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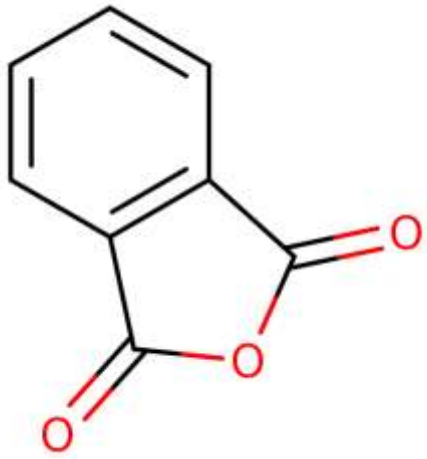
Office of Chemical Safety and
Pollution Prevention

Draft Systematic Review Protocol for Phthalic Anhydride

Systematic Review Support Document for the Draft Risk Evaluation

CASRN 84-55-9



March 2026

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INTRODUCTION

The U.S. EPA's Office of Pollution Prevention and Toxics (OPPT) applies systematic review principles in the development of risk evaluations under the amended Toxic Substances Control Act (TSCA). TSCA Section 26(h) requires EPA to use scientific information, technical procedures, measures, methods, protocols, methodologies, and models consistent with the best available science and base decisions under Section 6 on the weight of scientific evidence. Within the TSCA risk evaluation context, the weight of scientific evidence is defined as "a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance" (40 CFR 702.33).

To meet the TSCA Section 26(h) science standards, EPA used the TSCA systematic review process described in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (U.S. EPA, 2021) (hereinafter referred to as "2021 Draft Systematic Review Protocol"). Section 3 of the 2021 Draft Systematic Review Protocol depicts the steps in which information is identified and whether it undergoes the formal systematic review process (U.S. EPA, 2021). Information attained via the systematic review process is integrated with information attained from sources of information that do not undergo systematic review (*e.g.,* EPA-generated model outputs) to support the weight of scientific evidence analysis.

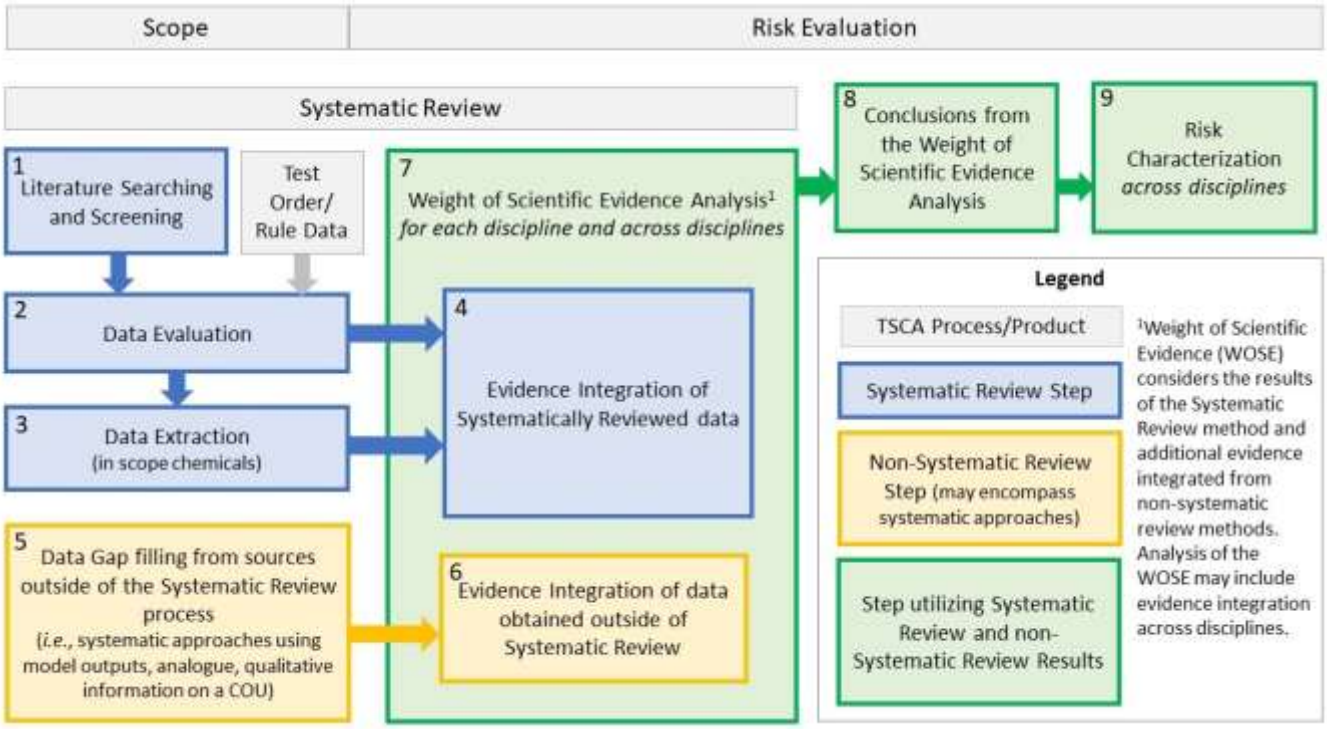

Figure 0-1. Overview of the TSCA Risk Evaluation Process with Identified Systematic Review Steps

The process complements the risk evaluation process in that it is used to develop the exposure and hazard assessments based on reasonably available information. EPA defines "reasonably available information" to mean information that EPA possesses or can reasonably obtain and synthesize for use in risk evaluations, considering the deadlines for completing the evaluation (40 CFR 702.33).

1 CLARIFICATIONS AND UPDATES TO THE 2021 DRAFT SYSTEMATIC REVIEW PROTOCOL

In 2021, EPA released the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (U.S. EPA, 2021), a framework of systematic review approaches under TSCA, to address comments received on a precursor systematic review approaches framework, the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018). In April 2022, the SACC provided comments on the 2021 Draft Systematic Review Protocol and additional comments on OPPT's systematic review approaches were garnered during the public comment period. In lieu of an update to the 2021 Draft Systematic Review Protocol, this systematic review protocol for the *Draft Risk Evaluation for Phthalic Anhydride* (U.S. EPA, 2026o) (hereinafter referred to as "Draft Risk Evaluation for Phthalic Anhydride") describes some clarifications and different approaches that were implemented than those described in the 2021 Draft Systematic Review Protocol in response to (1) SACC comments, (2) public comments, or (3) to reflect chemical-specific risk evaluation needs.

1.1 Clarifications

The chemical-specific systematic review protocol is used to transparently document any updates or clarifications made to the systematic review process used for considering information identified for a given TSCA risk evaluation, as compared to those published in the Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances (U.S. EPA, 2021). Throughout the 2021 Draft Systematic Review Protocol, there were some terms used that were not explicitly defined, resulting in their different uses within the document (U.S. EPA, 2021). Table 1-1 lists the terms that were updated to resolve some of the confusion expressed by the public and SACC comments regarding the implementation of the respective systematic review-related step. One main clarification is that *all references that undergo systematic review are considered for use in the risk evaluation*, even those that do not meet the various discipline and sub-discipline screening criteria or those that are categorized as supplemental information at title and abstract (TIAB) or full-text screening.

Section 4.2.5 of the 2021 Draft Systematic Review Protocol describes how data sources (*e.g.*, individual references, databases) may be tagged and linked when the same information is present in multiple publications (U.S. EPA, 2021). References will generally undergo data quality evaluation and extraction if there are data that pass screening criteria; however, to prevent the same data from being represented multiple times and conflating the amount of available information there is on a subject area, if two or more references contain the same results tables, EPA selects the reference(s) that most thoroughly describes the extractable results (indicated as the parent reference in DistillerSR). If two references portray the same information from the same dataset, only one is counted in the overall dataset (*i.e.*, deduplication). If two references contain information about the same dataset, but one of those references only provides additional contextual information or summary statistics (*e.g.*, mean), both data sources are linked but the extractable information from both may be combined in DistillerSR. This enables the capture of key information while avoiding double-counting the data of interest. The linked reference containing most of the data, which are evaluated and extracted, is identified in DistillerSR as the parent reference; the "complementary child reference" in DistillerSR does not undergo independent data evaluation and extraction but is evaluated and extracted in combination with the parent reference. Linking the references in DistillerSR allows the reference with more limited information or only contextual information to be tracked and utilized to evaluate the extracted data in the other related studies. The child reference may undergo data quality evaluation and extraction if there are additional unique and original data that pass screening criteria.

Section 4.5 of the 2021 Draft Systematic Review Protocol describes how data may be obtained using TSCA authorities and test orders. One update to that section is that in addition to requiring data reporting under TSCA Sections 4 (test order), 8(a) (Chemical Data Reporting) and 8(d) (Health and Safety Data Reporting), *EPA may also require data reporting under TSCA Section 8(c)* (Call-in of Adverse Reactions Records). Appendix 5.3 also describes how information may be submitted to EPA under other TSCA authorities (*e.g.*, TSCA Sections 4, 5, 6, 8(d) and 8(e), as well as FYI submissions).

Section 5 of the 2021 Draft Systematic Review Protocol describes how EPA conducts data quality evaluation of data/information sources considered for a respective chemical risk evaluation, with Section 5.2 specifically explaining the terminology used to describe both metric and overall data/information source quality determinations (U.S. EPA, 2021). To respond to both SACC and public comments regarding the inappropriate use of quantitative methodologies to calculate both "metric rankings" and "overall study rankings," *EPA decided to not implement quantitative methodologies to attain either metric and overall data/information source quality determinations* and therefore updated the terminology used for both metric ("metric ranking") and overall data/information source ("overall study ranking") quality determinations (Table 1-1). Subsequently terminology for both individual metric and overall information source quality determinations has been updated to "metric rating" and "overall quality determination," respectively. The word "level" was also often used synonymously and inconsistently with the word "ranking" in the 2021 Draft Systematic Review Protocol; that inconsistency has been rectified, resulting in the word "level" no longer being used to indicate either metric or overall data/information source quality determinations (U.S. EPA, 2021).

Sections 4.3.2.1.3 and 6 of the 2021 Draft Systematic Review Protocol describe when EPA may reach out to authors of data/information sources to obtain raw data or missing elements that are important to support the data evaluation and data integration steps (U.S. EPA, 2021). In such cases, the request(s) for additional data/information, number of contact attempts, and responses from the authors are documented. EPA's outreach is considered unsuccessful if those contacted do not respond to email or phone requests within one month of initial attempt(s) of contact. One important clarification to this guidance is that *EPA may reach out to authors anytime during the systematic review process for a given data/information source or reference, and that contacting authors does not explicitly happen during the data quality evaluation or extraction step.*

Table 1-1. Terminology Clarifications between the 2021 Draft Systematic Review Protocol and the Draft Risk Evaluation for Phthalic Anhydride

2021 Draft Systematic Review Protocol Term	Phthalic Anhydride Systematic Review Protocol Term Update	Clarification
"Title and abstract" or "title/abstract"	"Title and abstract"	To increase consistency, the term "title and abstract" will be used to refer to information specific to "title and abstract" screening.
Variations of how "include," "on topic" or "PECO[a]/PESO[b]/RESO[c] relevant" implied a reference was considered for use in the risk evaluation, whereas	Meets/does not meet PECO[a]/PESO[b]/RESO[c] screening criteria	The term "include" or "exclude" falsely suggests that a reference was or was not, respectively, considered in the risk evaluation. There was also confusion regarding whether "on topic" and "PECO[a]/PESO[b]/RESO[c] relevant" were synonymous and suggested those references were explicitly considered for use in the risk evaluation (and by

2021 Draft Systematic Review Protocol Term	Phthalic Anhydride Systematic Review Protocol Term Update	Clarification
"exclude," "off topic" or "not PECO[a]/PESO[b]/RESO[c] relevant" implied a reference was *not* considered for use in the risk evaluation.		default, "off topic" and "not PECO[a]/PESO[b]/RESO[c] relevant" references were not). References that meet the screening criteria proceed to the next systematic review step; however, all references that undergo systematic review at any time are considered in the risk evaluation. Information that is categorized as supplemental or does not meet screening criteria are generally less relevant for quantitative use in the risk evaluation but may be considered if there is a data need identified. For instance, mechanistic studies are generally categorized as supplemental information at either title and abstract or full-text screening steps but may undergo the remaining systematic review steps if there is a relevant data need for the risk evaluation (*e.g.*, dose response, mode of action).
Database source not unique to a chemical	Database	Updated term and definition of "Database": Data obtained from databases that collate information for the chemical of interest using methods that are reasonable and consistent with sound scientific theory and/or accepted approaches and are from sources generally using sound methods and/or approaches (*e.g.,* state or federal governments, academia). Example databases include STORET (STOrage and RETrieval) and the Massachusetts Energy and Environmental Affairs Data Portal. The term in the 2021 Draft Systematic Review Protocol (Table_Apx N-1) incorrectly suggested that databases that contain information on a singular chemical are not considered (U.S. EPA, 2021). Furthermore, the wording "large" was removed to prevent confusion and the incorrect suggestion that there is a data size requirement for databases that contain information that may be considered for systematic review.
Metric Ranking or Level	Metric Rating	As explained above, EPA is not implementing quantitative methodologies to indicate metric quality determinations, therefore the term "ranking" is inappropriate. The term "level" was inconsistently used to indicate metric quality determinations previously; therefore, EPA is removing the use of this term to reduce confusion when referring to metric quality determinations. The term "Rating" is more appropriate to indicate the use of professional judgement to determine a quality level for individual metrics.

2021 Draft Systematic Review Protocol Term	Phthalic Anhydride Systematic Review Protocol Term Update	Clarification
Overall Study Ranking or Level	Overall Quality Determination (OQD)	As explained above, EPA is not implementing quantitative methodologies to indicate overall data/information source quality determinations, therefore the term "ranking" is inappropriate. The term "level" was inconsistently used to indicate overall data/information source quality determinations previously; therefore, EPA is removing the use of this term to reduce confusion when referring to overall data/information source quality determinations. The term "Rating" is more appropriate to indicate the use of professional judgement to determine a quality level for the overall data/information source quality determination.
Sub-discipline	No change in term	Sub-discipline explicitly indicates the two categories of receptor-based studies relevant to evaluate human health hazard (discipline): epidemiological (human receptor) or human health animal model toxicological studies (non-human animal receptor). Although environmental hazard is a discipline, Appendix T incorrectly suggested that environmental hazard is a sub-discipline in the 2021 Draft Systematic Review Protocol.
Evidence Stream	No change in term	Evidence streams were updated for both environmental and human health hazard disciplines to more appropriately categorize the hazardous endpoints that were considered. Please see additional descriptions of the evidence stream updates in Section 5.5 below.

[a] "PECO" stands for Population, Exposure, Comparator or Scenario, and Outcomes.
[b] "PESO" stands for Pathways or Processes, Exposure, Setting or Scenario, and Outcomes.
[c] "RESO" stands for Receptors, Exposure, Setting or Scenario, and Outcomes.

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2 DATA SEARCH

As described in Section 4 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021), EPA conducts a comprehensive search for reasonably available information to support the TSCA risk evaluations. Chemical-specific literature searches are conducted as described in Section 4.2.1 of the 2021 Draft Systematic Review Protocol for all disciplines (*i.e.,* physical and chemical properties, environmental fate and transport properties, engineering, exposure, environmental hazard, and human health hazard) (U.S. EPA, 2021). Additional details on the chemical verification process, and the methodology used to search for chemical specific peer-reviewed and gray literature is available in Sections 4.2 and 4.3 of the 2021 Draft Systematic Review Protocol, respectively (U.S. EPA, 2021). The initial search for peer-reviewed and gray literature relevant references was completed in October 2020. Appendix Section C.1.15 of the 2021 Draft Systematic Review Protocol contains the specific search strings used to identify peer-reviewed literature on phthalic anhydride (U.S. EPA, 2021). All reasonably available information submitted to EPA under TSCA authorities was also considered.

An updated literature search for potential additional sources of information and data that might support the risk evaluation for phthalic anhydride was conducted in February 2025. Details for the updated literature search and consideration of the new information are described in Section 3.1 of this chemical-specific systematic review protocol.

2.1 Multi-Disciplinary Updates and Clarifications to the Data Search

For the *Draft Risk Evaluation for Phthalic Anhydride* (U.S. EPA, 2026o), the literature search was conducted as described in Section 4 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). The peer-reviewed and gray literature search followed the approach outlined in Sections 4.2 and 4.3 and used search strategies described in Appendix C of the 2021 Draft Systematic Review Protocol, respectively (U.S. EPA, 2021). Occasionally additional data sources relevant for the risk evaluation may be identified after the initial search for peer-reviewed and gray literature; these data sources will then undergo systematic review for the relevant discipline(s). Additionally, each discipline utilizes different strategies (*e.g.,* search strings) to attain their discipline-specific pools of data sources that undergo systematic review.

Updated Literature Search

An update to the peer-reviewed literature search to capture information published since the initial search in October 2020 was performed in February 2025 to identify any additional potential data sources across all disciplines that might have been identified since the initial literature search was conducted in 2020 for phthalic anhydride and *ortho-(o)*-phthalic acid. Table 2-1 and Table 2-2 list the details for the literature search strategies for phthalic anhydride and *o*-phthalic acid, respectively. To clarify, the literature search strategy was the same for the initial search in 2020 as for the search in February 2025. For full transparency, the literature results in Table 2-1 and Table 2-2 indicate the number of references obtained during the initial search, the updated search, as well as the total number of references identified for each chemical. The literature search strategies described in Table 2-1 and Table 2-2 are chemical-specific but discipline-agnostic. To identify discipline-specific pools of data sources that undergo systematic review, EPA applied the same discipline-specific strategies (*e.g.,* search strings) in the updated literature search performed in February 2025 as it did in the initial literature search in 2020. However, for the updated literature search to identify information considered for the evaluation of general population, consumer, and environmental exposure, additional search strategies were applied as described in Section 2.5.

Table 2-1. Peer Literature Search Strategies for Phthalic Anhydride

Source	Search Strategy
ProQuest	TIAB("Phthalic anhydride" OR "85-44-9" OR "Anidride ftalica" OR "Phthalsaureanhydrid" OR "Anhydride phtalique" OR "Phthalanhydride" OR "anhidrido ftalico" OR "1,2-benzenedicaboxylic acid anhydride" OR "1,3-Isobenzofurandione" OR "isobenzofuran-1,3-dione" OR ("phthalic anhydride" AND ("PA" OR "M 2" OR "PAN" OR "PSA" OR "PAD")) OR "Phthalandione")
PubMed	("Phthalic anhydride"[tw] OR "85-44-9"[rn] OR "Anidride ftalica"[tw] OR "Phthalsaureanhydrid"[tw] OR "Anhydride phtalique"[tw] OR "Phthalanhydride"[tw] OR "anhidrido ftalico"[tw] OR "1,2-benzenedicaboxylic acid anhydride"[tw] OR "1,3-Isobenzofurandione"[tw] OR "isobenzofuran-1,3-dione"[tw] OR ("phthalic anhydride"[tw] AND ("PA"[tw] OR "M 2"[tw] OR "PAN"[tw] OR "PSA"[tw] OR "PAD"[tw])) OR "Phthalandione"[tw])
Scopus	TITLE-ABS({Phthalic anhydride} OR {85-44-9} OR {Anidride ftalica} OR {Phthalsaureanhydrid} OR {Anhydride phtalique} OR {Phthalanhydride} OR {anhidrido ftalico} OR {1,2-benzenedicaboxylic acid anhydride} OR {1,3-Isobenzofurandione} OR {isobenzofuran-1,3-dione} OR ({phthalic anhydride} AND ({PA} OR {M 2} OR {PAN} OR {PSA} OR {PAD})) OR {Phthalandione})
WoS	(TS="Phthalic anhydride" OR TS="85-44-9" OR TS="Anidride ftalica" OR TS="Phthalsaureanhydrid" OR TS="Anhydride phtalique" OR TS="Phthalanhydride" OR TS="anhidrido ftalico" OR TS="1,2-benzenedicaboxylic acid anhydride" OR TS="1,3-Isobenzofurandione" OR TS="isobenzofuran-1,3-dione" OR (TS="phthalic anhydride" AND (TS="PA" OR TS="M 2" OR TS="PAN" OR TS="PSA" OR TS="PAD")) OR TS="Phthalandione")
Literature Results	Initial Search – 2,918, Update Search: 810, Total Literature: 3,728

Table 2-2. Peer Literature Search Strategies for *o*-Phthalic Acid

Source	Search Strategy
ProQuest	TIAB("Phthalic acid" OR "88-99-3" OR "Hydrogen phthalate" OR ("phthalic acid" AND ("PA" OR "M 2" OR "PAN" OR "PSA" OR "PAD")) OR "*o-p*hthalic acid" OR "ortho-phthalic acid" OR "Benzene-1,2-dicarboxylic acid" OR "Orthophthalic acid" OR "acido ftalico" OR "Enantic acid" OR "1,2-benzenedicaboxylic acid" OR "Acide phtalique")
PubMed	("Phthalic acid"[tw] OR "88-99-3"[rn] OR "Hydrogen phthalate"[tw] OR ("phthalic acid"[tw] AND ("PA"[tw] OR "M 2"[tw] OR "PAN"[tw] OR "PSA"[tw] OR "PAD"[tw])) OR "*o*-phthalic acid"[tw] OR "ortho-phthalic acid"[tw] OR "Benzene-1,2-dicarboxylic acid"[tw] OR "Orthophthalic acid"[tw] OR "acido ftalico"[tw] OR "Enantic acid"[tw] OR "1,2-benzenedicaboxylic acid"[tw] OR "Acide phtalique"[tw])
Scopus	TITLE-ABS({Phthalic acid} OR {88-99-3} OR {Hydrogen phthalate} OR ({phthalic acid} AND ({PA} OR {M 2} OR {PAN} OR {PSA} OR {PAD})) OR {*o*-phthalic acid} OR {ortho-phthalic acid} OR {Benzene-1,2-dicarboxylic acid} OR {Orthophthalic acid} OR {acido ftalico} OR {Enantic acid} OR {1,2-benzenedicaboxylic acid} OR {Acide phtalique})
WoS	(TS="Phthalic acid" OR TS="88-99-3" OR TS="Hydrogen phthalate" OR (TS="phthalic acid" AND (TS="PA" OR TS="M 2" OR TS="PAN" OR TS="PSA" OR TS="PAD")) OR TS="*o*-phthalic acid" OR TS="ortho-phthalic acid" OR TS="Benzene-1,2-dicarboxylic acid" OR TS="Orthophthalic acid" OR TS="acido ftalico" OR TS="Enantic acid" OR TS="1,2-benzenedicaboxylic acid" OR TS="Acide phtalique")
Literature Results	Initial Search – 8,071, Update Search: 4,270, Total Literature: 12,341

SWIFT-Review Validation

EPA received comments regarding the lack of detail on the use and validation of SWIFT-Review to determine discipline-specific peer-reviewed reference set considered for use in TSCA risk evaluations. In response to those comments, EPA conducted validation exercises to clarify the search process and build consistency among all the disciplines. The 2021 Draft Systematic Review Protocol contains

validation results for the use of SWIFT-Review to determine which peer-reviewed references may be relevant for the characterization of occupational exposure and environmental releases and general population, consumer, and environmental exposure for the respective chemical risk evaluations. However, to expand upon the information provided in the 2021 Draft Systematic Review Protocol, EPA validated references relevant for determining chemical specific peer-reviewed reference set for the characterization of physical and chemical properties, environmental fate and transport properties, and environmental and human health hazard. EPA manually screened the references that were found in the overall peer-reviewed search results that did not undergo TIAB screening (*i.e.*, references that were not identified using a discipline-specific search string). If a reference that did not undergo further review after TIAB screening was found to meet the screening criteria for a respective discipline (*e.g.*, data needs on physical chemical properties, environmental fate and transport properties, and environmental and human health hazard) and identified for the chemical of interest, it was flagged as a false negative. This analysis validated and verified the use of the search terms in SWIFT-Review, as it showed that less than five percent of references were false negatives across all three disciplines. This method was repeated for several of the TSCA High Priority Substances to build confidence in our discipline-specific search strings.

Additional Gray Literature Sources

Physical and Chemical Properties: In addition to the gray literature sources listed in Appendix E of the 2021 Draft Systematic Review Protocol, an additional database was added to the list of gray literature sources for physical and chemical properties. The National Institutes for Standards and Technology (NIST) Chemistry Webbook was searched in September 2021 to capture spectroscopic data, specifically ultra-violet and visible absorption (UV-Vis) data, if recorded. This source may also provide thermodynamic data that informs chemical stability and behavior under various conditions.

General Population, Consumer, and Environmental Exposure: In addition to the gray literature sources listed in Appendix E of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021), an additional source was added in 2023 to capture database outputs from a governmental source. Because the literature pool for many chemicals, including phthalic anhydride, includes a record from EPA's STORET database, which has been retired, EPA downloaded all the data for this chemical from the Water Quality Portal (WQP), which results from a collaboration between EPA, the U.S. Geological Survey, and the National Water Quality Monitoring Council, the successor database that now contains data from STORET. This data was uploaded into HERO and added to the literature pool that is considered for systematic review.

2.2 Physical and Chemical Properties

The search for peer-reviewed and gray literature are as described in Sections 4.2 and 4.3, respectively, in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). To identify pools of data sources that undergo systematic review for physical and chemical properties, EPA applied the same discipline-specific strategies (*e.g.,* search strings) in the updated literature search performed in February 2025 as it did in the initial literature search in 2020 SWIFT-Review was used to identify peer-reviewed references that are predicted to be the most relevant for evaluating physical and chemical properties for phthalic anhydride and *o*-phthalic acid. Specifically, the search string used to identify data sources that potentially contain physical and chemical property information on phthalic anhydride and *o*-phthalic acid in SWIFT-Review was developed by EPA's ORD in collaboration with Sciome and is presented in Appendix G, Section G-1, Table_Apx G-1 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). As mentioned above in Section 2.1, the search string used to identify potentially relevant peer-reviewed data references for evaluation of the physical and chemical properties of phthalic anhydride and *o*-phthalic acid were validated. When the search string terms are identified in the title, abstract or as

a keyword of a given reference in SWIFT-Review, those references proceed with title and abstract screening.

As described in Section 3.1, an update to the peer-reviewed literature search to capture information published since October 2020 was performed in February 2025 to identify any potential additional data sources for physical and chemical properties that might have been identified since the initial literature search was conducted in 2020 for phthalic anhydride and *o*-phthalic acid. The literature search strategy was the same for the initial search in 2020 as it was for the search in February 2025. From the update to the peer-reviewed literature search, EPA identified 77 new additional sources of data that were screened as described in Section 4.2.

2.3 Environmental Fate and Transport Properties

The search for peer-reviewed and gray literature are as described in Sections 4.2 and 4.3, respectively, in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). Specifically, SWIFT-Review was used to identify peer-reviewed references that are predicted to be the most relevant for evaluating environmental fate and transport properties for phthalic anhydride. The search string used for environmental fate and transport literature in SWIFT-Review was developed by EPA's ORD in collaboration with Sciome and is presented in Appendix G, Section G.2, Table_Apx G2 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). As mentioned above in Section 2.1, the search string used to identify potentially relevant peer-reviewed data references for evaluation of the environmental fate and transport properties of phthalic anhydride were validated. When the search string terms are identified in the title, abstract or as a keyword of a given reference in SWIFT-Review, those references proceed with TIAB screening.

As described in Section 3.1, an update to the peer-reviewed literature search to capture information published since October 2020 was performed in February 2025 to identify any potential additional data sources for environmental fate and transport properties that might have been identified since the initial literature search was conducted in 2020 for phthalic anhydride and *o*-phthalic acid. The literature search strategy was the same for the initial search in 2020 as it was for the search in February 2025. From the update to the peer-reviewed literature search, EPA identified 108 new additional sources of data that were screened as described in Section 4.3.

2.4 Environmental Release and Occupational Exposure

The searches for peer-reviewed and gray literature are described in Sections 4.2 and 4.3, respectively, in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). Specifically, SWIFT-Review was used to identify peer-reviewed references that are predicted to be the most relevant for evaluating environmental release and occupational exposure for the *Draft Risk Evaluation for Phthalic Anhydride* (U.S. EPA, 2026o). As described in Sections 4.2.4.2 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021), EPA identified relevant and not relevant references from the broad search results of the phthalic anhydride peer-reviewed literature as positive and negative "seeds" to classify which references contained environmental release and occupational exposure to prioritize for further review. When the relevant references were identified in SWIFT Review, those references proceeded with title and abstract screening.

As described in Section 3.1, an update to the peer-reviewed literature search to capture information published since October 2020 was performed in February 2025 to identify any potential additional data sources for environmental release and occupational exposure that might have been identified since the initial literature search was conducted in 2020 for phthalic anhydride and *o*-phthalic acid. The literature search strategy was the same for the initial search in 2020 as it was for the search in February 2025.

From the update to the peer-reviewed literature search, EPA identified 35 new additional sources of data that were screened as described in Section 4.4.

2.5 General Population, Consumer, and Environmental Exposure

The peer-reviewed and gray literature searches for general population, consumer, and environmental exposure are as described in Sections 4.2 and 4.3, respectively, in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). Specifically, SWIFT-Review was used to identify peer-reviewed references that are predicted to be the most relevant for evaluating general population, consumer, and environmental exposures to phthalic anhydride. As described in Sections 4.2.4.2 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021), EPA identified on-topic and off-topic references from the broad search results of the peer-reviewed literature as positive and negative "seeds" to classify which references on general population, consumer, and environmental exposures to prioritize for further review.

As noted previously in Section 2.1, one additional reference was added to the literature search protocol to capture database data from the WQP. The database data were compared to other databases and monitoring data found during the literature search to ensure no duplication of data. A record from a predecessor database to Water Quality Portal, EPA's STORET database, that was found during the literature search was not counted as a separate reference, to avoid double-counting data. There were no other changes to the process identified in the 2021 Draft Systematic Review Protocol for information considered for the evaluation of general population, consumer, and environmental exposure to phthalic anhydride (U.S. EPA, 2021).

2.5.1 General Population, Consumer, and Environmental Exposure Updated Literature Search Strings

As noted in Section 2.1, the updated literature search performed in February 2025 to identify information considered for the evaluation of general population, consumer, and environmental exposure, included additional search strategies to prioritize specific needs and to fill data gaps for the information supporting the risk evaluation of phthalic anhydride. The priority was to identify data sources from the U.S. and Canada. As such, references identified by any one of the targeted areas below and were also identified by the "U.S. & Canada" search strategy were sent forward to screening. The additional search strategies applied are listed in Table 2-3. A total of 57 references were identified using these search strings.

Table 2-3. Targeted Peer Literature Search Strategies for Phthalic Anhydride and *o*-Phthalic Acid

Targeted Area	Search Strategy
Ambient Air	tiab:(("airborne" OR "airflow" OR "air flow" OR "atmosphere" OR "atmospheric" OR "pm10" OR "pm(10)" OR "pm2.5" OR "pm(2.5)" OR ("air" AND ("particulate*" OR "outdoor" OR "particle" OR "gaseous" OR "sampl*")) OR "ambient air" OR "fume*") NOT "marine air")
Aquatic Species	tiab:(("aquatic species" OR "water dwelling" OR "aquatic animal*" OR "aquatic mammal*" OR "aquatic organism*" OR "seal" OR "seals" OR "manatee*" OR "otter*" OR "dolphin*" OR "whale" OR "orca" OR "porpoise*" OR "sea lion*" OR "dugong*" OR "amphibian*" OR "frog*" OR "salamander*" OR "newt" OR "newts" OR "turtle*" OR "toad*" OR "caecilian*" OR "fish" OR "fishes" OR "mollusk*" OR "sponge*" OR "scallops" OR "octopus" OR "clam" OR "clams" OR "cockle*" OR "oyster*" OR "squid" OR "snail*" OR "seafood") AND ("adipose tissue*" OR "blood" OR "egg" OR "feces" OR "liver" OR "muscle" OR "filet" OR "fillet" OR "whole organism" OR "blubber" OR "sampl*" OR "screen*")) OR ("food web" AND ("fish" OR "pelagic" OR "estuarine" OR "benthic" OR "aquatic"))

Biosolids	tiab:("biosolid*" OR "bio solid*" OR "sludge*" OR "soil amend*" OR "amended soil")
Drinking Water	tiab:("water*" AND ("distribution system" OR "raw" OR "filtration" OR "immediate consumption")) OR tiab:("community water*" OR "direct water*" OR "filtered water*" OR "potable water*" OR "tapwater*" OR "tap water*" OR "total water*" OR "water supply" OR "water supplies" OR "waterwork*" OR "water work*" OR "wellwater*" OR "well water*" OR "drinking water" OR "bottled water" OR "consumer tap water" OR "drinking water treatment plant") OR tiab:("water treatment" AND "drinking")
Groundwater	tiab:("groundwater*" OR "ground water*" OR "monitoring well" OR "wells" OR "well water" OR "wellwater" OR "recharge" OR "underground" OR "aquifer" OR "infiltration" OR "basin" OR ("field" AND "water"))
Landfills	tiab:("landfill" OR "landfills" OR "municipal solid waste" OR "municipal waste" OR ("waste" AND ("municipal" OR "worker*" OR "dump*" OR "disposal" OR "tip")) OR "dumping ground" OR "dumpsite")
Sediment	tiab:(("sediment*" OR ("bed" AND "sediment*") OR "bottom subsurface" OR "bottom surface" OR "porewater" OR "pore water") AND ("particulate matter" OR "bioconcentrat*" OR "concentrat*" OR "level" OR "levels" OR "suspended" OR "sampl*"))
Soil	tiab:("silt*" OR "soil*" OR "TSP" OR "porewater" OR "pore water" OR "soil gas" OR "soil vapor" OR "subsurface soil" OR "surface soil" OR "soil amendment" OR "amended soil*" OR "biosolid*" OR "compost" OR "fertilizer" OR "manure" OR "deposition")
Surface Water	tiab:("freshwater*" OR "fresh water*" OR "indirect water*" OR "irrigation water*" OR "meltwater*" OR "melt water*" OR "natural water*" OR "overland flow*" OR "recreation* water*" OR "riverine water*" OR "riverwater*" OR "river water*" OR "springwater*" OR "spring water*" OR "stormwater*" OR "storm water*" OR "surface runoff*" OR "surface water*" OR "marine air" OR "coast" OR "drinking water source*") OR ("sampl*" AND ("snow" OR "seawater" OR "lake" OR "river" OR "watershed" OR "stream*"))
U.S. & Canada	tiab:("U.S." OR "United States" OR "North America*" OR "American" OR "Canada" OR "Canadian" OR "Continental U.S." OR "Continental United States" OR "Alabama" OR "Alaska" OR "Arizona" OR "Arkansas" OR "California" OR "Colorado" OR "Connecticut" OR "Delaware" OR "Florida" OR "Georgia" OR "Hawaii" OR "Idaho" OR "Illinois" OR "Indiana" OR "Iowa" OR "Kansas" OR "Kentucky" OR "Louisiana" OR "Maine" OR "Maryland" OR "Massachusetts" OR "Michigan" OR "Minnesota" OR "Mississippi" OR "Missouri" OR "Montana" OR "Nebraska" OR "Nevada" OR "New Hampshire" OR "New Jersey" OR "New Mexico" OR "New York" OR "North Carolina" OR "North Dakota" OR "Ohio" OR "Oklahoma" OR "Oregon" OR "Pennsylvania" OR "Rhode Island" OR "South Carolina" OR "South Dakota" OR "Tennessee" OR "Texas" OR "Utah" OR "Vermont" OR "Virginia" OR "Washington" OR "West Virginia" OR "Wisconsin" OR "Wyoming")
Wastewater	tiab:("effluent*" OR "potw*" OR "reclaimed water*" OR "sewage*" OR "sewer*" OR "wastewater*" OR "wastewater*" OR "wrrf*" OR "wwtp*" OR "off-gas" OR "nonpotable" OR "industrial wastewater" OR "influent")
Total Results for Discipline	57 references

2.6 Environmental and Human Health Hazard

The search for peer-reviewed and gray literature are as described in Sections 4.2 and 4.3, respectively, in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). Specifically, SWIFT-Review was used to identify peer-reviewed references that are predicted to be the most relevant for evaluating environmental and human health hazard for phthalic anhydride. Specifically, search strings were developed for the two hazard disciplines by EPA's Office of Research and Development (ORD) in collaboration with SWIFT-

Review developer, Sciome. As mentioned above in Section 2.1, the search string used to identify potentially relevant peer-reviewed data references for evaluation of the environmental and human health hazard of phthalic anhydride were validated. When the search string terms are identified in the title, abstract or as a keyword of a given reference in SWIFT-Review, those references proceed with TIAB screening. The environmental and human health hazard search strings are provided online.

As described in Section 3.1, an update to the peer-reviewed literature search to capture information published since October 2020 was performed in February 2025 to identify any potential additional data sources for environmental and human health hazard that might have been identified since the initial literature search was conducted in 2020 for phthalic anhydride and *o*-phthalic acid. The literature search strategy was the same for the initial search in 2020 as it was for the search in February 2025. From the update to the peer-reviewed literature search, EPA identified 617 new additional sources of data that were screened as described in Section 4.4.

As described in Sections 5.5.1 and 5.5.2 of this protocol, data needs were identified during evidence integration, where information from sources that either did or did not undergo systematic review on phthalic ahydride was considered. EPA did not consider dermal absorption data further for when evaluating risks from phthalic anhydride; relevant dermal exposure to phthalic anhydride was evaluated through the dermal loading due to the conclusion that phthalic anhydride is a dermal sensitizer (*i.e.*, induction of skin sensitization is a local effect rather than a systemic one; skin sensitization arises from haptenation in the upper layers of skin) as further discussed in Section 4.5.2.3 and the *Draft Human Health Hazard Assessment for Phthalic Anhydride*.

3 DATA SCREENING

Sections 4.2.5 and 4.3.2 of the 2021 Draft Systematic Review Protocol describe how TIAB and full-text screening respectively, are conducted to identify references that may contain relevant information for use in risk evaluations under TSCA using discipline-specific screening criteria (U.S. EPA, 2021). Specifically, TIAB screening efforts may be conducted using the specialized web-based software programs DistillerSR[1] and SWIFT-Active-Screener,[2, 3] and the below sub-sections will describe whether TIAB screening was done manually in DistillerSR or utilized machine learning to help prioritize reference screening in SWIFT-Active-Screener. Additional details on how SWIFT Active-Screener utilizes a machine-learning algorithm to automatically compute which unscreened documents are most likely to be relevant[4] are available in Section 4.2.5 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). During TIAB screening, if it was unclear whether a reference met the screening criteria (*e.g.,* PECO/RESO/PESO statements) without having the full reference to review, or if a reference was determined to meet the screening criteria, that reference advanced to full-text screening if the full reference could be retrieved and generated into a Portable Document Format (PDF).

Literature inventory trees were introduced in the scoping process for the risk evaluations that began systematic review in 20 in response to comments received from the SACC and public to better illustrate how references underwent various systematic review steps (*e.g.,* TIAB and full-text screening). As explained in Section 2.1.2 of the *Final Scope of the Risk Evaluation for phthalic anhydride (1,3-isobenzofurandione)* (U.S. EPA, 2020b), literature inventory trees demonstrate how references that meet screening criteria progress to the next systematic review step. EPA used the Health Assessment Workplace Collaborative[5] (HAWC) tool to develop web-based literature inventory trees that enhance the transparency of the decisions resulting from the screening processes; details on the application of the tool were described by Shapiro *et al.* (2018).

Additional references identified outside of the literature searches in October 2020 or February 2025 on phthalic anhydride, but that EPA has obtained via public or other sources (*e.g.*, identified in searches for other chemicals undergoing risk evaluations, chemical assessor identified, backward searches) were also considered in the systematic review process and are reflected in the interactive HAWC hyperlinks available in the figure captions below each respective literature inventory tree. The web-based interactive literature inventory trees in HAWC also allow users to directly access the references in the Health & Environmental Research Online (HERO) database (more details available in Section 1 of the 2021 Draft Systematic Review Protocol). Instructions for accessing information about references and data sources in each node via HERO are available in HAWC for each respective literature inventory tree. Each node indicates whether a reference has met screening criteria at different screening steps

[1] As noted on the DistillerSR web page, this systematic review software "automates the management of literature collection, triage, and assessment using AI and intelligent workflows...to produce transparent, audit ready, and compliant literature reviews." EPA uses DistillerSR to manage the workflow related to screening and evaluating references; the literature search is conducted external to DistillerSR.

[2] SWIFT-Active Screener is another systematic review software that EPA is adopting in the TSCA systematic review process. From Sciome's SWIFT-Active Screener web page: "As screening proceeds, reviewers include or exclude articles while an underlying statistical model in SWIFT-Active Screener automatically computes which of the remaining unscreened documents are most likely to be relevant. This 'Active Learning' model is continuously updated during screening, improving its performance with each reference reviewed. Meanwhile, a separate statistical model estimates the number of relevant articles remaining in the unscreened document list."

[3] SWIFT is an acronym for "*Sciome Workbench for Interactive Computer-Facilitated Text-mining.*" SWIFT-Active Screener uses machine learning approaches to save screeners' time and effort.

[4] Description comes from the SWIFT-Active Screener web page.

[5] EPA HAWC is an application that allows to record and share the results of the systematic literature search, data extraction, and analyses that can then be publicly accessed online.

and/or contains types of content that may be discerned at that respective systematic review step (U.S. EPA, 2021). Furthermore, the sum of the numbers for the various nodes in the literature inventory trees may be smaller or larger than the preceding node because some studies may have unclear relevance or be relevant for many categories of information. The screening process for each discipline varies, and the nodes in the literature inventory tree indicate the screening decisions determined for each reference and whether specific content could be determined; if no references had a specific screening decision and/or contained specific content relevant for a respective discipline, a node will not be present on the literature tree to depict this.

Occasionally some references or data sources are identified in the literature search because of the availability of the title and abstract, however EPA may not be able to always locate the entire or original version. Therefore, references or data sources that meet TIAB screening criteria may be unattainable for full-text screening. The "PDF not available" node within the literature inventory tree refers to references that were identified in the literature search, but which EPA was unable to obtain the entire reference or source of information.

While all information contained in references that enter systematic review is considered for use in the risk evaluation, the references that satisfy the screening criteria are generally deemed to contain the most relevant and useful information for characterizing the uses of, exposure to, and hazards associated with a chemical of interest and are generally utilized in the risk evaluation or to identify further data needs. On the other hand, data or information sources that do not satisfy the screening criteria outlined below may undergo data quality evaluation and extraction should a data need arise for the risk evaluation.

3.1 Multi-disciplinary Updates and Clarifications to the Data Screening

As stated above in Section 2.1, all references that are found in the initial chemical-specific searches are considered for use in the respective chemical risk evaluation. Previously Section 4.2.5 of the 2021 Draft Systematic Review Protocol explained that references tagged as potentially having supplemental information may be considered for data quality evaluation and extraction. However, one clarification to that description is that even references that are tagged as not meeting TIAB or full-text screening criteria (*e.g.*, PECO/PESO/RESO) for a respective discipline or sub-discipline may also undergo additional screening to meet information needs that were not stated in the original screening criteria and be considered for data quality evaluation and extraction, should there be additional relevant information that may not have met the original screening criteria.

Section 3.1 described that an updated peer literature search was conducted in February 2025 to identify any potential additional data sources across disciplines that might not have been identified since the initial literature search was conducted in October 2020. References from the updated literature search identified to potentially have additional information were screened as previously described in Section 4.2.5 and Appendix H.4 of the 2021 Draft Systematic Review Protocol, except for references with information on environmental and human health hazard. As described in Section 4.6.1 an updated hazard PECO statement was developed to screen references from the updated literature search identified as potentially having hazard information related to environmental and human health hazard. This updated hazard PECO statement was employed to prioritize and narrow down references that were most relevant and filled data gaps for phthalic anhydride.

3.2 Physical and Chemical Properties

During data screening, EPA followed the process described in Appendix H, Section H-1 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021), to conduct title and abstract and full-text screening for phthalic anhydride guided by the data or information needs on various physical and chemical

properties or endpoints as listed in Table_Apx H-1 of the protocol. The same screening criteria was used during TIAB and full-text screening for references considered for the evaluation of physical and chemical properties of phthalic anhydride. Title and abstract screening was performed using SWIFT Active-Screener. Upon meeting screening criteria during full-text screening, data or information sources then undergo data quality evaluation and extraction. Figure 3-1 presents the number of references that report general physical and chemical property information that fulfilled the data needs for phthalic anhydride and passed these criteria for TIAB and full-text screening. EPA considered to have sufficient information gathered since the literature search conducted in 2020 in addition to information obtained via public or other sources (*e.g.*, chemical assessor identified, backward searches) on the physical and chemical properties to support the *Draft Risk Evaluation for Phthalic Anhydride* (U.S. EPA, 2026o) and did not proceed to screen the peer-reviewed literature from updated peer-reviewed literature search performed in February 2025.

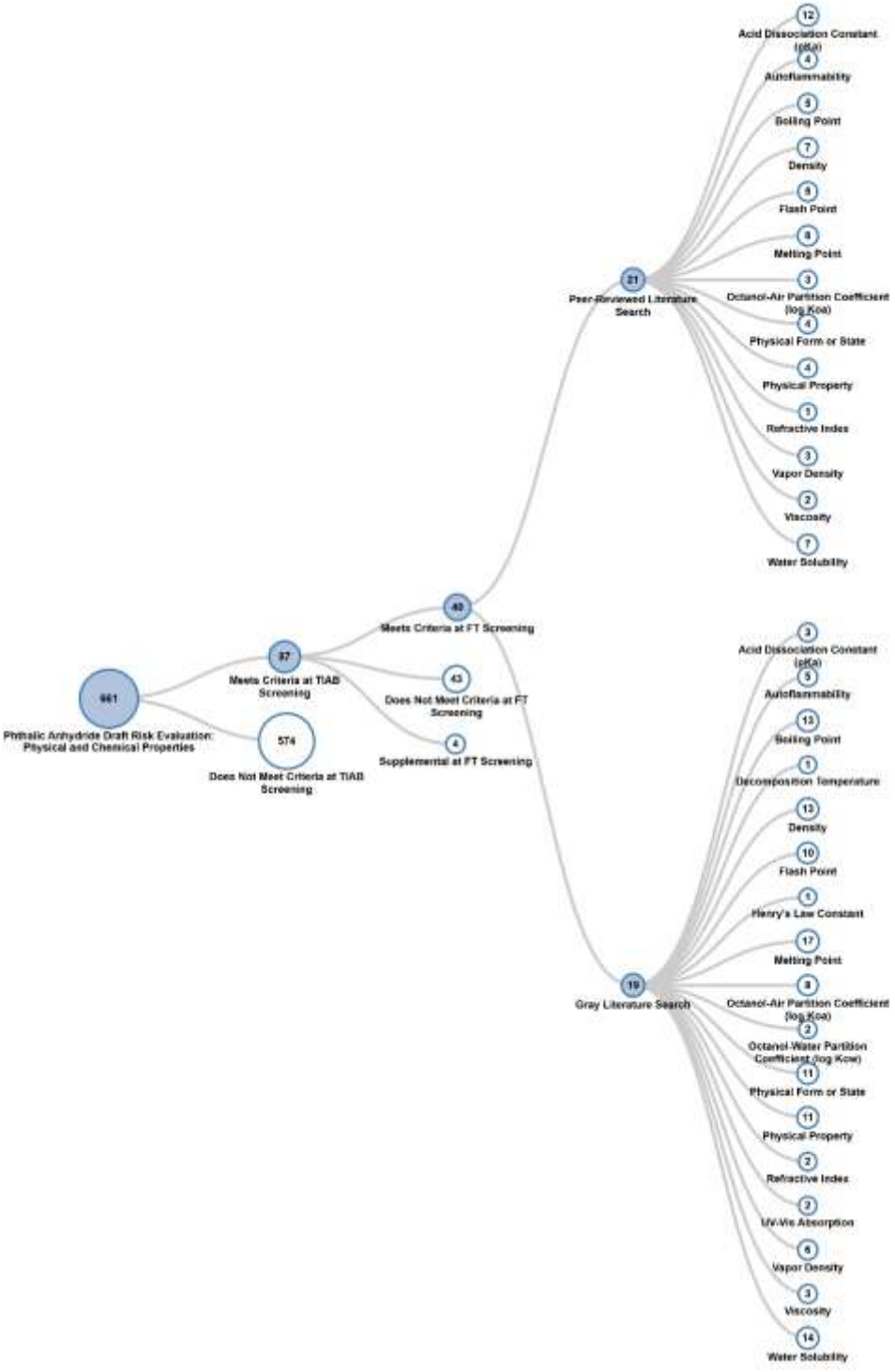

Figure 3-1. Literature Inventory Tree – Physical and Chemical Properties for Phthalic Anhydride

View the interactive literature inventory tree in HAWC. Data in this figure represent all references obtained from the publicly available databases and gray literature reference searches that were included in systematic review as of September 8, 2025. Additional data may be added to the interactive version as they become available. Some studies may be found through multiple searches and may have more than one source tag in HERO.

3.3 Environmental Fate and Transport Properties

During data screening, EPA followed the process described in Appendix H, Section H.2 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021), to conduct TIAB and full-text screening for literature search results, as guided by the PESO statement. PESO stands for **P**athways or **P**rocesses, **E**xposure, **S**etting or **S**cenario, and **O**utcomes (see Table_Apx H2 in 2021 Draft Systematic Review Protocol). The same PECO statement was used to screen references identified both in the initial search in October 2020 and the updated search in February 2025. Also, the same PESO screening criteria were used during TIAB and full-text screening for references considered for the evaluation of environmental fate and transport properties. TIAB screening was performed using SWIFT Active-Screener. Data or information sources that comply with the screening criteria specified in the PESO statement then undergo data quality evaluation and extraction. Figure 3-2 presents the number of references that report fate processes and endpoints, or environmental and exposure pathways that passed PESO screening criteria at TIAB and full-text screening.

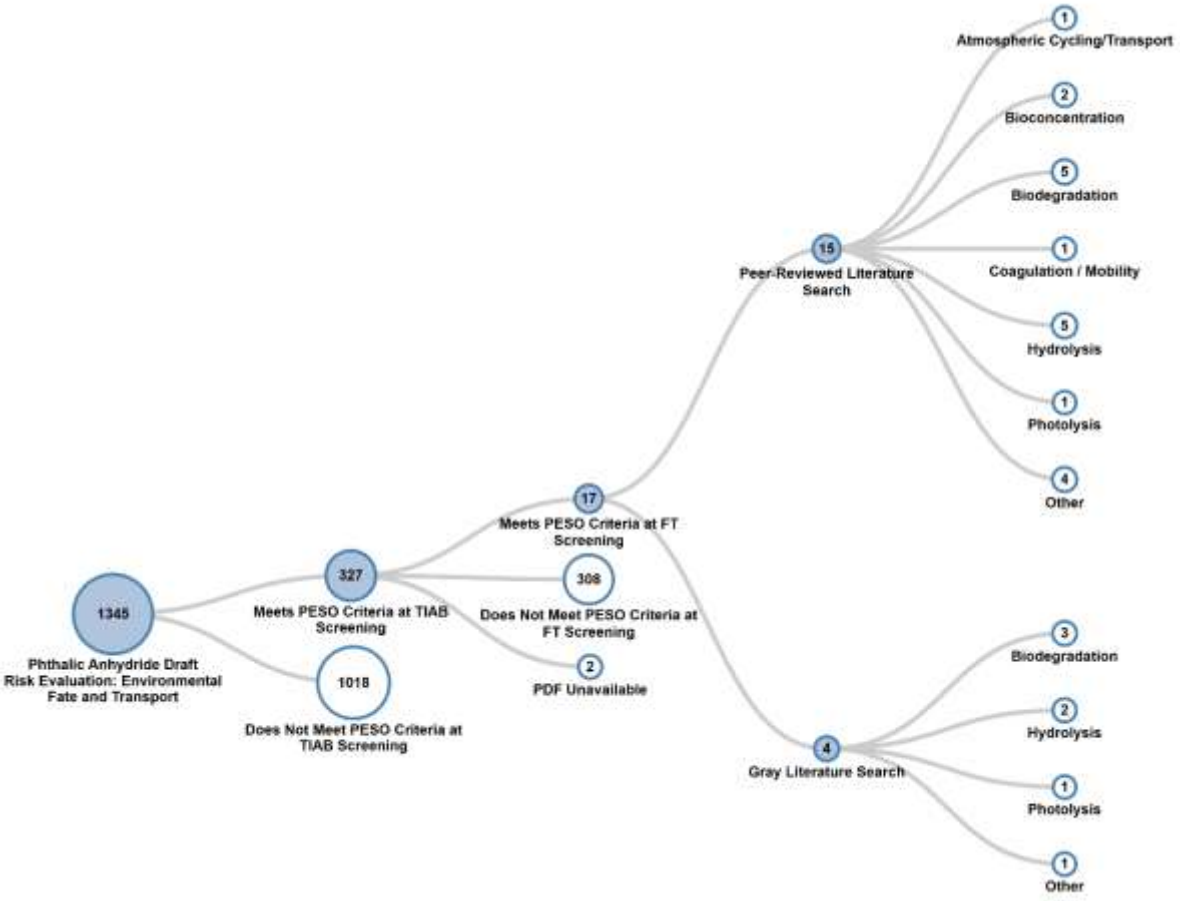

Figure 3-2. Literature Inventory Tree – Environmental Fate and Transport Properties for Phthalic Anhydride

View the interactive literature inventory tree in HAWC. Data in this figure represent all references obtained from the publicly available databases and gray literature references searches that were included in systematic review as of August 22, 2025. Additional data may be added to the interactive version as they become available.

Of the new additional sources of data that EPA identified for phthalic anhydride and *o*-phthalic acid from the update peer-reviewed literature search for environmental fate and transport properties, 123 references went through TIAB screening. Of these references 123 references, 5 references met the PESO

screening criteria during TIAB screening or were unclear to EPA whether the reference met the PECO screening criteria and moved to full-text screening. At the completion of full-text screening, of these 5 references EPA did not identify any studies for environmental fate and transport properties that met the full-text screening criteria.

3.4 Environmental Release and Occupational Exposure

During data screening, EPA followed the process described in Appendix H, Section H.3 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021), to conduct title and abstract, and full-text screening for phthalic anhydride literature search results, as guided by the RESO statement. RESO stands for **R**eceptors, **E**xposure, **S**etting or Scenario, and **O**utcomes. The same PECO statement was used to screen references identified both in the initial search in October 2020 and the updated search in February 2025. Also, the same RESO statement was used during title and abstract, and full-text screening for references considered for the evaluation of environmental release and occupational exposure information for phthalic anhydride. TIAB were performed using SWIFT Active-Screener. Data or information sources that comply with the screening criteria specified in the RESO statement then undergo data quality evaluation and extraction. Figure 3-3 presents the number of references that report general engineering data, environmental release, and occupational exposure data that passed RESO screening criteria at TIAB, and full-text screening.

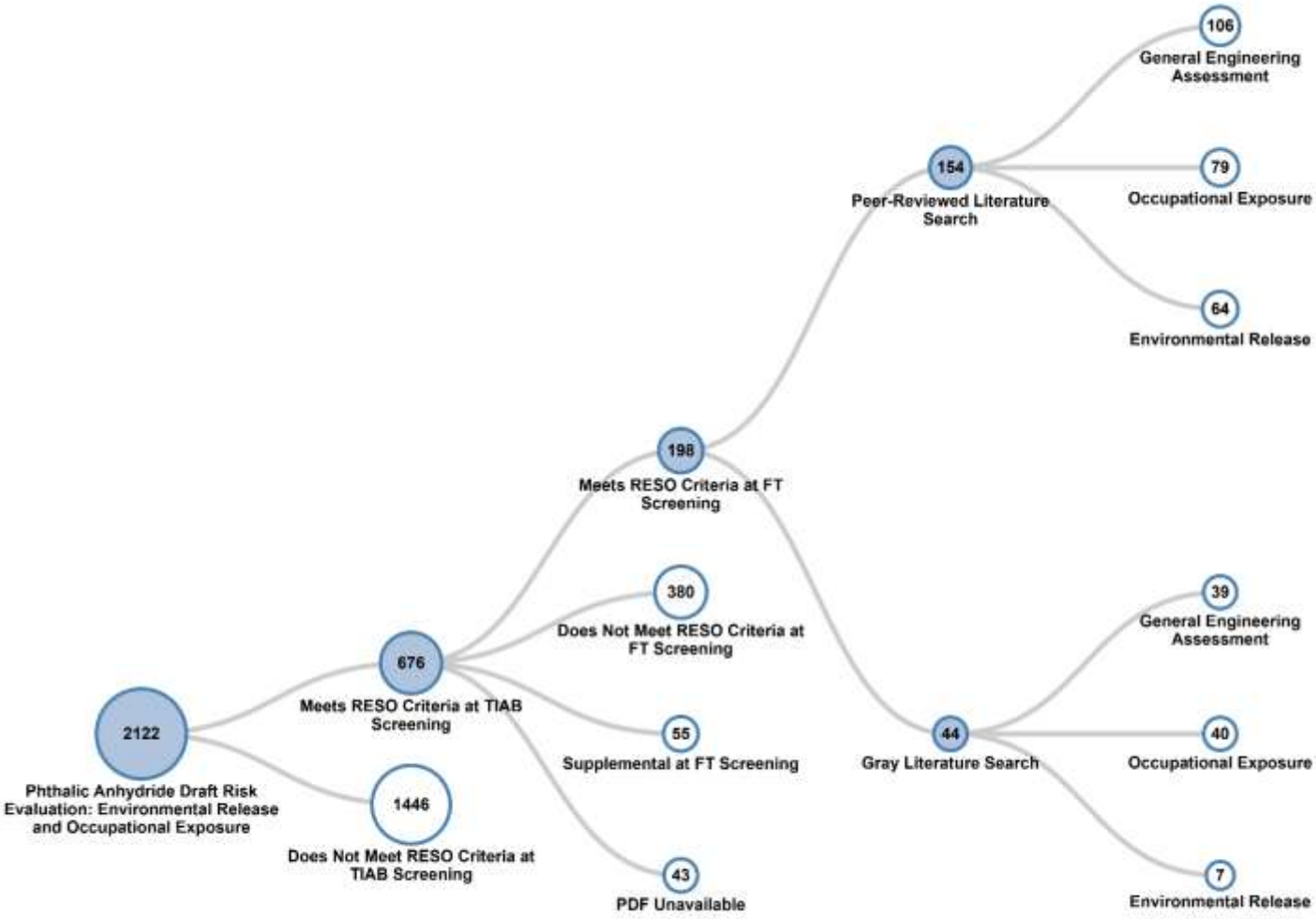

Figure 3-3. Literature Inventory Tree – Environmental Release and Occupational Exposure for Phthalic Anhydride

View the interactive literature inventory tree in HAWC. Data in this figure represents all references obtained from the publicly available databases and gray literature references searches that were included in systematic review as of January 28, 2026. Additional data may be added to the interactive version as they become available.

Of the new additional sources of data that EPA identified for phthalic anhydride and *o*-phthalic acid from the update peer-reviewed literature search for environmental release and occupational exposure information, 35 references went through TIAB screening. Of these 35 references, 16 references met the RESO screening criteria during TIAB screening or were unclear to EPA whether the reference met the PESO screening criteria and proceeded to full-text screening. Upon completion of full-text screening, EPA identified 6 references (63773, 10113574, 10191617, 11141340, 12191625, and 12193389) that met the full-text screening criteria and moved to the data evaluation and extraction step of the systematic review process.

3.5 General Population, Consumer, and Environmental Exposure

During data screening, EPA followed the process described in Appendix H.4 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021), to conduct TIAB and full-text screening for phthalic anhydride literature search results, as guided by the PECO statement. PECO stands for **P**opulation, **E**xposure, **C**omparator or Scenario, and **O**utcomes for Exposure Concentration or Dose. The same PECO statement was used to screen references identified both in the initial search in October 2020 and the updated search in February 2025. The priority, however, was to identify data sources from the U.S. and Canada. Also, the same PECO statement was used during TIAB and full-text screening for references considered for the evaluation of general population, consumer, and environmental exposure information for phthalic anhydride. TIAB screening was performed using SWIFT Active-Screener. Figure 3-4 presents the number of references that report general population, consumer, and environmental exposure data that passed PECO screening criteria at TIAB and full-text screening.

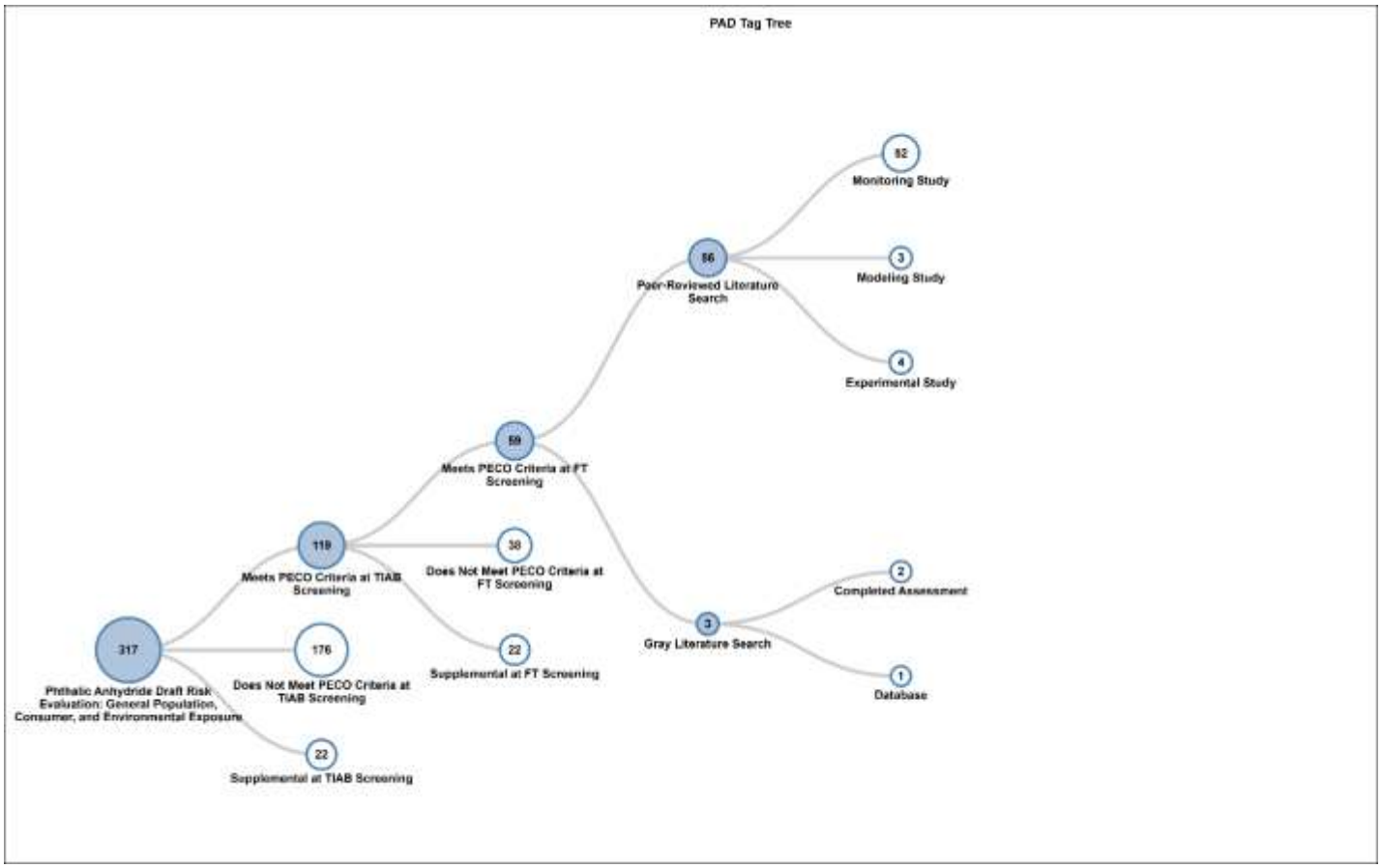

Figure 3-4. Literature Inventory Tree – General Population, Consumer, and Environmental Exposure Search Results for Phthalic Anhydride

View the interactive literature inventory tree in HAWC. Data in this figure represents all references obtained from the publicly available databases and gray literature references searches that were included in systematic review as of February 10, 2026. Additional data may be added to the interactive version as they become available.

Of the new additional sources of data that EPA identified for phthalic anhydride and *o*-phthalic acid from the update to the peer-reviewed literature search for general population, consumer, and environmental exposure information, 34 references went through TIAB screening. Of these 34 references, 12 references met the PECO screening criteria during TIAB screening or were unclear to EPA whether the reference met the PECO screening criteria and moved to full-text screening. At the completion of full-text screening, of these 12 references EPA identified 0 references that met the full-

text screening criteria and moved to the data evaluation and extraction step of the systematic review process.

3.6 Environmental and Human Health Hazard

During data screening of the literature search results from October 2020, EPA followed the process described in Appendix H, Section H.5.10 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021), to conduct TIAB and full-text screening for phthalic anhydride, as guided by the PECO statement. The PECO statement for phthalic anhydride in Appendix H.5.10 also included *o*-phthalic acid. PECO stands for **P**opulation, **E**xposure, **C**omparator or Scenario, and **O**utcomes for Exposure Concentration or Dose. The same PECO statement was used during TIAB and full-text screening for references considered for the evaluation of environmental and human health hazard resulting from exposure to phthalic anhydride. For TIAB screening, EPA utilized machine learning to help prioritize reference screening in SWIFT-Active-Screener. Full-text screening occurred in DistillerSR for references that either met the PECO screening criteria during TIAB screening or if it was unclear to EPA whether the reference would meet the PECO screening criteria based on the information available in the title and abstract.

As described in Sections 2.1 and 2.6, in addition to the sources identified in the initial literature search for phthalic anhydride and *o*-phthalic acid in October 2020, EPA conducted an updated literature search for peer-reviewed literature in February 2025. The PECO statement used to conduct TIAB and full-text screening for the updated literature search was updated from what was published in Appendix H.5.10 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021a). Specific updates to the PECO screening criteria that were used to screen references from the updated literature search in January 2025 are described below in Section 3.6.1. While the PECO statement used to conduct TIAB and full-text screening was updated to screen peer-reviewed literature from search results from February 2025, the screening process was the same as described in Section 4.2 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). For TIAB screening, EPA utilized machine learning to help prioritize reference screening in SWIFT-Active-Screener, and full-text screening occurred in DistillerSR.

Figure 3-5 presents the number of references that report environmental and human health hazard data that met PECO screening criteria at TIAB and full-text screening for phthalic anhydride. References identified in the updated literature search for peer-reviewed literature are also reflected in the literature inventory tree.

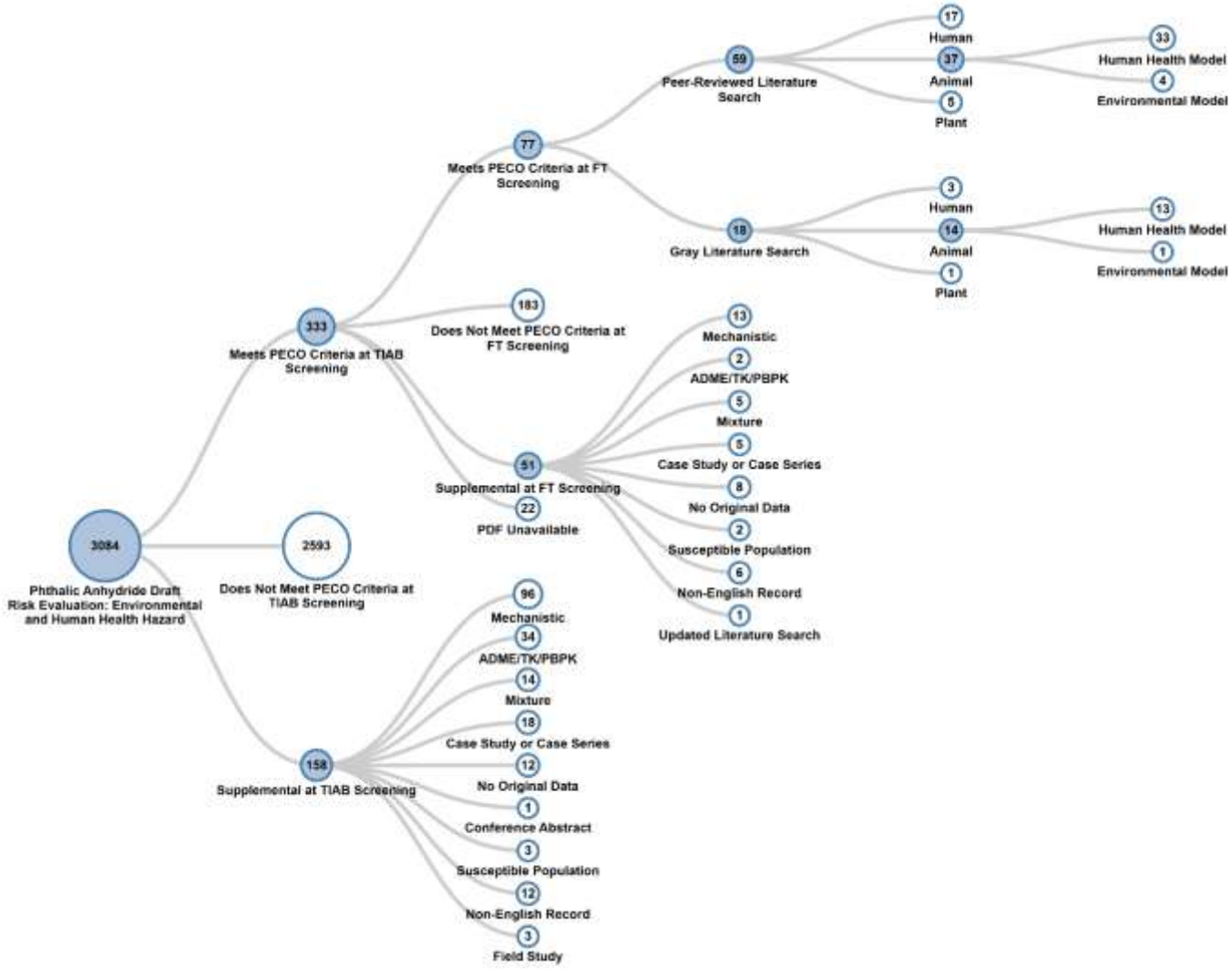

Figure 3-5. Literature Inventory Tree – Environmental and Human Health Hazard for Phthalic Anhydride

View the interactive literature inventory tree in HAWC. Data in this figure represents all references obtained from the publicly available databases and gray literature references searches that were included in systematic review as of February 3, 2026. Additional data may be added to the interactive version as they become available.

Of the new additional sources of data that EPA identified for phthalic anhydride and *o*-phthalic acid from the update to the peer-reviewed literature search for environmental and human health hazard, 617 references went through TIAB screening. Of these 617 references, 30 references met the PECO screening criteria during TIAB screening or were unclear to EPA whether the reference met the PECO screening criteria and moved to full-text screening. At the completion of full-text screening, of these 30 references EPA identified 1 hazard study (HERO IDs 61572) that met the full-text screening criteria and moved to the data evaluation and extraction step of the systematic review process. HERO ID 61572 was tagged during full-text screening as an animal, human health model study.

3.6.1 Hazard Targeted PECO Screening Criteria Updates

As stated in the previous paragraph, for references identified during the updated peer literature search in February 2025, EPA updated the PECO statement for phthalic anhydride (Table 3-1 and Table 3-2). The

screening criteria were developed as a targeted approach to prioritize the information that was most relevant and presented new information for characterizing both environmental and human health hazard for the risk evaluation for phthalic anhydride. To emphasize changes and/or clarifications added to the screening criteria published in Appendix H.5.10 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021), the following conventions are used in Table 3-1 and Table 3-2: text inserted is underlined, and text deleted is in ~~strikethrough.~~

Table 3-1. Updated PECO Criteria for Phthalic Anhydride (CASRN 85-44-9) and *o*-Phthalic Acid (CASRN 88-99-3)

PECO Element	Evidence
P	**Human:** Any population and lifestage (*e.g.,* occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any lifestage (*e.g.,* preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • **Human health models**: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, and pig~~, and hen (neurotox only)~~. • **Ecotoxicological models**: ~~invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles).~~ All animal studies (invertebrates and vertebrates) excluding the models listed above as a human health model. All hen studies (including neurotoxicity studies) will meet PECO screening criteria as ecotoxicological animal models. **Plant:** ~~All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species.~~ All aquatic and terrestrial species (live) (vascular and non-vascular plants), including but not limited to algal species, diatoms, cyanobacteria, moss, lichen and macro fungi (*e.g.*, mushrooms (Phylum: Basidiomycota)) species. **Screener notes:** • Human Health Animal Hazard and Environmental Hazard: To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential ecological hazard. For systematic review screening and data evaluation and extraction purposes, the human health models listed above will be tagged or identified as human health models and all other animal studies will be tagged as ecotoxicological animal models. Neurotoxicity studies performed in hens (*e.g.,* OECD 418 and 419) are considered relevant to both human health and environmental hazard, but all hen studies will be tagged only as ecotoxicological animal models for systematic review screening and data evaluation and extraction purposes. • Environmental Hazard: Ecotoxicological studies that assess exposure effects

PECO Element	Evidence
	on organisms such as protozoan, microbial fungi (*e.g.*, microsporidians) and molds do not meet PECO screening criteria because an environmental hazard assessment will unlikely be driven by unicellular organisms or microbial organisms which are low in the natural ecosystem hierarchy. • Human Health Animal Hazard and Environmental Hazard: Studies on gametes, embryos, or plant (*e.g.*, ungerminated seeds, harvested fruit, cut flowers, and potato tubers) or fungal sections capable of forming whole, new organisms will be tagged as potentially ***Supplemental, Mechanistic***. EXCEPTION: For environmental hazard, embryos for animal studies (*e.g.*, zebrafish, fathead minnow, copepod, bivalve embryos, chickens) and germinated seeds for plant studies (*e.g.*, seed germination in any plant) meet screening criteria if they also meet all other PECO criteria. • Human Health Animal Hazard and Environmental Hazard: Bacteria and yeast studies specific for assessing genotoxicity, mutagenicity (*e.g.*, Ames assay), or hormone assay will be tagged as potentially ***Supplemental, Mechanistic***. Otherwise, bacteria and yeast studies that are not used for assessing genotoxicity, mutagenicity, or hormone assays do **not** meet the PECO criteria. • Environmental Hazard: PECO considerations should be directed toward effects on target species only and not on the indirect effect expressed in taxa as a result of the chemical treatment (*e.g.,* substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Human Health Animal Hazard and Environmental Hazard: Tests of single toxicants in *in vitro* and *ex vivo* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.
E	**Relevant forms and isomers:** • Phthalic anhydride (CASRN 85-44-9) • *Ortho(o)*-Phthalic acid (CASRN 88-99-3) • No **isomers** were included for phthalic anhydride (CASRN 85-44-9) or *o*-phthalic acid (CASRN 88-99-3). **Human:** Any exposure to phthalic anhydride (CASRN 85-44-9) ~~or phthalic acid (CASRN 88-99-3)~~ singularly or in mixture, including exposure as measured by internal concentrations of these chemicals or metabolites in urine meet the screening criteria. Any exposure measured by internal concentrations of these chemicals or metabolites of these chemicals in additional biological matrices other than urine (*e.g.*, blood, semen, etc.) will be tagged ***Supplemental, Updated literature search: Meets original PECO criteria but does not fill a critical data gap***. Any exposure to *o*-phthalic acid (CASRN 88-99-3) will be tagged ***Supplemental, Updated literature search: Meets original***

PECO Element	Evidence
	PECO criteria but does not fill a critical data gap. **Animal Human Health Models:** Any exposure to phthalic anhydride (CASRN 85-44-9) ~~or phthalic acid (CASRN 88-99-3)~~ including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. Any exposure to *o*-phthalic acid (CASRN 88-99-3) will be tagged ***Supplemental, Updated literature search: Meets original PECO criteria but does not fill a critical data gap***. **Animal Ecotoxicological Models:** Any exposure to phthalic anhydride (CASRN 85-44-9) or *o*-phthalic acid (CASRN 88-99-3) including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plant:** Any exposure to phthalic anhydride (CASRN 85-44-9) or *o*-phthalic acid (CASRN 88-99-3) including via water, soil, and sediment. **Screener note:** • Human Epidemiology and Human Health Animal Hazard: Studies that report exposures to *o*-phthalic acid (CASRN 88-99-3) but not phthalic anhydride (CASRN 85-44-9) are to be tagged ***Supplemental, Updated literature search: Meets original PECO criteria but does not fill a critical data gap***. But studies that report exposures to phthalic anhydride (CASRN 85-44-9) in addition to reporting exposures to *o*-phthalic acid (CASRN 88-99-3) meet PECO screening criteria. • Environmental Hazard: Field studies with media concentrations (*e.g.,* surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as ***Supplemental, ADME, Field*** only if any biological effects are reported. • Human Health Animal Hazard and Environmental Hazard: Studies involving exposures to mixtures will be included only if they also include exposure to phthalic anhydride (CASRN 85-44-9) or *o*-phthalic acid (CASRN 88-99-3) alone. Otherwise, mixture studies will be tagged as ***Supplemental, Mixture Study***. • Environmental Hazard: Controlled outdoor experimental studies (*e.g.,* controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (**not field studies**) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.,* biomonitoring) where there is no prescribed exposure dose(s) will be **excluded** if there is no evaluated hazardous effect, and tagged as ***Supplemental, Field***, if there is an evaluated hazardous effect.

PECO Element	Evidence
C	**Human**: ~~A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of phthalic anhydride (CASRN 85-44-9) or phthalic acid (CASRN 88-99-3), or exposure to phthalic acid for shorter periods of time.~~ Any study with a comparison group, control group, or referent group, including: • A comparison group that does not have the disease or outcome of interest (such as a case-control study); or Any study comparing exposed individuals to unexposed or lower-exposed individuals including: • A comparison group with no exposure to the chemical of interest or exposure below detection limits, or • A comparison group exposed to lower levels of the chemical of interest; or • A comparison group exposed to the chemical of interest for shorter periods of time; or Any study assessing the association between a continuous measure of exposure and a health outcome; or For studies in which humans are intentionally exposed to the chemical of interest, an individual can serve as their own control. **Animal and Plant:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • Human Health Animal Hazard: If no control group is explicitly stated (implied (*e.g.,* by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during **Title/Abstract Screening.** During **Full-text Screening**, if no control group is explicitly stated, then the study does **not** meet PECO screening criteria**.** • Human Health Animal Hazard: For studies in which human health animal models are intentionally exposed to a chemical, the control could be a baseline measurement of the same individual (*i.e.*, the individual is assessed pre- and post-exposure), and these studies do meet the PECO screening criteria. Also, for studies in which human health animal models are intentionally exposed to a chemical, references that contain experimental designs that do not require a negative or vehicle control group (*i.e.*, skin sensitization (such as LLNA), LC50 and LD50 completed within an acute timeframe, or dermal irritation studies in which the experimental individual serves as their own control) do meet the PECO screening criteria.

PECO Element	Evidence
	• ~~Human (Epidemiology): All case series and case studies describing findings in a sample size of less than 20 people in any setting (e.g., occupation, general population) will be tracked as Supplemental Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, nested case-control study designs are meet screening criteria.~~
O	**Human**: All health outcomes (cancer and non-cancer) at the organ level or higher. **Animal and Plants**: All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth. **Screener note:** • Measurable biological effects relevant for humans, animals and plants may include but are not limited to: mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects. • Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.

Table 3-2. Major Categories of Potentially Relevant Supplemental Material for Phthalic Anhydride (CASRN 85-44-9) and *o*-Phthalic Acid (CASRN 88-99-3)

Category	Evidence
Mechanistic studies	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo*, *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Susceptible populations (no health outcome)	Epidemiology and Human Health Animal Hazard: Studies that identify potentially susceptible subgroups but do not report a health outcome. Screener note: If biological susceptibility issues are clearly present or *strongly* implied in the title/abstract, this supplemental tag may be applied at the Title/Abstract Screening. If uncertain at title/abstract, do not apply this tag to the reference during the Title/Abstract Screening.
Mixture studies	Experimental mixture studies that are not considered PECO-relevant

Category	Evidence
	because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Case reports or case series/studies	Epidemiology: ~~Case reports (n ≤ 3 cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.~~ Study designs such as case reports, case series, and case studies without a comparison group will be tagged as Supplemental. (This Supplemental category does NOT include cohort (prospective cohort, retrospective cohort, etc.), case-control, case-crossover, case-reference, case-cohort, cross-sectional, nested case control, regression, relative risk, risk ration, odds ratio, hazard ration, or standardized mortality ration (SMR) study designs, which if they report cancer related health outcomes will meet the PECO screening criteria but if they report health outcomes NOT related to cancer will be tagged as *Supplemental, Updated literature search: Meets original PECO criteria but does not fill a critical data gap*.
Non-English records	Non- English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries, but may cite secondary data on dermal absorption. This also includes studies of dermal exposure, risk, or modeling that may cite dermal absorption.
Abstract or summary	Records that do not contain sufficient documentation to support data evaluation and data extraction.
Field studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported.
Use of phthalic anhydride as a reference compound to induce a sensitization response	Phthalic anhydride is a known sensitizer and can be used as a reference compound to induce sensitization responses in experimental studies (*e.g.,* dermatitis, airway sensitization, or other allergenic response). Studies are to be tagged under this supplemental category in cases where (1) phthalic anhydride was used as a reagent to induce sensitization for the purpose of testing another compound (co-exposure); or (2) the endpoints evaluated were only mechanistic or biochemical and not apical (*e.g.,* cytokine mRNA levels). However, studies that focus on characterizing a sensitization response that included an apical outcome (*e.g.,* local lymph node assay) met the PECO screening criteria.

Category	Evidence
Updated literature search: Meets original PECO criteria but does not fill a critical data gap	Studies that met the original PECO screening criteria as published in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (U.S. EPA, 2021), however, they did not fill critical data gaps as per the additional criteria described in this revised PECO statement after the updated literature search was completed in 2025.

3.6.2 Further Filtering: Human Health Hazard

All references that met the PECO screening criteria and were categorized as having animal toxicity data relevant to human health hazard proceeded to data quality evaluation. References that met the PECO screening criteria and were categorized as having epidemiology information went through a fit-for-purpose further filtering step to determine which studies would move forward to data quality evaluation and data extraction.

3.6.2.1 Epidemiology Studies

To streamline the identification of relevant studies, modifications were implemented to the process described in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). Following PECO-based screening, references that met PECO screening criteria for epidemiology underwent a further filtering process to identify the subset of potentially relevant references that proceeded to data quality evaluation.

Urine is generally the only appropriate biomarker matrix for assessing exposure to short-chain phthalates and primary metabolites of long-chain phthalates such as *o*-phthalic acid. The IRIS Protocol for the Systematic Review of the Health Effects of Phthalate Exposure describes the reasons that biomarker matrices other than urine are inappropriate for assessing exposure. The IRIS Protocol states, "Phthalate metabolite concentration in urine is considered to be the best proxy of exposure from all sources (ingested/absorbed/inhaled). One of the problems with phthalates measured in blood and other tissues is the potential for contamination from outside sources, especially during the collection and processing of samples (Calafat et al., 2015). Phthalate diesters present from exogenous contamination can be metabolized to the monoester metabolites by enzymes present in blood and other tissues (but not urine). Thus, metabolite measures in samples other than urine may be erroneously reflecting external phthalate sources" (Radke et al., 2020; Radke et al., 2018).

Therefore, in the IRIS phthalates assessment, "biomarker measures based on samples other than urine *(e.g.*, serum, plasma, amniotic fluid, seminal fluid, amniotic fluid, breast milk) were considered to be critically deficient for all short-chain phthalates and for primary metabolites (*e.g.*, MEHP, MINP) of long-chain phthalates" (Radke et al., 2020; Radke et al., 2018). Although breast milk is not an appropriate biomarker matrix for assessing the exposure of the person who produced the milk, phthalate measures from breast milk are appropriate for assessing exposure to infants who are ingesting the breast milk.

The IRIS protocol states "Samples other than urine can be used for secondary metabolites of long-chain phthalates as the oxidative metabolism required to break down primary metabolites does not exist in these samples (personal communication, Antonia Calafat, 2016). Cord blood, as a sample matrix, is considered critically deficient for all metabolites, since DEHP containing plastics are widely used in medical settings, and thus, the concentrations of phthalates in cord blood may reflect exposure during delivery. In addition, studies that analyzed only phthalate diesters, rather than their metabolites, are

considered critically deficient due to the potential for contamination" (Radke et al., 2020; Radke et al., 2018). Therefore, data quality evaluation wasn't conducted for references that assessed exposure using only a biomarker matrix other than urine or breast milk without any other exposure assessment. Otherwise, all epidemiology references that met PECO screening criteria and used a potentially appropriate exposure assessment method proceeded to data quality evaluation.

Of the 18 references that met PECO screening criteria for epidemiology, one reference (Jung et al., 2013) was filtered out due to use of an inappropriate exposure biomarker. The remaining 17 references proceeded to data quality evaluation.

4 DATA EVALUATION AND DATA EXTRACTION

Data evaluation and extraction were conducted as described in Sections 5 and 6 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). Data evaluation is the systematic review step in which EPA assesses quality of the individual data sources using the evaluation strategies and criteria for each discipline (*e.g.,* physical and chemical property data; fate and transport data; occupational exposure and environmental release data; general population, consumer, and environmental exposure data; environmental hazard; human health hazard) or sub-discipline (*e.g.,* animal toxicity or epidemiology). The data quality evaluation method uses a structured framework with predefined criteria for each type of data/information source. Data extraction is the systematic review step in which EPA uses structured forms or templates to extract quantitative and qualitative data and information from references that meet screening criteria. The overall goal is to provide transparency, consistency, and as much objectivity as possible to the data quality evaluation and extraction processes along with meeting the TSCA scientific standards in section 26(h).

References that meet screening criteria following full-text screening will generally proceed to data quality evaluation and extraction steps, however one clarification to the procedures outlined in Section 6 of the 2021 Draft Systematic Review Protocol is that in situations where EPA is unable to extract data/information from sources that meet screening criteria (*e.g.,* formatting prohibits accurate extraction), that source may not have extracted data to present in the risk evaluation or respective supplemental documents. The systematic review supplemental files that contain results from the data quality evaluation and extraction systematic review steps may use updated templates from those that were provided in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021) because the purpose of these supplemental documents is to accommodate the data needs for each respective risk evaluation. The following sections describe the data quality and extraction process followed by each discipline or sub-discipline to address various information needs for the *Draft Risk Evaluation for Phthalic Anhydride* (U.S. EPA, 2026o) and any clarifications or updates regarding these systematic review steps as described in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021).

An additional clarification relates to falsified information. During the search for reasonably available information, EPA may identify and screen studies conducted by laboratories that had provided falsified information to the EPA (*e.g.*, studies conducted by Industrial Biotest Labs (IBT) between the years of 1965 and 1985). If such studies were identified and considered for TSCA Section 6 risk evaluations, EPA did not conduct data quality evaluation and data extraction for these references because the reported information regarding the study methodologies, results, and conclusions is not reputable and accurate. This is the systematic practice related to falsified information, but for clarification, EPA did not identify studies with falsified information for phthalic anhydride.

An important update to the data quality evaluation process as outlined in Section 5 of the 2021 Draft Systematic Review Protocol is that in unique circumstances EPA might use data evaluation reports (DERs) or data reviews instead of using the data quality evaluation method described in Section 5 of the 2021 Draft Systematic Review Protocol. If a DER is used to evaluate studies for risk evaluations under TSCA, EPA will only use it to evaluate and extract data for human health hazard studies. These DERs use a structured consistent framework with predefined criteria to evaluate studies under TSCA. While the use of DERs as part of the systematic review process under TSCA is new, EPA has used DERs to evaluate studies for decades in the Office of Pesticide Programs (OPP). Specifically, EPA's OPP and the Canadian Pest Management Regulatory Agency (PMRA) developed standard data evaluation templates. The templates have been in use since 2002 for writing data evaluation records (DERs) of studies submitted under the U.S. data requirements for pesticide registration (40 CFR, part 158) and the Canadian data codes (DACOs). A list of the templates used to write DERs can be found here:

https://www.epa.gov/pesticide-registration/oecd-data-evaluation-record-templates. The rationale for when EPA uses a DER to evaluate and extract data for human health hazard studies under TSCA is described in Section 4.5.2.3.

4.1 Physical and Chemical Properties

As described in the 2021 Draft Systematic Review Protocol, evaluation and extraction followed the steps outlined in Sections 5, 6, and 6.1 (U.S. EPA, 2021). The data quality criteria for physical and chemical property data are summarized in Appendix K of the 2021 Draft Systematic Review Protocol. The *Draft Data Quality Evaluation and Data Extraction Information for Physical and Chemical Properties for Phthalic Anhydride*(U.S. EPA, 2026g) provides details of the data extracted and evaluated, including metric ratings and the overall study quality determination for each data source.

4.2 Environmental Fate and Transport Properties

As described in the 2021 Draft Systematic Review Protocol, evaluation and extraction followed the steps outlined in Sections 5, 6, and 6.2 (U.S. EPA, 2021). The data quality criteria for environmental fate data are summarized in Appendix L of the systematic review protocol. Appendix L.4 describes how the overall quality of fate data or information were weighted according to an ordinal system corresponding to *High (1)*, *Medium (2)*, or *Low (3)* to quantitatively or qualitatively support the risk evaluations. EPA does not plan to use data rated as *Uninformative (4)*. Table_Apx L4 illustrates the possible quality rantings across the selected metrics for environmental fate data with examples in Table_Apx L5, Table_Apx L6 and Table_Apx L7 (U.S. EPA, 2021). Specific fate data quality rating quality criteria are in Table_Apx L8 (U.S. EPA, 2021). The *Draft Data Quality Evaluation and Data Extraction Information for Environmental Fate and Transport for Phthalic Anhydride* (U.S. EPA, 2026e) provides details of the data extracted and evaluated, including metric rating and the overall study quality determination for each data source.

4.3 Environmental Release and Occupation Exposure

As described in the 2021 Draft Systematic Review Protocol, evaluation and extraction followed the steps outlined in Sections 5, 6, and 6.2 (U.S. EPA, 2021). The data quality criteria for environmental release and occupational exposure data are summarized in Appendix M of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). The *Draft Data Quality Evaluation and Data Extraction Information for Environmental Release and Occupational Exposure for Phthalic Anhydride* (U.S. EPA, 2026f) details the data extracted and evaluated, including metric rating and the overall study quality determination for each data source.

4.4 General Population, Consumer, and Environmental Exposure

As described in the 2021 Draft Systematic Review Protocol, data quality evaluation and extraction generally followed the steps outlined in Section 5 and 6 (U.S. EPA, 2021). However, a few updates were made to the data quality evaluation metrics for some evidence streams (*i.e.*, study types) since the metrics were published in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). Most of the changes were editorial or minor clarifications, including the standardization of some metrics that apply to multiple evidence streams, where appropriate. For example, in the quality assurance/quality control (QA/QC) metric for evaluating monitoring and experimental evidence streams, the acronym QA/QC was defined and replaced all references to quality assurance and quality control when occurring separately or together, and the term “QA/QC techniques” was changed to “QA/QC measures,” which already appeared in the metrics.

A few metrics applicable to multiple evidence streams were slightly modified to better fit some of the unique situations that frequently arise for a certain type of evidence stream (*e.g.,* databases). For example, some metrics were updated to clarify the intent of the metric and better account for variation in types of evidence included in one grouping (*e.g.,* experiments involving chamber studies vs. product concentration assessments). The domains did not change, however see below the changes and updates made to the data evaluation metrics for the respective evidence types (*i.e.,* monitoring, experimental studies and databases) as presented in Section 4.4.1. No changes were made to the data evaluation metrics for modeling data, as described in Appendix N.6.2, or to the data evaluation metrics for completed exposure assessments and risk characterizations, as described in Appendix N.6.7 in the 2021 Draft Systematic Review Protocol, respectively (U.S. EPA, 2021). Data quality evaluations for references that met PECO screening criteria are included in the *Draft Data Quality Evaluation Information for General Population, Consumer, and Environmental Exposure for Phthalic Anhydride* (U.S. EPA, 2026h), referred to hereafter as the "Phthalic Anhydride Data Quality Evaluation Information for General Population, Consumer, and Environmental Exposure."

Data extraction of general population, consumer, and environmental exposure data and information was conducted as described in Section 6 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). However, with respect to information stored within databases, if EPA has access to the data tables, EPA does not conduct a separate data extraction because the data are more accessible and have additional context in the original database format. Data present in the database when the database underwent full-text screening are available in the HERO database, along with the date the data were downloaded. If a reference (*e.g.,* peer-reviewed reference) presents data from a database that did not undergo systematic review directly (*e.g.,* a foreign database that is not publicly accessible), the data would be extracted from the reference to the extent possible; this did not apply to references that underwent systematic review for this chemical.

References may not undergo data extraction, regardless of the overall quality determination, if they contain no extractable data points (*e.g.,* values are contained in a non-digitizable figure or are representative of unspecified media or treatment processes). On the other hand, there are references that have many reported endpoints that meet PECO screening criteria for a respective chemical risk evaluation, making it difficult to include all the data in the chemical-specific data extraction supplemental file. When a reference meets PECO screening criteria, the reference receives a data quality evaluation, and the data in the reference are still considered in the Risk Evaluation, whether or not the included data are extracted in DistillerSR and appear among the chemical-specific extractions in the Systematic Review Supplemental File: Data Extraction Information for General Population, Consumer, and Environmental Exposure. In addition, there may be other reasons that EPA decides not to extract all the data from a reference that undergoes data evaluation; EPA extracts the data that are most relevant, given the needs of the assessment. This constitutes an update to Section 6 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). Extraction forms, templates, and decisions are tailored to fit the data extraction needs for each risk evaluation.

The types of fields extracted vary by evidence stream and generally followed Section 6.3 of the 2021 Draft Systematic Review Protocol with regard to the data characteristics captured (U.S. EPA, 2021). Examples of types of data extracted and the extraction formats for the evidence streams identified through systematic review to evaluate environmental, general population, and consumer exposure data are listed in the extraction tables provided in the *Draft Data Quality Evaluation Information for General Population, Consumer, and Environmental Exposure for Phthalic Anhydride* (U.S. EPA, 2026h), referred to hereafter as the "Phthalic Anhydride Data Extraction Information for General Population, Consumer, and Environmental Exposure."

4.4.1 Data Quality Evaluation Metric Updates

The data evaluation metrics for the monitoring, experimental, and database evidence streams, are presented below in Table 4-1, Table 4-2, and Table 4-3, respectively. Each table shows which data evaluation metrics changed since the publication of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). Other data quality criteria for studies on consumer, general population, and environmental exposure appear in Appendix N of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). For the modeling, completed exposure assessments, and risk characterization evidence streams, there were no changes made to the data evaluation metrics since the 2021 Draft Systematic Review Protocol was published. The criteria for modeling studies appear in Table_Apx N-9 of the 2021 Draft Systematic Review Protocol, and criteria for completed exposure assessments and risk characterizations appear in Table_Apx N-19. In some cases, references can meet the criteria for two exposure evidence streams, and they can also be reviewed and meet criteria for other disciplines. Upon review, each study is evaluated and extracted using the criteria for the most appropriate and applicable evidence streams given the information therein. In order to make it easier for the reader to see changes made to the data evaluation metrics, the following conventions are used: text inserted is underlined, and text deleted is in ~~strikethrough~~.

Table 4-1. Updated Data Quality Evaluation Criteria for Monitoring Data Sources

Data Quality Rating	Description
Domain 1. Reliability	
Metric 1. Sampling methodology	
High	Samples were collected according to publicly available SOPs that are scientifically sound and widely accepted (*i.e.,* from a source generally ~~using~~ known to use sound methods and/or approaches) for the chemical and media of interest. Example SOPs include U.S. Geological Survey (USGS') "National Field Manual for the Collection of Water-Quality Data," EPA's "Ambient Air Sampling" (SESDPROC-303-R5), etc. OR The sampling protocol used was not a publicly available SOP from a source generally known to use ~~using~~ sound methods and/or approaches, but the sampling methodology is clear, appropriate (*i.e.,* scientifically sound), and similar to widely accepted protocols for the chemical and media of interest. All pertinent sampling information is provided in the data source or companion source. Examples include: • sampling equipment • sampling procedures/regimen • sample storage conditions/duration • performance/calibration of sampler • study site characteristics • matrix characteristics

Data Quality Rating	Description
Medium	Sampling methodology is discussed in the data source or companion source and is generally appropriate (*i.e.,* scientifically sound) for the chemical and media of interest; however, **one or more pieces of sampling information is not described.** The missing information is unlikely to have a substantial impact on results. OR Standards, methods, protocols, or test guidelines may not be widely accepted, but a successful validation study for the new/unconventional procedure was conducted prior to the sampling event and is consistent with sound scientific theory and/or accepted approaches. Or a review of information indicates the methodology is acceptable and differences in methods are not expected to lead to lower quality data.
Low	Sampling methodology is only briefly discussed; therefore, **most sampling information is missing** and likely to have a substantial impact on results. AND/OR The sampling methodology **does not represent best sampling methods, protocols, or guidelines** for the chemical and media of interest (*e.g.,* outdated [but still valid] sampling equipment or procedures, long storage durations). AND/OR There are **some inconsistencies** in the reporting of sampling information (*e.g.,* differences between text and tables in data source, differences between standard method and actual procedures reported to have been used, etc.) that led to a low confidence in the sampling methodology used.
Critically Deficient	The sampling methodology is not discussed in the data source or companion source. AND/OR Sampling methodology is not scientifically sound or is not consistent with widely accepted methods/approaches for the chemical and media being analyzed (*e.g.,* inappropriate sampling equipment, improper storage conditions). AND/OR There are **numerous inconsistencies** in the reporting of sampling information, resulting in high uncertainty in the sampling methods used.
Not rated/not applicable	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Metric 2. Analytical methodology	

Data Quality Rating	Description
High	Samples were analyzed according to publicly available analytical methods that are scientifically sound and widely accepted (*i.e.,* from a source generally ~~using~~ known to use sound methods and/or approaches) and are appropriate for the chemical and media of interest. Examples include EPA SW-846 Methods, NIOSH Manual of Analytical Methods 5th Edition, etc. OR The analytical method used was not a publicly available method from a source generally ~~using~~ known to use sound methods and/or approaches, but the methodology is clear and appropriate (*i.e.,* scientifically sound) and similar to widely accepted protocols for the chemical and media of interest. All pertinent sampling information is provided in the data source or companion source. Examples include: • extraction method • analytical instrumentation (required) • instrument calibration • limit of quantitation (LOQ), LOD, detection limits, and/or reporting limits • recovery samples • biomarker used (if applicable) • matrix-adjustment method (*i.e.,* creatinine, lipid, moisture)
Medium	Analytical methodology is discussed in detail and is clear and appropriate (*i.e.,* scientifically sound) for the chemical and media of interest; however, **one or more pieces of analytical information is not described**. The missing information is unlikely to have a substantial impact on results. AND/OR The analytical **method may not be standard/widely accepted, but a method validation study was conducted** prior to sample analysis and is expected to be consistent with sound scientific theory and/or accepted approaches. AND/OR Samples were collected at a site and immediately analyzed using an on-site mobile laboratory, rather than shipped to a stationary laboratory.
Low	Analytical methodology is only briefly discussed. Analytical instrumentation is provided and consistent with accepted analytical instrumentation/methods. However, **most analytical information is missing** and likely to have a substantial impact on results. AND/OR Analytical method **is not s**tandard/widely accepted, and method validation is limited or not available. AND/OR Samples were analyzed using field screening techniques. AND/OR LOQ, LOD, detection limits, and/or reporting limits not reported. AND/OR There are **some inconsistencies or possible errors** in the reporting of analytical information (*e.g.,* differences between text and tables in data source, differences between standard method and actual procedures reported to have been used, etc.) which leads to a lower confidence in the method used.

Data Quality Rating	Description
Critically Deficient	Analytical methodology is not described, **including analytical instrumentation** (*i.e.,* HPLC, GC). AND/OR Analytical methodology is not scientifically appropriate for the chemical and media being analyzed (*e.g.,* method not sensitive enough, not specific to the chemical, out of date). AND/OR There are numerous inconsistencies in the reporting of analytical information, resulting in high uncertainty in the analytical methods used.
Not rated/ Not applicable	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Metric 3. Selection of biomarker of exposure	
High	Biomarker in a specified matrix is known to have an accurate and precise quantitative relationship with external exposure, internal dose, or target dose (*e.g.,* previous studies (or the current study) have indicated the biomarker of interest reflects external exposures). AND Biomarker (parent chemical or metabolite) is derived from exposure to the chemical of interest.
Medium	Biomarker in a specified matrix has accurate and precise quantitative relationship with external exposure, internal dose, or target dose. AND Biomarker is derived from multiple parent chemicals, not only the chemical of interest, **but** there is a stated method to apportion the estimate to only the chemical of interest
Low	Biomarker in a specified matrix has accurate and precise quantitative relationship with external exposure, internal dose, or target dose. AND Biomarker is derived from multiple parent chemicals, not only the chemical of interest, **and** there is NOT an accurate method to apportion the estimate to only the chemical of interest. OR Biomarker in a specified matrix is a poor surrogate (low accuracy and precision) for exposure/dose.
Critically Deficient	Not applicable. A study will not be deemed critically deficient based on the use of biomarker of exposure.
Not rated/ applicable	Metric is not applicable to the data source.
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*

Data Quality Rating	Description
Domain 2. Representative	
Metric 4. Geographic area	
High	Geographic location(s) is reported, discussed, or referenced.
Medium	Not applicable. This metric is dichotomous (*i.e.,* high vs. critically deficient).
Low	Not applicable. This metric is dichotomous (*i.e.,* high vs. critically deficient).
Critically Deficient	Geographic location is not reported, discussed, or referenced.
Not rated/ not applicable	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Metric 5. Temporality	
High	Timing of sample collection for monitoring data is consistent with current or recent exposures **(within 5 years)** may be expected.
Medium	Timing of sample collection for monitoring data **is less consistent** with current or recent exposures **(>5 to 15 years)** may be expected.
Low	Timing of sample collection for monitoring data is not consistent with when current exposures **(>15 years old)** may be expected and likely to have a substantial impact on results.
Critically Deficient	Timing of sample collection for monitoring data is **not reported, discussed, or referenced.**
Not rated/ Not applicable	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Metric 6. Spatial and temporal variability	
High	Sampling approach accurately captures variability of environmental contamination in population/scenario/media of interest based on the heterogeneity/homogeneity and dynamic/static state of the environmental system. For example: • **Large sample size** (*i.e.,* ≥10 or more samples for a single scenario). • Use of replicate samples. • Use of systematic or continuous monitoring methods. • Sampling over a sufficient period of time to characterize trends. • For urine, 24-hour samples are collected (vs. first morning voids or spot). • For biomonitoring studies, the timing of sample collected is appropriate based on chemical properties (*e.g.,* half-life), the pharmacokinetics of the chemical (*e.g.,* rate of uptake and elimination), and when the exposure event occurred.

Data Quality Rating	Description
Medium	Sampling approach likely captures variability of environmental contamination in population/scenario/media of interest based on the heterogeneity/homogeneity and dynamic/static state of the environmental system. Some uncertainty may exist, but it is unlikely to have a substantial impact on results. For example: • **Moderate sample size** (*i.e.,* 5–10 samples for a single scenario), or • Use of judgmental (non-statistical) sampling approach, or • No replicate samples. • For urine, first morning voids or pooled spot samples.
Low	Sampling approach poorly captures variability of environmental contamination in population/scenario/media of interest. For example: • **Small sample size** (*i.e.,* <5 samples), or • Use of haphazard sampling approach, or • No replicate samples, or • Grab or spot samples in single space or time, or • Random sampling that does not include all periods of time or locations, or • For urine, un-pooled spot samples.
Critically Deficient	Sample size is not reported. **Single sample** collected per data set. For biomonitoring studies, the timing of sample collected is not appropriate based on chemical properties (*e.g.,* half-life), the pharmacokinetics of the chemical (*e.g.,* rate of uptake and elimination), and when the exposure event occurred.
Not rated/not applicable	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Metric 7. Exposure scenario	
High	The data closely represent relevant exposure scenario (*i.e.,* the population/scenario/media of interest). Examples include: • amount and type of chemical/product used • source of exposure • method of application or by-stander exposure • use of exposure controls • microenvironment (location, time, climate)
Medium	The data likely represent the relevant exposure scenario (*i.e.,* population/scenario/media of interest). **One or more key pieces of information may not be described** but the deficiencies are unlikely to have a substantial impact on the characterization of the exposure scenario. AND/OR If surrogate data, activities seem similar to the activities within scope.
Low	The data lack multiple key pieces of information, and the deficiencies are likely to have a substantial impact on the characterization of the exposure scenario. AND/OR

Data Quality Rating	Description
	There are **some inconsistencies or possible errors** in the reporting of scenario information (*e.g.,* differences between text and tables in data source, differences between standard method and actual procedures reported to have been used, etc.) which leads to a lower confidence in the scenario assessed. AND/OR If surrogate data, activities have lesser similarity but are still potentially applicable to the activities within scope.
Critically Deficient	If reported, the exposure scenario discussed in the monitored study does not represent the exposure scenario of interest for the chemical.
Not rated/ Not applicable	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
<u>Domain 3</u>. Accessibility/clarity	
<u>Metric 8</u>. Reporting of results	
High	Supplementary or raw data (*i.e.,* individual data points) are reported, allowing summary statistics to be calculated or reproduced. AND Summary statistics are detailed and complete. Example parameters include: • Description of data set summarized (*i.e.,* location, population, dates, etc.) • Range of concentrations or percentiles • Number of samples in data set • Frequency of detection • Measure of variation (coefficient of variation [CV], standard deviation) • Measure of central tendency (mean, geometric mean, median) • Test for outliers (if applicable) AND Both adjusted and unadjusted results are provided (*i.e.,* correction for void completeness in urine biomonitoring, whole-volume or lipid adjusted for blood biomonitoring, wet or dry weight for environmental tissue samples or soil samples) [only if applicable].
Medium	Supplementary or raw data (*i.e.,* individual data points) are not reported, and therefore summary statistics cannot be reproduced. AND/OR Summary statistics are reported but are missing one or more parameters (see description for high). AND/OR Only adjusted or unadjusted results are provided, but not both [only if applicable].
Low	Supplementary data are not provided, and summary statistics are missing most parameters (see description for high). AND/OR

Data Quality Rating	Description
	There are some inconsistencies or errors in the results reported, resulting in low confidence in the results reported (*e.g.,* differences between text and tables in data source, less appropriate statistical methods).
Critically Deficient	There are numerous inconsistencies or errors in the calculation and/or reporting of results, resulting in highly uncertain reported results.
Not Rated/ Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Metric 9. Quality assurance	
High	The study quality assurance/quality control (QA/QC) measures and all pertinent ~~quality assurance~~ QA/QC information is provided in the data source or companion source. Examples include: • Field, laboratory, and/or storage recoveries. • Field and laboratory control samples. • Baseline (pre-exposure) samples. • Biomarker stability • Completeness of sample (*i.e.,* creatinine, specific gravity, osmolality for urine samples) AND No QA/QC ~~quality control~~ issues were identified, or any identified issues were minor and adequately addressed (*i.e.,* correction for low recoveries, correction for completeness).
Medium	The study applied and documented ~~quality assurance/quality control~~ QA/QC measures; however, **one or more pieces of QA/QC information is not described.** Missing information is unlikely to have a substantial impact on results. AND No QA/QC ~~quality control~~ issues were identified, or any identified issues were minor and addressed (*i.e.,* correction for low recoveries, correction for completeness).
Low	QA/QC measures ~~Quality assurance/quality control techniques~~ and results were not directly discussed but are implied through the study's use of standard field and laboratory protocols. AND/OR Deficiencies were noted in ~~quality assurance/quality control~~ QA/QC measures that are likely to have a substantial impact on results. AND/OR There are some inconsistencies in the ~~quality assurance~~ QA/QC measures reported, resulting in low confidence in the QA/QC ~~quality assurance/control~~ measures taken and results (*e.g.,* differences between text and tables in data source).
Critically Deficient	QA/QC issues have been identified which significantly interfere with the overall reliability of the study.

Data Quality Rating	Description
Not Rated/ Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Domain 4. Variability and uncertainty	
Metric 10. Variability and uncertainty	
High	The study characterizes variability in the population/media studied. AND Key uncertainties, limitations, and data gaps have been identified. AND The uncertainties are minimal and have been characterized.
Medium	The study has limited characterization of variability in the population/media studied. AND/OR The study has limited discussion of key uncertainties, limitations, and data gaps. AND/OR Multiple uncertainties have been identified but are unlikely to have a substantial impact on results.
Low	The characterization of variability is absent. AND/OR Key uncertainties, limitations, and data gaps are not discussed. AND/OR Uncertainties identified may have a substantial impact on the exposure the exposure assessment
Critically Deficient	Estimates are highly uncertain based on characterization of variability and uncertainty.
Not Rated/ Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*

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Data Quality Rating	Metric Description
Domain 1. Reliability	
Metric 1. Sampling Methodology and Conditions	
High	Samples were collected according to publicly available SOPs, methods, protocols, or test guidelines that are scientifically sound and widely accepted from a source generally known to use sound methods and/or approaches such as EPA, NIST, American Society for Testing and Materials, ISO, and ACGIH.

Data Quality Rating	Metric Description
	OR The sampling protocol used was not a publicly available SOP from a source generally known to use sound methods and/or approaches, but the sampling methodology is clear, appropriate (*i.e.*, scientifically sound), and similar to widely accepted protocols for the chemical and media of interest. All pertinent sampling information is provided in the data source or companion source. Examples include: • sampling conditions (*e.g.*, temperature, humidity) • sampling equipment and procedures • sample storage conditions/duration • performance/calibration of sampler
Medium	Sampling methodology is discussed in the data source or companion source and is generally appropriate (*i.e.*, scientifically sound) for the chemical and media of interest, however, one or more pieces of sampling information is not described. The missing information is unlikely to have a substantial impact on results. OR Standards, methods, protocols, or test guidelines may not be widely accepted, but a successful validation study for the new/unconventional procedure was conducted prior to the sampling event and is consistent with sound scientific theory and/or accepted approaches.
Low	Sampling methodology is only briefly discussed. Therefore, most sampling information is missing and likely to have a substantial impact on results. AND/OR The sampling methodology does not represent best sampling methods, protocols, or guidelines for the chemical and media of interest (*e.g.*, outdated (but still valid) sampling equipment or procedures, long storage durations). AND/OR There are some inconsistencies in the reporting of sampling information (*e.g.*, differences between text and tables in data source, differences between standard method and actual procedures reported to have been used, etc.) which lead to a low confidence in the sampling methodology used.
Critically Deficient	The sampling methodology is not discussed in the data source or companion source. AND/OR Sampling methodology is not scientifically sound or is not consistent with widely accepted methods/approaches for the chemical and media being analyzed (*e.g.*, inappropriate sampling equipment, improper storage conditions). AND/OR There are numerous inconsistencies in the reporting of sampling information, resulting in high uncertainty in the sampling methods used.
Not Rated/Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*

Data Quality Rating	Metric Description
Metric 2. Analytical methodology	
High	Samples were analyzed according to publicly available analytical methods that are scientifically sound and widely accepted (*i.e.,* from a source generally using sound methods and/or approaches) and are appropriate for the chemical and media of interest. Examples include EPA SW-846 Methods, NIOSH Manual of Analytical Methods 5th Edition, etc. OR The analytical method used was not a publicly available method from a source generally known to use sound methods and/or approaches, but the methodology is clear and appropriate (*i.e.*, scientifically sound) and similar to widely accepted protocols for the chemical and media of interest. All pertinent analytical ~~sampling~~ information is provided in the data source or companion source. Examples include: • extraction method • analytical instrumentation (required) • instrument calibration • LOQ, LOD, detection limits, and/or reporting limits • recovery samples • biomarker used (if applicable) • matrix-adjustment method (*i.e.*, creatinine, lipid, moisture)
Medium	Analytical methodology is discussed in detail and is clear and appropriate (*i.e.*, scientifically sound) for the chemical and media of interest; however, one or more pieces of analytical information is not described. The missing information is unlikely to have a substantial impact on results. AND/OR The analytical method may not be standard/widely accepted, but a method validation study was conducted prior to sample analysis and is expected to be consistent with sound scientific theory and/or accepted approaches. AND/OR Samples were collected at a site and immediately analyzed using an on-site mobile laboratory, rather than shipped to a stationary laboratory.
Low	Analytical methodology is only briefly discussed. Analytical instrumentation is provided and consistent with accepted analytical instrumentation/methods. However, most analytical information is missing and likely to have a substantial impact on results. AND/OR Analytical method is not standard/widely accepted, and method validation is limited or not available. AND/OR Samples were analyzed using field screening techniques. AND/OR LOQ, LOD, detection limits, and/or reporting limits not reported. AND/OR There are some inconsistencies or possible errors in the reporting of analytical information (*e.g.*, differences between text and tables in data source, differences between standard method and actual procedures reported to have been used, etc.) which leads to a lower confidence in the method used.

Data Quality Rating	Metric Description
Critically Deficient	Analytical methodology is not described, including analytical instrumentation (*i.e.*, HPLC, GC). AND/OR Analytical methodology is not scientifically appropriate for the chemical and media being analyzed (*e.g.*, method not sensitive enough, not specific to the chemical, out of date). AND/OR There are numerous inconsistencies in the reporting of analytical information, resulting in high uncertainty in the analytical methods used.
Not Rated/Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Metric 3. Selection of biomarker of exposure	
High	Biomarker in a specified matrix is known to have an accurate and precise quantitative relationship with external exposure, internal dose, or target dose (*e.g.*, previous studies (or the current study) have indicated the biomarker of interest reflects external exposures). AND Biomarker (parent chemical or metabolite) is derived from exposure to the chemical of interest.
Medium	Biomarker in a specified matrix has accurate and precise quantitative relationship with external exposure, internal dose, or target dose. AND Biomarker is derived from multiple parent chemicals, not only the chemical of interest, **but** there is a stated method to apportion the estimate to only the chemical of interest
Low	Biomarker in a specified matrix has accurate and precise quantitative relationship with external exposure, internal dose, or target dose. AND Biomarker is derived from multiple parent chemicals, not only the chemical of interest, **and** there is NOT a stated method to apportion the estimate to only the chemical of interest. OR Biomarker in a specified matrix is a poor surrogate (low accuracy and precision) for exposure/dose.
Critically Deficient	Not applicable. A study will not be deemed critically deficient based on the use of biomarker of exposure. ~~Biomarker in a specified matrix is a poor surrogate (low accuracy and precision) for exposure/dose.~~
Not Rated/Not Applicable	Metric is not applicable to the data source.

Data Quality Rating	Metric Description
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Domain 2. Representative	
Metric 4. Testing scenario	
High	Testing conditions closely represent relevant exposure scenarios (*i.e.,* population/scenario/media of interest). Examples include: • amount and type of chemical/product used • source of exposure/test substance • method of application or by-stander exposure • use of exposure controls • microenvironment (location, time, climate, temperature, humidity, pressure, airflow) AND Testing conducted under a broad range of conditions for factors such as temperature, humidity, pressure, airflow, and chemical mass/weight fraction (if appropriate).
Medium	The data likely represent the relevant exposure scenario (*i.e.,* population/scenario/media of interest). One or more key pieces of information may not be described but the deficiencies are unlikely to have a substantial impact on the characterization of the exposure scenario. AND/OR If surrogate data, activities seem similar to the activities within scope.
Low	The data lack multiple key pieces of information, and the deficiencies are likely to have a substantial impact on the characterization of the exposure scenario. AND/OR There are some inconsistencies or possible errors in the reporting of scenario information (*e.g.,* differences between text and tables in data source, differences between standard method and actual procedures reported to have been used, etc.) which leads to a lower confidence in the scenario assessed. AND/OR If surrogate data, activities have lesser similarity but are still potentially applicable to the activities within scope. AND/OR Testing conducted under a single set of conditions, except for experiments to determine a weight fraction or concentration in a product.
Critically Deficient	Testing conditions are not relevant to the exposure scenario of interest for the chemical.
Not Rated/Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*

Data Quality Rating	Metric Description
Metric 5. Sample size and variability	
High	Sample size is reported and large enough (*i.e.,* ≥ 10 samples) to be reasonably assured that the samples represent the scenario of interest. AND Replicate tests performed and variability across tests is characterized (if appropriate).
Medium	Sample size is moderate (*i.e.,* 5 to ~~10~~ <10 samples), thus the data are likely to represent the scenario of interest. AND Replicate tests performed and variability across tests is characterized (if appropriate).
Low	Sample size is small (*i.e.,* <5 samples), thus the data are likely to poorly represent the scenario of interest. AND/OR Replicate tests were not performed.
Critically Deficient	Sample size is not reported. AND/OR Single sample collected per data set, except for experiments to determine a weight fraction or concentration in a product. AND/OR For biomonitoring studies, the timing of sample collected is not appropriate based on chemical properties (*e.g.,* half-life), the pharmacokinetics of the chemical (*e.g.,* rate of uptake and elimination), and when the exposure event occurred.
Not Rated/Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Metric 6. Temporality	
High	Source(s) of tested items appears to be current (within 5 years).
Medium	Source(s) of tested items is less consistent with when current or recent exposures (>5 to 15 years) are expected.
Low	Source(s) of tested items is not consistent with when current or recent exposures (>15 years) are expected or is not identified.
Critically Deficient	Temporality of tested items is not reported, discussed, or referenced.
Not Rated/Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*

Data Quality Rating	Metric Description
Domain 3. Accessibility/clarity	
Metric 7. Reporting of results	
High	Supplementary or raw data (*i.e.*, individual data points) are reported, allowing summary statistics to be calculated or reproduced. AND Summary statistics are detailed and complete. Example parameters include: • Description of data set summarized (*i.e.*, location, population, dates, etc.) • Range of concentrations or percentiles • Number of samples in data set • Frequency of detection • Measure of variation (CV, standard deviation) • Measure of central tendency (mean, geometric mean, median) • Test for outliers (if applicable) AND Both adjusted and unadjusted results are provided (*i.e.,* correction for void completeness in urine biomonitoring, whole-volume or lipid adjusted for blood biomonitoring) [only if applicable].
Medium	Supplementary or raw data (*i.e.,* individual data points) are not reported, and therefore summary statistics cannot be reproduced. AND/OR Summary statistics are reported but are missing one or more parameters (see description for high). AND/OR Only adjusted or unadjusted results are provided, but not both [only if applicable].
Low	Supplementary data are not provided, and summary statistics are missing most parameters (see description for high). AND/OR There are some inconsistencies or errors in the results reported, resulting in low confidence in the results reported (*e.g.*, differences between text and tables in data source, less appropriate statistical methods).
Critically Deficient	There are numerous inconsistencies or errors in the calculation and/or reporting of results, resulting in highly uncertain reported results.
Not Rated/Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*

Data Quality Rating	Metric Description
Metric 8. Quality assurance	
High	The study applied quality assurance/quality control (QA/QC) measures and all pertinent QA/QC ~~quality assurance~~ information is provided in the data source or companion source. Examples include: • Laboratory, and/or storage recoveries. • Laboratory control samples. • Baseline (pre-exposure) samples. • Biomarker stability • Completeness of sample (*i.e.,* creatinine, specific gravity, osmolality for urine samples) AND No QA/QC ~~quality control~~ issues were identified, or any identified issues were minor and adequately addressed (*i.e.,* correction for low recoveries, correction for completeness).
Medium	The study applied and documented ~~quality assurance/quality control~~ QA/QC measures; however, one or more pieces of QA/QC information is not described. Missing information is unlikely to have a substantial impact on results. AND No QA/QC ~~quality control~~ issues were identified, or any identified issues were minor and addressed (*i.e.,* correction for low recoveries, correction for completeness).
Low	QA/QC ~~Quality assurance/quality control techniques~~ measures and results were not directly discussed but are ~~can be~~ implied through the study's use of standard field and laboratory protocols. AND/OR Deficiencies were noted in QA/QC ~~quality assurance/quality control~~ measures that are likely to have a substantial impact on results. AND/OR There are some inconsistencies in the QA/QC ~~quality assurance~~ measures reported, resulting in low confidence in the ~~quality assurance/control~~ QA/QC measures taken and results (*e.g.,* differences between text and tables in data source).
Critically Deficient	QA/QC issues have been identified which significantly interfere with the overall reliability of the study.
Not Rated/Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Domain 4. Variability and uncertainty	
Metric 9. Variability and uncertainty	
High	The study characterizes variability in the population/media studied. AND

Data Quality Rating	Metric Description
	Key uncertainties, limitations, and data gaps have been identified. AND The uncertainties are minimal and have been characterized.
Medium	The study has limited characterization of variability in the population/media studied. AND/OR The study has limited discussion of key uncertainties, limitations, and data gaps. AND/OR Multiple uncertainties have been identified but are unlikely to have a substantial impact on results.
Low	The characterization of variability is absent. AND/OR Key uncertainties, limitations, and data gaps are not discussed. AND/OR Uncertainties identified may have a substantial impact on ~~the exposure~~ the exposure assessment
Critically Deficient	Estimates are highly uncertain based on characterization of variability and uncertainty.
Not Rated/Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*

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Data Quality Rating	Description
Domain 1. Reliability	
Metric 1. Sampling methodology	
High	Widely accepted sampling methodologies (*i.e.,* from a source generally known to use ~~using~~ sound methods and/or approaches) were used to generate the data presented in the database. Example SOPs include USGS's "National Field Manual for the Collection of Water-Quality Data," EPA's "Ambient Air Sampling" (SESDPROC-303-R5), etc.
Medium	One or more pieces of sampling methodology information is not described, but missing information is unlikely to have a substantial impact on results. OR The sampling methodologies were consistent with sound scientific theory and/or accepted approaches based on the reported sampling information but may not have followed published procedures from a source generally known to use sound methods and/or approaches.
Low	The sampling methodology was not reported in data source or readily available companion data source.

Data Quality Rating	Description
Critically Deficient	The sampling methodologies used were not appropriate for the chemical/media of interest in the database (*e.g.,* inappropriate sampling equipment, improper storage conditions).
Not Rated/Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Metric 2. Analytical methodology	
High	Widely accepted analytical methodologies (*i.e.,* from a source generally using sound methods and/or approaches) were used to generate the data presented in the database. Example SOPs include EPA SW-846 Methods, NIOSH Manual of Analytical Methods 5th Edition, etc.
Medium	The analytical methodologies were consistent with sound scientific theory and/or accepted approaches based on the reported analytical information but may not have followed published procedures from a source generally known to use sound methods and/or approaches.
Low	The analytical methodology was not reported in data source or companion data source.
Critically Deficient	The analytical methodologies used were not appropriate for the chemical/media of interest in the database (*e.g.,* method not sensitive enough, not specific to the chemical, out of date).
Not Rated/Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Domain 2. Representative	
Metric 3. Geographic area	
High	Geographic location(s) is reported, discussed, or referenced.
Medium	Not applicable. This metric is dichotomous (*i.e.,* high vs. critically deficient).
Low	Not applicable. This metric is dichotomous (*i.e.,* high vs. critically deficient).
Critically Deficient	Geographic location is not reported, discussed, or referenced.
Not Rated/Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Metric 4. Temporal	

Data Quality Rating	Description
High	The data reflect current conditions (within 5 years) AND/OR Database contains robust historical data for spatial and temporal analyses (if applicable).
Medium	The data are less consistent with current or recent exposures (>5 to 15 years) AND/OR Database contains sufficient historical data for spatial and temporal analyses (if applicable).
Low	Data are not consistent with when current exposures (>15 years old) may be expected AND/OR Database does not contain enough historical data for spatial and temporal analyses (if applicable).
Critically Deficient	Timing of sample data is not reported, discussed, or referenced.
Not Rated/Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Metric 5. Exposure scenario	
High	The data closely represent relevant exposure scenario (*i.e.,* the population/scenario/media of interest). Examples include: • Amount and type of chemical/product used • Source of exposure • Method of application or by-stander exposure • Use of exposure controls • Microenvironment (location, time, climate)
Medium	The data likely represent the relevant exposure scenario (*i.e.,* population/scenario/media of interest). **One or more key pieces of information may not be described** but the deficiencies are unlikely to have a substantial impact on the characterization of the exposure scenario. AND/OR If surrogate data, activities seem similar to the activities within scope.
Low	The data lack multiple key pieces of information and the deficiencies are likely to have a substantial impact on the characterization of the exposure scenario. AND/OR There are **some inconsistencies or possible errors** in the reporting of scenario information (*e.g.,* differences between text and tables in data source, differences between standard method and actual procedures reported to have been used, etc.) which leads to a lower confidence in the scenario assessed. AND/OR

Data Quality Rating	Description
	If surrogate data, activities have lesser similarity but are still potentially applicable to the activities within scope.
Critically Deficient	If reported, the exposure scenario discussed in the monitored study does not represent the exposure scenario of interest for the chemical.
Not Rated/Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Domain 3. Accessibility/clarity	
Metric 6. Availability of database and supporting documents	
High	Database is widely accepted and/or from a source generally known to use sound methods and/or approaches (*e.g.,* raw data from NHANES, STORET).
Medium	The database may not be widely known or accepted (*e.g.,* state-maintained databases), but the database is adequately documented with most or all of the following information: 1. Within the database, metadata is present (sample identifiers, annotations, flags, units, matrix descriptions, etc.) and-data fields are generally clear and defined. 2. A user manual and other supporting documentation is available, or there is sufficient documentation in the data source or companion source. Database quality assurance and data quality control measures are defined and/or a QA/QC protocol was followed.
Low	The database may not be widely known or accepted, and only limited database documentation is available (see the medium rating).
Critically Deficient	No information is provided on the database source or availability to the public.
Not Rated/ Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Metric 7. Reporting of results	
High	The database or information source reporting the analysis of the database data is well organized and understandable by the target audience. AND Summary statistics in the data source are detailed and complete. Example parameters include: • Description of data set summarized (*i.e.,* location, population, dates, etc.) • Range of concentrations or percentiles • Number of samples in data set • Frequency of detection

Data Quality Rating	Description
	• Measure of variation (CV, standard deviation) • Measure of central tendency (mean, geometric mean, median) • Test for outliers (if applicable)
Medium	The database or information source reporting the analysis of the database data is well organized and understandable by the target audience. AND/OR Summary statistics are missing one or more parameters (see description for high).
Low	The database or information source reporting the analysis of the database data is unclear or not well organized. AND/OR Summary statistics are missing most parameters (see description for high) AND/OR There are some inconsistencies or errors in the results reported, resulting in low confidence in the results reported (*e.g.,* differences between text and tables in data source, less appropriate statistical methods).
Critically Deficient	There are numerous inconsistencies or errors in the calculation and/or reporting of results, resulting in highly uncertain reported results. AND/OR The information source reporting the analysis of the database data is missing key sections or lacks enough organization and clarity to locate and extract necessary information.
Not Rated/Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Domain 4. Variability and uncertainty	
Metric 8. Variability and uncertainty	
High	Variability, key uncertainties, limitations, and/or data gaps have been identified. AND/OR The uncertainties are minimal and have been characterized.
Medium	The study has limited discussion of variability, key uncertainties, limitations, and/or data gaps. AND/OR Multiple uncertainties have been identified but are unlikely to have a substantial impact on results.
Low	Variability, key uncertainties, limitations, and data gaps are not discussed. AND/OR Uncertainties identified may have a substantial impact on the exposure the exposure assessment

Data Quality Rating	Description
Critically Deficient	Estimates are highly uncertain based on characterization of variability and uncertainty.
Not Rated/Not Applicable	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*

4.5 Environmental and Human Health Hazard

Details regarding the evaluation and extraction of environmental and human health hazard information from references that met PECO screening criteria are available in Sections 5 and 6.4 of the 2021 Draft Systematic Review Protocol. Data quality criteria for environmental studies, animal and *in vitro* toxicity studies and epidemiological studies are available in Appendix P, Q, and R in the 2021 Draft Systematic Review Protocol, respectively (U.S. EPA, 2021). Any updates made to the data quality evaluation and extraction forms for human health hazard information since the 2021 Draft Systematic Review Protocol was published (U.S. EPA, 2021) are described below in Section 4.5.2. The below-listed supplemental documents provide details of the data evaluated and extracted. Data evaluation information for each discipline (*i.e.,* environmental and human health hazard) is contained in separate supplemental documents and includes metric ratings and the overall study quality determination for each data source. On the other hand, data extraction information for both disciplines are contained in a single supplemental document to increase the ease of accessing hazard data that may be relevant for both environmental- and human health-related receptors. One clarification that applies to the data extraction of human health hazard data is that all the data extraction was conducted in DistillerSR. In regard to the environmental hazard data, for references that meet PECO screening criteria at full text screening, the available environmental hazard data were extracted from those references in the ECOTOXicology Knowledgebase (ECOTOX) database and then imported into DistillerSR.

- *Draft Data Evaluation Information for Environmental Hazard for Phthalic Anhydride* (U.S. EPA, 2026b)
- *Draft Data Quality Evaluation Information for Human Health Hazard Epidemiology for Phthalic Anhydride* (U.S. EPA, 2026j)
- *Draft Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for Phthalic Anhydride* (U.S. EPA, 2026i)
- *Draft Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology for Phthalic Anhydride* (U.S. EPA, 2026d)

As stated at the beginning of Section 0 of this chemical-specific systematic review protocol, an important update to the data quality evaluation and extraction process as outlined in Section 5 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021) is that in unique circumstances EPA might use DERs to evaluate studies for risk evaluations under TSCA instead of using the data quality evaluation and extraction method described in Section 5 of the 2021 Draft Systematic Review Protocol. The rationale for when EPA has used a DER to evaluate and extract data for human health hazard studies for phthalic anhydride is described in Section 4.5.2.3 of this systematic review protocol. The DERs are available in a separate supplemental document of the risk evaluation for phthalic anhydride listed below and provide details of how each study was evaluated and whether the study was acceptable or unacceptable.

- *Draft Data Evaluation Record Information for in chemico, in vitro, and in vivo assays for Human Health Hazard for Phthalic Anhydride* (U.S. EPA, 2026c)

4.5.1 Environmental Hazard

As described in Appendix R of the 2021 Draft Systematic Review Protocol, references that met PECO criteria at full text screening underwent data quality evaluation (U.S. EPA, 2021). Likewise, references that met PECO criteria at full text screening underwent data extraction as described in Section 6.4.1 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). This section describes any updates made to the data quality evaluation and data extraction process since the 2021 Draft Systematic Review Protocol was published.

For phthalic anhydride, toxicity data gaps were identified for mammalian wildlife relevant to the terrestrial compartment of the environmental hazard assessment and thus rodent data were used as surrogate data for mammalian wildlife. The rodent data were evaluated following the human health hazard animal toxicity evaluation process as described below in Section 4.5.2 and underwent data extraction as described in Section 6.4.1 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). Additional data for health outcomes most relevant for environmental hazard assessment were also extracted for these rodent studies and are listed in detail in the *Draft Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology for Phthalic Anhydride* (U.S. EPA, 2026d).

Data Evaluation and Data Extraction Cross Walk

As per the established systematic review process described in the 2021 Draft Systematic Review Protocol, data extraction is completed for all health outcomes regardless of the overall quality determination a study has received during data quality evaluation (*i.e.*, rating of high, medium, low, or uninformative). Moreover, initial data extractions for environmental hazard are completed outside of DistillerSR by contractors that support ECOTOX, database managed by EPA's ORD. Data extraction QC for phthalic anhydride was completed within DistillerSR by experts in environmental hazard data.

Since the 2021 Draft Systematic Review Protocol was published, an additional process improvement step has been incorporated into the environmental hazard TSCA systematic review process. Experts that perform the data extraction QC need to cross walk data evaluation forms to data extraction forms to ensure that health outcomes for each experimental condition reported in the study match in both the data evaluation and extraction forms; this step is necessary because the initial data extractions are completed outside of DistillerSR independently of the data evaluation process within DistillerSR. In addition, experts completing the cross walk during the data extraction QC need to ensure that the rating for the health outcome in the data evaluation forms is also reported in the data extraction forms.

To maximize efficiency for the completion of the data evaluation and data extraction cross walk, an external (outside of DistillerSR) automated function has been added. Figure 4-1 summarizes the steps that a study that meets the PECO screening criteria for environmental hazard (green circle in Figure 4-1) follows until completion of the data evaluation and data extraction cross walk (gray oval with check mark in Figure 4-1). The initial data extractions by ECOTOX contractors occur outside of DistillerSR (orange ECOTOX box in Figure 4-1), and data converted into a JSON file are later imported into DistillerSR in preparation for the data extraction QC by EPA staff (second blue square in the red DistillerSR box in Figure 4-1).

The light purple box with the label "External processing" in Figure 4-1 illustrates the steps that occur outside of DistillerSR including the automated crosswalk function (blue square with an asterisk).

Specifically, this automated function starts with a data extraction form and compares to the corresponding data evaluation form by first filtering by HERO ID, then filtering by species name, followed by lifestage of the organism, exposure duration, health outcome and chemical type. For each of these filtering levels as the matching function is run, if there is a data evaluation form that corresponds to the data extraction criteria, there is a successful match and the health outcomes in the data extraction form and data evaluation forms are aligned, the rating is also added in the data extraction forms. On the contrary, if there is no data evaluation that corresponds to the data extraction criteria, the automated cross walk stops, and the outcome of the function is "No Match". If there is no match by the automated function, the cross walk is completed manually at the final step. Once the automated cross walk function is complete, the data are converted to a JSON file that is uploaded into DistillerSR. For the final step, the Quality Control reviewer checks the data extraction forms for the successful automated matches and completes the cross walk manually for the forms that did not match (blue square with double asterisks in Figure 4-1), at which point the data evaluation and data extraction cross walk is complete.

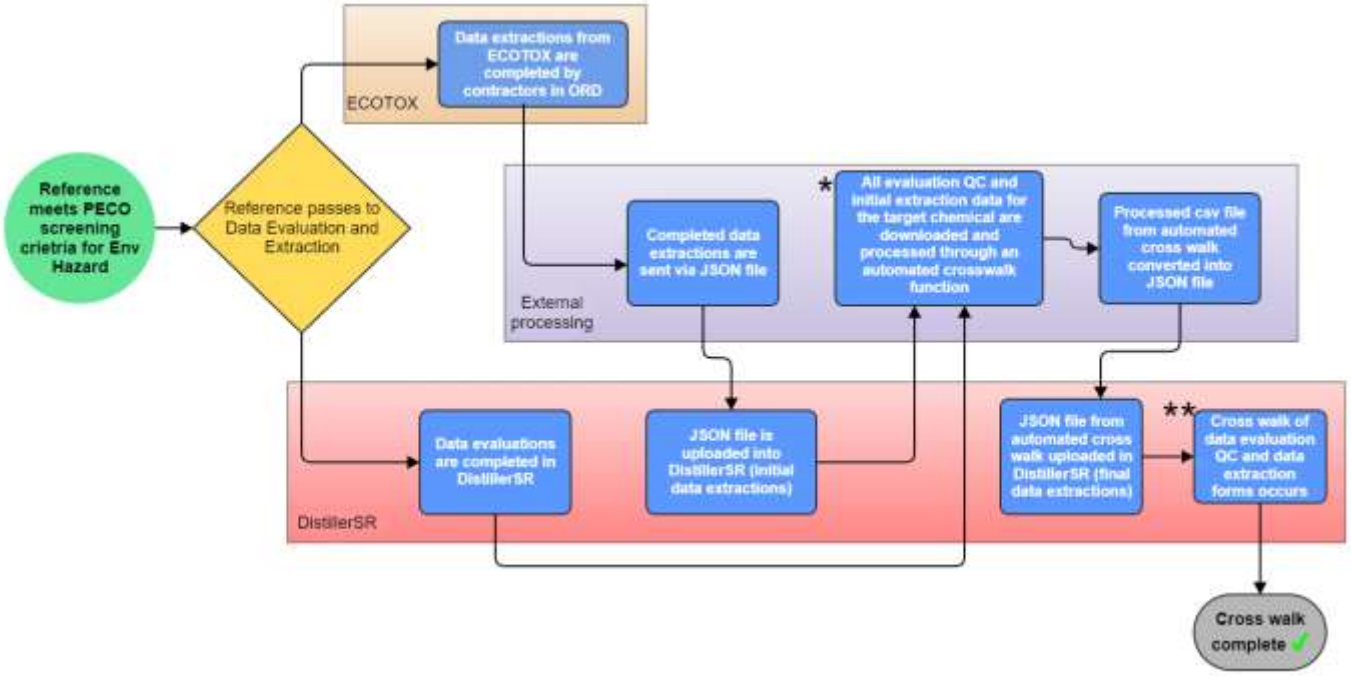

Figure 4-1. Data Evaluation and Data Extraction Cross Walk Workflow for Environmental Hazard

At the completion of the data evaluation and data extraction cross walk for phthalic anhydride, the data extraction information was included in the *Draft Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology for Phthalic Anhydride* (U.S. EPA, 2026d).

4.5.2 Human Health Hazard

As described in Section 3.6.1 references that met PECO screening criteria and further filtering criteria underwent data quality evaluation and extraction. This section describes updates made to the data quality evaluation and extraction forms since the 2021 Draft Systematic Review Protocol was published (U.S. EPA, 2021). Clarifications or updates regarding the data quality evaluation or extraction of data are discussed further below for epidemiological and animal toxicity studies.

As stated above in Section 4.5.2.3, an important update made to the data quality evaluation and extraction framework as described in Section 5 of the of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021) is the use of DERs for evaluating and extracting data for studies that report human health hazard outcomes. The DER contains a study profile documenting study information such as materials, methods, results, applicant's conclusions and the evaluator's conclusions on the quality of the study. Templates to DERs that EPA might use applicable to human health hazard can be found here: https://www.epa.gov/pesticide-registration/oecd-data-evaluation-record-templates. As part of the systematic process for the completion of DERs, phthalic anhydride studies were first evaluated and extracted by an initial reviewer and a QC step was completed by a secondary reviewer.

For phthalic anhydride, EPA used DERs to evaluate ten non-*in vivo* studies (Table 4-4). First, *in vitro* studies could not be evaluated effectively with the data evaluation forms in DistillerSR, EPA's tool and repository to complete data evaluation and extraction as described in Section 5 of the of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). The data evaluation forms currently implemented in DistillerSR are most appropriate for *in vivo* studies, and while data evaluation forms for *in vitro* studies were described in Appendix Q of the 2021 Draft Systematic Review Protocol, they were not implemented in DistillerSR, and EPA opted to proceed with data evaluation and extraction of these *in vitro* studies using data review templates. Second, the set of the ten studies listed below collectively reported data on potential skin sensitization effects following exposure to phthalic anhydride. The collective information the studies provided is of interest in assessing if the dermal route of exposure for phthalic anhydride is a significant route or not for human health hazard assessment. Each study individually as well as data from all studies collectively were evaluated following OECD's adverse outcome pathway (AOP) for skin sensitization assessment: www.oecd.org/content/dam/oecd/en/publications/reports/2014/09/the-adverse-outcome-pathway-for-skin-sensitisation-initiated-by-covalent-binding-to-proteins_g1g48567/9789264221444-en.pdf. Table 4-4 lists the OECD test guideline followed to evaluate each study, and the data evaluation was documented using EPA's data review templates which are formatted to evaluate data quality as described in standard test guidelines such as OECD test guidelines and OCSPP test guidelines. All ten data evaluations and the conclusion of whether the studies were acceptable or not is available in the *Draft Data Evaluation Record Information for in chemico, in vitro, and in vivo assays for Human Health Hazard for Phthalic Anhydride* (U.S. EPA, 2026c).

Table 4-4. List of Studies for Phthalic Anhydride Evaluated Using a TSCA Section 5 Data Review Template [a]

OECD Test Guideline	HERO ID of the Study	Study Title
442c	8310407	Putting the parts together: Combining *in vitro* methods to test for skin sensitizing potentials
442c	8356995	Development of a peptide reactivity assay for screening contact allergens
442c	6789397	Prediction of skin sensitization potency sub-categories using peptide reactivity data
442d	8315696	A dataset on 145 chemicals tested in alternative assays for skin sensitization undergoing prevalidation

OECD Test Guideline	HERO ID of the Study	Study Title
442e	8238790	Prediction of skin sensitization potency of chemicals by human Cell Line Activation Test (h-CLAT) and an attempt at classifying skin sensitization potency
429	1943046	A quantitative method for assessing the sensitizing potency of low molecular weight chemicals using a local lymph node assay: Employment of a regression method that includes determination of the uncertainty margins
429	5353562	Comparison of the local lymph node assay with the guinea-pig maximization test for the detection of a range of contact allergens
429	1222879	The respiratory local lymph node assay as a tool to study respiratory sensitizers
429	5178449	Characterization in mice of the immunological properties of five allergenic acid anhydrides
429	117458	Identifying airway sensitizers: cytokine mRNA profiles induced by various anhydrides

[a] To provide transparency, individual data reviews were compiled into a single file that provides details and is available to the public as a supplemental document: *Draft Data Evaluation Record Information for in chemico, in vitro, and in vivo assays for Human Health Hazard for Phthalic Anhydride* (U.S. EPA, 2026c).

4.5.2.1 Epidemiology Studies

As described above in Section 3.6.2.1, all references containing epidemiological information that met PECO screening criteria during full-text screening proceeded to an additional further filtering screening step. References that met the further filtering screening criteria then proceeded to data quality evaluation and extraction. There were no changes to the data evaluation domains and metrics or data extraction methodologies since the 2021 Draft Systematic Review Protocol was published.

4.5.2.2 Animal Toxicity Studies

Although there were no updates made to the data extraction methodologies described in the 2021 Draft Systematic Review Protocol for references with potentially relevant animal toxicity studies for the evaluation of human health hazard, EPA did update language in some of the metrics used to conduct data quality evaluation for those references. Updates to the data evaluation metrics from the versions published in Appendix Q.4.2 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021) are shown below in Table 4-5. Language that was inserted since the draft protocol was published is **bolded**, and language removed is shown in ~~strikethrough~~. Language was removed from metric 12 to ensure the metric rating was not discounted due to assessment of liver metabolism via an injection pathway. The description for the rating of high for metric 12 was updated to clarify that the caveat of 10 or more air changes/hour applies only to dynamic whole-body chambers. For metrics not listed below, no changes were made since the 2021 was published (U.S. EPA, 2021).

1052 **Table 4-5. Updated Data Quality Evaluation Criteria for Animal Toxicity Studies**

Data Quality Rating	Description
Metric 12. Exposure route and method Were the route and method of exposure reported and suited to the test substance (*e.g.,* accounting for volatility, ~~injection was not used for assays of liver metabolism~~, an appropriate vehicle was used when necessary)? For nose-only or head-only inhalation studies, were the animals appropriately acclimated or was the lack of acclimation controlled for?	
High	The route and method of exposure were reported and were suited to the test substance (see above) For inhalation studies, a dynamic, nose-only or head-only chamber was used~~. with greater than 10 or more air changes/hour~~. While dynamic nose-only (or head-only) studies are generally preferred, dynamic whole-body chambers are acceptable for gases **as long as there were 10 or more air changes/hour**.
Medium	There were minor limitations regarding the route and method of exposure, but the researchers took appropriate steps to mitigate the problem (*e.g.,* attempted to minimize headspace for volatile compounds in drinking water). These limitations are unlikely to have a substantial impact on results. For inhalation studies, a dynamic whole-body chamber was used for vapors that may condense (assume most will condense at high concentrations unless otherwise stated) or for aerosols, having 10 or more air changes/hour. A medium rating can also be assigned if the study indicates a dynamic chamber but not the number of air changes.
Low	There were deficiencies regarding the route and method of exposure that are likely to have a substantial effect on results. Researchers may have attempted to correct the problem, but the success of the mitigating action was unclear. For inhalation studies, there are significant flaws in the design or operation of the inhalation chamber, such as uneven distribution of test substance in a whole-body chamber, having less than 10 air changes/hour in a whole-body chamber, or using a whole-body chamber that is too small for the number and volume of animals exposed. OR Only very minimal if any details about the methods for inhalation exposure administration (as described above) were reported, resulting in significant uncertainty about the true exposure parameters.
Critically Deficient	The route or method of exposure was not reported OR An inappropriate route or method (*e.g.,* administration of a volatile organic compound via the diet) was used for the test substance without taking steps to correct the problem (*e.g.,* mixing fresh diet). These are serious flaws that makes the study unusable. For inhalation studies, either a static chamber was used, there is no description of the inhalation chamber, or an atypical exposure method was used, such as allowing a container of test substance to evaporate in a room.
Not Rated/Not Applicable	Do not select for this metric.
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*

The data evaluation and extraction information for all phthalic anhydride references, and relevant isomers (including trimellitic anhydride), with the exception of the data evaluation records for dermal studies described in Section 4.5.2.3, can be found in the supplemental files:

- *Draft Data Evaluation Information for Environmental Hazard for Phthalic Anhydride* (U.S. EPA, 2026b)
- *Draft Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology for Phthalic Anhydride* (U.S. EPA, 2026d)

4.5.2.3 Data Evaluation Records for Dermal Studies

OPPT's data quality evaluation process was not intended to evaluate several of the study types that were ultimately used quantitatively in the dermal sensitization dose-response assessment described in Section 4.2.1.3 of the *Draft Human Health Hazard Assessment* (U.S. EPA, 2026n). Therefore, EPA developed data evaluation records (DERs) for these study types, which include *in chemico* direct peptide reactivity assays (DPRAs) and kinetic DPRAs (kDPRA), as well as *in vitro* h-CLAT, *in vitro* KeratinoSens assays, and local lymph node assays (LLNAs). For studies in which DERs were developed, DERs can be found in *Draft Data Evaluation Record Information for in chemico, in vitro, and in vivo Assays for Human Health Hazard for Phthalic Anhydride* (U.S. EPA, 2026c).

5 EVIDENCE INTEGRATION

As described in Section 7 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021), evidence integration refers to the consideration of evidence obtained from systematic review and scientific information obtained from sources that did not undergo systematic review to implement a weight of scientific evidence approach. The weight of scientific evidence is defined as "a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance" (40 CFR 702.33). The consideration of the quality and relevance of the data, while considering the strengths and limitations of the data, to appropriately evaluate the evidence for this supplement, is described in Section 7 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021).

5.1 Physical and Chemical Properties

The systematic review process identified multiple data for each of the physical-chemical properties analyzed in the risk evaluation. Relevant data types used for the physical-chemical assessment are discussed in Appendix K of the Draft Systematic Review Protocol (U.S. EPA, 2021). When a specific datum is cited for a given physical-chemical parameter, priority is given to data from expert-curated, peer-reviewed databases that have been identified as "trusted sources". Sources of uncertainty are discussed, when appropriate, in the risk evaluation.

5.2 Environmental Fate and Transport

Relevant data types used for environmental fate and transport assessment are listed in Table 7-1 of the Draft Systematic Review Protocol (U.S. EPA, 2021). Systematic review data as well as data gaps filled using evidence streams outside systematic review are incorporated as described in Figure 7-1. Quality of these data are determined based on whether they are measured or estimated data, and further broken down based on consistency, study design, study conditions and uncertainty (Figure 7-2).

5.3 Environmental Release and Occupational Exposure

To evaluate environmental releases and occupational exposures for the various conditions of use (COUs), EPA first mapped the COUs to broader occupational exposure scenario (OES) categories, as shown in the *Draft Environmental Release and Occupational Exposure Assessment for Phthalic Anhydride* (U.S. EPA, 2026m). Specifically, EPA developed OES categories to group processes or applications with similar sources of environmental releases and occupational exposures. For each OES, EPA integrated the occupational exposure results for various job classifications to be representative of all U.S. workers and sites within that OES.

The EPA utilized release data from programmatic databases (TRI and NEI databases) and used identified air, water, and land release data to estimate releases for OESs where they were applicable (U.S. EPA, 2024, 2023). To estimate the number of sites using phthalic anhydride within an OES, EPA primarily relied on the Chemical Data Reporting (CDR) database for manufacturing, import, and processing sites (U.S. EPA, 2020a). For all other OESs, EPA used GS and ESD inputs to estimate the number of sites and used U.S. Census Bureau data where necessary to provide a bounding estimate.

EPA assessed OES-specific exposures to workers and occupational non-users (ONUs) based on monitoring data, surrogate monitoring data, and modeling approaches. EPA developed worker activity information using GSs, ESD, SpERCs and other systematic review literature, as described in the *Draft Environmental Release and Occupational Exposure Assessment for Phthalic Anhydride* (U.S. EPA,

2026m). When sufficient monitoring data for an OES were available, EPA gave preference to monitoring data more recent than 1989, as the Occupational Safety and Health Administration (OSHA) set a permissible exposure limit (PEL) for phthalic anhydride of 12 mg/m^3 from 1989.

EPA identified inhalation monitoring data from industry submissions and published and peer-reviewed literature for manufacturing, processing, plastics converting, application of non-spray paints and coatings, use of laboratory chemicals, fabrication or use of final product or articles, and disposal/recycling. EPA used monitoring data from application of non-spray paints and coatings as surrogate for the use of lubricants and functional fluids based on similar exposure conditions. For spray application of paints and coatings, EPA utilized the relevant ESD to determine input parameters and approaches to model the defining exposure activity. The *Draft Environmental Release and Occupational Exposure Assessment for Phthalic Anhydride* (U.S. EPA, 2026m) describes all data and approaches for estimating occupational exposures. Where available, EPA used NEI data to estimate the number of exposure days (U.S. EPA, 2023). EPA relied on the BLS and U.S. Census Bureau data (U.S. BLS, 2023; U.S. Census Bureau, 2015) to estimate the number of workers and ONUs potentially exposed to phthalic anhydride within each OES.

For the assessment of dermal exposures, EPA quantified the dermal loading of materials being handled (mg product/cm^2), as well as phthalic anhydride weight fraction of the materials being handled (mg phthalic anhydride/mg product), in order to estimate the dermal exposure of phthalic anhydride as described in Section 2.4.3 of the *Environmental Release and Occupational Exposure Assessment for Phthalic Anhydride* (U.S. EPA, 2026m).

5.4 General Population, Consumer, and Environmental Exposure

Phthalic anhydride concentrations in ambient air, surface water, sediment, soil, landfills, and biosolids were gathered and summarized within each environmental media pathway within the *Draft Environmental Media and General Population and Environmental Exposure for Phthalic Anhydride* (U.S. EPA, 2026l). The sources and approaches to gather monitoring data from peer-reviewed publications, government reports, and/or databases were classified as monitoring and mainly used to compare with modeling results or to support qualitative assessments. Consumer products containing phthalic anhydride were identified through review and searches of a variety of sources, such as completed assessments, online retailers, and SDSs . General population and environmental exposures were evaluated for the ambient air, surface water, drinking water, and fenceline exposure pathways based on environmental release data.

5.4.1 Consumer Exposure Assessment

EPA assessed consumer exposure to phthalic anhydride for both users and bystanders, resulting from use of consumer products (*i.e.*, adhesives and sealants, crafting resins, and paints and coatings) and articles (*i.e.*, cured/solidified crafting resins) (U.S. EPA, 2026a). The major routes of exposure considered were via ingestion, inhalation, and dermal exposure. Consumer Conditions of Use were initially identified considering Chemical Data Reporting (CDR) submissions for phthalic anhydride from the last two CDR cycles (2020 & 2024) for and other reasonably available information, including stakeholder engagements, published literature, company websites, government and commercial trade databases and publications. Consumer products containing phthalic anhydride were identified through review and searches of a variety of sources, such as completed assessments, , in addition to chemical safety data sheets (SDSs) identified through product-specific internet searches. Chemical weight fractions were gathered from SDSs and used to tailor COU-specific consumer exposure scenarios for products and articles identified in the consumer market. The dermal assessment was based on U.S. EPA

(1992), which conducted experiments to obtain liquid product dermal loading values used as a surrogate for direct dermal contact with products.

Altogether, EPA screened over 34 exposure studies with potential relevance to the phthalic anhydride risk evaluation. Out of this total, 4 studies were of most relevance to the consumer exposure assessment but did not contain COU-specific data for the phthalic anhydride. One study was used in the indoor exposure assessment with an OQD assignment of medium per systematic review exposure evaluation metrics (U.S. EPA, 2021). Data from this study was extracted to inform the consumer indoor exposure assessment of phthalic anhydride.

5.4.2 Other Data Sources

The exposure models relied heavily on the physical chemical and fate properties as input parameters. Sections 4.1 and 4.2 describe how the physical chemical and fate properties were selected. Where applicable, EPA relied on model defaults, exposure factors and activity patterns available from EPA's Exposure Factors Handbook (U.S. EPA, 2017). As mentioned previously, these physical chemical and fate parameters are used as inputs for PSC modeling of surface water concentrations of phthalic anhydride and as inputs for AERMOD modeling.

5.5 Environmental and Human Health Hazard

Sections 7.4 and 7.5, the 2021 Draft Systematic Review Protocol explain how information from data sources that undergo systematic review and those that do not are considered for use in risk evaluations under TSCA, specifically, for evaluating environmental and human health hazard, respectively (U.S. EPA, 2021).

The environmental hazard evidence streams, as described in Table 7-8 of the 2021 Draft Systematic Review Protocol, have been updated to increase the level of clarity and consistency of granularity (U.S. EPA, 2021). Table 5-1 reflects the updated environmental hazard evidence streams that parses out the types of mechanistic data evidence streams.

5.5.1 Environmental Hazard

Section 7.4.1 of the 2021 Draft Systematic Review Protocol describes how environmental hazard integration is organized into different evidence streams. The environmental hazard evidence streams for risk evaluations conducted under TSCA, as described in Table 7-8 of the 2021 Draft Systematic Review Protocol, have been updated (Table 5-1; updates are represented in bold text) to increase the level of clarity and consistency of granularity (U.S. EPA, 2021). These updated environmental hazard evidence streams more clearly reflect how apical and mechanistic hazardous endpoints (as defined by the screening PECO statement) that result from either controlled field/laboratory or uncontrolled exposure field studies are binned to better consider the relevancy of the data for the respective risk evaluation.

Table 5-1. Querying the Evidence to Organize Integration for Environmental Data and Information

Evidence Stream	Questions
Apical endpoints (controlled field/laboratory conditions)	Of the available data, are there endpoints that could have population level effects such as reproduction, growth, and/or mortality?

Evidence Stream	Questions
Mechanistic data **(controlled field/laboratory conditions)**	Is the mechanistic endpoint linked to an apical endpoint? Is it part of an AOP? If not, can you instead use it qualitatively? If a transcriptomic point of departure (tPOD) is available, is it appropriate to use quantitatively?
Apical endpoints (uncontrolled exposure field conditions)	Are there any field studies available showing adverse effects? How does exposure to the chemical of interest affect the community of organisms? Are there any co-occurring adverse environmental conditions other than exposure to the chemical of interest that should be taken into consideration?
Mechanistic endpoints (uncontrolled exposure field conditions)	**Is the mechanistic endpoint linked to an apical endpoint? Is it part of an AOP? If not, can you instead use it qualitatively? If a transcriptomic point of departure (tPOD) is available, is it appropriate to use quantitatively? Are there any co-occurring adverse environmental conditions other than exposure to the chemical of interest that should be taken into consideration?**

As described in the *Draft Environmental Hazard Assessment for Phthalic Anhydride* (U.S. EPA, 2026k), streams for environmental hazard included empirical data with apical endpoints for aquatic and terrestrial organisms that were reviewed following the TSCA systematic review process.

EPA reviewed potential environmental health hazards associated with phthalic anhydride (U.S. EPA, 2026k). Studies identified as meeting PECO screening criteria and evaluated for data quality (see Section 2 of the *Phthalic Anhydride Environmental Hazard Assessment* for details) received an overall quality determination of high, medium, low, or uninformative. Although all studies were considered in the hazard characterization, only high and medium-quality studies were used for quantitative risk characterization (U.S. EPA, 2025). An OQD of high and medium were assigned to four aquatic studies and two terrestrial plant studies. Due to a lack of wildlife terrestrial mammalian studies, controlled laboratory studies that used rats as human health model organisms were used to assess terrestrial hazards.

Using empirical and modeled evidence streams, EPA characterized the environmental hazards of phthalic anhydride to surrogate species representing various receptor groups (U.S. EPA, 2026k), including aquatic vertebrates (acute and chronic); aquatic invertebrates (acute); aquatic plants and algae; terrestrial vertebrates ((mammalian (rat): oral routes of exposure)); soil invertebrates; and terrestrial plants.

Evaluations of the strength of evidence and weight of scientific evidence for environmental hazard was conducted as described within Section 7.4.2 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). For additional details on the application of this methodology, please see Appendix B of the *Draft Environmental Hazard Assessment for Phthalic Anhydride* (U.S. EPA, 2026k) and Section 5 of the *Draft Risk Evaluation for Phthalic Anhydride* (U.S. EPA, 2026o).

5.5.2 Human Health Hazard

Section 7.5 of the 2021 Draft Systematic Review Protocol describes how EPA considers individual evidence streams (human, animal toxicity, and mechanistic/supplemental studies) when integrating

evidence (U.S. EPA, 2021). For risk evaluations conducted under TSCA, the human health hazard evidence streams were updated (Table 5-2) to more clearly reflect how apical and mechanistic hazard endpoints (as defined by the screening PECO statement) are binned to better consider the relevancy of the data for the risk evaluation.

Table 5-2. Querying the Evidence to Organize Integration for Human Health Hazard Data and Information

Evidence Stream	Questions
Studies of Exposed Humans	Is there any qualitative data in human studies that can be used to support PODs used for risk estimates?
In Vivo Mammalian Animal Studies Considered for Deriving Toxicity Values	Is there dose-response information and/or endpoints that could be used as PODs? Are there differences/similarities in toxicity across studies of different exposure durations and routes? Is there concordance across species and studies for observed endpoints?
Mechanistic and *In Vitro* Studies and Supplemental Information	Is the mechanistic endpoint linked to an apical endpoint? Is it part of an AOP? If not, can it be used qualitatively?

However, a modified fit for purpose approach was employed for phthalic anhydride. Rather than evaluating and integrating all evidence examining exposure to phthalic anhydride and/or *o*-phthalic acid and all health outcomes, EPA focused on identifying studies that could inform an updated dose-response assessment for all routes of exposure or that supported identification of a new human health hazard. To do this, EPA first reviewed existing assessments of phthalic anhydride by the U.S. EPA Integrated Risk Information System (IRIS) Program (U.S. EPA, 1988), California Office of Environmental Health Hazard Assessment (OEHHA, 2008), the Organization for Economic Co-operation and Development (OECD, 2005), Australia National Industrial Chemicals Notification and Assessment Scheme (NICNAS, 2013), Health Canada (2019), and the American Conference of Government Industrial Hygienists (ACGIH, 2023), which have all consistently identified dermal and respiratory sensitization as the most sensitive hazards associated with dermal and inhalation exposure to phthalic anhydride, respectively. Further, assessments by OECD (2005), Australia NICNAS (2013), and Health Canada (2019) have concluded that phthalic anhydride has low systemic toxicity via the oral exposure route. Therefore, EPA focused its evidence integration on dermal and respiratory sensitization through the dermal and inhalation routes, while all reasonably available evidence was considered following exposure through the oral route.

EPA considered that key studies used to support POD selection in existing assessments would also be important for its updated hazard and dose-response assessment of phthalic anhydride. For purposes of this assessment, EPA considered key studies from existing assessments of phthalic anhydride to be those considered for dose-response assessment and/or those used to establish a POD for subsequent use in risk characterization. Key studies were evaluated for data quality consistent with EPA's Draft Systematic Review Protocol (U.S. EPA, 2021). Because existing assessments of phthalic anhydride have consistently identified dermal and respiratory sensitization as the most sensitive effects to phthalic anhydride, evidence streams were integrated for these health outcomes. Because existing assessments of

phthalic anhydride have consistently concluded that it has low systemic toxicity through the oral route, evidence streams were integrated for all outcomes that may support a new human health hazard (*i.e.*, target organ toxicity).

As further described in Section 4.5.2.3 above and in the *Draft Human Health Hazard Assessment for Phthalic Anhydride* (U.S. EPA, 2026n), EPA also identified new dermal sensitization studies that provided data from experimental animal models, *in chemico,* and *in vitro* test methods that provide data for key events (KEs) in the OECD (2014) adverse outcome pathway (AOP) for skin sensitization. DERs were completed for these studies, which were then fully integrated (qualitative or quantitative) into the human health hazard assessment as part of the weight of scientific evidence for phthalic anhydride.

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