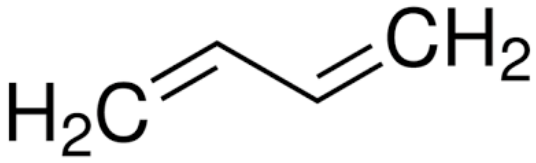
United States
Environmental Protection Agency

December 2025
Office of Chemical Safety and
Pollution Prevention

Systematic Review Protocol for 1,3-Butadiene

CASRN 106-99-0



December 2025

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1 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 (or "the Agency") 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, Version 1.0: A Generic TSCA Systematic Review Protocol with Chemical-Specific Methodologies* (U.S. EPA, 2021) (also called the "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 a weight of scientific evidence analysis.

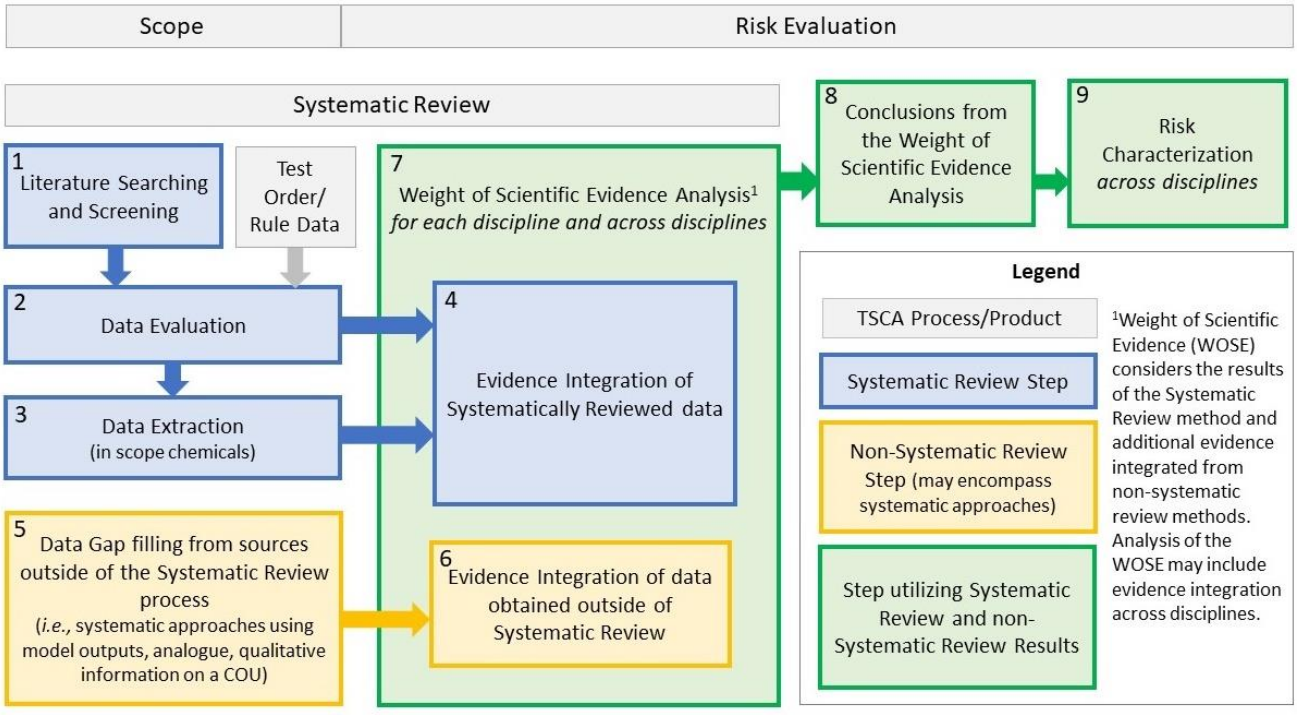

Figure 1-1. Overview of the TSCA Risk Evaluation Process with Identified Systematic Review Steps

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).

2 CLARIFICATIONS AND UPDATES TO THE 2021 DRAFT SYSTEMATIC REVIEW PROTOCOL

In 2021, EPA released the 2021 Draft Systematic Review Protocol (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 Scientific Advisory Committee on Chemicals (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 *Risk Evaluation for 1,3-Butadiene* (U.S. EPA, 2025n) (also referred to as the "risk evaluation") 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.

2.1 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 2021 Draft Systematic Review Protocol (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 2-1 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 in 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 data set, only one is counted in the overall data set (*i.e.*, deduplication). If two references contain information about the same data set, 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 2-1). 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 2-1. Terminology Clarifications Between the 2021 Draft Systematic Review Protocol and the Risk Evaluation for 1,3-Butadiene

2021 Draft Systematic Review Protocol Term	1,3-Butadiene 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 "exclude," "off topic" or "not PECO[a]/PESO[b]/RESO[c] relevant" implied a reference was *not* considered for use in the risk evaluation.	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 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.

2021 Draft Systematic Review Protocol Term	1,3-Butadiene Systematic Review Protocol Term Update	Clarification
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.
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 (nonhuman 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 1 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.

3 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 search for peer-reviewed and gray literature relevant references was completed in September and May 2019, respectively. Appendix Section C.1.9 contains the specific search strings used to identify peer-reviewed literature on 1,3-butadiene (U.S. EPA, 2021). All reasonably available information submitted to EPA under TSCA authorities was considered.

3.1 Multi-Disciplinary Updates and Clarifications to the Data Search

For the Risk Evaluation for 1,3-Butadiene (U.S. EPA, 2025n), the literature search was conducted as described in Section 4 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021), where the peer-reviewed and gray literature updated search followed the approach outlined in Sections 4.2 and 4.3 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.

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 and 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 5 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.

Supplemental Filtering of 2019 Literature Search for Dermal Absorption
EPA uses dermal absorption studies to accurately assess dermal exposure resulting from certain conditions of use (COUs). These studies are identified as supplemental studies within the human health hazard discipline. However, dermal absorption data may not meet screening criteria for other disciplines and even for the human health discipline (see criteria in Appendix H of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021)). Therefore, EPA developed search strings specific for dermal absorption (see Section 3.7) that were used to filter data sources excluded from the original literature search conducted in 2019. This filtering method was conducted using SWIFT-Review and the general process is explained in Section 4.2.4 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021).

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), two sources were added in 2023 to capture database outputs from several governmental sources. The two data sets were accessed directly and uploaded into HERO. EPA downloaded data from EPA's Ambient Monitoring Technology Information Center (AMTIC) and EPA's Third Unregulated Contaminant Monitoring Rule (UCMR3).

EPA's AMTIC is an ambient monitoring archive for hazardous air pollutants (HAPs) data records. These data are collected from various primary data sources including federal, state, local, and Tribal monitoring agencies, and other academic, community, and short-term studies. This repository also includes EPA's Air Quality System (AQS) and National Air Toxics Trends Station (NATTS) Network. The 2020 Archive for HAPs data from 1990 to 2020 was downloaded from AMTIC for 1,3-butadiene.

Additionally, EPA used data it collected in support of compliance with the Safe Drinking Water Act. This includes data for 1,3-butadiene collected pursuant to UCMR3. UCMR monitoring is also designed to produce a data set that is nationally representative of unregulated contaminants in finished water from public water systems (PWSs) across the country.

Between Draft and Final Risk Evaluation for 1,3-Butadiene, EPA also considered additional data sources relevant for the risk evaluation that were received through public comments and/or recommended by SACC; relevant data sources for each discipline underwent systematic review.

3.2 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). SWIFT-Review was used to identify peer-reviewed references that are predicted to be the most relevant for evaluating physical and chemical properties for 1,3-butadiene. Specifically, the search string used to identify data sources that potentially contain physical and chemical property information on 1,3-butadiene in SWIFT-Review was developed by EPA's Office of Research and Development (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 3.1, the search string used to identify potentially relevant peer-

reviewed data references for evaluation of the physical and chemical properties of 1,3-butadiene was 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.

3.3 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 1,3-butadiene. 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 3.1, the search string used to identify potentially relevant peer-reviewed data references for evaluation of the environmental fate and transport properties of 1,3-butadiene 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.

3.4 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 Risk Evaluation for 1,3-Butadiene (U.S. EPA, 2025n). 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 1,3-butadiene 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.

3.5 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 1,3-butadiene. 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 3.1, two additional references were added to the literature search protocol to capture database data from the AMTIC and UCMR3. The database data were compared to other database and monitoring data found during the literature search to ensure no duplication of data. The AQS and NATTS databases were found during the literature search, but they were not counted as separate references from AMTIC. 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 1,3-butadiene (U.S. EPA, 2021).

3.6 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 1,3-butadiene. 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 3.1, the search strings used to identify potentially relevant peer-reviewed data references for evaluation of the environmental and human health hazard of 1,3-butadiene 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.

In 2024, prior to completion of the draft risk evaluation, EPA selectively updated the literature pool with studies published after the September 2019 literature cutoff date through manual PubMed keyword searching, reviewing key studies and dose-response analyses provided by stakeholders, and backwards searching of references cited in those stakeholder comments. More specifically, EPA searched for recent information on 1,3-butadiene hemoglobin adducts and metabolites to inform the modes of action for each health outcome, and EPA also incorporated all updates to the original occupational cancer cohort (Delzell et al., 1996) to support an updated cancer hazard value. Among the studies identified were two updates to the cancer cohort that were used for the cancer dose-response analysis. There were not any animal toxicology studies with apical or other adverse outcome data identified post-2019, and all key studies that informed the weight of evidence were captured within the (U.S. EPA, 2002) and/or (ATSDR, 2012) assessments. Following peer review of the draft risk evaluation in April 2025, EPA reviewed all studies referenced in SACC or public comments to identify any studies that may have been missed. Following this review, three additional epidemiology/mechanistic studies recommended by the SACC panel were screened for PECO relevance and added to the literature pool.

3.7 Dermal Absorption

EPA did not filter/screen the literature search results for dermal absorption because dermal exposure was not considered a relevant exposure route for 1,3-butadiene.

4 DATA SCREENING

Sections 4.2.5 and 4.3.2 of the 2021 Draft Systematic Review Protocol describe how TIAB and full-text (FT) 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 2019 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 1,3-Butadiene; CASRN 106-99-0* (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 (HAWC) tool to develop web-based literature inventory trees that enhance the transparency of the decisions resulting from the screening processes. Additional references that EPA has obtained via public comments and other sources 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 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

[1] As noted on the DistillerSR web page (accessed November 26, 2025), 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 (accessed November 26, 2025) 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 (accessed November 26, 2025) web page.

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.

Although 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 hazard 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.

4.1 Multi-Disciplinary Updates and Clarifications to the Data Screening

As stated above in Section 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.

4.2 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 1,3-butadiene 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 FT screening for references considered for the evaluation of physical and chemical properties of 1,3-butadiene. 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 4-1 presents the number of references that report general physical and chemical property information that fulfilled the data needs for 1,3-butadiene and passed these criteria for TIAB and FT screening.

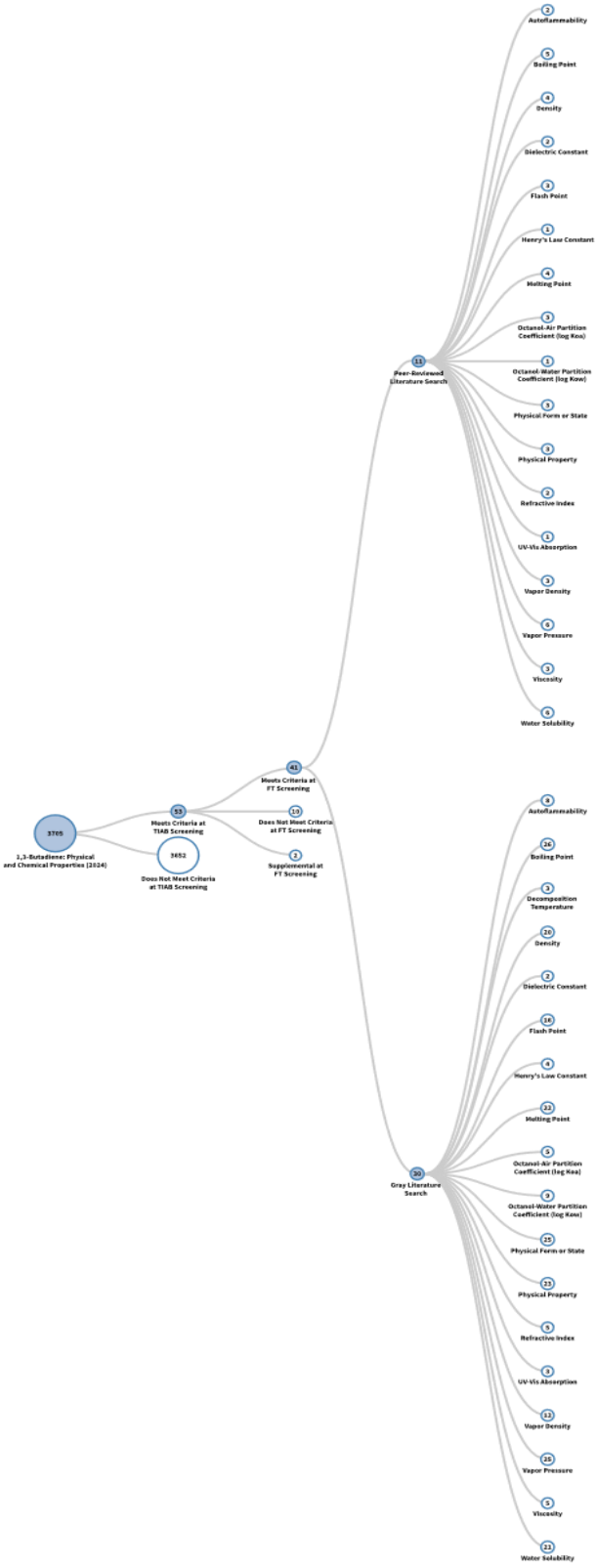

Figure 4-1. Literature Inventory Tree – Physical and Chemical Properties for 1,3-Butadiene
View the interactive literature inventory tree in HAWC. Data in this figure represent all references obtained from the publicly available databases and gray literature reference searches that were included in systematic review as of May 24, 2024. 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.

4.3 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 FT screening for 1,3-butadiene 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 PESO screening criteria was used during TIAB and FT screening for references considered for the evaluation of environmental fate and transport properties of 1,3-butadiene. 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 4-2 presents the number of references that report 1,3-butadiene fate processes and endpoints, or environmental and exposure pathways that passed PESO screening criteria at TIAB and FT screening.

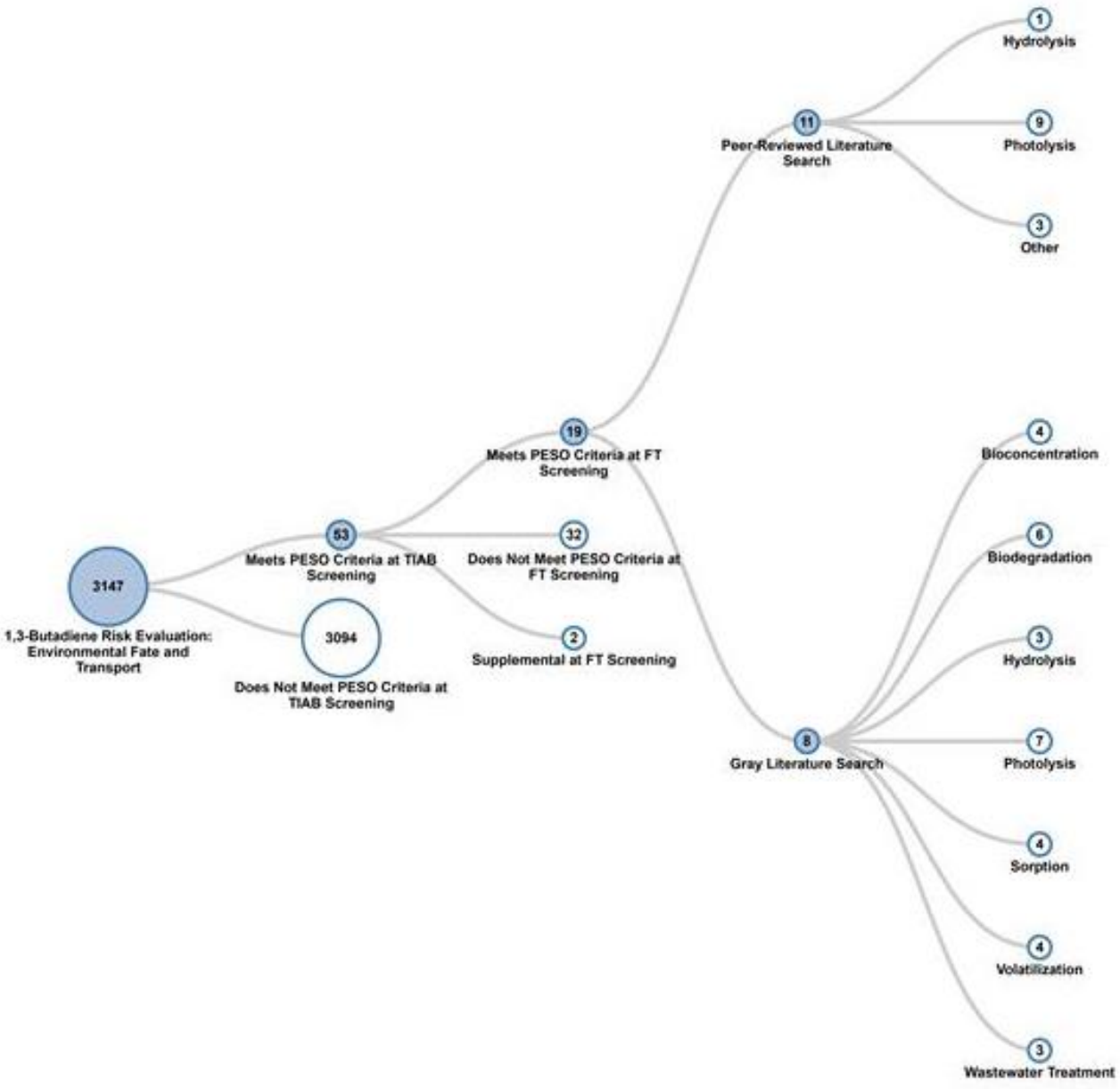

Figure 4-2. Literature Inventory Tree – Environmental Fate and Transport Properties for 1,3-Butadiene

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 September 25, 2025. Additional data may be added to the interactive version as they become available.

4.4 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 1,3-butadiene 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 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 1,3-butadiene. 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 4-3 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.

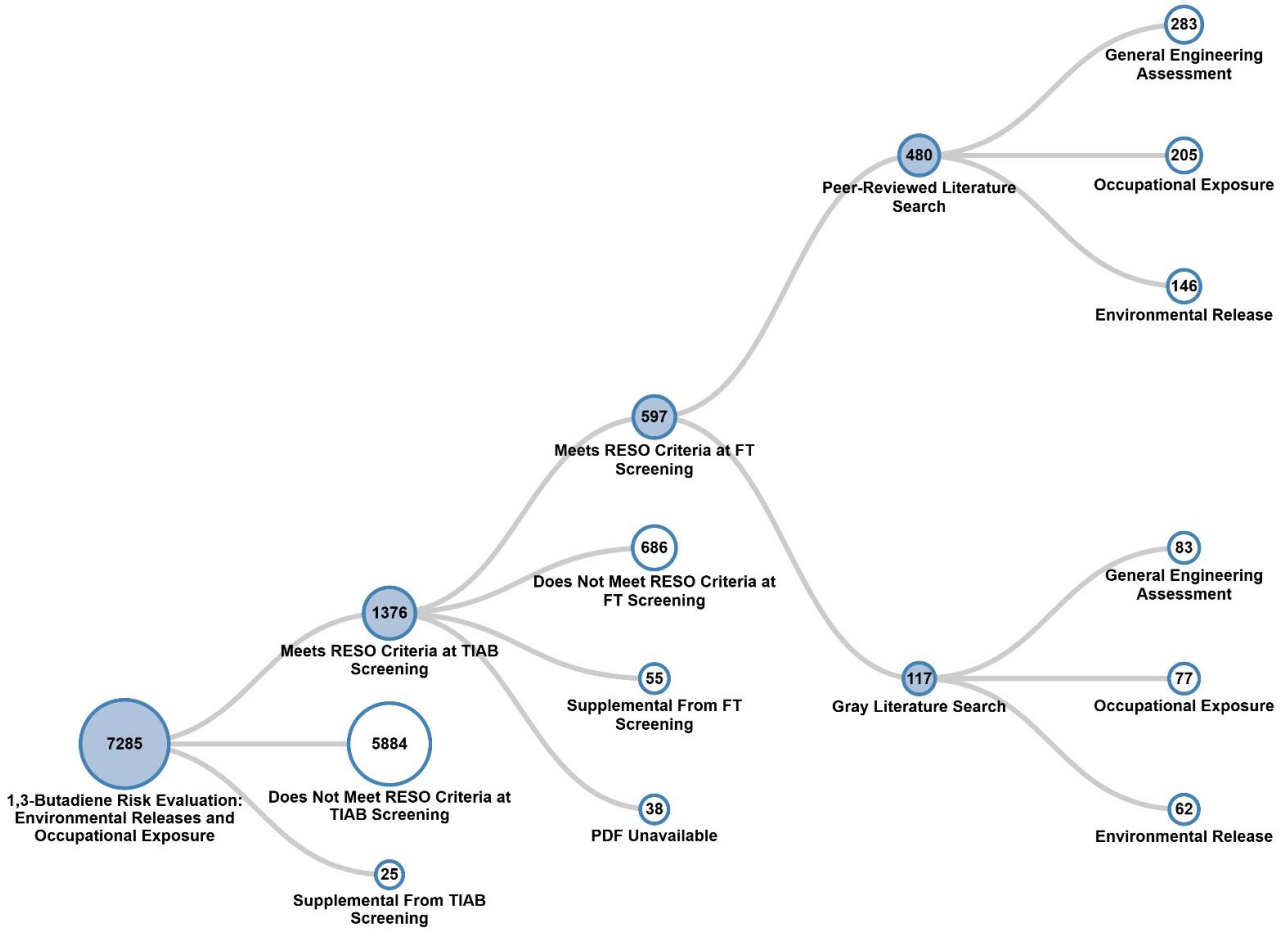

Figure 4-3. Literature Inventory Tree – Environmental Release and Occupational Exposure for 1,3-Butadiene

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 September 23, 2025. Additional data may be added to the interactive version as they become available.

4.5 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 1,3-butadiene 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 during TIAB and full-text screening for references considered for the evaluation of general population, consumer, and environmental exposure information for 1,3-butadiene. TIAB screening was performed using SWIFT Active-Screener. Figure 4-4 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. Six studies submitted by the SACC (4 consumer and 2 general population) were determined to have relevant information for the risk evaluation. One consumer study was evaluated and extracted in DistillerSR as it contains elevated 1,3-butadiene concentration of concern in consumer products, which is reflected in the below literature inventory tree (Abe et al., 2013). The 2 general population exposure study were screened in DistillerSR but not evaluated or extracted as qualitative information was used, and is also reflected in the literature tree (Padilla et al, 2024; Masoud et al, 2025).The remaining studies were contextually referenced and not included in the literature inventory tree: (Danish EPA, 2019; Omarova et al, 2021; Startin, 1984).

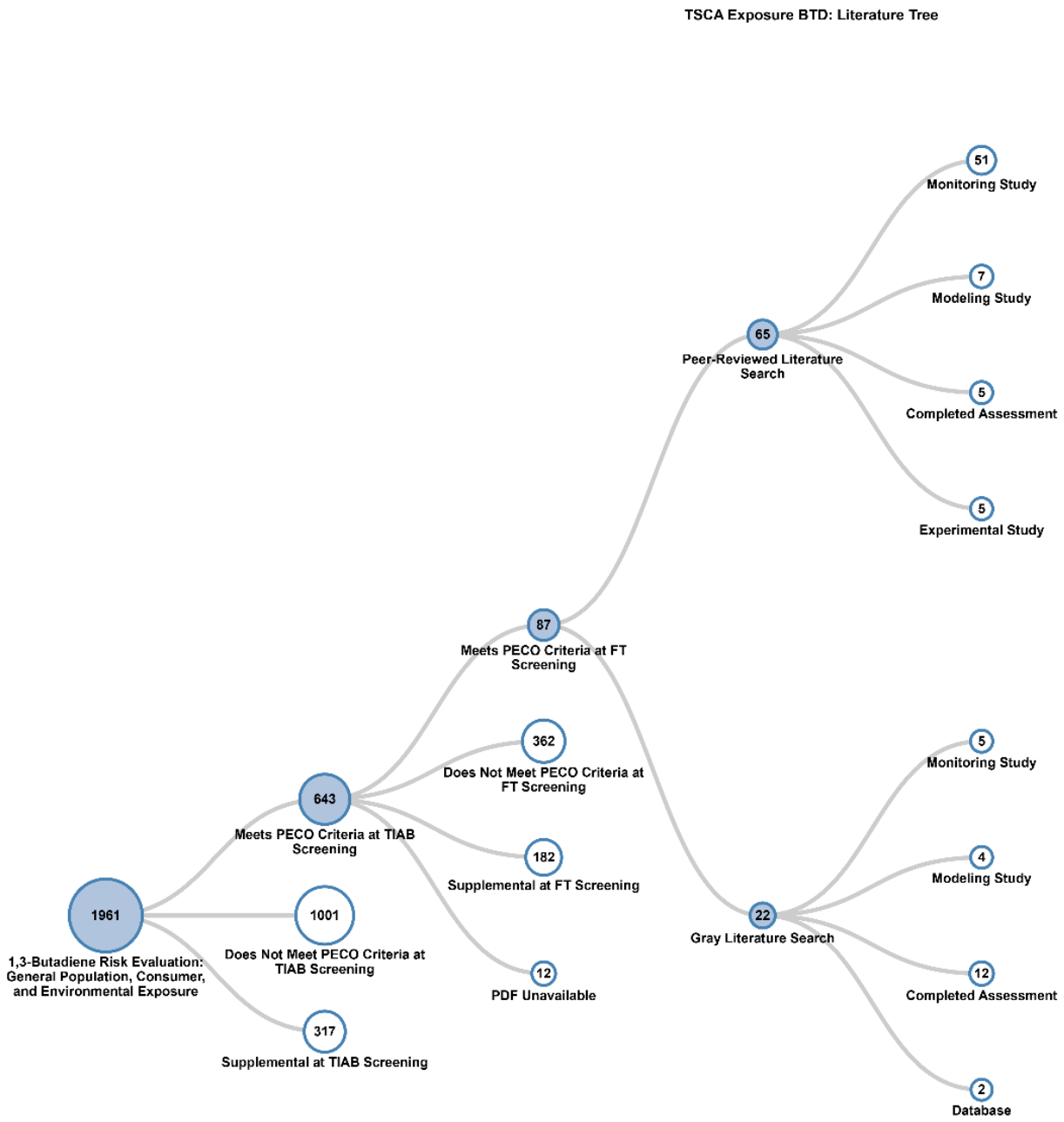

Figure 4-4. Literature Inventory Tree – General Population, Consumer, and Environmental Exposure Search Results for 1,3-Butadiene

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 October 16, 2025. Additional data may be added to the interactive version as they become available.

4.6 Environmental and Human Health Hazard

During data screening, EPA followed the process described in Appendix H, Section H.5.11 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021), to conduct TIAB and full-text screening for 1,3-butadiene 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 during TIAB and full-text screening for references considered for the evaluation of environmental and human health hazard resulting from exposure to 1,3-butadiene. 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. Figure 4-5 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 1,3-butadiene. Following peer review of the draft risk evaluation, EPA reviewed individual 1,3-butadiene-specific studies recommended by the SACC or public comments. Many of these studies were already considered in the existing systematic review pool, but the following three references were added, all under the epidemiology evidence stream: HERO IDs 12095563, 12381562, and 12392229.

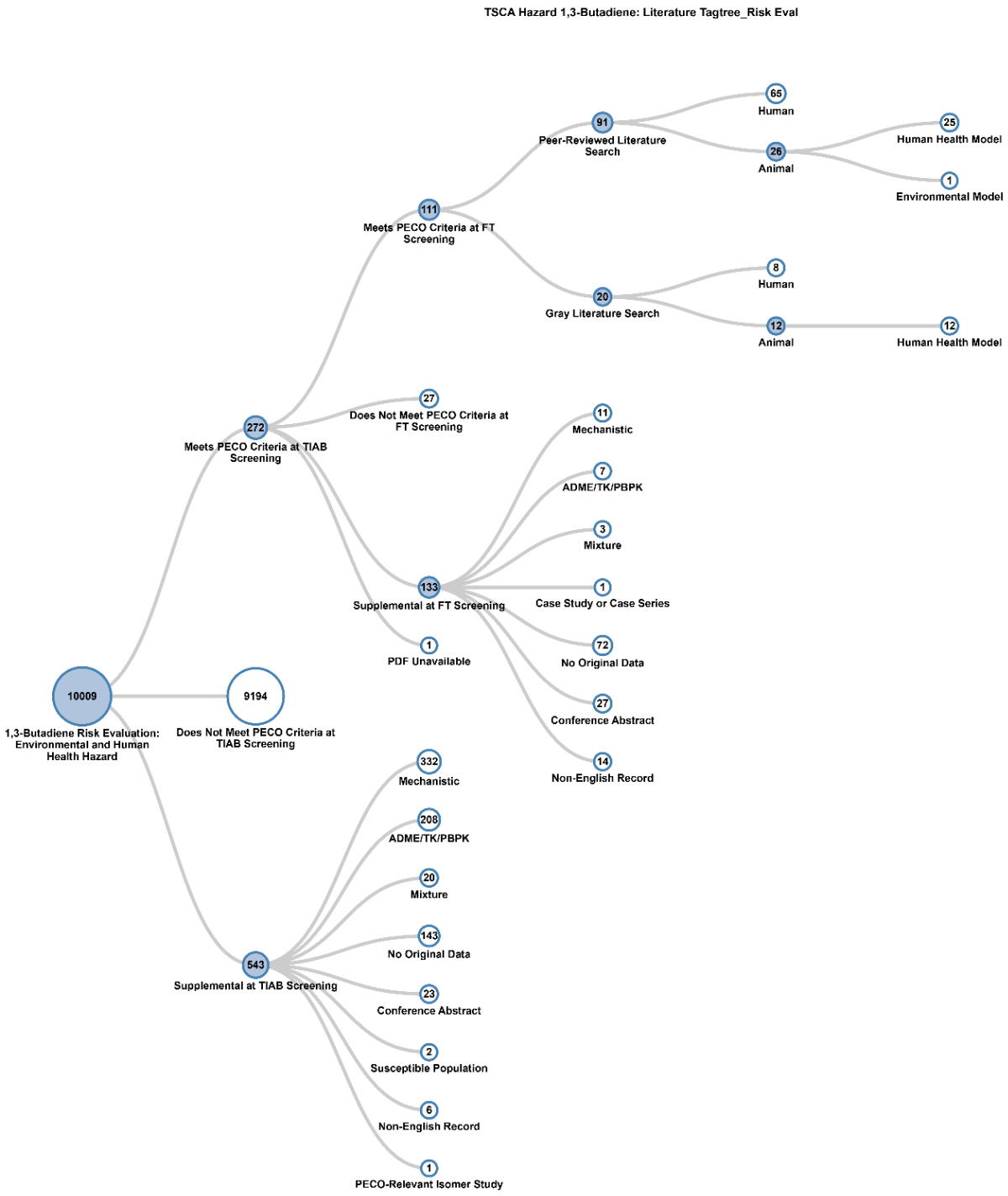

Figure 4-5. Literature Inventory Tree – Environmental and Human Health Hazard for 1,3-Butadiene

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 October 17, 2025. Additional data may be added to the interactive version as they become available.

4.6.1 Further Filtering: Human Health Hazard

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

4.6.1.1 De-Duplication of Reference Pool

In addition to further filtering studies as described above, EPA also identified studies and their respective HERO entries that were either duplicates or alternative versions of the same data, similar to the process described in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). For example, separate HERO entries for both the OECD guideline and academic peer-reviewed version of the same study may have both independently met the PECO screening criteria allowing them to move forward to data evaluation and extraction. In other cases, an entry may have represented only a supplemental analysis to the main study. In this case, only the most detailed, inclusive, and/or most recent version would be utilized for data evaluation and extraction while the other study was marked as supplemental and used to help contextualize the data presented in the study utilized. The study numbers listed in Figure 4-6 and Figure 4-7 represent the results following removal of these duplicate entries.

4.6.1.2 Further Filtering for Epidemiology Studies

To streamline the identification of studies containing dose-response data, 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 and extraction.

4.6.1.2.1 Epidemiology Further Filtering Process

All epidemiology references (peer-reviewed and gray literature) that met PECO screening criteria proceeded to a further filtering form in DistillerSR. For each reference, two independent assessors completed the further filtering form and differences in responses between assessors were resolved via conflict resolution discussions.

The questions on the further filtering form are presented in Table 4-1 below. This form includes questions to confirm that the initial PECO-based screening determination was correct; identify whether the reference was included in the IRIS assessment and if so whether it was used for dose-response assessment in the IRIS assessment; identify the exposure routes in the study and the duration for inhalation exposures; tag cancer and non-cancer studies; determine whether the reference contains dose-response data; and identify intentional dosing studies.

References that were identified on the further filtering form as having been incorrectly screened as meeting PECO criteria were pushed back to the screening level and retagged based on the correct screening results, and those references are not included in the counts of further filtered references discussed below. The remaining references that met PECO screening criteria were checked to determine whether they were included in the IRIS assessment. References that were included in the IRIS assessment but were not used to determine points of departure (POD) for dose-response in the IRIS assessment didn't proceed to the remaining questions on the further filtering form and didn't proceed to data quality evaluation and extraction. References that met PECO screening criteria and also met further filtering criteria proceeded to data quality evaluation and extraction. To proceed to data quality evaluation and extraction, references had to meet either of the following further filtering criteria:

- References that were used for dose-response assessment in the IRIS assessment
  OR
- References that were not included in the IRIS assessment that contained potentially relevant dose-response data, which was defined based on the study using quantitative information to determine three or more levels of exposure that were used in the analysis or an exposure-response model using a continuous measure of exposure.

Table 4-1. Epidemiology Further Filtering Form

Epidemiology Further Filtering Form
Check PECO screening - should this study be:
• Meets PECO Screening Criteria – Epi Study   o Comments (optional) [free text] If this answer is selected, then proceed to the next questions below.

• PECO Supplemental
  o Specify which supplemental category
  ▪ Mechanistic studies or studies with below organ-level effects
  ▪ ADME, PBPK, and toxicokinetic
  ▪ Case reports, case series, case-case, or case-only study designs
  ▪ Susceptible populations (no health outcomes)
  ▪ Mixture studies
  ▪ Non-English records
  ▪ Records with no original data
  ▪ Conference abstracts
  ▪ Field studies
  ▪ Isomer
  o Please include the reason for the determination [free text]
 	
The form ends here if this answer is selected.

• Does not meet PECO Screening Criteria   o Please include the reason for the determination [free text] The form ends here if this answer is selected.
• Other Discipline (Not an Epi study)   o Please include the reason and specify if the study should be sent to a different discipline (Animal, Ecotox) [free text] The form ends here if this answer is selected.
Was this reference included in the IRIS assessment?
• No
• Yes, but the reference was NOT used for POD The form ends here if this answer is selected.
• Yes, and the reference WAS used for POD
• Assessor identified the reference as associated with a study that was used for POD

Epidemiology Further Filtering Form
Potential Exposure Routes for the Condition of Use (COU) in the study (select <u>all</u> potential routes via which exposure could have occurred in the study population) ***Use your best judgment to decide the appropriate exposure route(s).***
• Inhalation
• Dermal/Skin
• Ocular/Eye
• Food
• Drinking water
• Teeth or dental patient
• Comment if there is substantial uncertainty on your selection [free text]
Exposure Routes <u>specifically assessed via exposure measurement</u> (select all routes that were specifically assessed via exposure measurement in the study)

• Inhalation (air sampling, personal air monitoring, area air monitoring, inhalation chamber studies, shower studies, questionnaire assessing inhalation exposure, lung tissue exposure biomarkers, etc.)
Check all inhalation exposure durations that apply:
• acute inhalation (exposure duration of 24 hours or less) (For a study to be classified as an acute exposure study, the exposure duration must be 24 hours or less at the time of outcome measurement. The outcome doesn't need to be measured immediately after exposure ends, but further exposure cannot occur before outcome measurement. Examples of exposures that might be 24 hours or less include accidental spills and studies in which participants are intentionally dosed with the chemical of interest for 24 hours or less.)
• short-term inhalation (exposure duration of more than 24 hours and up to and including 28 days)
• chronic inhalation (exposure duration of more than 28 days)
• If the duration of exposure is unclear, please select the most relevant choice from the list above.
  • Acute inhalation (≤24 hours)
  • Short-term inhalation (>24 hours and ≤28 days)
  • Chronic inhalation (>28 days)

Dermal/Skin (wipe sampling, questionnaire assessing dermal exposure, patch testing (intentional dosing), dermal chamber studies, shower studies, skin permeability coefficient, skin exposure biomarkers, etc.)
Ocular/Eye (ocular chamber studies, etc.)
Food (duplicate diet, food sampling, etc.)
Drinking water (water sampling, etc.)
Teeth or dental patient
Other (duration, non-route-specific biomarker (matrices such as blood, urine, etc.), etc.)
Does the study assess occupational exposure? *Office workers in their workplace <u>are</u> occupational exposures.*
• Yes
• No

Epidemiology Further Filtering Form
Endpoints Analyzed (check all that apply)
• Cancer/carcinogenesis Select all **cancer** health outcome categories included in the study (CANCER ONLY) • Neurological/behavioral • Cardiovascular • Thyroid • Cancer of the Reproductive System • Childhood cancer (before birth through age 18) • Gastrointestinal • Immune/hematological • Hepatic/liver • Mortality • Musculoskeletal • Nutritional/metabolic • Ocular/sensory • Renal/kidney • Lung/respiratory • Skin & connective tissue • Other [free text to specify]
• Non-cancer Select all **non-cancer** health outcome categories included in the study (NON-CANCER ONLY) • Neurological/behavioral • Cardiovascular • Thyroid • Reproductive/developmental • Gastrointestinal • Immune/hematological • Hepatic/liver • Mortality • Musculoskeletal • Nutritional/metabolic • Ocular/sensory • Renal/kidney • Lung/respiratory • Skin & connective tissue • Irritation • Sensitization • Other
What type(s) of quantitative measurement of exposure does the study <u>report</u> (check all that apply)?
• None - no quantitative measurement
• Duration of exposure
• Biomarker of exposure with only binary data (detected/undetected)

• Quantitative measurement or estimate of concentration or dose of the chemical of interest
  o Please select any of the following quantitative methods that apply.
  ▪ Measured concentration or dose
  ▪ Modeled concentration or dose

Epidemiology Further Filtering Form
▪ Job-Exposure Matrix (JEM) or similar ▪ Concentration or dose per time period (ex: mg/day, mg/kg/day, ml/hour, ml/year, TWA, etc.) ▪ Biomarker of exposure with quantitative data ▪ Other (please specify) [free text]
Did the study <u>report</u> any of the following exposure levels (check all that apply)?
• Three or more levels of exposure (*i.e.*, referent group + 2 or more groups) but didn't use these levels in any analyses of the association between the chemical of interest and a health outcome
• Three or more levels of exposure (*i.e.*, referent group + 2 or more groups), which were used in the analyses of the association between the chemical of interest and a health outcome
• A continuous measure of exposure but didn't use this measurement in any model or analyses of the association between the chemical of interest and a health outcome
• An exposure-response model using a continuous measure (or estimate) of exposure
• Other
Does the study <u>assess the association</u> between exposure to the chemical of interest and a health outcome?
• Yes
• No o Please specify (check all that apply): ▪ No, focus on exposure to a different chemical with the chemical of interest as an effect modifier ▪ No, focus on a third variable's effect on the relationship between exposure to the chemical of interest and an outcome ▪ No, the only exposure assessed is smoking and the specific contribution of the chemical of interest is not separated out (*i.e.*, the chemical of interest is a component of the mixture of cigarette smoke; the effect of smoking plus exposure to the chemical is not assessed). ▪ No, other
Did the study report a quantitative measurement or estimate of concentration or dose of the chemical of interest (as defined in previous questions) AND Use this quantitative information to define three or more levels of exposure (*i.e.*, referent group + 2 or more groups) or an exposure-response model using a continuous measure of exposure, which were used in the analyses of the association between exposure to the chemical of interest and a health outcome (as defined in previous questions)? THIS ANSWER IS AUTO-CALCULATED > DO NOT EDIT ANSWER
• Yes
• No
Please comment on whether the study contains potentially useful dose-response data and note any questions you have. [free text]
Select all study designs that apply:
• This is an observational epidemiology study
• This is an intentional dosing epidemiology study or a controlled exposure epi study in which people were intentionally exposed to the chemical of interest

Epidemiology Further Filtering Form
Please select all {Potentially Exposed and Susceptible Subpopulations} PESS categories mentioned in the reference (Select all that apply. If the reference mentions the category, select it)
Lifestage (select all that apply) (Specific ages for the categories below may vary. Select the category if the study included analyses for that particular category) Select all lifestages • Pregnant people (parent) or embryo/fetus (developmental) (conception through birth) • Infants (birth through <12 months) • Children (age 1 year through <11 years) • Adolescents (age 11 years through <21 years) • Older adults (≥65 years) • Other PESS lifestage specified in the reference (such as studies specifying a certain age range as being more likely to be either exposed or susceptible)
• Studies focusing on reproductive parameters
• Pre-existing Disease (ex. altered metabolism, behaviors, treatments related to condition)
• Lifestyle Activities (ex. exercise, smoking)
• Occupational
• Consumers of targeted/niche products
• Geography/site-specific (ex. downstream of release sites)
• Sociodemographic status (ex. home near exposure source)
• Nutrition (ex. contaminated food source)
• Genetics/Epigenetics (ex. genetic variants that increase susceptibility, knockout
• Unique Activities (ex. sweat lodges)
• Aggregate Exposures (ex. multiple air exposure sources)
• Other Chemical and Non-chemical stressors (ex. exposure to other substances that affect same organ as test chemical)
• Tribal
• Other PESS category specified in the reference
Should this reference move on to data quality evaluation and extraction?
• Yes
• No

4.6.1.2.2 Epidemiology Further Filtering Results

The epidemiology further filtering results are presented in the *Further Filtering Results for Human Health Hazard Animal Toxicology and Epidemiology for 1,3-Butadiene* (U.S. EPA, 2025k). An overview of the epidemiology further filtering results is presented in Figure 4-6 below. There were 72 references that met PECO screening criteria that were considered in the Risk Evaluation for 1,3-Butadiene. One additional reference that met PECO screening criteria was identified based on SACC comments. Of the 73 references that met PECO screening criteria, 17 references were found to be included in the IRIS assessment. Of these 17 references, 16 were not used for IRIS dose-response assessment and one reference was used for IRIS dose-response assessment. The one reference that was

used for IRIS dose-response assessment proceeded to TSCA data quality evaluation and extraction. Of the remaining 56 references that were not included in the IRIS assessment, 35 were found to contain sufficient dose-response data to proceed to data quality evaluation and extraction. Thus, a total of 36 references underwent data quality evaluation and extraction as described below. Only the 36 references that underwent data quality evaluation and extraction were considered for use in dose-response assessment, but all 73 references that met PECO screening criteria were included in hazard identification and evidence integration.

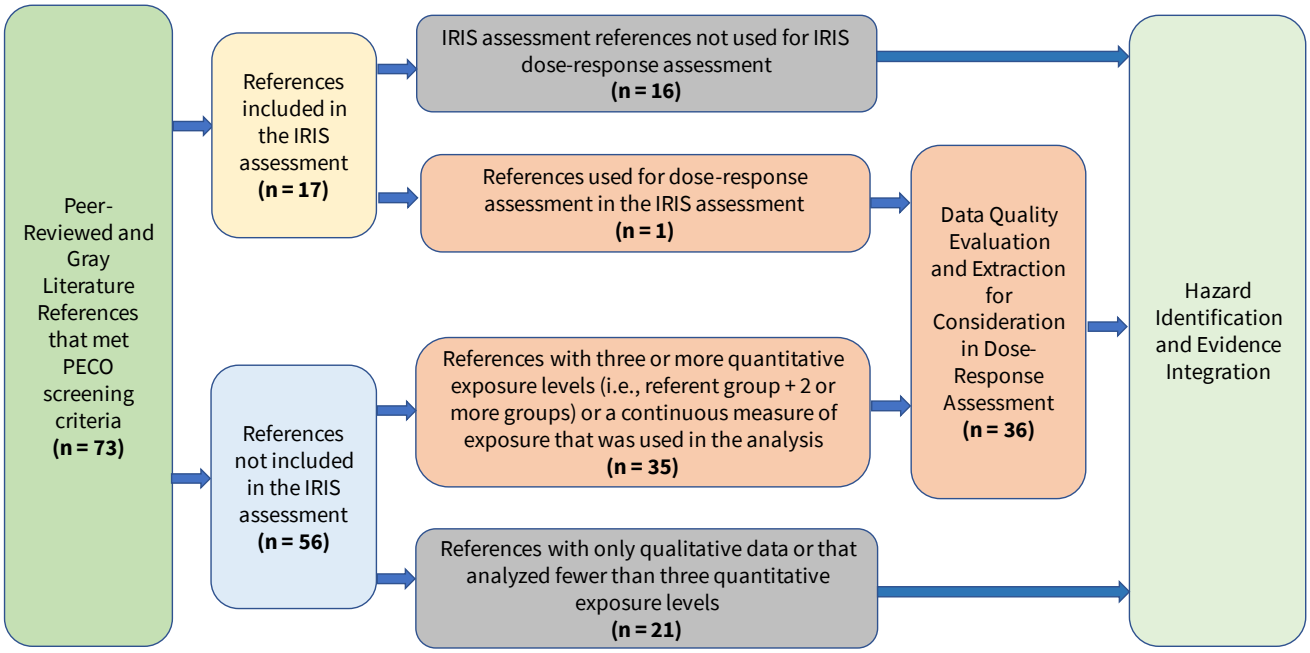

Figure 4-6. Results of the Further Filtering Process for Human Health Epidemiology Studies That Met PECO Screening Criteria

4.6.1.3 Further Filtering for Animal Toxicity Studies

Studies that met the PECO screening criteria and were categorized as having animal toxicity information for the evaluation of human health hazard were assessed through the further filtering process. This process involved use of an "Animal Toxicity Further Filtering Form," presented in Table 4-2, to extract basic study-level information followed by a subsequent two-step filtering process to identify and prioritize animal toxicity studies with quantitative information most useful for the human health hazard assessment. Throughout the screening and further filtering process, the studies from both gray and peer-reviewed literature sources were checked for potential use of the same data in more than one assessment (study duplicate), or alternative versions of the same data set (data duplicate). This "de-duplication" process is described in further detail within sections 4.2.3 and 4.3.2 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). A brief description is provided in Section 4.6.1.1. All animal toxicology references (peer-reviewed and gray literature) that met PECO screening criteria proceeded to a further filtering form in DistillerSR. For each reference, two independent assessors completed the further filtering form and differences in responses between assessors were resolved via conflict resolution discussions.

Table 4-2. Animal Toxicology Further Filtering Form

Animal Toxicity Further Filtering Form	
Does the article meet PECO criteria? If NO, PLEASE STOP SCREENING.	
• Yes – PECO-relevant	• No – not PECO relevant
• PECO relevance unclear	• Supplemental
What is the animal species?	
• Cat	• Pig
• Dog	• Primate
• Guinea Pig	• Rabbit
• Hamster	• Rat
• Mouse	• Other [free text]
What is the experiment exposure route? (select all that apply)	
• Inhalation	• Subcutaneous injection
• Dermal/Skin	• Ocular/Eye
• Oral o If 'Yes' ▪ Gavage, Drinking Water, or Food	• Intraamniotically
• Intraperitoneal injection	• Other [free text]
Is this a reproductive/developmental study?	
• Yes	
• No	
Select the study duration category:	
• Acute (≤ 24 h)	
• Short-Term (>1–30 days)	
• Sub-Chronic (>30–90 days)	
• Chronic (>90 days)	
• Not Reported	
Does this study contain 2 or more dose groups in addition to a control?	
• Yes	
• No	
Please inventory target organs/systems with outcomes reported (qualitative or quantitative, including negative outcomes):	
• Neurological/Behavioral	• Immune/Hematological
• Cancer/Carcinogenesis	• Hepatic/Liver
• Cardiovascular	• Mortality
• Thyroid	• Musculoskeletal
• Reproductive/Developmental	• Nutritional/Metabolic
• Gastrointestinal	• Ocular/Sensory

Animal Toxicity Further Filtering Form	
• Renal/Kidney	• Lung/Respiratory
• Skin/Connective Tissue	• Irritation
• Sensitization	• Other [free text]
Does this study have a LOEL?	

• Yes
  ○ What is the experiment LOEL dose value [free text]
  ○ What is the experiment LOEL Units (mg/kg-bw/day, mg/kg, etc.)
  ○ Briefly describe the LOEL outcome [free text]	

• No	
• Other ○ [free text]	
Does this study report only negative outcomes (*i.e.* no change seen in animals following exposure)?	
• Yes	
• No	
Does the experiment show different effects among subpopulations (age/sex/etc), where specific groups seem to have higher susceptibility to the test chemical? If so, which of the following PESS categories may be relevant? (select all that may apply, tag for all possibly relevant PESS categories regardless of study results)	
• Lifestage (ex. reproductive studies, accumulation in milk)	• Nutrition (ex. contaminated food source)
• Pre-existing Disease (ex. altered metabolism, behaviors, treatments related to condition)	• Genetics/Epigenetics (ex. genetic variants that increase susceptibility; knockout animals)
• Lifestyle Activities (ex. exercise, smoking)	• Unique Activities (ex. sweat lodges)
• Occupational and Consumer Exposures (ex. byproduct of work)	• Aggregate Exposures (ex. multiple air exposure sources)
• Geography/Site-specific (ex. downstream of release sites)	• Other Chemical and Non-chemical stressors (ex. exposure to other substances that affect same organ as test chemical)
• Sociodemographic Status (ex. home near exposure source)	• Other [free text]
Should this reference move on to data extraction and evaluation?	
• Yes	
• Not at this time	
Comments (optional)	
• [free text]	

4.6.1.3.1 Animal Toxicology Further Filtering Step 1: Identification of Whether or Not Studies were Considered for Hazard Value Derivation in a Recent Authoritative Assessment

During full-text screening, 37 studies were identified to have met the PECO screening criteria for animal toxicity informing human health hazard across both gray and peer-reviewed literature (Figure 4-5). Previous 1,3-butadiene risk/hazard assessments have been conducted by authoritative sources, most notably EPA IRIS (2002) and ATSDR (2012). OPPT used these previous assessments to facilitate an

efficient and scientific risk evaluation by better focusing and refining the efforts for data evaluation and extraction and evidence integration. Studies that these previous assessments used in a quantitative context (*e.g.,* discussed hazard values and/or considered for dose-response analysis of key endpoints) were sent directly to data evaluation and extraction without consideration of other factors described in Section 4.6.1.3.2.

EPA considered excluding any other older studies cited in these assessments from consideration for data evaluation and extraction, since they were already determined to not be relevant for hazard value derivation. However, due to the relatively low number of studies meeting PECO criteria (<40) in the 1,3-butadiene database, EPA did not restrict the studies sent through further filtering Step 2 (Section 4.6.1.3.2). Therefore, all studies that met the PECO screening criteria were either directly sent to data evaluation and extraction due to their use in previous assessments or further filtered based on dose group criteria described in the following section.

4.6.1.3.2 Animal Toxicology Further Filtering Step 2: Number of Dose Groups Tested

For the remaining studies that were not already sent forward to data evaluation and extraction in the previous step (Section 4.6.1.3.1), they underwent a basic study-level extraction (Table 4-2). This included information such as species, exposure route, study duration, organ systems assessed, relevant PESS categories, the most sensitive lowest-observable-effect level (LOEL) (if any effects were observed), and whether the study used two dose groups in addition to a control. EPA considered many factors for filtering studies including selected data evaluation metrics and selective data gap-filling needs but eventually decided on a less restrictive approach. Studies undergoing further filtering only moved forward to data evaluation and extraction if they contained at least two dose groups in addition to a designated control. This resulted in the majority of studies moving forward (Figure 4-7) and therefore a broader pool of studies under consideration for dose-response analysis. The use of further filtering criteria in this manner for 1,3-butadiene is considered a pilot approach and may be modified in the future as EPA evaluates the relative benefits of more or less restrictive filtering considerations.

Studies that contained only one dose group in addition to a control, or only a single dose group without a control (*e.g.,* a limit test) did not move forward through the data evaluation or extraction process (Penn and Snyder, 1996; Elovaara et al., 1994; U.S. EPA, 1990; Irons et al., 1986; Chemical Manufacturers Association, 1985; Mobil Environmental and Health Science Laboratory, 1985; Bio/dynamics, 1980). The study-wide information extracted in the further filtering form from these studies was used for supporting evidence integration (Section 6.5) and describing the hazard database in the risk evaluation.

4.6.1.3.3 Animal Toxicology Further Filtering Results

Step 1

A total of 11 key studies were prioritized for data evaluation and extraction based on their quantitative use in prior risk assessments (Anderson et al., 1998; Brinkworth et al., 1998; Pacchierotti et al., 1998; Anderson et al., 1996; Bevan et al., 1996; NTP, 1993; Hackett et al., 1988b; Hackett et al., 1988a; Battelle PNL, 1987; Thurmond et al., 1986; Shugaev, 1969). Thus, these 11 studies automatically moved directly to the data evaluation and extraction step (Figure 4-7). Even though some of these studies only used a single dose group and would not have passed further filtering if they were not prioritized in Step 1 (Section 4.6.1.3.1), but due to their importance for informing the key endpoints identified in authoritative assessments the number of dose groups was not a consideration.

Step 2

Out of 26 remaining studies that went through the Animal Toxicity Further Filtering Form (Table 4-2), 8 were excluded due to not containing 2 or more dose groups plus a control (Penn and Snyder, 1996; Elovaara et al., 1994; U.S. EPA, 1990; Irons et al., 1989; Irons et al., 1986; Chemical Manufacturers Association, 1985; Mobil Environmental and Health Science Laboratory, 1985; Bio/dynamics, 1980). The results from further filtering for these studies are presented in Further Filtering Results for Human Health Hazard Animal Toxicology and Epidemiology for 1,3-Butadiene (U.S. EPA, 2025k). All other studies moved forward to data evaluation and extraction (Figure 4-7).

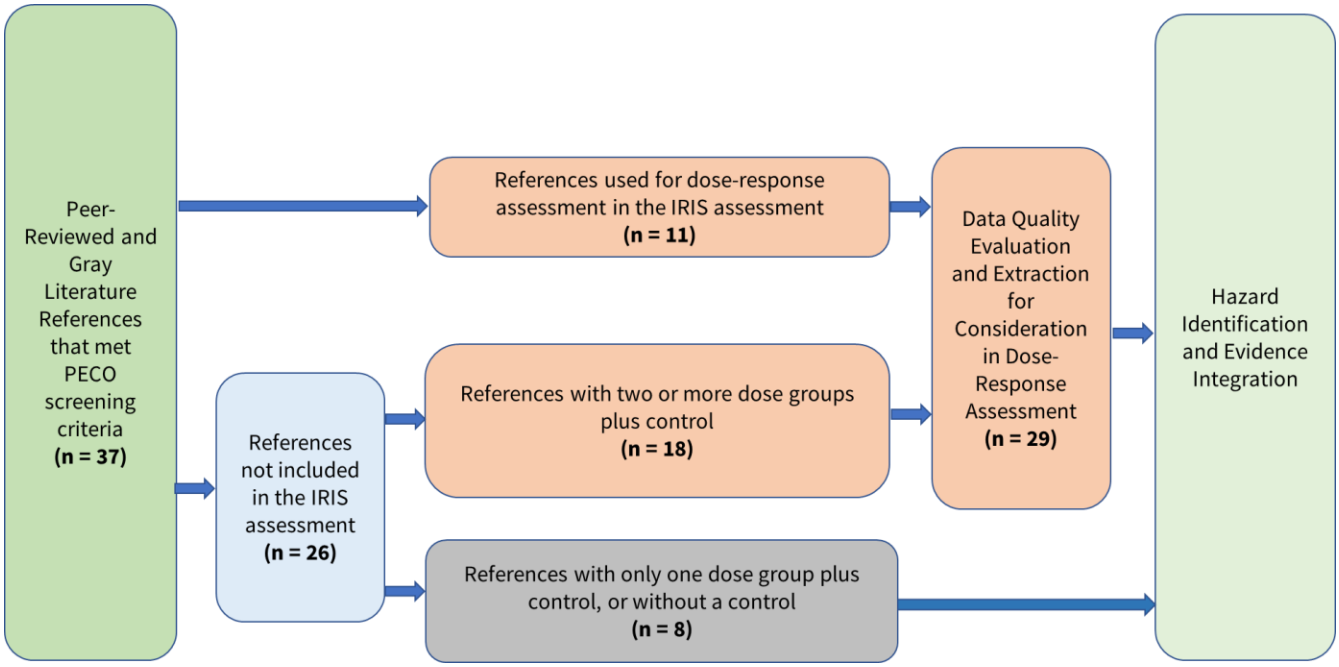

Figure 4-7. Results of Further Filtering Process for Human Health Animal Toxicology Studies That Met PECO Criteria

4.7 Dermal Absorption

EPA did not perform screening for dermal absorption because dermal exposure was not considered a relevant exposure route for 1,3-butadiene.

5 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 Risk Evaluation for 1,3-Butadiene (U.S. EPA, 2025n) and any clarifications or updates regarding these systematic review steps as described in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021).

5.1 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 of the Protocol. The data quality criteria for physical and chemical property data are summarized in Appendix K of the 2021 Draft Systematic Review Protocol. The *Data Quality Evaluation and Data Extraction Information for Physical and Chemical Properties for 1,3-Butadiene* (U.S. EPA, 2025e) provides details of the data extracted and evaluated, including metric ratings and the overall study quality determination for each data source.

Nineteen references were used to come to conclusions on melting and boiling points for 1,3-butadiene. Twelve references were used to come to conclusions on density. Five references were used to come to conclusions on vapor density. Eight references were used to come to conclusions on vapor pressure. Four references were used to come to conclusions on water solubility. Ten references were used to come to conclusions on an octanol:water partition coefficient. Seven references were used to come to conclusions on Henry's Law coefficient/constant. Eleven references were used to come to conclusions on flash point. Four references were used to come to conclusions on auto flammability. Four references were used to come to conclusions on viscosity. Four references were used to come to conclusions on refractive index and one references were used to come to conclusions on dielectric constant.

5.2 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 rankings 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 ranking quality criteria are in Table_Apx L8. The *Data Quality Evaluation and Data Extraction Information for Environmental Fate and Transport for 1,3-Butadiene* (U.S. EPA, 2025c) provides details of the data extracted and evaluated, including metric rating and the overall study quality determination for each data source.

A total of 15 references were used to complete the fate assessment for 1,3-butadiene. Seven references were used to come to conclusions on photodegradation rates. Five references were used to come to conclusions on transformation products for 1,3-butadiene in air. For Biodegradation in water and hydrolysis in water, two references were used each. One reference each was used for indirect photolysis in water, and biodegradation in soil and sediments. Wastewater treatment efficiency, bioconcentration factor, organic carbon:water partition coefficient and octanol:air partition coefficient were estimated using EPI Suite™ (U.S. EPA, 2012). The selected values for the physical-chemical properties were used in the fate assessment.

5.3 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 *Data Quality Evaluation and Data Extraction Information for Environmental Release and Occupational Exposure for 1,3-Butadiene* (U.S. EPA, 2025d) details the data extracted and evaluated, including metric rating and the overall study quality determination for each data source.

5.4 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 for 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 5.4.1. 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 *Data Quality Evaluation Information for General Population, Consumer, and Environmental Exposure for 1,3-Butadiene* (U.S. EPA, 2025a), referred to hereafter as the "1,3-Butadiene 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.

As mentioned above in Section 1, 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. As seen in Figure 4-5, the extracted 1,3-butadiene data are from targeted evaluated references that have an OQD of High assuming that such studies would be distinctly supportive to the 1,3-butadiene exposure assessment. The extracted data provide a high level of confidence for characterizing general population, consumer, and environmental exposure and for meeting assessment needs. 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 *Data Extraction Information for General Population, Consumer, and Environmental Exposure for 1,3-Butadiene* (U.S. EPA, 2025a), referred to hereafter as the "1,3-Butadiene Data Extraction Information for General Population, Consumer, and Environmental Exposure."

5.4.1 Data Quality Evaluation Metric Updates

The data evaluation metrics for the monitoring, experimental, and database evidence streams, are presented below in Table 5-1, Table 5-2, Table 5-3, 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 5-1. 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]*
Domain 2. Representative	
Metric 4. Geographic area	

Data Quality Rating	Description
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.

Data Quality Rating	Description
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.
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 8. 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 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).

Data Quality Rating	Description
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.
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	Description
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]*

Table 5-2. Updated Evaluation Criteria for Experimental Data Sources

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. 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

Data Quality Rating	Metric 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.
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.
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 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]*
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).

Data Quality Rating	Metric Description
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 Key uncertainties, limitations, and data gaps have been identified. AND The uncertainties are minimal and have been characterized.

Data Quality Rating	Metric Description
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]*

Table 5-3. Updated Data Evaluation Criteria for Database Data

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.
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	

Data Quality Rating	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]*
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	
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).

Data Quality Rating	Description
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 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]*

Data Quality Rating	Description
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/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. 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 • 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).

Data Quality Rating	Description
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
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]*

5.5 Environmental and Human Health Hazard

Details regarding the evaluation and extraction of 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 animal and *in vitro* toxicity studies and epidemiological studies are available in Appendix 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 5.5.2. The below-listed supplemental documents provide details of the data evaluated and extracted. Data evaluation information for each sub-discipline (*i.e.*, human health hazard epidemiology or animal toxicology) 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 sub-disciplines are contained in a single supplemental document. All of the data extraction for human health hazard data was conducted in DistillerSR.

- *Data Quality Evaluation Information for Human Health Hazard Epidemiology for 1,3-Butadiene* (U.S. EPA, 2025h)
- *Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for 1,3-Butadiene* (U.S. EPA, 2025g)
- *Data Extraction Information for Human Health Hazard Animal Toxicology and Epidemiology for 1,3-Butadiene* (U.S. EPA, 2025b)

5.5.1 Environmental Hazard

Only one ecotoxicological animal model reference was identified during screening. However, data evaluation and data extraction were not conducted for environmental hazard because an environmental hazard assessment was not conducted in the risk evaluation of 1,3-butadiene.

5.5.2 Human Health Hazard

As described in Section 4.6.1, references that met further filtering criteria underwent data quality evaluation, with separate evaluations performed for each outcome in the study (in addition to species and duration for animal toxicology). Each of these components underwent data extraction; data were not extracted from Uninformative evaluations (other components from the same reference may still be extracted). 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).

As a result of feedback from NASEM, the SACC, and multiple external stakeholders, OPPT explored ways to harmonize its Systematic Review Protocol with the *IRIS Systematic Review Handbook*. Besides being responsive to feedback, this effort was envisioned to have several additional benefits. It would facilitate the sharing of systematic review outputs between programs. This would not only make reviews reusable by other Agency units but also could mean that chemical-specific assessments could be split up into modules, with each Agency unit sharing their results to form a final assessment. This in turn would conserve Agency resources. Harmonization of the protocols would also avoid waste of government funds (which is an imperative for all Agency managers) by not having employees and contractors in different EPA offices performing substantially similar reviews on the same references. Finally, it would prevent divergent conclusions from being reached by different parts of the Agency within a very limited timeframe, supporting the vision of "One EPA."

The process of harmonizing the TSCA Systematic Review Protocol with the *IRIS Systematic Review Handbook* was a collaborative effort between OPPT and ORD. The OPPT team developed an IRIS/TSCA crosswalk that mapped corresponding IRIS and TSCA data quality evaluation domains. The IRIS data quality evaluation tool has fewer metrics compared to the old TSCA tool – an IRIS domain consisting of one metric might have a corresponding domain on the old TSCA form that consisted of several metrics; hence, multiple old TSCA metrics were mapped into a smaller number of IRIS metrics (many-to-one). Systematic review practitioners in both offices reviewed the mapping and confirmed that the data quality considerations on the old TSCA form were captured in the IRIS form. Therefore, harmonized TSCA forms were developed based on the mapping of IRIS metrics to TSCA domains.

Once general agreement was reached, a small number of references were used for calibration of the new forms to ensure (1) that the results were concordant between OPPT and IRIS, and (2) that the results were concordant between the old TSCA data quality evaluation form and the harmonized data quality evaluation form. Once both the systematic review project managers and the teams of practitioner/ evaluators were satisfied, the harmonized TSCA forms were finalized and put into use. Further details on the forms are described in the discipline-specific sections below (see Section 5.5.2.1 for details on the

data evaluation forms for epidemiology studies and Section 5.5.2.2 for details on the data evaluation forms for animal toxicity studies used in assessing human health hazard).

5.5.2.1 Epidemiology Studies

As described above in Section 4.6.1.1, 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. An update to the 2021 Draft Systematic Review Protocol is that the criteria for extracting data were refined. The criteria for extracting data from 1,3-butadiene epidemiology studies identified by the literature search were that the reference met PECO screening criteria and further filtering criteria, and had an overall quality determination of High, Medium, or Low, and found statistically significant associations between 1,3-butadiene and an adverse health outcome. For additional data sources relevant for the risk evaluation that were received through public comments and/or recommended by SACC, the criteria for data extraction were that the reference met PECO screening criteria and further filtering criteria, and had an overall quality determination of High, Medium, or Low, found statistically significant associations, and was used for dose-response assessment in the risk evaluation. However, all studies were included in the evidence integration and considered for their contribution to the weight of scientific evidence in the human health hazard assessment.

Epidemiology references that met the further filtering criteria were evaluated using the OPPT data quality evaluation form, which was modified to be more consistent with the IRIS data quality evaluation form, as described above. This modified form is referred to as the harmonized TSCA epidemiology data quality evaluation form.

The old TSCA epidemiology data quality evaluation form used for other chemicals included 6 data quality evaluation domains, each of which included 3 or more metrics, such that the entire form included consideration of 22 different metrics. The harmonized TSCA epidemiology data quality evaluation form used for 1,3-butadiene includes the first five domains from the old TSCA data quality evaluation form, but the metrics are collapsed and streamlined with each domain having just one or two metrics. The harmonized TSCA data quality evaluation form does not include the Biomarker domain from the old TSCA data quality evaluation form because biomarker considerations are now included in other domains. In particular, biomarkers of exposure are evaluated in Metric 2A of the Exposure Characterization Domain, biomarkers of effect are evaluated in Metric 3A of the Outcome Assessment Domain, and analytical components of biomarker assessments are evaluated in Metric 5A of the Analysis Domain. The evaluator assesses predefined criteria on the form to rate each metric as High, Medium, Low, or Critically Deficient for the reference.

The first step in developing the harmonized data quality evaluation form was an IRIS-TSCA crosswalk that compared IRIS and TSCA domains, metrics, and criteria. Table 5-4 below summarizes the correspondence between IRIS and TSCA data quality evaluation domains. A more detailed crosswalk and discussion with experts from the ORD IRIS program indicated that all of the criteria that were assessed on the old TSCA form corresponded with components of the criteria assessed on the IRIS data quality evaluation form. Therefore, data quality evaluation criteria from the IRIS Handbook were used on the harmonized TSCA forms. These criteria were further modified based on calibration discussions. The data quality evaluation instructions, domains, metrics, and criteria for the harmonized TSCA Epidemiology Data Quality Evaluation form are presented below in Table 5-5.

The assessment of each of the metrics contributes to an OQD of High, Medium, Low, or Uninformative for the reference. Some references contain multiple health outcomes; therefore, a given reference may have multiple data quality evaluation forms and respective OQDs.

In addition to these updates to the data quality evaluation form, the data extraction form for epidemiology studies was updated to add additional relevant data. Additional fields were added to the extraction form, as can be seen in the extraction table in the supplemental file *Data Extraction Information for Human Health Hazard Animal Toxicology and Epidemiology for 1,3-Butadiene, Systematic Review Support Document for the Risk Evaluation*.

Table 5-4. Summary of Crosswalk of IRIS Domains, TSCA Domains, Old TSCA Form Metrics, and Harmonized TSCA Form Metrics for Epidemiology Studies

IRIS Domain (1 Metric per Domain)	TSCA Domain	Old TSCA Form Metrics	Harmonized TSCA Form Domains and Metrics
Participant Selection	1. Study Participation	1, 2, 3	Domain 1, Metric 1A
Exposure Measurement	2. Exposure Characterization	4, 5, 6	Domain 2, Metric 2A
Outcome Ascertainment	3. Outcome Assessment	7. Outcome Measurement or Characterization	Domain 3, Metric 3A
Confounding	4. Potential Confounding / Variability Control	9, 10, 11	Domain 4, Metric 4A
Analysis	5. Analysis	12, 14, 15	Domain 5, Metric 5A
Selective Reporting	3. Outcome Assessment	8. Reporting Bias	Domain 3, Metric 3B
Sensitivity	5. Analysis	13. Statistical Power	Domain 5, Metric 5B
Part of Other Domains	6. Biomarkers	16, 17, 18, 19, 20, 21, 22	Part of Domains 2, 3, and 5

Table 5-5. Harmonized TSCA Epidemiology Data Quality Evaluation Form

Data Quality Rating	Description
Domain 1. Study participation (Combines/Collapses old TSCA Metrics 1, 2, and 3 into one metric - Metric 1A)	
Metric 1A. Participant Selection (Combines Old TSCA Form Metrics 1, 2, and 3)	
High	*Mark as high/good if:* *For all study types:* - There is minimal concern for selection bias based on description of recruitment process (*e.g.*, selection of comparison population, population-based random sample selection, recruitment from sampling frame including current and previous employees). - Exclusion and inclusion criteria for participants specified and would not induce bias. - Participation rate is reported at all steps of study (*e.g.*, initial enrollment, follow-up, selection into analysis sample). If rate is not high, there is appropriate rationale for why it is unlikely to be related to exposure (*e.g.*, comparison between participants and nonparticipants or other available information indicates differential selection is not likely).
Medium	*Mark as medium/adequate if:* - Enough of a description of the recruitment process to be comfortable that there is no serious risk of bias. - Inclusion and exclusion criteria for participants specified and would not induce bias. - Participation rate is incompletely reported but available information indicates participation is unlikely to be related to exposure.
Low	*Mark as low/deficient if:* - Little information on recruitment process, selection strategy, sampling framework and/or participation OR aspects of these processes raises the potential for bias (*e.g.*, healthy worker effect, survivor bias).
Critically Deficient	*Mark as uninformative/critically deficient if:* - Aspects of the processes for recruitment, selection strategy, sampling framework, or participation result in concern that selection bias is likely to have had a large impact on effect estimates (*e.g.*, convenience sample with no information about recruitment and selection, cases and controls are recruited from different sources with different likelihood of exposure, recruitment materials stated outcome of interest and potential participants are aware of or are concerned about specific exposures).
Not Rated/Not Applicable	*Mark as N/A if:* - 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.*
Domain 2. Exposure characterization (Combines/Collapses old TSCA metrics 4, 5, and 6 into one metric – Metric 2A)	
Metric 2A. Exposure Measurement (Combines Old TSCA Form Metrics 4, 5, and 6)	
High	*Mark as high/good if:* - Valid exposure assessment methods were used, which represent the etiologically relevant time period of interest. - Exposure misclassification is expected to be minimal.

Data Quality Rating	Description
Medium	*Mark as medium/adequate if:* - Valid exposure assessment methods were used, which represent the etiologically relevant time period of interest. - Exposure misclassification may exist but is not expected to greatly change the effect estimate.
Low	*Mark as low/deficient if:* - Valid exposure assessment methods were used, which represent the etiologically relevant time period of interest. Specific knowledge about the exposure and outcome raise concerns about reverse causality, but there is uncertainty whether it is influencing the effect estimate. - Exposed groups are expected to contain a notable proportion of unexposed or minimally exposed individuals, the method did not capture important temporal or spatial variation, or there is other evidence of exposure misclassification that would be expected to notably change the effect estimate.
Critically Deficient	*Mark as uninformative/critically deficient if:* - Exposure measurement does not characterize the etiologically relevant time period of exposure or is not valid. - There is evidence that reverse causality is very likely to account for the observed association. - Exposure measurement was not independent of outcome status.
Not Rated/Not Applicable	*Mark as N/A if:* - 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.*
Domain 3. Outcome assessment (Includes corresponding IRIS metrics for old TSCA Metrics 7 and 8 – Metrics 3A and 3B, respectively)	
Metric 3A. Outcome Ascertainment (Corresponds to Old TSCA Form Metric 7. Outcome Measurement or Characterization)	
High	*Mark as high/good if:* - High certainty in the outcome definition (*i.e.*, specificity and sensitivity), minimal concerns with respect to misclassification. - Assessment instrument was validated in a population comparable to the one from which the study group was selected.
Medium	*Mark as medium/adequate if:* - Moderate confidence that outcome definition was specific and sensitive, some uncertainty with respect to misclassification but not expected to greatly change the effect estimate. - Assessment instrument was validated but not necessarily in a population comparable to the study group.
Low	*Mark as low/deficient if:* - Outcome definition was not specific or sensitive. - Uncertainty regarding validity of assessment instrument.
Critically Deficient	*Mark as uninformative/critically deficient if:* - Invalid/insensitive marker of outcome. - Outcome ascertainment is very likely to be affected by knowledge of, or presence of, exposure. Note: Lack of blinding should not be automatically construed to be critically deficient.

Data Quality Rating	Description
Not rated/Not Applicable	*Mark as N/A if:* - 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.*
Metric 3B. Selective Reporting (Corresponds to Old TSCA Form Metric 8. Reporting Bias) Note: It is currently rare that a study would cite a registered methods paper. Because we often can't know whether there is selective reporting, consistent with IRIS, this metric will often be rated as Medium/Adequate rather than Good/High. Ensure that the study's OQD is not getting downgraded from High to Medium solely because of the Selective Reporting Metric. But the metric itself will often be rated as Medium/Adequate.	
High	*Mark as high/good if:* - The results reported by study authors are consistent with the primary and secondary analyses described in a registered protocol or methods paper.
Medium	*Mark as medium/adequate if:* - The authors described their primary (and secondary) analyses in the methods section and results were reported for all primary analyses.
Low	*Mark as low/deficient if:* - Concerns were raised based on previous publications, a methods paper, or a registered protocol indicating that analyses were planned or conducted that were not reported, or that hypotheses originally considered to be secondary were represented as primary in the reviewed paper. - Only subgroup analyses were reported suggesting that results for the entire group were omitted. - Only statistically significant results were reported.
Critically Deficient	*Mark as uninformative/critically deficient if:* - Do not select for this metric
Not Rated/Not Applicable	*Mark as N/A if:* - 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.*
Domain 4. Potential confounding/Variable control Potential Confounding / Variability Control (Combines/Collapses old TSCA metrics 9,10, and 11 into one metric – Metric 4A)	
Metric 4A. Potential Confounding (Combines Old TSCA Form metrics 9,10, and 11)	

Data Quality Rating	Description
High	*Mark as high/good if:* - Conveys strategy for identifying key confounders. This may include a priori biological considerations, published literature, causal diagrams, or statistical analyses; with recognition that not all "risk factors" are confounders. - Inclusion of potential confounders in statistical models not based solely on statistical significance criteria (*e.g.*, $p < 0.05$ from stepwise regression). - Does not include variables in the models that are likely to be influential colliders or intermediates on the causal pathway. - Key confounders are evaluated appropriately and considered to be unlikely sources of substantial confounding. This often will include: Presenting the distribution of potential confounders by levels of the exposure of interest and/or the outcomes of interest (with amount of missing data noted); Consideration that potential confounders were rare among the study population, or were expected to be poorly correlated with exposure of interest; Consideration of the most relevant functional forms of potential confounders; Examination of the potential impact of measurement error or missing data on confounder adjustment; Presenting a progression of model results with adjustments for different potential confounders, if warranted.
Medium	*Mark as medium/adequate if:* - Similar to high/good but may not have included all key confounders, or less detail may be available on the evaluation of confounders (*e.g.*, sub-bullets in high/good). It is possible that residual confounding could explain part of the observed effect, but concern is minimal.
Low	*Mark as low/deficient if:* - Does not include variables in the models that are likely to be influential colliders or intermediates on the causal pathway. And any of the following: - The potential for bias to explain some of the results is high based on an inability to rule out residual confounding, such as a lack of demonstration that key confounders of the exposure-outcome relationships were considered; - Descriptive information on key confounders (*e.g.*, their relationship relative to the outcomes and exposure levels) are not presented; or - Strategy of evaluating confounding is unclear or is not recommended (*e.g.*, only based on statistical significance criteria or stepwise regression [forward or backward elimination]).
Critically Deficient	*Mark as uninformative/critically deficient if:* - Includes variables in the models that are colliders and/or intermediates in the causal pathway, indicating that substantial bias is likely from this adjustment; or - Confounding is likely present and not accounted for, indicating that all of the results were most likely due to bias.
Not Rated/Not Applicable	*Mark as N/A if:* - 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.*
Domain 5. Analysis (Combines/Collapses old TSCA Metrics 12, 14, and 15 into one metric and includes the corresponding IRIS metric for TSCA Metric 13 – Metrics 5A and 5B, respectively)	

Data Quality Rating	Description
Metric 5A. Analysis (Combines Old TSCA Form Metrics 12, 14, and 15: Study Design and Methods, Reproducibility of Analyses, and Statistical Models)	
High	*Mark as high/good if:* - Use of an optimal characterization of the outcome variable. - Quantitative results presented (effect estimates and confidence limits or variability in estimates; *i.e.*, not presented only as a p-value or "significant"/ "not significant"). - Descriptive information about outcome and exposure provided (where applicable). - Amount of missing data noted and addressed appropriately (discussion of selection issues—missing at random vs. differential). - Where applicable, for exposure, includes LOD (and percentage below the LOD), and decision to use log transformation. - Includes analyses that address robustness of findings, *e.g.*, examination of exposure-response (explicit consideration of nonlinear possibilities, quadratic, spline, or threshold/ceiling effects included, when feasible); relevant sensitivity analyses; effect modification examined based only on a priori rationale with sufficient numbers. - No deficiencies in analysis evident. Discussion of some details may be absent (*e.g.*, examination of outliers).
Medium	*Mark as medium/adequate if:* Same as high/good except: - Descriptive information about exposure provided (where applicable) but may be incomplete; might not have discussed missing data, cut-points, or shape of distribution. - Includes analyses that address robustness of findings (examples in high/good), but some important analyses are not performed.
Low	*Mark as low/deficient if:* - Does not conduct analysis using optimal characterization of the outcome variable. - Descriptive information about exposure levels not provided (where applicable). - Effect estimate and p-value presented, without standard error or confidence interval. - Results presented as statistically "significant"/"not significant." - Sufficient details on test or model assumptions were not provided and there is some indication that the test or model might have been inappropriate.
Critically Deficient	*Mark as uninformative/critically deficient if:* - Results of analyses of effect modification examined without clear a priori rationale and without providing main/principal effects (*e.g.*, presentation only of statistically significant interactions that were not hypothesis driven). - Analysis methods are not appropriate for design or data of the study.
Not Rated/Not Applicable	*Mark as N/A if:* - 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.*
Metric 5B. Sensitivity (Corresponds to Old TSCA Form Metric 13. Statistical Power)	
High	*Mark as high/good if:* - Study sensitivity was high due to sufficient exposure contrast, large sample size and examination of a relevant and sensitive population and minimal bias related to sensitivity in other domains.

Data Quality Rating	Description
Medium	*Mark as medium/adequate if:* - The range of exposure levels provides adequate variability to evaluate primary hypotheses in study. - The population was exposed to levels expected to have an impact on response. - The study population was sensitive to the development of the outcomes of interest (*e.g.*, ages, lifestage, sex). - The timing of outcome ascertainment was appropriate given expected latency for outcome development (*i.e.*, adequate follow-up interval). - The study was adequately powered to observe an effect, with a moderate sample size. - No other concerns raised regarding study sensitivity.
Low	*Mark as low/deficient if:* - Study sensitivity was deficient due to insufficient exposure contrast and/or small sample size in a non-sensitive or non-relevant population
Critically Deficient	*Mark as uninformative/critically deficient if:* - There is a lack of critical information needed to inform the ability of the study to detect an effect if it exists, [and/or] there is indication that the study was unlikely to be able to do so.
Not Rated/Not Applicable	*Mark as N/A if:* - 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*
Overall Quality Determination (OQD)	
Additional Comments	Additional comments:
Based on your professional judgement, would you upgrade or downgrade this study's OQD?	*Select one of the following:* Yes, I would upgrade the paper Briefly describe why you decided to upgrade this study: Yes, I would downgrade the paper Briefly describe why you decided to downgrade this study: Neither – Keep quality rating as is
Specify which OQD you would give this paper (either confirm the auto calculated judgement OR suggest a new one based on your professional judgement?	High Medium Low Uninformative

5.5.2.2 Animal Toxicity Studies

Data quality evaluation of human health animal toxicity studies was conducted using the harmonized data quality evaluation form. The impetus for development of this form was to harmonize the data evaluation form from the existing TSCA Systematic Review Protocol with that from the IRIS Systematic Review Handbook. Table 5-6 describes the 6 domains and lists the number of metrics in

each domain included in the harmonized TSCA form. Since there are fewer domains in the IRIS Systematic Review Handbook than the TSCA Systematic Review Protocol, there was a many-to-one mapping from the old TSCA data quality evaluation form to the harmonized TSCA data quality evaluation form as illustrated in the far-right column in Table 5-7. The far-right column depicts the individual metrics from the old TSCA data quality evaluation form that were mapped to the harmonized TSCA data quality evaluation form. Moreover, Table 5-6 defines the domains in the harmonized TSCA data quality evaluation form and describes how the old TSCA evaluation form metrics align with this new language. Detailed descriptions of each old TSCA form metrics in Table 5-6 can be found in Appendix Q of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021).

The harmonized TSCA data quality evaluation form is described in Table 5-7 below. This form is applicable to the data quality evaluation of animal toxicity studies beyond 1,3-butadiene and thus will also be used in the systematic review of studies reporting exposure to other TSCA High Priority Substances.

With the impetus of preserving historic context and educating evaluators, explanatory text summarizing the origin of the harmonized forms and how the old TSCA metrics map to the harmonized TSCA domains in data evaluation forms can be found in the header row of Table 5-7. Extensive calibration sessions were completed to ensure the team of contractors and EPA staff were trained and confident that the two forms (*i.e.*, old TSCA form and harmonized TSCA form) produced equivalent results. Finally, all metrics in the data quality evaluation form include a comment box for reviewers to catalogue reference details not otherwise captured in the metric text, reading: "Reviewer comments: Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance."

Table 5-6. Summary of Harmonized TSCA Domains and Domain Definitions, Harmonized TSCA Form Metrics, and Old TSCA Form Metrics for Human Health Animal Toxicity Studies

Harmonized TSCA Form Domains	Harmonized TSCA Form Domain Definition	Harmonized TSCA Form Metrics	Old TSCA Form Metrics
Domain 1. Reporting quality	Domain 1 evaluates the reporting of details in the study. It uses two main categories of information: (1) critical, and (2) important. Critical information is considered essential and without it, the quality of the study may not be sufficiently evaluated. Important information is not required for evaluation, but it supports the critical information.	Single metric	Metrics 13, 14, and 15
Domain 2. Selection and performance	Domain 2 evaluates the risk of bias using metrics that assess allocation methods and observational bias. The randomization of the study design ensures that the effect observed is due to the exposure. Bias in observational measurements may lead to questions about the validity and reliability about the results of an experiment.	Metrics 2.1 and 2.2	Metrics 6 and 19

Harmonized TSCA Form Domains	Harmonized TSCA Form Domain Definition	Harmonized TSCA Form Metrics	Old TSCA Form Metrics
Domain 3. Confounding/variable control	Domain 3 evaluates the use of appropriate controls and/or comparators to discern the relationship between exposure to the test substance and the outcome(s)/endpoint(s) of interest. The use of controls and comparator and accounting for confounding variables minimizes bias so that the effect can be specifically attributed to the exposure.	Single metric	Metrics 4 and 5, 20, and 21
Domain 4. Selective reporting and attrition	Domain 4 evaluates the risk of bias due to selective reporting and attrition. The study should report intended sample sizes for all outcome(s)/endpoint(s) of interest, and discrepancies between the number of animals used to generate data points should also be adequately addressed. Attrition of animals during the experiment should be explained and transparent.	Single metric	Metric 22
Domain 5. Exposure methods sensitivity	Domain 5 evaluates the chemical administration and characterization. The information reported on the test substance should verify that exposure is in fact to the substance of interest, and the route and method of administration should be appropriate for the measured outcome(s)/endpoint(s) of interest. The timing, frequency, and duration of exposure should be suitable for all outcome(s)/endpoint(s) of interest.	Metrics 5.1 and 5.2	Metrics 1, 2, 3, 7, 8, 9, 10, and 12
Domain 6. Outcome measures and results display	Domain 6 evaluates the sensitivity of the experiments that are used to characterize or measure the specific endpoint(s)/outcome(s) of interest. The methods used should reliably and reproducibly detect a response due to exposure for the specific endpoint(s)/outcome(s) of interest. The analysis and presentation of the results should be interpretable and transparent for the specific endpoint(s)/outcome(s) of interest.	Metrics 6.1 and 6.2	Metrics 11, 16, 17, 18, 23, and 24

Table 5-7. Harmonized TSCA Data Quality Evaluation Form for Human Health Animal Toxicity Studies

Data Quality Rating	Description
Domain 1. Reporting Quality (Combines Old TSCA Form Metrics 13, 14, and 15 from the Test Animals Domain)	
Does the study report information for evaluating the design and conduct of the study for the endpoint(s)/outcome(s) of interest? This Domain uses two main categories of information: 1) critical, and 2) important. Critical information necessary to perform study evaluation: Test animals' species, test article identity (*i.e.*, CASRN, chemical name, and/or structure), dose/concentration levels and duration of exposure, route (*e.g.*, oral; inhalation), qualitative or quantitative results for at least one endpoint of interest Important information for evaluating the study methods: Test animal characteristics: source (*e.g.*, commercial source or laboratory-maintained colony), strain, age and/or life stage, sex, starting body weight, and/or parity (whether the test animals have been previously pregnant). For example, reporting animals to be 'mature' prior to starting the study leaves uncertainty and potential impact to results and may not be considered high quality. General animal husbandry conditions and procedures: temperature, humidity, light/dark cycle, diet, water availability, number of animals per cage throughout the study Exposure methods: test substance source, purity (or grade), method of administration Experimental design: frequency of exposure (*e.g.*, hours/day, days/week), number of animals per study group, animal age and life stage during exposure and at endpoint/outcome evaluation, as applicable to the study purpose/objective Endpoint evaluation methods: assays or procedures used to measure the endpoints/outcomes of interest. The presence or absence of all critical information determines whether a ranking is acceptable, or not. If/when critical information is missing, this Domain receives an uninformative ranking. The confidence level of acceptable, *e.g.*, high, medium, or low, corresponds to the amount of important information provided, in addition to the critical information. The confidence ranking for acceptable information should be justified and the assessor should identify which important information was provided in the study to support the assigned ranking. Note: This domain is limited to reporting. Other aspects (*i.e.*, appropriateness) of the exposure methods, experimental design, and endpoint evaluation methods are evaluated using the domains related to risk of bias and study sensitivity. The considerations below typically do not need to be refined by assessment teams, although in some instances the important information may be refined depending on the endpoints/outcomes of interest or the chemical under investigation. As for any study quality domain/metric, assessor judgment and rationale for ranking this domain should be given for the study and in the form of comments. Typically, a ranking given for this domain will not change across endpoints/outcomes investigated by the study. In the rationale, reviewers should indicate whether the study adhered to GLP, OECD, or other testing guidelines.	
High	*Mark as high/good if*: All critical and important information is reported or for the endpoints/outcomes of interest. The information could also be inferred from a reference document (*e.g.*, cited paper, manufacturer's website, guideline).
Medium	*Mark as medium/adequate if*: All critical information is reported but some combination important information is missing. However, the missing information is not expected to significantly impact the study evaluation.
Low	*Mark as low/deficient if*: All critical information is reported but important information is missing that is expected to significantly reduce the ability to evaluate the study.

Data Quality Rating	Description
Critically Deficient	*Mark as critically deficient if*: Study report is missing any pieces of critical information.
Not Rated/Not Applicable	*Mark as N/A if*: 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]*
Domain 2. Selection and Performance (Corresponds to Old TSCA Form Metrics 6 and 9)	
Metric 2.1. Allocation Were animals assigned to experimental groups using a method that minimizes selection bias? The considerations below typically do not need to be refined by assessment teams. A judgment and rationale for this domain should be given for each cohort or experiment in the study. Did each animal or litter have an equal/random chance of being assigned to any experimental group (*i.e.*, random allocation)? Is the allocation method described? Aside from randomization, were any steps taken to balance variables and/or pre-study test animal characteristics or other modifying factors across experimental groups during allocation? What is the expected and extent of the impact on study results if there is failure to randomize and/or normalize animal allocation? Is it significant or negligible?	
High	*Mark as high/good if*: Experimental groups were randomized, and any specific randomization procedure was described or inferable from a reference document (*e.g.*, cited paper, manufacturer's website, guideline). (*e.g.*, computer-generated scheme). Normalization of body weight to make sure average body weight is similar across doses if combined with a randomization scheme can be rated as *High*.
Medium	*Mark as medium/adequate if*: Authors report that groups were randomized but do not describe the specific procedure used (*e.g.*, "animals were randomized"). Alternatively, authors used a nonrandom method to control for important modifying factors across experimental groups (*e.g.*, body-weight normalization without use of randomization).
Low	*Mark as low/deficient if*: No indication of randomization of groups or other methods (*e.g.*, normalization) to control for important modifying factors across experimental groups.
Critically Deficient	*Mark as critically deficient if*: Bias in the animal allocations was explicitly reported or inferable from a reference document.
Not Rated/Not Applicable	*Mark as N/A if*: 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]*

Data Quality Rating	Description
Metric 2.2. Observational bias/Blinding Did the study implement measures to reduce observational bias? The considerations below typically do not need to be refined by the assessment teams. It is recommended that project assessors collectively build consensus to identify highly subjective measures of endpoints/outcomes where observational bias may strongly influence results prior to performing evaluations. A judgment and rationale for this domain should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study. Does the study report blinding or other methods/procedures for reducing observational bias? This can apply to endpoints/outcomes that require heavy research practitioner handling or awareness of treatment/exposure groups during outcome assessment that may significantly impact study results. If not, did the study describe a design or approach for quality control of observational bias, for which such procedures can be inferred from a reference cited in the document? What is the expected and extent of the impact on study results of failure to implement (or report implementation) of these methods/procedures? Is it significant or negligible?	
High	*Mark as high/good if*: Measures to reduce observational bias were described (*e.g.*, blinding to conceal treatment groups during endpoint evaluation; consensus-based evaluations of histopathology-lesions).
Medium	*Mark as medium/adequate if*: Methods for reducing observational bias (*e.g.*, blinding) can be inferred from a cited reference (*e.g.*, cited paper or guideline) or were reported but were described incompletely. OR Measures to reduce observational bias were not described AND the potential concern for bias was mitigated because the outcomes were not subjective and/or based on use of automated/computer-driven systems, standard laboratory kits, simple objective measures (*e.g.*, body or tissue weight), or screening-level evaluations of histopathology.
Low	*Mark as low/deficient if*: Measures to reduce observational bias were not described AND the potential impact on the results is significant (*e.g.*, outcome measures are subjective).
Critically Deficient	*Mark as critically deficient if*: Strong evidence for observational bias that impacted the results.
Not Rated/Not Applicable	*Mark as N/A if*: 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]*
Domain 3. Confounding/Variable Control (Combines TSCA Metrics 4 and 5 from the Test Design Domain, Metric 20, and Metric 21 from the Confounding/Variable Control Domain)	

Data Quality Rating	Description
Are variables with the potential to confound or modify results controlled for and consistent across all experimental groups? The considerations below may need to be refined by assessment teams, as the specific variables of concern can vary by experiment or chemical. A judgment and rationale for this domain should be given for each cohort or experiment in the study, noting when the potential for confounding is restricted to specific endpoints/outcomes. Are there differences across the study groups (*e.g.*, co-exposures, vehicle, diet, palatability, husbandry) that could bias the results or introduce an unaccounted for or confounding variable? What is the expected extent of the impact on study results if confounding variables are identified? Is it significant or negligible?	
High	*Mark as high/good if*: Outside of the exposure of interest, variables that are likely to confound or modify results appear to be controlled for and consistent across experimental groups.
Medium	*Mark as medium/adequate if*: Some concern that variables that were likely to confound or modify results were uncontrolled or inconsistent across groups but are expected to have a minimal impact on the results.
Low	*Mark as low/deficient if*: Notable concern that potentially confounding variables were uncontrolled or inconsistent across groups and are expected to substantially impact the results.
Critically Deficient	*Mark as critically deficient if*: One or more confounding variables is known or presumed to be uncontrolled or inconsistent across groups and is expected to be a primary driver of the results and/or to distort the relationship between the exposure and outcome(s) of interest.
Not Rated/Not Applicable	*Mark as N/A if*: 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]*
Domain 4. Selective Reporting and Attrition (Combines TSCA Metric 22 from the Confounding/Variable Control Domain)	
Did the study report results for all prespecified outcomes and tested animals? Note: This domain does not consider the appropriateness of the analysis/results presentation. This aspect of study quality is evaluated in another domain. The considerations below typically do not need to be refined by assessment teams. A judgment and rationale for this domain should be given for each cohort or experiment in the study. Selective reporting bias: Are all results presented for endpoints/outcomes described in the methods? Attrition bias: Are all animals accounted for in the results? If there are discrepancies, do the authors provide an explanation (*e.g.*, death or unscheduled sacrifice during the study)? If unexplained results omissions and/or attrition are identified, what is the expected impact on the interpretation of the results?	

Data Quality Rating	Description
High	*Mark as high/good if*: Quantitative or qualitative results were reported for all prespecified outcomes (explicitly stated or inferred from a cited reference, such as a guideline or methodology peer-reviewed paper), exposure groups and evaluation time points. Data not reported in the primary article are available from supplemental material. If results omissions or animal attrition are identified, the authors provide an explanation, and these are not expected to impact the interpretation of the results.
Medium	*Mark as medium/adequate if*: Quantitative or qualitative results were reported for most prespecified outcomes (explicitly stated or inferred from a cited reference, such as a guideline or methodology peer-reviewed paper), exposure groups and evaluation time points. Omissions and/or attrition are not explained but are not expected to significantly impact the interpretation of the results.
Low	*Mark as low/deficient if*: Quantitative or qualitative results are missing for two or more prespecified endpoints (explicitly stated or inferred from a cited reference, such as a guideline or peer-reviewed methodology paper), exposure groups, and evaluation time points and/or there is high animal attrition; omissions and/or attrition are not explained and may significantly impact the interpretation of the results.
Critically Deficient	*Mark as critically deficient if*: Extensive results omission and/or animal attrition are identified and prevents comparisons of results across treatment groups.
Not Rated/Not Applicable	*Mark as N/A if*: 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]*
Domain 5. Exposure Methods Sensitivity (Combines TSCA Metrics from the Test Substance and Exposure Characterization Domains (Metrics 1,2,3,7,8,9,10, and 12))	

Data Quality Rating	Description
Metric 5.1. Chemical administration and characterization Did the study adequately characterize exposure to the chemical of interest and the exposure administration methods? Was the route and method of exposure appropriate? Note: Relevance and utility of the routes of exposure are considered in the PECO criteria for study inclusion and during evidence synthesis. It is essential that the considerations below are considered, and potentially refined, by assessment teams, as the specific variables of concern can vary by chemical (*e.g.*, stability may be an issue for one chemical but not another). A judgment and rationale for this domain should be given for each cohort or experiment in the study. Are there concerns [specific to this chemical] regarding the source and purity and/or composition (*e.g.*, identity and percent distribution of different isomers) of the chemical? If so, can the purity and/or composition be obtained from the supplier (*e.g.*, as reported on the website)? Was independent analytical verification of the test article purity and composition performed? Did the authors take steps to ensure the reported exposure levels were accurate (*e.g.*, reporting by the authors of calculated doses in feeding/drinking water studies or sufficient information to independently calculate doses from concentrations in feed or water)? Are there concerns about the methods used to administer the chemical (*e.g.*, inhalation chamber type, gavage volume) or methods of test substance preparation or storage? For inhalation studies: Were target concentrations confirmed using reliable analytical measurements in chamber air? For oral studies: If necessary, based on consideration of chemical specific-knowledge (*e.g.*, instability in solution; volatility) and/or exposure design (*e.g.*, the frequency and duration of exposure), were chemical concentrations in the dosing solutions or diet/drinking water analytically confirmed? ** *If methods were cited to another publication, review the relevant methods in the original publication and consider this information as you rank this metric. Methods papers will be linked in HERO to the publication being evaluated.*	
High	*Mark as high/good if*: Chemical administration and characterization are complete (*i.e.*, test substance source and purity are appropriate, and analytic verification of the test article are provided). There are no concerns about the composition, stability, or purity of the administered chemical, or the specific methods of administration. For inhalation studies, chemical concentrations in the exposure chambers are verified using reliable analytical methods.
Medium	*Mark as medium/adequate if*: Some uncertainties in the chemical administration and characterization are identified but these are expected to have minimal impact on interpretation of the results (*e.g.*, source and vendor-reported purity are presented, but not independently verified; purity of the test article is suboptimal but not concerning; for inhalation studies with gases, actual exposure concentrations are missing or verified with less reliable methods; for oral and dermal studies, there are minor uncertainties about precision of dose levels or exposure concentrations).
Low	*Mark as low/deficient if*: Uncertainties in the exposure characterization are identified and are expected to substantially impact the results (*e.g.*, source of the test article was not reported; levels of impurities are substantial or concerning; deficient administration methods, such as use of static inhalation chambers or a gavage volume considered too large for the species and/or lifestage at exposure; for inhalation studies with aerosols or vapors, actual exposure concentrations are missing or verified with less reliable methods; for oral and dermal studies, there is substantial ambiguity about precision of dose levels or exposure concentrations).

Data Quality Rating	Description
Critically Deficient	*Mark as critically deficient if*: Uncertainties in the exposure characterization are identified and there is reasonable certainty that the results are largely attributable to factors other than exposure to the chemical of interest (*e.g.*, identified impurities are expected to be a primary driver of the results).
Not Rated/Not Applicable	*Mark as N/A if*: 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]*
Metric 5.2. Exposure timing, frequency, and duration Was the timing, frequency, and duration of exposure sensitive for the endpoint(s)/outcome(s) of interest? Considerations for this domain are highly variable depending on the endpoint(s)/outcome(s) of interest and must be refined by assessment teams. A judgment and rationale for this domain should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study. Does the exposure period include the critical window of sensitivity (*e.g.*, to detect developmental effects of interest)? Was the duration and frequency of exposure sensitive for detecting the endpoint of interest?	
High	*Mark as high/good if*: The timing, duration, and frequency of the exposure was sensitive, and the exposure included the critical window of sensitivity (if known).
Medium	*Mark as medium/adequate if*: The duration and frequency of the exposure was sensitive, and the exposure covered most of the critical window of sensitivity (if known).
Low	*Mark as low/deficient if*: The timing, duration, and frequency of the exposure is not sensitive or did not include most of the critical window of sensitivity (if known). These limitations are expected to bias the results towards the null.
Critically Deficient	*Mark as critically deficient if*: The exposure design is inappropriate for evaluating the outcome(s) of interest and is expected to strongly bias the results towards the null. The rationale should indicate the specific concern(s).
Not Rated/Not Applicable	*Mark as N/A if*: 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]*
Domain 6. Outcome Measures and Results Display (Combines TSCA Metrics from the Outcome Assessment and Data Presentation and Analysis Domains, and Metric 23 from the Data Presentation and Analysis Domain) (Metrics 11, 16, 17, 18, 23, and 24)	

Data Quality Rating	Description
Metric 6.1. Are the procedures sensitive and specific for evaluating the endpoint(s)/outcome(s) of interest? Considerations for this domain are highly variable depending on the endpoint(s)/outcome(s) of interest and must be refined by assessment teams. A judgment and rationale for this domain should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study. Are there concerns regarding the sensitivity, specificity, and/or validity of the protocols? Is the species appropriate? Are there serious concerns regarding the sample size? Are there concerns regarding the timing of the endpoint assessment? Examples of potential concerns include: Selection of protocols that are insensitive or nonspecific for the endpoint of interest Evaluations did not include all treatment groups (*e.g.*, only control and high dose) Use of unreliable methods to assess the outcome Assessment of endpoints at inappropriate or insensitive ages, or without addressing known endpoint variation (*e.g.*, due to circadian rhythms, estrous cyclicity) The study was conducted appropriately in relation to the evaluation domain, and any deficiencies, if present, are minor and would not be expected to influence the study results Decreased specificity or sensitivity of the response due to the timing of endpoint evaluation, as compared to exposure (*e.g.*, short acting depressant or irritant effects of chemicals; insensitivity due to prolonged period of non-exposure prior to testing) **** If methods were cited to another publication, review the relevant methods in the original publication and consider this information as you rank this metric. Methods papers will be linked in HERO to the publication being evaluated.*	
High	*Mark as high/good if*: The study was conducted appropriately in relation to the evaluation domain, and any deficiencies, if present, are minor and would not be expected to influence the study results.
Medium	*Mark as medium/adequate if*: There are methodological limitations relating to the evaluation domain, but that those limitations are not likely to be severe or have a notable impact on the results.
Low	*Mark as low/deficient if*: Biases or deficiencies were identified that are interpreted as likely to have had a notable impact on the results or that may prevent reliable interpretation of the study findings.
Critically Deficient	*Mark as critically deficient if*: The conduct of the study introduced a serious flaw that makes the observed effect(s) uninterpretable. Note: Sample size alone is not a reason to conclude an individual study is critically deficient.
Not Rated/Not Applicable	*Mark as N/A if*: 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]*

Data Quality Rating	Description
Metric 6.2. Results presentation Are the results presented in a way that makes the data usable and transparent? Considerations for this domain are highly variable depending on the outcomes of interest and must be refined by assessment teams. A judgment and rationale for this domain should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study. Does the level of detail allow for an informed interpretation of the results? Are the data analyzed, compared, or presented in a way that is inappropriate or misleading? Examples of potential concerns include: Nonpreferred presentation (*e.g.*, developmental toxicity data averaged across pups in a treatment group, when litter responses are more appropriate; presentation of absolute organ-weight data when relative weights are more appropriate) Failing to present quantitative results either in tables or figures Lack of full presentation of the data (*e.g.*, presentation of mean without variance data; concurrent control data are not presented)	
High	*Mark as high/good if*: There was a full quantitative presentation of results (*e.g.*, means and SE or SD for continuous data; incidence data for categorical data; or individual animal results were presented). Any omissions are minor and are not expected to impact the interpretation of the results.
Medium	*Mark as medium/adequate if*: Some details of the results are missing, but the missing information is not expected to have a notable impact on the interpretation of the results.
Low	*Mark as low/deficient if*: Data were analyzed, compared, or presented in a way that is inappropriate or misleading (*e.g.*, the authors report a treatment-related effect on a quantitative endpoint, but only qualitative results are provided).
Critically Deficient	*Mark as critically deficient if*: Deficiencies in results presentation make the observed effect(s) uninterpretable.
Not Rated/Not Applicable	*Mark as N/A if*: 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]*
Overall Quality Determination (OQD)	
Additional Comments	Additional Comments:
Based on your professional judgement, would you upgrade or downgrade this study's OQD?	*Select one of the following:* Yes, I would upgrade the paper Briefly describe why you decided to upgrade this study: Yes, I would downgrade the paper Briefly describe why you decided to downgrade this study: Neither – Keep quality rating as is

Data Quality Rating	Description
Specify which OQD you would give this paper (either confirm the auto calculated judgement OR suggest a new one based on your professional judgement?	High Medium Low Uninformative

For 1,3-butadiene, EPA additionally instituted a unique data extraction form as a pilot that was not utilized for other chemicals with 2019 scoping documents. In addition to the typical extraction form collecting a study summary and overall study lowest-observed-adverse-effect-level (LOAEL), EPA extracted dose information, sample size, and points of departure for every endpoint assessed in the reference. Additionally, EPA indicated whether the findings are definitively adverse, dose-responsive, and either measured or nominal (reviewers could indicate yes, no, or ambiguous). A free text box for comments was also included. This more detailed data extraction was used to better inform evidence integration and dose-response analysis. This detailed endpoint extraction was only performed on studies that did not score *uninformative for dose response.* These *uninformative* studies did receive an extraction of basic study-level summary data; however, endpoint extraction was not performed. The data evaluation and extraction results from 29 studies are presented in the following supplemental files: *Quality Evaluation Information for Human Health Hazard Animal Toxicology for 1,3-Butadiene* (U.S. EPA, 2025g) and the *Data Extraction Information for Human Health Hazard Animal Toxicology and Epidemiology for 1,3-Butadiene* (U.S. EPA, 2025b)

5.6 Dermal Absorption

EPA did not perform data evaluation or extraction for dermal absorption because dermal exposure was not considered a relevant exposure route for 1,3-butadiene.

6 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 taking into account 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).

6.1 Physical and Chemical Properties

The systematic review process identified multiple data for each of the physical and chemical properties analyzed in the risk evaluation. Relevant data types used for the physical and chemical assessment are discussed in Appendix K of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). When a specific datum is cited for a given physical and 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.

6.2 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).

6.3 Environmental Release and Occupational Exposure

To evaluate environmental releases and occupational exposures for the various COUs, EPA first mapped the COUs to broader occupational exposure scenario (OES) categories, as shown in the *Environmental Release and Occupational Exposure Assessment for 1,3-Butadiene* (U.S. EPA, 2025j). 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 facility-specific release data from programmatic databases (such as the TRI and NEI databases) and estimated the daily release by averaging the annual release over the expected release days per year. Releases from an OES were calculated by taking the 50th and 95th percentile of the relevant facilities' releases. In cases where an OES had no programmatic data, EPA used data from the systematic review literature, Emission Scenario Documents (ESDs), Generic Scenarios (GSs), and Specific Environmental Release Categories (SpERCs) to determine model input parameters for each OES. As described in the *Environmental Release and Occupational Exposure Assessment for 1,3-Butadiene* (U.S. EPA, 2025j), EPA ran Monte Carlo simulations with 100,000 iterations and the Latin Hypercube sampling method, using the statistical distribution for each input parameter to calculate a full distribution of the final release results for each modeled OES. EPA selected the 50th and 95th percentiles of the resulting distributions to represent central tendency and high-end releases,

respectively. To estimate the number of sites using 1,3-Butadiene within an OES, EPA relied on the Chemical Data Reporting (CDR) database as well as TRI and NEI. 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 and surrogate monitoring data. EPA developed worker activity information using industry information, GSs, ESDs, and systematic review literature, as described in the *Environmental Release and Occupational Exposure Assessment for 1,3-Butadiene* (U.S. EPA, 2025j). When sufficient monitoring data for an OES were available, EPA gave preference to monitoring data under 20 years old, as the Occupational Safety and Health Administration (OSHA) has not set a permissible exposure limit (PEL) for 1,3-butadiene. Dermal exposure data were not available for any of the OES considered in this assessment, however dermal exposure is not considered relevant for 1,3-butadiene.

EPA identified inhalation monitoring data for the manufacturing and PVC plastic converting OESs from industry submissions and published and peer-reviewed literature. EPA used this monitoring data as a surrogate for other OES with similar expected exposure conditions. Where available, EPA used literature data to estimate the number of exposure days. EPA relied on U.S. Census Bureau data and OES-assigned NAICS codes to estimate the number of workers and ONUs potentially exposed to 1,3-butadiene within each OES.

6.4 General Population, Consumer, and Environmental Exposure

1,3-Butadiene concentrations in ambient air, surface water, groundwater and drinking water were gathered and summarized within each environmental media pathway within the *Environmental Media Concentrations for 1,3-Butadiene* Technical Support Document (U.S. EPA, 2025i). 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 were found to contain polymers of 1,3-butadiene rather than the 1,3-butadiene monomer. The polymer form of 1,3-butadiene will not result in exposure to the monomer form thus no quantitative analyses were carried out for consumer exposure. General population and environmental exposures were evaluated for the inhalation pathway based on environmental release data. In summary, modeled environmental release estimates were used as inputs for the general population exposure modeling.

6.4.1 General Population and Environmental Exposure: Surface, Groundwater, and Drinking Water

Measured concentrations of 1,3-butadiene within published literature are summarized in the *Environmental Media Concentrations for 1,3-Butadiene* Technical Support Document (U.S. EPA, 2025i). Section 3 summarizes surface water concentrations, Section 4 summarizes drinking water concentrations, and Section 5 summarizes groundwater concentrations. No modeling was done for concentrations of 1,3-butadiene in water based on its low frequency of detection in water and the low release amounts to water. See details of this justification in the *Environmental Media Concentrations for 1,3-Butadiene* Technical Support Document (U.S. EPA, 2025i).

6.4.2 General Population and Environmental Exposure: Ambient Air

EPA evaluated general population and environmental exposures based on measured, monitored, and modeled concentrations of 1,3-butadiene in ambient air. Sections 2.1 and 2.2 of the *Environmental Media Concentrations for 1,3-Butadiene* (U.S. EPA, 2025i) summarizes measured concentrations in ambient air and other media (indoor air, landfill gas and personal inhalation, respectively, reported from

peer-reviewed studies from systematic review. Section 2.3 of the *Environmental Media Concentrations for 1,3-Butadiene* (U.S. EPA, 2025i) summarizes monitored concentrations reported and archived in EPA's AMTIC database and includes discussion on monitored concentrations from the Houston Regional Monitoring (HRM) and Shell Norco monitoring networks, which were presented by the SACC. In addition to measured and monitored data, EPA modeled ambient air concentrations based on facility releases reported to TRI and NEI data using IIOAC and HEM to assess general population exposure. A full description of input parameters is provided in Section 3.1 and the appendix of the *General Population Exposures for 1,3-Butadiene* (U.S. EPA, 2025l) for both IIOAC and HEM. Modeled ambient air concentrations were used to estimate inhalation exposure. Where available, EPA compared reported environmental monitoring or systematic review data with IIOAC and HEM modeled ambient air concentrations.

6.4.3 Consumer Exposure Assessment

EPA assessed consumer exposure to 1,3-butadiene for both users and bystanders, resulting from use of consumer products and articles. The major routes of exposure considered were via ingestion, inhalation, and dermal exposure. Consumer products containing 1,3-butadiene were identified through review and searches of a variety of sources, such as completed assessments, 2016 and 2020 Chemical Data Reporting (U.S. EPA, 2020a, 2016), in addition to chemical safety data sheets (SDSs) identified through product-specific internet searches. Chemical weight fractions were gathered from SDSs and completed assessments and used to tailor COU-specific consumer exposure scenarios for products and articles identified in the consumer market.

Altogether, EPA screened over 633 exposure studies with potential relevance to the 1,3-butadiene risk evaluation. Out of this total, three studies were of most relevance to the consumer exposure assessment and contained COU-specific data for the 1,3-butadiene. These seven studies had a various OQD assignment of high and medium (U.S. EPA, 2025f) per systematic review exposure evaluation metrics (U.S. EPA, 2021). Data from these five studies were extracted to inform the consumer inhalation, ingestion, and dermal assessment of 1,3-butadiene.

6.4.4 Other Data Sources

The exposure models relied heavily on the physical and chemical and fate properties as input parameters. Sections 5.1 and 5.2 describe how the physical and 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 and chemical and fate parameters are used as inputs for PSC modeling of surface water concentrations of 1,3-butadiene and as inputs for AERMOD modeling.

6.5 Human Health Hazard

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

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 6-1) to more clearly reflect how apical and mechanistic hazard

endpoints (as defined by the screening PECO statement) that result from either animal toxicology or epidemiology studies are binned to better consider the relevancy of the data for the risk evaluation.

Table 6-1. Querying the Evidence to Organize Integration for Human Health Hazard Data and Information

Evidence Stream	Questions
Studies of Exposed Humans Considered for Deriving Toxicity Values	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?

As discussed in Sections 4.6.1.2.2 and 4.6.1.3.3, information from all PECO-relevant human and animal toxicity studies were utilized for evidence integration. For studies that went through data evaluation and extraction, formal extraction results (see *Data Extraction Information for Human Health Hazard Animal Toxicology and Epidemiology for 1,3-Butadiene* (U.S. EPA, 2025b)) were referenced. For studies that did not pass further filtering, study-level extraction information from the further filtering form were used (see *Further Filtering Results for Human Health Hazard Animal Toxicology and Epidemiology for 1,3-Butadiene* (U.S. EPA, 2025k)). EPA did not perform formal data evaluation or extraction (including study-level extraction) of any supplemental data (*e.g.*, toxicokinetic or mechanistic studies). Therefore, mechanistic evidence relied primarily on EPA IRIS (U.S. EPA, 2002) and ATSDR (2012) supplemented by manual review of relevant individual peer-reviewed literature studies identified by hazard assessors. Evidence integration results are presented in Sections 4, 5, and 6 of the *Human Health Hazard Assessment for 1,3-Butadiene* (U.S. EPA, 2025m), with detailed evidence integration tables (Appendix A of that document) created for the organ systems with larger datasets.

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