb in ambient air and originating from air-related sources are the focus of the appendix, studies containing Pb concentrations in other media (soil, dietary sources, consumer products, occupational sources, and ammunition) were included because cumulative body burden can occur as a result of contributions from

multiple exposure pathways (e.g., ingestion of Pb-containing soil by children) and the origin of Pb can be difficult to determine as stemming from an air-related source.

12.4.3. Health

Relevance for studies that evaluate the relationship between Pb exposure and health effects was assessed using scoping statements that define the relevant Population, Exposure, Comparison, Outcome, and Study Design (PECOS). Discipline-specific PECOS statements for epidemiologic and experimental studies (i.e., animal toxicology studies) were developed to establish inclusion criteria based on the objectives of the review, facilitating identification of the most relevant literature to inform the Pb ISA (Table 12-2 and Table 12-3). In some cases, PECOS statements differ by health outcome depending on well-established areas of research; gaps in the literature; and inherent uncertainties in specific populations, exposure metrics, comparison groups, and study designs identified in the 2013 Pb ISA. Additionally, some epidemiologic PECOS statements were further refined to emphasize the strongest recent epidemiologic studies that address key uncertainties from the previous review; these PECOS refinements are identified and described in detail in the relevant appendices. The use of PECOS statements is widely accepted and often applied in the health disciplines for systematic review in risk assessment. PECOS statements for the 2024 Pb ISA can also be found in each health effects appendix.

12.4.3.1. Experimental Studies

For experimental studies (specifically animal exposure studies), the relevance evaluation focused on studies with appropriate study designs and relevant exposure concentrations (Table 12-2). The scope of the experimental evidence used for the 2024 Pb ISA encompassed studies of nonhuman mammalian animal species with exposures that are relevant to the range of human exposures (blood Pb levels [BLLs] up to 30 μg/dL, which is about one order of magnitude above the 95th percentile of the 2011–2016 National Health and Nutrition Examination Survey [NHANES] distribution of BLLs in children) (Egan et al., 2021).

Table 12-2 Population, Exposure, Comparison, Outcome, and Study Design statement to define the parameters and provide a framework for identifying relevant experimental studies

Concept	Application
Population	Laboratory nonhuman mammalian animal species (i.e., mouse, rat, Guinea pig, minipig, rabbit, cat, dog; whole organism) at any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages).
Exposure	Oral, inhalation, or intravenous routes administered to a whole animal (in vivo) that results in a BLL of 30 µg/dL or below.[a,b]
Comparison	A concurrent control group exposed to vehicle-only treatment or untreated control.
Outcome	Cancer and noncancer health outcomes including cardiovascular, dermal, developmental, endocrine system, gastrointestinal, hematological, hepatic, immunological, metabolic syndrome, musculoskeletal, neurological, ocular, renal, reproductive, or respiratory effects.
Study Design	Controlled exposure studies of animals in vivo.

BLL = blood lead level; Pb = lead.
[a]Pb mixture studies are included if they employ an experimental arm that involves exposure to Pb alone.
[b]This level is approximately an order of magnitude above the upper end of the distribution of U.S. young children's BLLs. The 95th percentile of the 2011–2016 NHANES distribution of BLL in children (1–5 years; n = 2,321) is 2.66 µg/dL (Egan et al., 2021), and the proportion of individuals with BLLs that exceed this concentration varies depending on factors including housing age, geographic region, and a child's age, sex, and nutritional status.

12.4.3.2. Epidemiologic Studies

To identify the most relevant epidemiologic literature, the body of evidence from the 2013 Pb ISA was considered in the development of the PECOS statements. Specifically, the scope of the current assessment is informed by well-established areas of research, gaps in the literature, inherent uncertainties in specific populations, exposure metrics, comparison groups, and study designs identified in the 2013 Pb ISA. The evaluation of epidemiologic studies focused on the association between exposure to Pb (as indicated by Pb levels in blood, bone, and teeth; validated environmental indicators of Pb exposure; or intervention groups in randomized trials and quasi-experimental studies) and an ensemble of health effects, including effects on the nervous system, cardiovascular effects, and reproductive and developmental outcomes (Table 12-3). Emphasis was placed on studies conducted in non-occupationally exposed populations, but recent longitudinal studies of occupational exposure to Pb published since the literature cutoff date for the 2013 Pb ISA were considered insofar as they addressed a topic that was of particular relevance to the NAAQS review (e.g., longitudinal studies designed to examine recent versus historical Pb exposure). Additionally, the following types of epidemiologic studies are generally considered to fall outside the scope and are not included in the ISA: review articles (which typically present summaries or interpretations of existing studies rather than bringing forward new information in the form of original research or new analyses); Pb poisoning studies or clinical reports (e.g., involving accidental exposures to very high amounts of Pb described in clinical reports that may be extremely unlikely to be experienced under ambient air exposure conditions); and risk or benefit analyses (e.g., that apply existing concentration-response functions or effect estimates to exposure estimates for differing

cases). Although review articles are not typically included in the health sections of the ISA, they are identified and tracked during the literature searching and study selection phase of the assessment. These reviews are often consulted to ensure that all relevant literature has been identified and to track key issues related to a particular evidence base.

For some health outcomes for which the evidence assessed in the 2013 Pb ISA supported a "causal" relationship, the epidemiologic PECOS statements were refined in order to further emphasize the strongest recent epidemiologic studies that address the key uncertainties from the previous review and the scientific questions in Volume 2 of the IRP (U.S. EPA, 2022). These PECOS refinements, which are identified and described in detail in the relevant appendices, generally focus on the most informative study designs and relevant BLLs, and emphasize control for important potential confounders that were identified in the 2013 Pb ISA. Studies that met the broader PECOS criteria in Table 12-3, but were no longer relevant under the refined criteria were still included in evidence inventories that summarize key study details, including study population, exposure assessment, confounders, and select results.

Table 12-3 Population, Exposure, Comparison, Outcome, and Study Design statement to define the parameters and provide a framework for identifying relevant epidemiologic studies

Population: Any human population, including specific populations or lifestages that might be at increased risk of a health effect.

Exposure: Exposure to Pb[a] as indicated by biological measurements of Pb in the body, with a specific focus on Pb in blood, bone, and teeth; validated environmental indicators of Pb exposure, or intervention groups in randomized trials and quasi-experimental studies.

Comparison: Populations, population subgroups, or individuals with relatively higher versus lower levels of the exposure metric (e.g., per unit or log unit increase in the exposure metric, or categorical comparisons between different exposure metric quantiles).

Outcome

Nervous System	*Cardiovascular*	*Renal*	*Immune*	*Hematological*	*Reproductive*	*Developmental*	*Cancer*	*Other*
Nervous system effects including cognitive function (e.g., IQ decrement), externalizing and internalizing behaviors, psychopathological effects, sensory organ function, motor function, and neurodegenerative diseases.	Cardiovascular effects including coronary heart disease, hypertension and increased blood pressure, and cardiovascular-related mortality.	Renal effects including elevated serum creatinine levels and lower GFR.	Immune system effects including immunotoxicity, systemic inflammation, and immune-based diseases.	Hematological effects including disruption of heme synthesis and RBC function.	Reproductive effects, including altered age of puberty onset, reduced fertility, poor semen quality or motility, and miscarriage.	Developmental effects, including adverse pregnancy outcomes (e.g., reduced fetal growth, preterm birth, small for gestational age, birth defects), as well as postnatal developmental effects.	Cancer incidence, mortality, or related biomarkers.	Effects on the hepatic system, gastrointestinal system, endocrine system, bone and teeth, ocular health, and respiratory system.

Study Design: Epidemiologic studies consisting of longitudinal and retrospective cohort studies, case-control studies, cross-sectional studies with appropriate timing of exposure for the health endpoint of interest, randomized trials, and quasi-experimental studies examining interventions to reduce exposures.

GFR = glomerular filtration rate; IQ = intelligence quotient; Pb = lead; RBC = red blood cell.

[a]The focus was on populations with nonoccupational Pb exposures, though recent longitudinal studies of occupational exposure to Pb were considered insofar as they addressed a topic that was of particular relevance to the NAAQS review (e.g., longitudinal studies designed to examine recent versus historical Pb exposure).

[b]Studies that estimate Pb exposure by measuring Pb concentrations in particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 μm (PM_{10}) and particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$) ambient air samples are only considered for inclusion if they also include a relevant biomarker of exposure (e.g., Pb in blood, bone, or teeth). Given that size distribution data for Pb-PM are fairly limited, it is difficult to assess the representativeness of these concentrations to population exposure [Section 2.5.3 (U.S. EPA, 2013a)]. Moreover, data illustrating the relationships of Pb-PM_{10} and Pb-$PM_{2.5}$ with blood Pb levels are lacking.

12.4.4. Welfare—Effects on Terrestrial and Aquatic Ecosystems

For welfare effects (i.e., on terrestrial and aquatic ecosystems), scoping statements defining the Level of Biological Organization, Exposure, Comparison, Endpoint, and Study Design (LECES) were used. U.S. EPA developed the LECES based on the PECOS with some concepts substituted to provide a better fit with ecological science. In the LECES, "population" (**P**ECOS) is replaced with "level of biological organization" (**L**ECES) and "outcome" (PEC**O**S) is replaced with "endpoint" (LEC**E**S). A LECES statement was developed for terrestrial and aquatic ecosystems.

For research evaluating ecological effects, emphasis was placed on recent studies published since the literature cutoff date of the 2013 Pb ISA that: (1) evaluated effects at concentrations at or near current environmental concentrations of Pb in soil, water, and sediment and (2) investigated effects on species, subspecies, or study populations of algae and plants, microbes, invertebrates, or vertebrates at any lifestage or in any biological community or ecosystem. Exposure concentrations, endpoints, and study types considered for the 2024 Pb ISA that inform understanding of the ecological effects of Pb in terrestrial and aquatic systems are summarized further in the LECES statement (Table 12-4). For exposure concentrations, guidelines were used when screening studies for inclusion. These guidelines took into consideration data that was current at the time of the 2013 Pb ISA on Pb concentrations in soils, water, and sediments in the United States (Table 1-1 from the 2013 Pb ISA). The concentration guideline for literature screening in the 2024 Pb ISA is approximately one order of magnitude higher than upper bound values from available environmental surveys for soils, water, and sediment (refer to the footnotes in Table 12-4). For soil, the concentration guideline for screening of terrestrial studies of Pb exposure and effects was set at approximately 230 mg Pb/kg of soil, although higher concentrations were considered if the study added new information on a mechanism of action, or if the higher concentration was part of a series that contributed exposure-response information and included other concentrations below 230 mg Pb/kg. For aqueous exposures, the concentration guideline for study screening was approximately 10 μg Pb/L, although higher concentrations were considered if the study added new information on a mechanism of action or if the higher concentration was part of a series that contributed exposure-response information. For sediments, the concentration guideline for study screening was approximately 300 mg Pb/kg dry weight or lower. Studies at very high concentrations of Pb in soils, water, and sediments were excluded unless they were part of a series in an experimental exposure-response study and at least one concentration in the test series was in the ranges stated above (Table 12-4).

In addition to the biological effects described in the LECES statement, other topics within scope included how chemical and biological modifying factors affect bioavailability in terrestrial, freshwater, and saltwater environments, as well as studies that address key uncertainties and limitations in the evidence identified in the 2013 Pb ISA. Site-specific studies in non-U.S. locations that do not contribute to novel insights into Pb biogeochemistry or effects are considered outside of the scope of the 2024 Pb

ISA. Studies on mine tailings, biochar, industrial effluent, sewage, ship breaking, bioremediation of highly contaminated sites, and ingestion of Pb shot, fishing tackle, or pellets are also outside the scope of the 2024 Pb ISA due to the high concentration of Pb and lack of a connection to an air-related source or process.

Table 12-4 Level of Biological Organization, Exposure, Comparison, Endpoint, and Study Design statement to define the parameters and provide a framework for identifying relevant ecological studies

Terrestrial	**Level of Biological Organization:** Species or subspecies, study populations of vegetation, microbes, invertebrates, or vertebrates, at any lifestage, or any biological community or ecosystem in terrestrial environments present in the United States or similar to those in the United States.
	Exposure: Short or long-term Pb concentrations in exposure media (e.g., soil or diet) that are most relevant to environmental concentrations of Pb in the United States.[a] For soil, the guideline for screening of terrestrial studies of Pb exposure and effects was defined as a concentration of approximately 230 mg Pb/kg,[b] with higher concentrations considered if the study elucidates a mechanism or is an acute exposure and at least one concentration in the test series is in the range described above. Analytically verified exposure concentrations preferred; nominal concentrations considered in some cases.
	Comparison: A comparison to an unexposed laboratory control, a reference population, or site with no detectable exposure or with lower Pb exposure.
	Endpoint: Species or population effects including effects on growth, reproduction or development, neurobehavioral effects, reduced survival or fitness, carbon fixation and photosynthesis. At higher levels of biological organization endpoints include changes in community composition, altered ecosystem processes and functions, such as productivity, community composition, or shifts in genotypes or species, species extirpation, declines in total number of species or biomass, or decreased species richness.
	Study Design: Laboratory, mesocosm, observational or experimental field or gradient studies, or mechanistic modeling studies that estimate the effect of Pb on an organism, biological population, community, or ecosystem whose processes may be represented quantitatively (e.g., in a dynamic or steady state).
Aquatic	**Level of Biological Organization:** Species and subspecies, study populations of vegetation, microbes, invertebrates, or vertebrates, at any lifestage, or any biological community or ecosystem in freshwater or saltwater environments and transition zones present in the United States, or similar to those in the United States, excluding the open ocean.
	Exposure: Short or long-term Pb concentrations in exposure media (e.g., water, sediment, or diet) that are most relevant to environmental concentrations of Pb in the United States.[a] For freshwater or saltwater, the guideline for screening of Pb exposure and effects was defined as a concentration of approximately 10 µg Pb/L[c] with higher concentrations considered if the study elucidates a mechanism plausibly relevant at lower concentrations. For sediments, exposure concentration of approximately 300 mg Pb/kg, dry weight.[d] For dietary pathways, at least one experimental group (prey) exposed to approximately 10 µg Pb/L (aqueous guideline for screening) prior to a feeding study. If a study provides toxicity data on a previously untested organism grouping (such as Class, Order, Family) or for lower concentration studies of an organism with a protected status, studies were included even if concentrations exceeded the guideline. Analytically verified exposure concentrations preferred; nominal concentrations considered in some cases.
	Comparison: A comparison to an unexposed laboratory control, a reference population, or site with no detectable exposure or with lower Pb exposure.
	Endpoint: Species or population effects including effects on growth, reproduction or development, neurobehavioral effects, reduced survival or fitness, carbon fixation and photosynthesis. At higher levels of biological organization endpoints include changes in community composition, altered ecosystem processes and functions, such as productivity, or shifts in genotypes or species, species extirpation, declines in total number of species or biomass, or decreased species richness.

	Study Design: Laboratory, mesocosm, observational or experimental field or gradient studies or mechanistic modeling studies that estimate the effect of Pb on an organism, biological population, community, or ecosystem whose processes may be represented quantitatively (e.g., in a dynamic or steady state).

Pb = lead.

[a]Studies on mine tailings, industrial effluent, land-applied sewage sludge, ship breaking, bioremediation of highly contaminated sites, and ingestion of Pb shot or pellets are not within the scope of the ISA due to a high concentration of Pb or lack of a connection to an air-related source or process. Generally excluded are studies of metal mixtures for which a specific effect of Pb was not separated unless conducted in biological systems with limited experimental evidence. Lastly, most site-specific studies conducted outside of North America that do not contribute novel insights on Pb biogeochemistry or effects are excluded.

[b]The guideline for screening of terrestrial studies of Pb exposure and effects is based on the values reported for soils of the conterminous United States in the 2013 United States Geological Survey report "Geochemical and mineralogical data for soils of the conterminous United States" (Smith et al., 2013). This survey was conducted between 2007 and 2013 and sampled three soil horizons (surface, A, and C) at 4,857 nonurban, non-near-road sites. The Q1, median, mean, and Q3 values in surface soil (0–5 cm) for 4841 locations for which Pb data was available in North American Soil Geochemical Landscapes Project (NASGLP) were 13.5, 18.1, 25.8, and 23.9 mg Pb/kg soil. The Q1, median, mean, and Q3 values in the A horizon (relevant for plants, invertebrates, and microorganisms as well as burrowing mammals and reptiles) for 4,841 locations for which Pb data was available in NASGLP were 13.2, 17.8, 22.2, and 23.2 mg Pb/kg soil. The 230 mg Pb/kg soil concentration guideline is approximately one order of magnitude higher than the Q3 values from the survey.

[c]The guideline for screening of Pb concentration in water is based on United States Geological Survey National Water Quality Assessment sampling for which the 2006 Pb AQCD reported summary statistics as of the time (U.S. EPA, 2006). The 99th and 95th percentile dissolved Pb values were 5.44 µg/L and 1.1 µg/L, respectively (see Table 6-2 in the 2013 Pb ISA) (U.S. EPA, 2013a). A more relevant upper bound value for dissolved Pb would be closer to 1 µg/L, and 10 µg/L is one order of magnitude above that value. As dissolved Pb concentrations in saltwater would be expected to be no higher—and generally, lower—than concentrations in freshwater (due to odds of greater proximity of freshwaters to anthropogenic sources and less access to mixing), an upper bound for saltwater would reasonably be expected to be lower than that for freshwater concentrations.

[d]The guideline for Pb screening in sediment is based on an older survey of urban and reference lake sediments across the United States. (Mahler et al., 2006) and further supported by evidence from more recent regional survey data. A median 1990s concentration for 35 U.S. sites (Table 2 of (Mahler et al., 2006)) of 73 mg Pb/kg was reported and the paper concluded that Pb had decreased since 1970s, with the 1990s median being 40% lower than the 1970s median. For saltwater, Kim et al. (2004) reported samples in a lower Delaware coastal saltmarsh that would be expected to have much less historic and non-air contamination. The concentrations for the upper depths (0 to 5 cm), dated to reflect the 90s through the early 2000s, range from 20 to 30 mg/kg. Thus, 30 mg/kg appears to be a more appropriate upper bound value for freshwater and saltwater sediments, and 300 mg Pb/kg is one order of magnitude above that value.

12.5 Literature Search

The U.S. EPA uses a structured approach to identify relevant studies for consideration and inclusion in the ISAs. The search for relevant literature in this review began with publishing a Request for Information FRN (July 7, 2020, 85 FR 40641). This FRN announced the initiation of this Pb NAAQS review and invited the public to submit relevant research studies and data that have been published, accepted for publication, or presented at a public scientific meeting since January 1, 2011, providing overlap with the 2013 Pb ISA wherein the literature considered extended to September 2011. Literature submitted by the public in response to this FRN can be viewed in the U.S. EPA's HERO database. U.S. EPA reviewed these studies for relevance following the literature screening process described in this appendix.

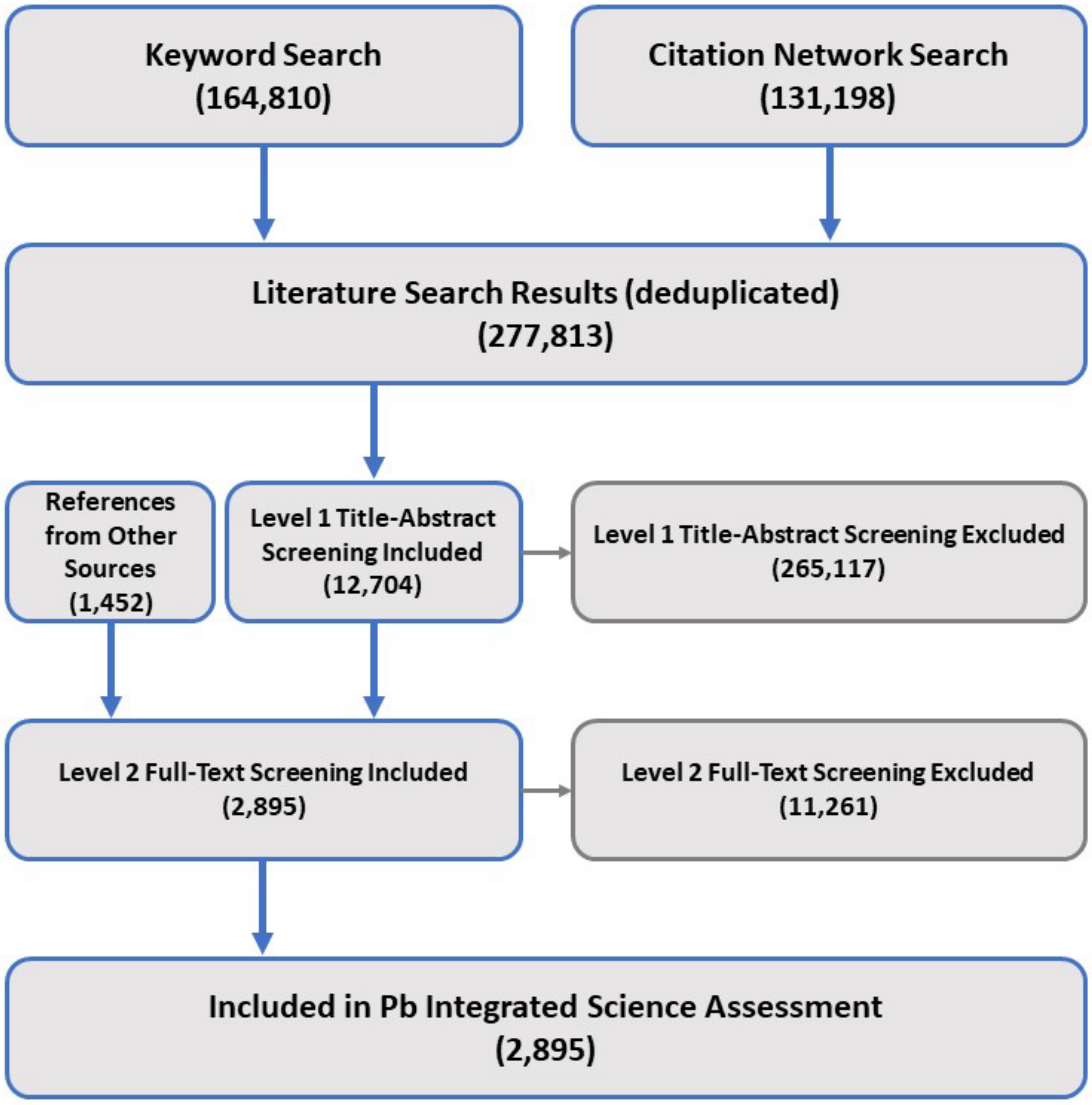
In addition to the Request for Information FRN, the U.S. EPA applied systematic review methodologies to identify peer-reviewed scientific literature relevant to the 2024 Pb ISA. The literature searching and screening methodology used for the 2024 Pb ISA generally followed the process depicted in Figure 12-2. The process began with a combination of keyword searches and citation network searches to find relevant literature in PubMed and Web of Science published between September 2011 and December 2020. This literature search strategy was designed to maximize precision[2] and recall[3] for each discipline (i.e., health, welfare effects, atmospheric sciences, and exposure). The literature then went through two levels of screening to identify relevant studies: (1) title and abstract screening using SWIFT-Active Screener (SWIFT-AS), and (2) full-text screening if the peer-reviewed paper was deemed potentially relevant after title and abstract screening.

Keyword searches were developed for each appendix using strings of relevant search terms to capture literature relevant to Pb and the topics in each appendix. For human health search results, automatic topic classification, a process that uses machine learning to classify references based on a set of already identified relevant papers, was then used to separate epidemiologic references from experimental references. In addition to keyword searches, topic-specific citation network searches for all disciplines were used to identify publications that cite references included in the 2013 Pb ISA. This approach allows for relevance ranking: given a set of seed references from the 2013 Pb ISA, the more seed references that a new reference cites, the more likely that new reference is to be relevant. In addition, a small number of references were also identified for consideration in the 2024 Pb ISA through identification of relevant literature by U.S. EPA expert scientists; recommendations received in response to the Request for Information and the Peer Input Workshop; and by review of citations included in previous assessments or in newly identified literature. Reviewers during the Peer Input Workshop were asked to provide a list of

[2]Precision is the proportion of relevant references relative to all references retrieved in a literature search.
[3]Recall is the proportion of relevant references identified by screening, relative to the total number of relevant references that exist.

additional references (if any) that the U.S. EPA should consider for the ISA, including those published since the initial literature search.

Following the 2022 Peer Input Workshops and prior to the release of the *External Review Draft*, the U.S. EPA updated the initial literature searches. These searches were conducted in response to comments received on the IRP Volume 2 from the CASAC consultation, and feedback received during the Peer Input Workshops. The updated literature searches targeted key, policy-relevant topics (i.e., "scientific information and analyses that address key questions related to the adequacy of the standards" (U.S. EPA, 2022)) most informative to reviewing the Pb NAAQS to ensure that literature published since the cutoff date of the initial literature searches was captured. For the selected health effects (i.e., nervous system, cardiovascular, and reproductive and developmental health effects) the updated literature search captured epidemiologic and experimental literature published between December 2020 and June 2022. For effects of Pb in terrestrial and aquatic ecosystems, the updated literature search included the date range of August 2020 to June 2022 and focused on studies reporting effects on growth, reproduction, and development or survival. For atmospheric sciences, the same search strings used for the original search were applied to the date range of August 2020 to June 2022. The U.S. EPA then conducted title and abstract and full-text screening steps to these additional references.



Pb = lead.

Figure 12-2 Literature flow diagram for the Pb Integrated Science Assessment.

12.5.1. Title and Abstract Screening

Consistent with the 2020 Ozone ISA (U.S. EPA, 2020b), the U.S. EPA used SWIFT-AS to perform the first-level screening of the search results for relevance, based on the title and abstract.

SWIFT-AS is a web-based literature screening software application that uses machine learning to allow screeners to efficiently screen literature for relevance (Howard et al., 2020). It ranks search results by descending likely relevance using a bag-of-words approach and Latent Dirichlet Allocation, trained by both the screener's inclusion and exclusion decisions and a positive training set, when supplied (Howard et al., 2016). The U.S. EPA used such a set of "seed references" (references known to be relevant from the 2013 Pb ISA). As references are screened and tagged as relevant or not relevant, the ranking model is further trained to sort the remaining literature, pushing predicted relevant literature to the top of the queue of references to be screened. U.S. EPA screened literature until SWIFT-AS estimated that 95% of relevant literature was included, a threshold considered comparable to human error rates (Howard et al., 2020; Cohen et al., 2006).

12.5.1.1. Atmospheric Science

Initial literature related to air quality, atmospheric chemistry, fate, and transport discussed in Appendix 1 of the 2024 Pb ISA, *Lead Source to Concentration,* was identified using a strategy consistent with the approach described in Volume 2 of the IRP (U.S. EPA, 2022). The search involved both a citation network search and a keyword search component. For all air sections (Appendix 1, Sections 1.2, 1.3.1, 1.3.4, 1.4, and 1.5), the citation network search identified all publications that cited any references from the 2013 Pb ISA chapter, *Ambient Lead: Source to Concentration* (U.S. EPA, 2013a), and a keyword search was developed to capture additional relevant publications in the Web of Science database that did not cite any 2013 Pb ISA references. The search string was tested to confirm it would achieve greater than 99% recall when applied to the 2013 Pb ISA chapter references. Literature for the fate and transport sections on soil and water (Appendix 1, Sections 1.3.2 and 1.3.3) was obtained in a similar manner, using the citation network and keyword searches used for terrestrial and aquatic ecosystems (Section 12.5.1.4). SWIFT-AS was used for title and abstract screening with seed references from the 2013 Pb ISA. Decisions about inclusion or exclusion were guided by the PICOC statement (Table 12-1).

After the Peer Input Workshop (Section 12.7.3), the literature search was updated using the same two search strings originally applied to the Web of Science database for references published after the original cutoff date. Consistent with the initial literature search, the U.S. EPA screened these additional studies for relevance using SWIFT-AS; decisions about relevance were guided by the PICOC statement.

12.5.1.2. Exposure Assessment

Initial literature related to ambient Pb exposure, toxicokinetics, and biomarkers discussed in Appendix 2 of the 2024 Pb ISA, *Exposure, Toxicokinetics, and Biomarkers,* was identified using a keyword search strategy consistent with the approach described in Volume 2 of the IRP (U.S. EPA, 2022). This search involved both a citation network search and a keyword search. The citation network

search was designed to identify all publications that cited any references from *Chapter 3: Exposure, Toxicokinetics, and Biomarkers* of the 2013 Pb ISA (U.S. EPA, 2013a).

Two separate keyword searches were developed to capture additional relevant publications that did not cite any 2013 Pb ISA references from the Web of Science and PubMed databases, respectively. The inclusion and exclusion terms used for each search were developed independent of one another to maximize the relevance for each database. Given the extensive overlap between publications that contained information on Pb exposure, biomarkers, and toxicokinetics, both keyword searches were performed on all topics in the appendix. Results from both searches were combined and literature was de-duplicated.

SWIFT-AS was used for title and abstract screening. The SWIFT-AS algorithm was initially trained using references from *Chapter 3: Exposure, Toxicokinetics, and Biomarkers* of the 2013 Pb ISA (U.S. EPA, 2013a) as seed references. Literature tags were developed to organize results by subsection. Judgments of inclusion and exclusion were based on guidelines described in the Relevance and Scope section above (Section 12.4.2).

Following the 2022 Peer Input Workshop, peer input reviewers determined that the U.S. EPA had identified most of the relevant literature. Suggested additions were screened for relevance and judgments of inclusion and exclusion were based on guidelines described in the Relevance and Scope section above (Section 12.4.2).

12.5.1.3. Health

Epidemiologic and experimental studies (i.e., animal toxicology studies) examining health effects from Pb exposure were targeted using a broad keyword search and citation network search strategy consistent with Volume 2 of the IRP (U.S. EPA, 2022). U.S. EPA screened the identified literature for relevance against PECOS statements for each health endpoint (see Section 12.4.3), using SWIFT-AS. The SWIFT-AS algorithm was trained initially using seed references from the 2013 Pb ISA (U.S. EPA, 2013a).

During this first phase of screening, the U.S. EPA tagged experimental studies reporting health outcome-related literature that potentially informs the biological or chemical events associated with phenotypic effects, including in vitro, in vivo (by various routes of exposure), ex vivo, and in silico studies. Although these studies do not necessarily meet PECOS criteria, they were tracked as a supplemental evidence stream to inform biological plausibility.

Following the 2022 Peer Input Workshop, the U.S. EPA updated the literature search for the following health outcome categories using the same keyword and citation network search strategy: nervous system effects (Appendix 3); cardiovascular effects (Appendix 4); and reproductive and developmental effects (Appendix 8). The updated literature search focused on key, policy-relevant health

outcomes for which a substantial body of recent literature conducted at relevant Pb biomarker levels was expected, as suggested by results from the initial search. Consistent with the initial literature search, the U.S. EPA screened these additional studies for relevance using SWIFT-AS and the PECOS statements.

12.5.1.4. Welfare—Effects on Terrestrial and Aquatic Ecosystems

Studies potentially relevant to Pb effects in terrestrial or aquatic ecosystems (freshwater and saltwater) were identified using a broad keyword search and citation network search strategy consistent with the approach described in Volume 2 of the IRP (U.S. EPA, 2022). The U.S. EPA screened the identified literature for relevance against LECES statements using SWIFT-AS (Table 12-4). The SWIFT-AS algorithm was trained initially using seed references from the 2013 Pb ISA (U.S. EPA, 2013a). Studies that were not within the scope of the ISA or that did not meet the criteria for inclusion based on title and abstract screening (Section 12.4.4 and Table 12-4) were excluded from further consideration. Following the 2022 Peer Input Workshop, the U.S. EPA updated the literature search and screened additional studies in SWIFT-AS for relevance using the LECES statements.

12.6 Study Selection: Full-Text Screening and Evaluation of Studies

The U.S. EPA performed a second level of screening based on assessment of the full text of the references remaining after the first-level screening (title and abstract). The U.S. EPA continued to use relevance criteria outlined in Section 12.4 during full-text screening. Studies selected for inclusion based on relevance were evaluated for study quality, as described below.

12.6.1. Individual Study Quality

After selecting studies for inclusion based on relevance, individual study quality was evaluated by considering the design, methods, conduct, and documentation of each study, but not the study results. For ISAs, the overall individual study quality evaluation process is described in the Preamble (U.S. EPA, 2015b), which outlines a base set of questions for consideration when evaluating the scientific quality of studies, intended for use in both human health and ecological studies:

- Were the study designs, study groups, methods, data, and results clearly presented in relation to the study objectives to allow for study evaluation? Were limitations and any underlying assumptions of the design and other aspects of the study stated?

- Were the ecosystems, study site(s), study populations, subjects, or organism models adequately selected, and are they adequately defined to allow for meaningful comparisons between study or exposure groups?
- Are the air quality, exposure, or dose metrics of adequate quality and are they sufficiently representative of or pertinent to ambient air?
- Are the welfare effect measurements meaningful, valid, and reliable?
- Were likely covariates or modifying factors adequately controlled or taken into account in the study design and statistical analysis?
- Do the analytical methods provide adequate sensitivity and precision to support conclusions?
- Were the statistical analyses appropriate, properly performed, and properly interpreted?

Worldwide, formal methods for individual study quality evaluation are much better developed for human health research than for ecological, atmospheric, and exposure studies. The study quality approach for health and welfare are described further below. For the 2024 Pb ISA, atmospheric and exposure studies were considered acceptable if they were published in a peer-reviewed journal, though further scrutiny was applied during full-text screening of exposure studies to identify whether the exposure assessment methods were clearly described; the selected exposure assessment methods were appropriate for the research question evaluated; the assumptions of the method(s) were clearly stated; the uncertainties and limitations of the methods were clearly stated; and QA testing had been performed. No studies in the atmospheric or exposure, toxicokinetics, and biomarkers appendices were deemed to have unacceptable study quality.

Study quality was a final step in full-text screening to decide whether to include a study in the ISA. Any references that did not pass the study quality review and deemed uninformative for the purposes of this assessment were excluded from the ISA. Studies that passed both the relevance screening and the study quality evaluation were included in the ISA. The combination of approaches described in this section are intended to produce a comprehensive collection of pertinent studies needed to address the key scientific issues that are examined in the ISA.

12.6.1.1. Health

As described in the Preamble (U.S. EPA, 2015b), causality determinations are informed by integrating evidence across scientific disciplines (e.g., exposure, animal toxicology, epidemiology) and related outcomes, and by judgments of the strength of inference in individual studies. For health outcomes, study quality is evaluated using a uniform approach that considers study strengths and limitations, including the possible roles of chance, confounding, and other biases that may influence results. The process for individual study quality evaluation has been refined by discipline with each

successive ISA based on input and feedback from numerous reviews by CASAC. Recent ISAs have developed study quality criteria tables to provide clarity on important aspects of study quality for health outcomes and serve as the foundation for the review of individual health studies (U.S. EPA, 2020b, 2019, 2017, 2016). These aspects describe the characteristics of study elements (e.g., study design, exposure assessment, potential confounding factors) that can increase or decrease confidence in the study results. Where possible, study elements, such as exposure assessment and confounding (i.e., bias due to a relationship with the outcome and correlation with exposures to Pb) are tailored to address factors specific to health studies of Pb exposure. Thus, judgments on the ability of a study to inform the relationship between an air pollutant and health vary depending on the specific pollutant being assessed.

Table 12-5 describes the aspects considered in evaluating study quality of animal toxicological and epidemiologic studies considered for inclusion in the 2024 Pb ISA. The specific aspects of each domain listed in Table 12-5 are consistent with current best practices for reporting or evaluating health science data.[4] Additionally, the aspects are compatible with published U.S. EPA guidelines related to cancer, neurotoxicity, reproductive toxicity, and developmental toxicity (U.S. EPA, 2005, 1998, 1996, 1991). These aspects were not used as a checklist to determine if a study should be included or excluded; the presence or absence of particular features in a study did not necessarily lead to the conclusion that a study was less informative or should be excluded from consideration in the ISA. Instead, reviewers considered each element of a study and made a final binary judgment (include or exclude) based on overall study quality. Study quality considerations for individual studies may be discussed within the health appendices of the 2024 Pb ISA in instances when specific aspects affect the interpretation of a study, either increasing or decreasing confidence in study results. Importantly, judgments were made without considering the outcome of a study (e.g., whether an adverse health outcome was observed), and these aspects were not used as criteria for determining the causal relationship between Pb exposure and health effects. As described in the Preamble (U.S. EPA, 2015b), causality determinations were based on judgments of the overall strengths and limitations of the *collective* body of available studies and the coherence of evidence across scientific disciplines. Table 12-5 is not intended to be a complete list of aspects that define a study's ability to inform the relationship between Pb and health effects, but it describes the major aspects considered in the 2024 Pb ISA to evaluate studies.

A limited number of studies have been excluded based on consideration of the study quality aspects described in Table 12-5. For example, specific epidemiologic studies have been excluded due to the evaluation (solely) of univariate models; lack of statistical power to detect an association; and inadequate or missing description of methods. In addition, specific toxicological studies were excluded from consideration because observed effects could not be reliably attributed to Pb exposure; application of an experimental model that was not intended for use with animals; reporting data that directly conflict with results of different experiments described in the same publication without explanation, along with

[4]For example, the National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT) approach (Rooney et al., 2014), Integrated Risk Information System (IRIS) Preamble (U.S. EPA, 2013b), ToxRTool (Klimisch et al., 1997), Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (von Elm et al., 2007), aand Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines (Kilkenny et al., 2010).

mislabeled figures, which together reduce confidence in the conclusions of the study; and for conducting experiments performed in animals that were not approved by an institutional animal care and use committee.

To document the study quality evaluation for a subset of the most policy-relevant health studies, a narrative approach was used to provide nuanced and transparent documentation of the strengths and limitations that support expert judgment for individual studies. Narrative reviews were completed for epidemiologic studies of Pb exposure and full-scale IQ in children, which played a significant role in the development of the Policy Assessment in the 2016 Pb NAAQS review. The study quality tables (Table 12-5) were used to develop prompting questions for each study domain designed to assist in the narrative documentation of study quality, ensuring the inclusion of consistent information across reviewers. The narrative reviews, along with the prompting questions, were recorded in HAWC and can be accessed on the HAWC project page.

Table 12-5 Scientific considerations for evaluating the strength of inference from studies on the health effects of Pb

Study Design
Epidemiology
Inference is stronger for studies that clearly describe the primary and any secondary aims of the study, or specific hypotheses being tested. Information including the age of the population studied, study period, and study location is used to aid in the interpretation of findings because Pb exposure has declined over time and exposures vary depending on proximity to Pb sources. For observational studies of Pb exposure and health outcomes, inference is considered to be stronger for prospective cohort studies and case control studies nested within a cohort (e.g., for rare diseases) than other case control, cross sectional, or ecologic studies. Cohort studies can better inform the temporality of exposure and effect. Other designs can have uncertainty related to the appropriateness of the control group or validity of inference about individuals from group level data. Study design limitations can bias health effect associations in either direction.
Animal Toxicology
The primary and any secondary objectives of the study, or specific hypotheses being tested should be clearly described. Studies should include appropriately matched control exposures (e.g., to clean filtered air, time matched). Studies should use experimental conditions that provoke little concern for uncontrolled variables or different practices across groups. Groups should be subjected to identical experimental procedures, conditions, and animal care (e.g., housing and husbandry).
Study Population/Test Model
Epidemiology
There is greater confidence in results for study populations that are recruited from and representative of the target population. Studies with high participation and low dropout over time that is not dependent on exposure or health status are considered to have low potential for selection bias. Clearly specified criteria for including and excluding subjects, and the reporting of baseline information on participants that are lost to follow up can aid assessment of selection bias. For populations with an underlying health condition, independent, clinical assessment of the health condition is valuable, but self-report of physician diagnosis generally is considered to be reliable for respiratory and cardiovascular diseases.[a] Comparisons of groups with and without an underlying health condition are more informative if groups are from the same source population. Selection bias can influence results in either direction or may not affect the validity of results but rather reduce the generalizability of findings to the target population.
Animal Toxicology
The animal species and strain used for toxicology investigations must be appropriate for the study goals and have relevance to a corresponding outcome in humans. Ideally, studies should report species, strain, substrain, genetic background, age, sex, and weight. Where applicable, approval of study protocols by appropriate institutional animal care and use committees must be obtained. Unless data indicate otherwise, PECOS-relevant laboratory nonhuman mammalian species and strains are considered appropriate for evaluating effects of Pb exposure. It is preferred that the authors test for effects in both sexes across multiple lifestages and report the result for each group separately.

Pollutant
Epidemiology
The focus is on studies evaluating Pb exposure.
Animal Toxicology
Studies should focus on the effects of Pb exposure on health outcomes; however, information from mixture studies in which Pb is a component may be informative if the study employs a Pb-only treatment arm with appropriate control group. Ideally, studies should report the source, purity, and form of Pb (e.g., lead acetate) used.
Exposure Assessment or Assignment
Epidemiology
General population studies using Pb biomarkers (e.g., blood, bone, or tooth Pb concentrations) are emphasized. The most useful biomarker of exposure is one that reflects the exposure timing and duration that is appropriate to the underlying pathogenetic processes (e.g., recent, cumulative over lifetime, or cumulative over a developmentally sensitive window). Blood Pb concentration (PbB) is typically measured in venous or capillary blood specimens using a variety of laboratory analytical techniques. Validated analytical methods with lower LODs, such as inductively coupled plasma mass spectrometry or graphite furnace atomic absorption spectrometry, are preferred. Capillary blood Pb determinations have greater potential for contamination during collection, resulting in greater measurement error, particularly at concentrations approaching the LOD. While PbB is most commonly measured in samples of whole blood, the small fraction of Pb in plasma (<1%) is the more toxicologically active fraction of the circulating Pb. Bone Pb is most commonly measured in the tibia, calcaneus, patella, or finger bone via X-ray fluorescence. Recent studies favor measurement of the patella for estimating trabecular bone Pb, because it has more bone mass and may afford better measurement precision than the calcaneus. Bone measurements are typically expressed in units of µg Pb per g bone mineral. This convention may potentially introduce variability into the bone Pb measurements related to variation in bone density. Notably, lower bone mineral density is associated with greater measurement uncertainty in bone Pb, which can have important implications for studies in populations for whom low bone mineral density is more common (e.g., older women). Measurements of Pb in hair, saliva, nails, urine, and feces suffer from high interlaboratory variability, low reproducibility, and a lack of reliable reference values. A more detailed discussion of exposure biomarkers can be found in Appendix 2.
Animal Toxicology
For this assessment, the administration of Pb by oral, inhalation, or intravenous routes are considered relevant. Studies that resulted in measured blood Pb levels <30 µg/dL will be used in the health section narratives.[b] Studies should characterize Pb concentration, environmental temperature and relative humidity, and/or have measures in place to adequately control the exposure conditions. All studies should include exposure control groups (e.g., dosing vehicle, or no Pb treatment) that are appropriate to the route, duration of exposure, and study design. Studies should randomize assignment to exposure groups and, where possible, conceal allocation to research personnel. Blinding of research personnel to study group may not be possible due to animal welfare and experimental considerations; however, differences in the monitoring or handling of animals in all groups by research personnel should be minimized.

Outcome Assessment
Epidemiology
Inference is stronger when outcomes are assessed or reported without knowledge of exposure status. Knowledge of exposure status could produce artifactual associations. Confidence is greater when outcomes assessed by interview, self-report, clinical examination, or analysis of biological indicators are defined by consistent criteria and collected by validated, reliable methods. Independent, clinical assessment is valuable for incidence of disease, but report of physician diagnosis has shown good reliability. Validated questionnaires for subjective outcomes such as symptoms are regarded to be reliable,[c] particularly when collected frequently and not subject to long recall. For biological samples, the stability of the compound of interest and the sensitivity and precision of the analytical method is considered. If not based on knowledge of exposure status, errors in outcome assessment tend to bias results toward the null.
Animal Toxicology
Endpoints should be assessed in the same manner for control and exposure groups (e.g., time after exposure, evaluation methods/procedures, endpoint evaluation) using valid, reliable methods. Wherever possible, the limit of detection for quantitative assays should be given. For each experiment and each experimental group, including controls, precise details of all procedures carried out should be provided. Time of the endpoint evaluations is a key consideration that will vary depending on endpoint evaluated. Endpoints should be assessed at time points that are appropriate for the research questions. Additionally, in order to preclude reporting bias, studies should report results for all experimental procedures conducted. All animals used in a study should be accounted for, and rationale for exclusion of animals (e.g., attrition) or data should be specified and reasonable given the study design.
Other Potential Confounding Factors[d]
Epidemiology
Factors are considered to be potential confounders if demonstrated in the scientific literature to be related to health effects and correlated with Pb. Not accounting for confounders can produce artifactual associations; thus, studies that statistically adjust for multiple factors or control for them in the study design are emphasized. Less weight is placed on studies that adjust for factors that mediate the relationship between Pb and health effects, which can bias results toward the null. Confounders vary according to study design and health effect of interest, and may include, but are not limited to the following: socioeconomic status, parental caregiving, race (as a proxy measure for a complex set of social factors), age, medication use, smoking status, noise, urbanicity, and environmental and/or occupational exposures.
Animal Toxicology
Preference is given to studies using experimental and control groups that are matched for individual level characteristics (e.g., strain, sex, body weight, litter size, and food and water consumption) and time varying factors (e.g., seasonal and diurnal patterns).

Statistical Methodology
Epidemiology
Multivariable regression models that include potential confounding factors are emphasized. Studies of pollutant mixtures can be informative if health effects of exposure to Pb, presumably a component of the mixture, are also examined separately. Such studies can provide insight into potential modification of the criteria pollutant's effect by other individual pollutants or by a broader pollutant mixture. Models with interaction terms aid in the evaluation of potential confounding as well as effect modification. Sensitivity analyses with alternate specifications for potential confounding inform the stability of findings and aid in judgments of the strength of inference from results. In the case of multiple comparisons, consistency in the pattern of association can increase confidence that associations were not found by chance alone. Statistical methods that are appropriate for the power of the study carry greater weight. For example, categorical analyses with small sample sizes can be prone to bias results toward or away from the null. Statistical tests such as correlation coefficients, *t* tests, and chi-squared tests are not considered sensitive enough for adequate inferences regarding Pb health effect associations. For all methods, the effect estimate and precision of the estimate (i.e., width of 95% CI) are important considerations rather than statistical significance.
Animal Toxicology
Statistical methods should be clearly described and appropriate for the study design and research question (e.g., correction for multiple comparisons). Specific sample sizes are not criteria for inclusion or exclusion; ideally, the sample size should provide adequate power to detect hypothesized effects. Because statistical tests have limitations, consideration is given to both trends in data and reproducibility of results. Results should be presented quantitatively in the appropriate format for the data (e.g., continuous data ideally should not be presented as categorical or dichotomized) and separately by sex and cohort.

CI = confidence interval; LOD = limit of detection; Pb = lead; PbB = blood lead concentra

[a]Murgia et al. (2014); Weakley et al. (2013); Yang et al. (2011); Heckbert et al. (2004); Barr et al. (2002); Muhajarine et al. (1997); Toren et al. (1993).

[b]Studies not including a blood lead biomarker were tracked during study screening but were not included/evaluated in the health section narratives.

[c]Burney et al. (1989).

[d]Many factors evaluated as potential confounders can be effect measure modifiers (e.g., season, comorbid health condition) or mediators of health effects related to Pb (e.g., comorbid health condition).

12.6.1.2. Welfare—Effects on Terrestrial and Aquatic Ecosystems

Generally, the field of study quality evaluation is much more robust for human health research than for ecological research. However, study quality is still very important for ecological research, and U.S. EPA staff have relied on the criteria listed in the Preamble as criteria for reviewing the quality of individual studies within the 2024 Pb ISA. A limited number of studies were excluded based on consideration of these study quality questions and application of the LECES statement. The main reasons studies were eliminated: exposure concentrations that exceeded concentration guidelines, as specified in the LECES (Table 12-4); no report of Pb concentration; Pb was part of a mixture of metals with no testing of the independent effect of Pb; a lack of statistical testing for endpoints of interest; inadequate or missing description of methods; or inadequate study design.

12.7 Peer Review and Public Participation

Peer review is an important component of any scientific assessment, as formalized in the guidance found in the U.S. EPA's Peer Review Handbook (U.S. EPA, 2015a). The 2024 Pb ISA follows the policies and procedures identified therein. Additionally, the 2024 Pb ISA is designated as a Highly Influential Scientific Assessment, which is defined by the Office of Management and Budget's *Final Information Quality Bulletin for Peer Review* (hereafter, "Peer Review Bulletin") as:

> A subset of Influential Scientific Information that is a scientific assessment (i.e., an evaluation of a body of scientific or technical knowledge, which typically synthesizes multiple factual inputs, data, models, and assumptions and applies the best professional judgment to bridge uncertainties in the available information) that "could have a potential impact of more than $500 million in any year on either the public or private sector" or "is novel, controversial, or precedent-setting, or has significant interagency interest." (https://obamawhitehouse.archives.gov/omb/memoranda_fy2005_m05-03/).

As such, there are additional review and transparency steps required in the release of this information (e.g., public comment). These review and public participation steps are described in the subsequent sections.

12.7.1. Request for Information

Consistent with the Preamble (U.S. EPA, 2015b), a Request for Information was published in the Federal Register on July 7, 2020 (85 FR 40641). The purpose of this Request for Information was announcing the beginning of the review cycle of the air quality criteria and the Pb NAAQS and inviting the public to submit relevant research studies and data that had been published, accepted for publication, or presented at a public scientific meeting since January 1, 2011. The public was given 60 days to respond

to this FRN; the U.S. EPA received eight comments via the Federal eRulemaking Portal (http://www.regulations.gov, Docket ID: EPA-HQ-OAR-2020-0312). Literature submitted by the public in response to this FRN can be viewed in the U.S. EPA's HERO database.

12.7.2. Integrated Review Plan

Following the Request for Information, the U.S. EPA prepared a multi-volume IRP: Volume 1 provides background information on the air quality criteria and standards for Pb; Volume 2 addresses the general approach for the review and planning of the ISA; and Volume 3 is the planning document for quantitative analyses considered in the policy assessment. Volume 2 of the IRP (U.S. EPA, 2022), which describes the plan for developing the ISA, was discussed by CASAC at a public meeting on April 8, 2022. Availability of Volume 2 of the IRP for public comment was announced in the Federal Register on March 10, 2022 (87 FR 13732). The public was given the opportunity to respond, and the U.S. EPA received one public comment via the Federal eRulemaking Portal (http://www.regulations.gov, Docket ID: EPA-HQ-OAR-2020-0312-0010).

Following the April CASAC public meeting, documentation of the meeting and written comments from individual CASAC members were sent to the U.S. EPA Administrator in a letter dated April 22, 2022 (https://casac.epa.gov/ords/sab/f?p=113:12:17516491975646:::12).

12.7.3. Peer Input

The role of peer input is described in the Preamble, as well as the Peer Review Handbook (U.S. EPA, 2015a, b). After a thorough literature search and screening process, the U.S. EPA developed preliminary draft appendices for initial peer input. Causality determinations had yet to be developed. Peer input is a process that allows the U.S. EPA to gather early-in-the-process feedback from subject-matter experts, internal and external to the U.S. EPA, to ensure that the ISA captures relevant new literature and is focused on the most policy-relevant findings. Peer input serves as a supplement to other peer-review mechanisms and does not replace a thorough external peer review by CASAC.

Peer input for the 2024 Pb ISA occurred as a series of four webinar workshops, which the U.S. EPA announced in an FRN on May 6, 2022 (87 FR 27147, Docket ID: EPA-HQ-ORD-2020-0701). The four workshops were organized by subject: Effects of Pb in Terrestrial and Aquatic Ecosystems; Epidemiologic and Toxicological Evidence for Health Effects of Pb Exposure; Ambient Pb: Source to Concentration; and Exposure, Toxicokinetic, and Pb Biomarkers. Workshops were facilitated by U.S. EPA's contractor, ICF. Peer input reviewers were selected by ICF, with input from U.S. EPA, in accordance with U.S. EPA's Peer Review Handbook (U.S. EPA, 2015a).

Peer input reviewers were given the following charges:

- Correct technical errors and identify critical gaps.
- Consider how clearly and logically the appendices and content within the sections are organized.
- Indicate how accurately scientific information is characterized, whether advances in knowledge in the recent literature have been adequately highlighted, and whether emphasis has been placed on the most informative, policy-relevant literature.
- Identify any key studies missing, (including those published after the early 2021 literature search dates for the draft materials), especially any associated with the effects of Pb from ambient air. Provide full citations for suggested references.
- Indicate any specific issues that should be considered or highlighted that will be important for integrating evidence across disciplines.

There were additional topic-specific charge questions. Peer input reviewers were not asked to correct typos or grammatical errors.

During the workshops, peer input reviewers affirmed that the U.S. EPA included the relevant literature, though some additional studies were identified for U.S. EPA's consideration. Following the workshop, the U.S. EPA considered comments and incorporated revisions based on the reviewers' feedback. Suggested studies were screened for relevance as described for the initial literature searches and incorporated if they met the inclusion criteria (see Sections 12.4 and 12.5.1).

12.7.4. Internal Technical Review and Clearance

The U.S. EPA guidelines, such as the U.S. EPA's Peer Review Handbook (U.S. EPA, 2015a), recommend an internal technical review process prior to any external dissemination of scientific information. Consistent with this guidance, the draft ISA was reviewed by U.S. EPA subject-matter experts. Following the technical review, the U.S. EPA revised the document based on the reviewers' comments prior to submitting this document for formal U.S. EPA clearance. This final document was cleared for public release following clearance policy and procedures.

12.7.5. Clean Air Scientific Advisory Committee Peer Review

CASAC served as the official peer review mechanism for the 2024 Pb ISA. Two sections of the Clean Air Act, Sections 108 and 109 [42 U.S.C. 7408 and 7409], govern the periodic review and establishment of the NAAQS (U.S. EPA, 2020a). With respect to CASAC, Section 109(d)(2) addresses the appointment and advisory functions of an independent scientific review committee. Section

109(d)(2)(A) requires the Administrator to appoint this committee, which is to be composed of "seven members including at least one member of the National Academy of Sciences, one physician, and one person representing State air pollution control agencies." Section 109(d)(2)(B) states that the independent scientific review committee periodically "shall complete a review of the criteria… and the national primary and secondary ambient air quality standards… and shall recommend to the Administrator any new… standards and revisions of existing criteria and standards as may be appropriate…" Since the early 1980s, this independent review function has been performed by CASAC. More information on the CASAC peer review can be found on the U.S. EPA CASAC website.

The draft ISA was released for public comment and CASAC review on March 31, 2023. It was posted on U.S. EPA's website and its availability was announced in a Federal Register Notice (88 FR 19302). CASAC met on June 13–14, 2023, to review the draft ISA, and met virtually on August 23–24, 2023, to further discuss its consensus comments. The final CASAC letter was sent to the U.S. EPA Administrator on September 18, 2023. The letter conveyed the committee's consensus advice as well as comments from individual committee members. The Administrator responded to CASAC's letter on the draft ISA on October 30, 2023. CASAC's letter and U.S. EPA's response are viewable on CASAC's website.

CASAC, in its letter, found the ISA "to be a comprehensive assessment of the available science relevant to understanding the health and welfare effects of lead (Pb)" (EPA-CASAC-23-003; https://casac.epa.gov/ords/sab/r/sab_apex/casac/activity?p18_id=2637&clear=18&session=22281838571132#report). CASAC shared recommendations for strengthening and improving the ISA and noted that "with these recommended changes, the [ISA] will serve as a scientifically-sound foundation for the agency's review of the National Ambient Air Quality Standards (NAAQS) for Pb." The CASAC recommended clarifying text to strengthen the characterization of health and exposure evidence as well as revisions to the causality determinations for some health outcomes. In response to that advice, the U.S. EPA revisited the evidence supporting the draft determinations for several outcomes, including adult cognitive function, pregnancy and birth outcomes, female reproductive function, immune system effects, and mortality. In addition, across the exposure and health appendices, the U.S. EPA clarified the lines of evidence and rationales that support causality determinations; bolstered the ISA's characterization of the strengths and limitations of various study designs, analytic approaches, and exposure biomarkers; expanded discussion of the relationship of particle size to exposure pathways, absorption of Pb into the blood, and models of Pb exposure-blood Pb relationships; and improved consistency in how the ISA characterizes study results.

CASAC expressed general agreement with the U.S. EPA's characterization of the sources, fate and transport, and measurement of Pb, as well as its effects on terrestrial and aquatic biota. In response to CASAC's advice on Appendix 1 *(Lead Source to Concentration)*, the U.S. EPA included additional figures on emission and concentration trends; added more detail on aviation gas and fire emissions; expanded the discussion of monitoring requirements and the Pb monitoring network; and recognized

monitoring needs and interventions related to high daily concentrations identified by CASAC. In response to CASAC's advice on ecological effects, the U.S. EPA provided additional clarification on a few specific topics as indicated, edited other content for brevity, and revisited the evidence supporting the draft causality determination for neurobehavioral effects in freshwater invertebrates.

12.8 Quality Assurance and Quality Control

QA helps ensure that the U.S. EPA conducts high-quality science that can be used to inform policymakers, industry, and the public. Agency-wide, the U.S. EPA Quality Program provides the framework for planning, implementing, documenting, and assessing work performed by the Agency, and for carrying out required quality assurance and quality control (QA/QC) activities. Additionally, the Quality Program covers the implementation of the U.S. EPA Information Quality Guidelines and the U.S. EPA Environmental Information Quality Policy and Procedures (U.S. EPA, 2023a, b, 2002). The 2024 Pb ISA follows all Agency guidelines to ensure a high-quality document.

For the ISA Program, management of quality assurance is documented in a Program Quality Assurance Project Plan (PQAPP), which describes the technical approach and QA/QC procedures associated with the ISA Program. QA objectives and measurement criteria detailed in the PQAPP have been employed in developing the 2024 Pb ISA. QC checks were conducted on numerical entries throughout the ISA. At a minimum, numerical values from every fifth citation were verified for accuracy by an independent U.S. EPA staff member against the original source, and any errors were subsequently corrected. Furthermore, the U.S. EPA's HERO database has its own QC processes, as documented in HERO's Quality Assurance Project Plan (QAPP).

The 2024 Pb ISA is classified as QA Category A, which requires at least one audit to be completed. During assessment development, the Pb ISA underwent two Technical System Audits in July 2022 and July 2023 by an independent contractor, Neptune and Company, Inc. The auditor identified no major findings and verified that QC procedures were adequately performed and documented in accordance with QA procedures.

12.9 Conclusion

This appendix describes the overall process of developing the Pb ISA: literature search and screening methods; study quality evaluation; peer input and peer review; documentation; and QA. Overall, the U.S. EPA has a robust set of policies and procedures in place to ensure the highest quality products. In developing the 2024 Pb ISA, the U.S. EPA has followed all the appropriate processes and endeavored to add additional steps as practicable and needed (e.g., use of SWIFT-AS, scoping statements, and documentation of individual study quality).

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