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Office of Chemical Safety and
Pollution Prevention

Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances Version 1.0

A Generic TSCA Systematic Review Protocol with Chemical-Specific Methodologies

December 2021

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Docket

This document can be found in EPA docket number EPA-HQ-OPPT-2021-0414.

Disclaimer

Any mention of trade names or commercial products should not be interpreted as an endorsement by EPA.

ABBREVIATIONS AND ACRONYMS

ACGIH	American Conference of Governmental Industrial Hygienists
ADD	Average Daily Dose
ADME	Absorption, Distribution, Metabolism, and Elimination
AEGL	Acute Exposure Guideline Levels
AHRQ	Agency for Healthcare Research and Quality
AICIS	Australian Industrial Chemicals Introduction Scheme
AIHA	American Industrial Hygiene Association
AOP	Adverse Outcome Pathway
AP-42	Compilation of Air Pollutant Emissions Factors
AQS	Air Quality System
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	Area under the curve
BAF	Bioaccumulation factor
BBP	Butyl benzyl phthalate - 1,2-Benzene- dicarboxylic acid, 1- butyl 2(phenylmethyl) ester
BCF	Bioconcentration factor
BLS	U.S. Bureau of Labor Statistics
BMD	Benchmark dose
BMR	Benchmark response
BW	Body weight
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service Registry Number
CBI	Confidential Business Information
CCL	Contaminant Candidate List
CCOHS	Canadian Center for Occupational Health and Safety
CDC	Centers for Disease Control and Prevention
CDR	Chemical Data Reporting
CEC	Cation exchange capacity
CEM	Consumer Exposure Model
CFR	Code of Federal Regulations
CICAD	Concise International Chemical Assessment Documents
COC	Concentration of Concern
CONSEXPO	Consumer Exposure Model
COU	Conditions of Use
CPDAT	Chemicals and Products Database
CPSC	Consumer Product Safety Commission
CRC	Chemical Rubber Company
CRED	Criteria for Reporting and Evaluating Ecotoxicity Data
CV	Coefficient of Variation
D4	Octamethylcyclotetra- siloxane
DBP	Dibutyl phthalate (1,2-Benzene- dicarboxylic acid, 1,2- dibutyl ester)
DEHP	Di-ethylhexyl phthalate - (1,2-Benzene- dicarboxylic acid, 1,2- bis(2-ethylhexyl) ester)

DIBP	Di-isobutyl phthalate - (1,2-Benzene- dicarboxylic acid, 1,2- bis-(2-methylpropyl) ester)
DIDP	Diisodecyl phthalate
DINP	Diisononyl phthalate
DIY	Do it yourself
DO	Dissolved oxygen
DOI	Digital object identifier
EC	Effective concentration
ECx	Effect concentration at which x% effect is observed compared to the control group
EC_{50}	Half Maximal Effective Concentration
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
ECOTOX	Ecotoxicology Knowledgebase
E-FAST	Exposure and Fate Assessment Screening Tool
EINECS	European Inventory of Existing Commercial Substances
ELG	Effluent limit guideline
EPA	U.S. Environmental Protection Agency
EPI	Estimation programs interface
ESD	Emission Scenario Documents
EUSES	European Union System for the Evaluation of Substances
FDA	U.S. Food and Drug Administration
FTC	Federal Trade Commission
FYI	For your information
GC	Gas chromatography
GC-ECD	Gas chromatography-electron capture detector
GC-FID	Gas chromatography-flame ionization detector
GC-HRMS	Gas chromatography-high resolution mass spectrometry
GC-MS	Gas chromatography-mass spectrometry
GEAE	Generic ecological assessment endpoints
GLP	Good Laboratory Practice
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GSPC	Gold Standard Publication Checklist
HAP	Hazardous air pollutant
HAWC	Health Assessment Workplace Collaborative
HBCD	Hexabromocyclododecane
HEC	Human Equivalent Concentration
HED	Human Equivalent Dose
HERO	Health and Environmental Research Online (database)
HHCB	1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran
HHE	Health Hazard Evaluations
HPLC	High-performance liquid chromatography
HPV	High Production Volume
HPVIS	High Production Volume Information System

HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IC_{50}	Half Maximal Inhibitory Concentration
ICC	Intra-Class Correlation Coefficient
ILO	International Labour Organization
IPCHEM	Information Platform for Chemical Monitoring Data
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System (IRIS)
ISO	International Organization for Standardization
JSON	JavaScript Object Notation
K_{AW}	Air:Water Partitioning Coefficient
K_{OC}	Organic Carbon: Water Partitioning Coefficient
K_{OW}	Octanol: Water Partitioning Coefficient
LADD	Lifetime average daily dose
LC_{50}	Half maximal lethal concentration
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LOAEC	Lowest-Observed-Adverse-Effect Concentration
LOAEL	Lowest-Observed-Adverse-Effect Level
LOD	Limit of detection
LOEC	Lowest-Observed-Effect Concentration
LOQ	Limit of quantitation
MCCEM	Multi-Chamber Concentration and Exposure Model
MeSH	Medical Subject Heading
MITI	Ministry of International Trade and Industry
MMAD	Mass Median Aerodynamic Diameter
MOA	Mode of action
MOCA	4,4’-Methylenebis(2-chloroaniline)
MOE	Margin of exposure
MRRE	Manufacturer-requested risk evaluations
MS	Mass spectrometry
MW	Molecular weight
NAFTA	North American Free Trade Association
NAICS	North American Industry Classification System
NAS	National Academy of Sciences (now NASEM)
NASEM	National Academies of Sciences, Engineering, and Medicine
NATA	National-Scale Air Toxics Assessments
ND	Non-detect (values)
NEI	National Emissions Inventory
NESHAP	National Emissions Standards for Hazardous Air Pollutants
NHANES	National Health and Nutrition Examination Survey
NICNAS	National Industrial Chemicals Notification and Assessment Scheme (Australian Government Department of Health)
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health

NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology
NITE	Japanese National Institute of Technology and Evaluation
NMP	N-Methylpyrrolidone
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
NR	Not reported
NRC	National Research Council (formerly part of NAS)
NSC	National Safety Council
NTP	National Toxicology Program
OARS	Occupational Alliance for Risk Science
OC	Organic carbon
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organisation for Economic Cooperation and Development
OECD TG	Organisation for Economic Cooperation and Development Testing Guideline
OEL	Occupational Exposure Limit
OHAT	Office of Health Assessment and Translation
OPPT	Office of Pollution Prevention and Toxics
ORD	Office of Research and Development
OSHA	Occupational Safety and Health Administration
PAH	Polycyclic aromatic hydrocarbon
PAN	Pesticide Action Network
PBPK	Physiologically-based pharmacokinetic
PBT	Persistence, bioaccumulation, and toxic
PDF	Portable document format
PECO	Populations, Exposures, Comparators, and Outcomes
PEL	Permissible Exposure Limit
PESO	Pathways and Processes, Exposure, Setting or Scenario, and Outcomes
PESS	Potentially exposed or susceptible subpopulation
PK	Pharmacokinetic
PKWG	Pharmacokinetics Workgroup
PMID	PubMed Identifier
PMN	Pre-manufacture notices
POD	Point of departure
POTW	Publicly owned treatment works
PPDB	Pesticide Properties Database
PPE	Personal protective equipment
PPRTV	Provisional Peer-Reviewed Toxicity Values
QA/QC	Quality assurance/quality control
QAPP	Quality Assurance Project Plan
QSAR	Quantitative structure-activity relationship
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RED	Reregistration Eligibility Decision

RESO	Receptors, Exposure, Setting or Scenario, and Outcomes
RIVM	Rijksinstituut Voor Volksgezondheid En Milieu
RTECS	Registry of Toxic Effects of Chemical Substance
SAR	Structure-activity relationship
SciRAP	Science in Risk Assessment and Policy
SDS	Safety data sheets
SE	Standard error
SG	Specific gravity
SHEDS	Stochastic Human Exposure and Dose Simulator
SIDS	Screening Information Dataset
SMILES	Simplified Molecular-Input Line-Entry System
SOM	Soil organic matter
SOP	Standard operating procedure
SR	Systematic review
STEL	Short-Term Exposure Limit
STN	Scientific & Technical Information Network
STORET	STORage and RETrieval; EPA's Water Quality Monitoring Database
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SWIFT	Sciome Workbench for Interactive Computer-Facilitated Text-Mining
TBBPA	4,4'-(1-Methylethylidene)bis[2, 6-dibromophenol]
TCEP	Tris(2-chloroethyl) phosphate
TDI	Toluene diisocyanate
TEM	Total Exposure Model
TG	Testing guideline
TIAB	Title and abstract
TLV	Threshold Limit Value
TPP	Phosphoric acid, triphenyl ester
TOXNET	Toxicology Data Network
TRA	Targeted risk assessment
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TW	Tissue weight
TWA	Time-weighted average
UCRM	Unregulated Contaminant Monitoring Rule
UF	Uncertainty Factor
UNEP	United Nations Environment Programme
UNIFY	Reference Module of the ECOTOX Knowledgebase
UNII	Unique Ingredient Identifier
URL	Uniform Resource Locator
USDA	U.S. Department of Agriculture
USGS	U.S. Geological Survey
WEEL	Workplace environmental exposure level
WHO	World Health Organization
WOS	Web of Science

WoSE	Weight of the scientific evidence
WQP	Water Quality Portal
WQX	Water Quality Exchange

See also GLOSSARY OF SELECT TERMS.

1 INTRODUCTION AND OVERVIEW

U.S. EPA's Office of Pollution Prevention and Toxics (OPPT) applies systematic review principles in the development of its risk evaluations of existing chemicals designated to be of high-priority or requested by manufacturers under the amended Toxic Substances Control Act (TSCA). This new TSCA systematic review protocol documents the specific systematic review approaches used for identifying and evaluating evidence for the hazard and exposure assessments that support OPPT's risk evaluations, including evidence within other disciplines underpinning the hazard and exposure assessments (*i.e.*, engineering, physical and chemical properties, environmental fate). This protocol (1) responds to key recommendations received from the National Academies of Sciences, Engineering, and Medicine (NASEM) on the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a); (2) is a product of collaboration with the EPA Office of Research and Development's Integrated Risk Information System (IRIS) Program, and (3) will continue to be improved by public feedback, examination of the recent NASEM report (NASEM, 2021a) on the *ORD Staff Handbook for Developing IRIS Assessments* (U.S. EPA, 2020), and evolution of the state of the science in the field of systematic review. This protocol reflects the current TSCA systematic review approaches at the time of its writing. It also provides specific details of the systematic reviews for the individual chemicals listed in Table 1-1. EPA invites the public to provide input on this document via docket No EPA-HQ-OPPT-2021-0414.

Table 1-1. Chemicals Undergoing TSCA Systematic Review for Which Details Are Included in this TSCA Systematic Review Protocol Version 1.0

Chemical Name	CASRN(s)
o-Dichlorobenzene	95-50-1
p-Dichlorobenzene	106-46-7
1,2-Dichloroethane	107-06-2
trans-1,2- Dichloroethylene	156-60-5
1,1,2-Trichloroethane	79-00-5
1,2-Dichloropropane	78-87-5
1,1-Dichloroethane	75-34-3
Ethylene dibromide	106-93-4
1,3-Butadiene	106-99-0
1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (HHCB)	1222-05-5
4,4'-(1-Methylethylidene)bis[2, 6-dibromophenol] (TBBPA)	79-94-7
Tris(2-chloroethyl) phosphate (TCEP)	115-96-8
Phosphoric acid, triphenyl ester (TPP)	115-86-6
Formaldehyde	50-00-0

Chemical Name	CASRN(s)
Phthalic anhydride	85-44-9
Dibutyl phthalate (DBP) (1,2-Benzene- dicarboxylic acid, 1,2- dibutyl ester)	84-74-2
Butyl benzyl phthalate (BBP) - 1,2-Benzene- dicarboxylic acid, 1-butyl 2(phenylmethyl) ester	85-68-7
Di-ethylhexyl phthalate (DEHP) - (1,2-Benzene- dicarboxylic acid, 1,2- bis(2-ethylhexyl) ester)	117-81-7
Di-isobutyl phthalate (DIBP) - (1,2-Benzene- dicarboxylic acid, 1,2-bis-(2methylpropyl) ester)	84-69-5
Dicyclohexyl phthalate	84-61-7
Diisodecyl phthalate (DIDP)	26761-40-0 68515-49-1
Diisononyl phthalate (DINP)	28553-12-0 68515-48-0
Octamethylcyclotetra- siloxane (Cyclotetrasiloxane, 2,2,4,4,6,6,8,8-octamethyl-) (D4)	556-67-2
Asbestos 2 (including Libby Amphibole Asbestos [LAA] and its tremolite, winchite, and richterite constituents)	1332-21-4 12001-29-5 12001-28-4 12172-73-5 17068-78-9 12172-67-7 1318-09-8 (12425-92-2, 17068-76-7, 14567-73-8)
1,4-Dioxane supplement	123-91-1

The following narrative text summarizes the principal additions to or changes from the 2018 Systematic Review methodology that was reviewed by NASEM.

Transparency and Documentation

Previously, EPA did not have a complete clear and documented TSCA systematic review (SR) Protocol. EPA is addressing this lack of *a priori* protocol by releasing this TSCA SR Protocol. In its development, EPA considered existing systematic review approaches for hazard/epidemiology data (*e.g.*, Office of Health Assessment and Translation [OHAT], IRIS Handbook, and the Navigation Guide) and occupational exposure data/studies (*e.g.*, World Health Organization [WHO] and International Labour Organization [ILO] collaboration). EPA adopted many features of these mostly hazard-only systematic review approaches in developing this TSCA SR Protocol while also customizing the SR approaches to meet TSCA-specific needs—most importantly the systematic review of more than just hazard data (*e.g.*,

data streams for fate and transport, exposure, environmental and workplace monitoring, engineering). To transparently show the similarities and adaptations of existing methods to TSCA data streams, this TSCA SR Protocol provides a crosswalk detailing how EPA adopted and incorporated the best practices from other approaches/frameworks into the TSCA SR Protocol (see Appendix A).

The TSCA SR Protocol also includes a glossary of important terms to provide consistency and transparency about how EPA uses terms with TSCA-specific meaning (*e.g.*, Weight of the Scientific Evidence) and terms that are used frequently in the systematic review field in the TSCA SR context (see GLOSSARY OF SELECT TERMS). Development and inclusion of a glossary of terms is consistent with a recent recommendation made by the NASEM regarding the NASEM report on the TSCA SR approach as well as EPA's *ORD Staff Handbook for Developing IRIS Assessments* (IRIS Handbook)—a large part of which is dedicated to systematic review.

In response to NASEM's critique that EPA had not previously documented how TSCA prioritization and problem formulation relate to the TSCA SR, this TSCA SR Protocol clearly presents the alignment of the TSCA prioritization and scoping (problem formulation) processes with the steps of the TSCA SR Protocol. The TSCA SR Protocol further shows how EPA's systematic review efforts identify data gaps and data needs related to TSCA chemical risk evaluations. Identifying these data gaps and data needs provides EPA with the information needed to strategically exercise TSCA authorities to require testing or information collection for use in TSCA prioritization and risk evaluation (Section 2).

New Literature Search Process

For the 20 high-priority substances and manufacturer-requested risk evaluations (MRREs) currently undergoing TSCA risk evaluation, EPA implemented a new, unified literature search process, which is described in this TSCA SR Protocol. It uses a comprehensive set of chemical identifiers to capture as much of the literature relevant for all given disciplines, thereby providing consistency and efficiency to the literature search step of systematic review. In addition, EPA's TSCA SR Protocol now leverages additional SR tools (*e.g.,* SWIFT-Review, SWIFT-Active, Health Assessments Workspace Collaborative [HAWC]) to provide structure, documentation, efficiency, and transparency to searching, filtering, and screening (see Sections 3, 4, and 5). The TSCA SR Protocol also includes a description of the use of machine learning to prioritize literature screening, updates to the search and screening approach, PECO/PESO/RESO statement refinement prior to title/abstract screening, and improvements to the screening criteria and templates. All of these approaches are in direct response to the NASEM recommendations, particularly those encouraging harmonization with the IRIS Program.

Reducing Bias and Improving Consistency

The TSCA SR Protocol incorporates the use of the interactive HAWC to generate literature inventory trees and evidence maps (see Appendix I). These inventory trees and evidence maps are also linked to Health and Environmental Research Online (HERO) database to provide access to specific titles and abstract of sources and pdf if freely available. These visualizations are "evergreen" in nature and provide greater transparency, access, and utility to the public and peer reviewers. EPA incorporated this technology after close collaboration and technology transfer with EPA's IRIS Program, consistent with NASEM's recommendation. EPA is fully implementing these tools for the 20 high-priority chemical substances and MRRE risk evaluations currently underway, as evidenced by the chemical-specific search terms (Appendix C), PECO statements (Appendix H), and evergreen literature trees and evidence maps (Appendix I).

This TSCA SR Protocol also includes new methods to reduce bias and improve evaluation consistency between reviewers and across chemicals, included in response to NASEM recommendations, SACC

comments, and public comments. These improvements include coordinated data evaluation training and calibration exercises for reviewers (both contractor support staff and in-house experts), the development of additional internal evaluation guidance, and enhanced use of fields for screener notes within DistillerSR evaluation forms for all metric rankings. To ensure internal consistency and transparency, whenever EPA revises data evaluation criteria for any discipline, EPA pilot tests their application and undertakes multiple rounds of calibration. Further, as recommended by NASEM and SACC, EPA's data quality evaluation now involves two levels of review for each study for every discipline—a primary review and a secondary quality control review, which may be followed by an explicit conflict resolution step in cases where the two reviewers are not in agreement.

Data Evaluation and Evidence Integration

In response to a variety of commenters, including NASEM and SACC, the TSCA SR Protocol does not include a quantitative/weighted scoring system for data evaluation. Rather, the TSCA SR Protocol applies ordinal rankings to guide the *qualitative* categorization of *high*, *medium*, *low*, or *critically deficient* for each data evaluation metric. The ordinal rankings for individual metrics are used to derive an overall study qualitative ranking of *high*, *medium*, *low*, *or uninformative*. This approach provides for objectivity, consistency, and transparency in comparing studies (Section 5). These updates to the evaluation criteria have been made across all disciplines (*e.g.*, fate, exposure, engineering, environmental, human health hazard).

The TSCA SR Protocol is significantly different in that it includes descrition of the Evidence Integration process (Section 7), which was not previously included in the 2018 TSCA SR document (U.S. EPA, 2018a). This substantial addition was in direct response to recommendations by the NASEM and the SACC. The Evidence Integration approach included in the TSCA SR Protocol relies on approaches similar to those in EPA's IRIS Handbook but extended to other disciplines, where appropriate, in the TSCA SR Protocol.

In summary, EPA has carefully considered the important peer review recommendations and public comments received on the 2018 TSCA SR document. In close collaboration with colleagues in EPA's IRIS Program, EPA has adopted—to the extent possible and adapted when necessary to meet unique TSCA needs—many of the approaches, procedures, and state-of-the-art technology tools operationalized at EPA for conducting systematic review of data and information to be used to support risk evaluations under TSCA.

2 STATUTORY AND REGULATORY CONTEXT GUIDING PROTOCOL DEVELOPMENT

On June 22, 2016, the "Frank R. Lautenberg Chemical Safety for the 21st Century Act" was signed into law, amending the 1976 Toxics Substances Control Act (TSCA) (15 U.S.C. § 2601 et seq., 2016). TSCA, administered by EPA's Office of Pollution Prevention and Toxics (OPPT), required EPA to initiate risk evaluations for 10 chemical substances drawn from the 2014 update of the TSCA Work Plan for Chemical Assessments (U.S. EPA, 2014b), in 2016. Thereafter, TSCA imposes additional statutory requirements to ensure that risk evaluations and potential risk management rules continue on a rolling basis as the risk evaluations are completed. After the first 10 chemical substances, EPA must designate substances as high-priority for risk evaluation before initiating risk evaluations on those substances. Additionally, manufacturers can request that EPA evaluate a chemical substance, subject to the payment of fees pursuant to TSCA section 26(b). If granted by EPA, these MRREs are treated similarly to high-priority designated substances with regards to applying systematic review approaches, and any minor differences are detailed in this protocol or the examples in the appendices for the next 20 high-priority substances and manufacturer-requested risk evaluations.

Under TSCA section 6(b)(4)(A), OPPT "conduct[s] risk evaluations… to determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other nonrisk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation [(PESS)] identified as relevant to the risk evaluation by the Administrator, under the conditions of use." [1]

TSCA section 6(b)(4)(F) also identifies the minimum components EPA must include in all chemical risk evaluations: (1) "integrate and assess available information on hazards and exposures for the conditions of use of the chemical substance, including information that is relevant to specific risks of injury to health or the environment and information on potentially exposed or susceptible subpopulations identified as relevant by the Administrator;" (2) "describe whether aggregate or sentinel exposures to a chemical substance under the conditions of use were considered, and the basis for that consideration;" (3) "not consider costs or other nonrisk factors;" (4) "take into account, where relevant, the likely duration, intensity, frequency, and number of exposures under the conditions of use of the chemical substance;" and (4) "describe the weight of the scientific evidence for the identified hazard and exposure." The statute provides that the scope of the risk evaluation must be published no later than 6 months after the initiation of the risk evaluation (TSCA section 6(b)(4)(D)).

Moreover, the statute requires that EPA adhere to specific provisions regarding Scientific Standards, Weight of the Scientific Evidence, and Reasonably Available Information as articulated in TSCA sections 26 (h), (i), and (k), respectively. These provisions are applicable to TSCA risk evaluations and state

> *"(h) SCIENTIFIC STANDARDS.—In carrying out sections 4, 5, and 6, to the extent that the Administrator makes a decision based on science, the Administrator shall use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science, and shall consider as applicable—*

[1] TSCA section 3(12) states that "the term 'potentially exposed or susceptible subpopulation' [PESS] means a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly."

> *(1) the extent to which the scientific information, technical procedures, measures, methods, protocols, methodologies, or models employed to generate the information are reasonable for and consistent with the intended use of the information;*
> *(2) the extent to which the information is relevant for the Administrator's use in making a decision about a chemical substance or mixture;*
> *(3) the degree of clarity and completeness with which the data, assumptions, methods, quality assurance, and analyses employed to generate the information are documented;*
> *(4) the extent to which the variability and uncertainty in the information, or in the procedures, measures, methods, protocols, methodologies, or models, are evaluated and characterized; and*
> *(5) the extent of independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies, or models.*
>
> *(i) WEIGHT OF SCIENTIFIC EVIDENCE.—The Administrator shall make decisions under sections 4, 5, and 6 based on the weight of the scientific evidence.*
>
> *…*
>
> *(k) REASONABLY AVAILABLE INFORMATION*
> *In carrying out sections 2603, 2604, and 2605 of this title, the Administrator shall take into consideration information relating to a chemical substance or mixture, including hazard and exposure information, under the conditions of use, that is reasonably available to the Administrator."*

In the final rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (hereafter Risk Evaluation Rule), 82 Fed. Reg. 33726 (July 20, 2017), EPA defined best available science as "science that is reliable and unbiased. Use of best available science involves the use of supporting studies conducted in accordance with sound and objective science practices, including, when available, peer-reviewed science and supporting studies and data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data . . . ." (40 CFR 702.33). Also, TSCA risk evaluations are required to rely on the weight of the scientific evidence [15 U.S.C. § 2625(i)] that is defined in the Risk Evaluation Rule 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). EPA believes that integrating systematic review methods into the TSCA risk evaluations is critical to meet the scientific standards as described in TSCA.

The current protocol updates, supplants, and significantly expands upon the procedures outlined in EPA's *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a) and other associated materials published for the first 10 risk evaluations. These updates include developments that respond to scientific peer review and public comments.

In February 2020, the National Academies of Sciences, Engineering, and Medicine (NASEM) began their review of EPA's systematic review process with a series of workshops and provided their final report in 2021 (NASEM, 2021b). These important NASEM recommendations were implemented in the development of this draft protocol (see response to comments in Table_Apx A-1). During the scientific peer review of the first 10 risk evaluations, the Science Advisory Committee on Chemicals (SACC) also provided peer review comments on existing TSCA systematic review approaches. EPA also received public comments on the 2018 *Application of Systematic Review in TSCA Risk Evaluations* document (U.S. EPA, 2018a). EPA received numerous public comments on this 2018 document, including that the document was not a protocol. EPA responded to public comments and posted responses at that time.

Overarching comments on EPA's early systematic review process and EPA's responses are provided in Appendix A. Table_Apx A-1 lists the comments received by EPA and Table_Apx A-2 lists major updates EPA has implemented in response to the peer review and public comments.

TSCA requires that EPA designate at least 20 chemical substances as a high priority for risk evaluation. EPA finalized the designation of 20 chemical substances as a high priority for upcoming risk evaluations effective as of December 20, 2019. (*High-Priority Substance Designations Under the Toxic Substances Control Act and Initiation of Risk Evaluation on High-Priority Substances; Availability*, 84 Fed. Reg. 71924 (Dec. 30, 2019)). The prioritization process includes a risk-based screening process considering criteria including: the hazard and exposure potential of the chemical substance; persistence and bioaccumulation; PESS; storage near significant sources of drinking water; the conditions of use or significant changes in the conditions of use of the chemical substance; and the volume or significant changes in the volume of the chemical substance manufactured or processed. (TSCA section 6(b)(1)(A)). This screening process includes a systematic search and screening of chiefly peer-reviewed secondary sources relevant to the TSCA prioritization considerations described in TSCA section 6(b)(1)(A), and the information is used to inform EPA's identification of candidate chemicals for prioritization and proposed priority designations. Note that this systematic approach used to inform priority designations is not a systematic review and does not include data evaluation of the peer-reviewed sources. The prioritization process does include two opportunities for public comments on, and submission of, data identified for use in prioritization. This systematic approach is foundational for future scoping exercises, including problem formulation development, which follow high priority designation by forming the basis of information supporting the Population, Exposure, Comparator, and Outcomes (PECO) as well as Receptors, Exposure, Setting or Scenario, and Outcomes (RESO) statements for engineering and exposures of interest (see Figure 2-1).

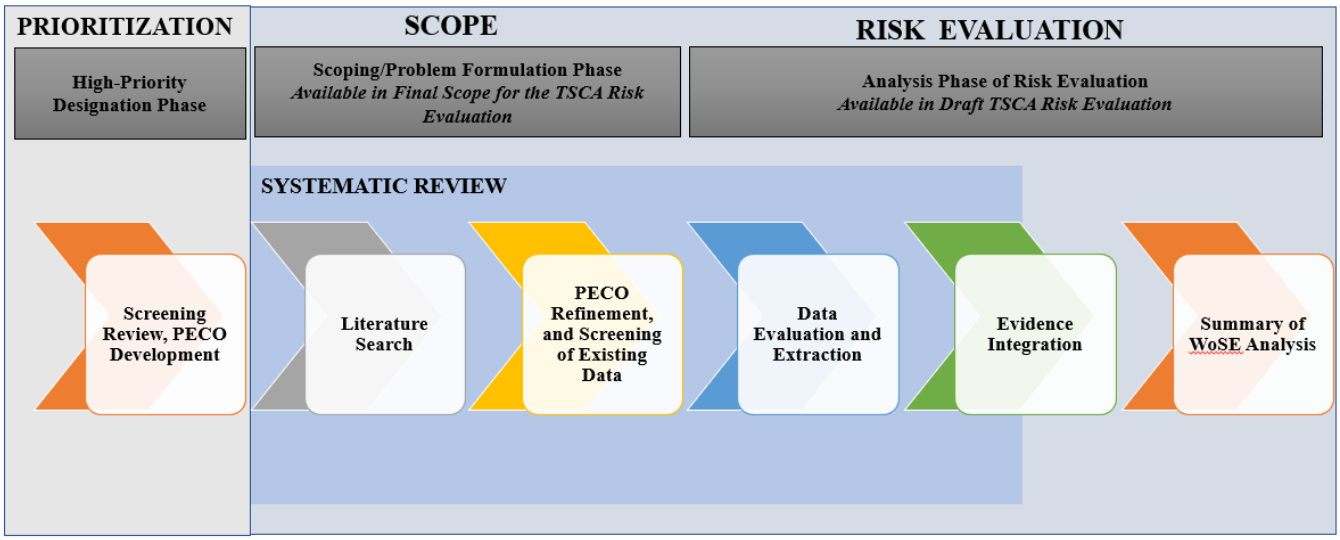

Figure 2-1. Overview of the TSCA Prioritization, Scoping, and Risk Evaluation Process with Parallel Systematic Review Steps Identified

Scoping is required under TSCA and the systematic review effort is an important part of the analytical framework for the TSCA risk evaluations. It is during scoping that EPA develops conceptual models and analysis plans for each risk evaluation, as required by EPA's final Risk Evaluation Rule (40 CFR Part 702). Under EPA's risk evaluation guidance, the conceptual model and the analysis plan are the outcomes of conducting problem formulation (U.S. EPA, 2019, 2014a, 1998a). The TSCA scopes include these conceptual model(s) that illustrate the exposure pathways, receptor populations, including

PESS, and effects that EPA expects to consider for the conditions of use in the scope of the risk evaluation. Scoping is the first stage of the TSCA risk evaluation process and is intended to convey EPA's expectations regarding the overall scope of the risk evaluation (*e.g.,* level of detail and approach for the risk evaluation). This planning effort is critical to developing clear objectives and assessment questions to support quantitative risk analyses, and to defining the steps that EPA expects to take to conduct the different components of the risk evaluation including the searching and screening strategies for systematic review. These efforts are critical to development and refinement of PECO for screening of reasonably available information. The analysis plan of the TSCA scope presents the proposed approach for the risk evaluation. Scoping helps shape the systematic review approaches and/or methods that are used to identify, evaluate, analyze, and integrate evidence. Thus, scoping under TSCA has essentially the same function as problem formulation outlined in the Agency's risk assessment guidelines, such that EPA expects the scope for a TSCA risk evaluation to generally align with the components of a problem formulation in other EPA risk assessment guidance (U.S. EPA, 2019, 2014a, 1998a).

With this context in mind, the chemical-specific systematic review activities supporting TSCA existing chemical risk evaluations are guided by the corresponding scoping activities, as documented in TSCA scope documents. The scoping document for each chemical includes the initial search strategy and screening criteria and specific products from these efforts, including literature trees and evidence tables for each discipline. This approach for development of literature trees and evidence maps was adapted from innovations developed by the IRIS Program for human health hazard (U.S. EPA, 2020) and applied across all disciplines and data streams assessed in TSCA risk evaluations. The application of systematic review principles is generally expected to be consistent across risk evaluations, as outlined in this generic protocol, with customized criteria and approaches applied, as necessary, to meet the assessment needs of individual risk evaluations as noted in chemical specific appendices.

EPA acknowledges significant collaboration and coordination with the IRIS Program to inform the TSCA systematic review process especially for hazard evaluation and is considering the recent NASEM report on the IRIS Handbook (U.S. EPA, 2020). OPPT will be working closely with IRIS on incorporating key recommendations into revisions of its protocol as appropriate to assure inter-operability and facilitate incorporation of ongoing systematic review efforts by ORD into TSCA evaluations (*e.g.,* phthalates and formaldhyde systematic review products).

The evidence maps obtained from these exercises also serve other purposes by identifying obvious data gaps in the reasonable available information. These systematic review screening efforts and identified data gaps can inform EPA's assessment of the criticality of data needs and inform data collection efforts under other TSCA authorities, including test orders and test rules.

This protocol also applies to systematic review efforts for supplemental evaluations for asbestos fibers (Appendix C and Appendix H) and 1,4-dioxane (Appendix H) with specifics described in chemical specific appendices.

3 OBJECTIVES AND AIMS OF THE SYSTEMATIC REVIEW

This systematic review protocol describes the process and methods that EPA is using to identify, evaluate, and integrate the exposure and hazard evidence for TSCA risk evaluations. The aims of the systematic literature review are to

- Conduct literature searches to identify relevant information in key disciplines, including information supporting all discipline-specific topic areas (see Table 3-1).
- Screen studies according to discipline-specific screening criteria to identify those pertinent to understanding the potential exposure and hazards of the chemical substance (Appendix H).
- Produce literature inventory trees and evidence tables to summarize the extent and nature of the evidence that meets the screening criteria for each discipline.
- Evaluate the quality of the studies for each key discipline using the method and criteria described in Section 5 and Appendix K through Appendix T.
- Extract information from studies containing relevant data/information for the risk evaluation.
- Integrate the identified exposure and hazard information using the methods described in Section 7. Integration includes a characterization of the strengths, limitations, and relevance of the available data within and across data/information types, as necessary and appropriate.

Section 1 through Section 6 outlined in this protocol provide details on the identification, evaluation and extraction of information attained via systematic review processes. Section 7 describes the integration of evidence obtained both within and outside of a formal systematic review process to support a Weight of the Scientific Evidence analysis.

Figure 3-1 illustrates the steps leading from data gathering to risk characterization and which of these steps are covered formally within EPA's systematic review approach.

Table 3-1. Data/Information Needs across All Disciplines

Disciplines	Discipline-Specific Topic Areas	Data/Information Needs
Physical and chemical properties	Physical and chemical properties	Collection of physical and chemical properties of the substance being evaluated to inform the fate, exposure, and hazard assessments of the risk evaluation
Environmental fate and transport	Environmental fate and transport	Environmental mobility Environmental degradation Bioaccumulation and environmental persistence Wastewater removal processes
Engineering	Occupational exposure and environmental release	Conditions of use, lifecycle, and process-related information Facility production parameters Exposure routes Occupational exposure data Occupational exposure controls Environmental releases data Environmental release/emission controls

Disciplines	Discipline-Specific Topic Areas	Data/Information Needs
Exposure	Environmental, general population, consumer exposure	Lifecycle information to inform environmental (ecological), general population and consumer exposures Media concentrations in the environment Biomonitoring data Information to identify potentially exposed or susceptible subpopulations
Environmental hazard	Environmental hazard	Information about environmental hazards associated with acute and chronic toxic effects on aquatic and terrestrial species
Human health hazard	Human health hazard	Information about health hazards including critical health effects and corresponding points of departure associated with exposure via all routes, durations, sources, and pathways Characterization of hazard for general population and potentially exposed or susceptible subpopulations Toxicokinetics Mode(s) of action (MOA) Information to identify PESS

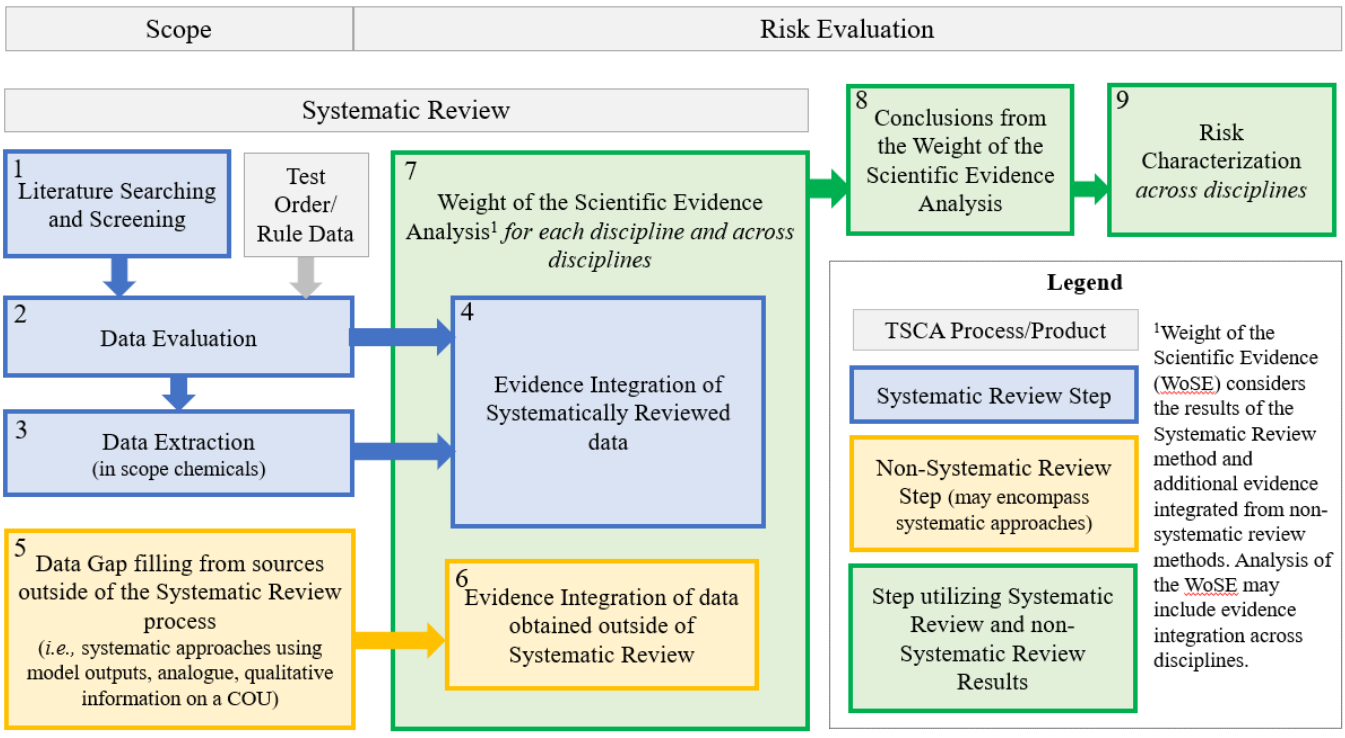

Figure 3-1. Overview of the TSCA Risk Evaluation Process with Identified Systematic Review Steps

The following steps fall within the TSCA Systematic Review Process:

1. Literature Searching and Screening Search for and Selection of Studies for Inclusion (Section 4)
2. Data Evaluation and Risk of Bias of Individual Studies (Section 5)
3. Data Extraction for Inclusion of Individual Studies (Section 6)
4. Evidence Integration of Systematically Reviewed Quality Studies (Section 7)

Steps that fall outside of the TSCA Systematic Review Process, but may include systematically reviewed information, include the following:

5. Data Gap Filling from sources outside of the Systematic Review process
6. Evidence Integration of information that may have been reviewed using systematic review methods (*e.g.*, incorporation of evidence from read-across and modeling; Section 7)
7. Weight of the Scientific Evidence Analysis (*i.e.*, consideration of information from Evidence Integration)
8. Weight of the Scientific Evidence Conclusion (*i.e.*, conclusions, uncertainty)
9. Integration of Exposure and Hazard Information for Risk Characterization

4 LITERATURE SEARCH AND SCREENING STRATEGIES

EPA conducts a comprehensive search for reasonably available information to support the TSCA risk evaluations. This search includes the following general categories of sources:

1. Databases containing publicly available, peer-reviewed literature (*e.g.,* PubMed, Web of Science, ProQuest; hereafter "peer-reviewed literature").
2. Gray literature, which is defined as the broad category of data/information sources not found in standard, peer-reviewed literature databases. Gray literature includes data/information sources such as white papers, conference proceedings, technical reports, reference books, dissertations, information on various stakeholder websites and various databases.
3. Relevant data and information submitted under TSCA sections 4, 5, 6, 8(d), and 8(e), as well as for your information (FYI) submissions (a subset of gray literature).
4. Data/information sources generated from backward searches of existing documents containing data/information likely to be relevant to the risk evaluations.
5. Public comments that EPA receives during the risk evaluation process that include references or published or unpublished data proposed for consideration during risk evaluation.

EPA also leverages the data and information sources that are collected in preliminary searches and found in the documents supporting high-priority substance designations. Once EPA conducts searches of these sources, EPA assesses the data for relevancy to the risk evaluations using title/abstract and full-text screening steps, as appropriate. Screening criteria for hazard and exposure studies are described as PECO statements because they describe criteria specific to study details of Population, Exposure, Comparator, and Outcome. Similarly, environmental fate studies are screened according Processes, Exposure, Setting or Scenario, and Outcomes (PESO) statements and engineering studies are screened according to Receptors, Exposure, Setting or Scenario, and Outcomes (RESO) statements.

Gray literature requires pre-screening steps using a decision tree to determine whether a source should be screened. This decision tree is described in Figure 4-3 and Section 4.3.2 describes the decision logic. Once a gray literature source has gone through this decision tree and determined to be relevant for the risk evaluation, it advances to full-text screening.

The subsequent sections describe the literature search and screening strategies for the categories of sources listed above as well as additional steps as needed.

4.1 Software Used in Searching/Screening Workflow

Several specialized software applications are used to streamline the literature search, filtering search results, study screening (both at the title and abstract and full text levels), and data visualization steps of the TSCA systematic review process. An overview of these applications and their role in the systematic review of literature is illustrated in Figure 4-1. The HERO application is an EPA product that manages project references and has deduplication and tagging features. SWIFT-Review and SWIFT-Active Screener are Sciome products which leverage novel technologies such as text-mining and machine learning. SWIFT-Review applies filters based on key words and Medical Subject Heading (MeSH) terms/fields to titles, abstracts, and keywords in peer-reviewed publications to predict relevance to a TSCA discipline or discipline-specific evidence stream. SWIFT-Review can also be used to predict the relevance of new studies based on the keywords found in their titles and abstracts corresponding to keywords in a set of *a priori* identified relevant studies to the topic (*i.e.,* discipline) of interest. SWIFT-Active screener uses machine learning and keywords in titles and abstracts to predict the relevance of unscreened literature in a pool based on manual screening results of studies in this same initial pool. DistillerSR is an Evidence Partners product which manages screening decisions and is used at Title and

Abstract (TIAB) screening when a pool of literature is too small to use SWIFT-Active screener as well as full text screening. Data visualizations of the screening results are displayed using Tableau software and EPA's HAWC features. The details of how these software applications are used in the TSCA systematic review process and differences across disciplines are provided in Sections 4.2 and 4.6.

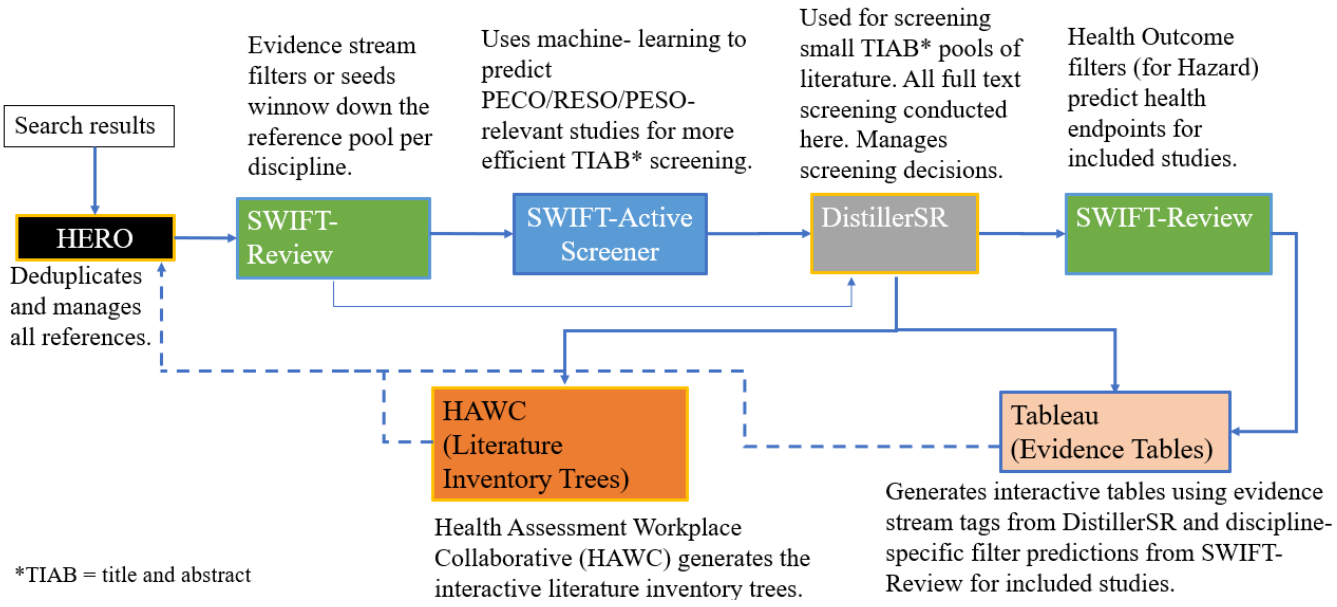

Figure 4-1. Workflow and Software Used in Searching and Screening

4.2 Searching, Categorizing/Filtering, and Screening Strategy for Peer-Reviewed Literature

EPA broadly searches and screens the peer-reviewed literature to capture data and/or information that may be relevant to the risk evaluation based on the general data/information needs described in Table 3-1. The chemical-specific search and screening process involves the following general steps:

- *Step 1* – Search databases that house peer-reviewed literature for potentially relevant studies across all disciplines for a given chemical using search strings based on chemical name, synonyms and identifiers.
- *Step 2* – Categorize/filter references into separate disciplines using key word filters available in the software SWIFT-Review.
- *Step 3* – Screen titles and abstracts of filtered studies according to relevance criteria (*i.e.*, PECO, RESO, or PESO statements) using the SWIFT-Active Screener or DistillerSR according to *a priori* developed relevance criteria.
- *Step 4* – Screen the studies which passed title and abstract screening at the full-text level using DistillerSR.

These steps are outlined in Figure 4-2 and described in detail in the sections below.

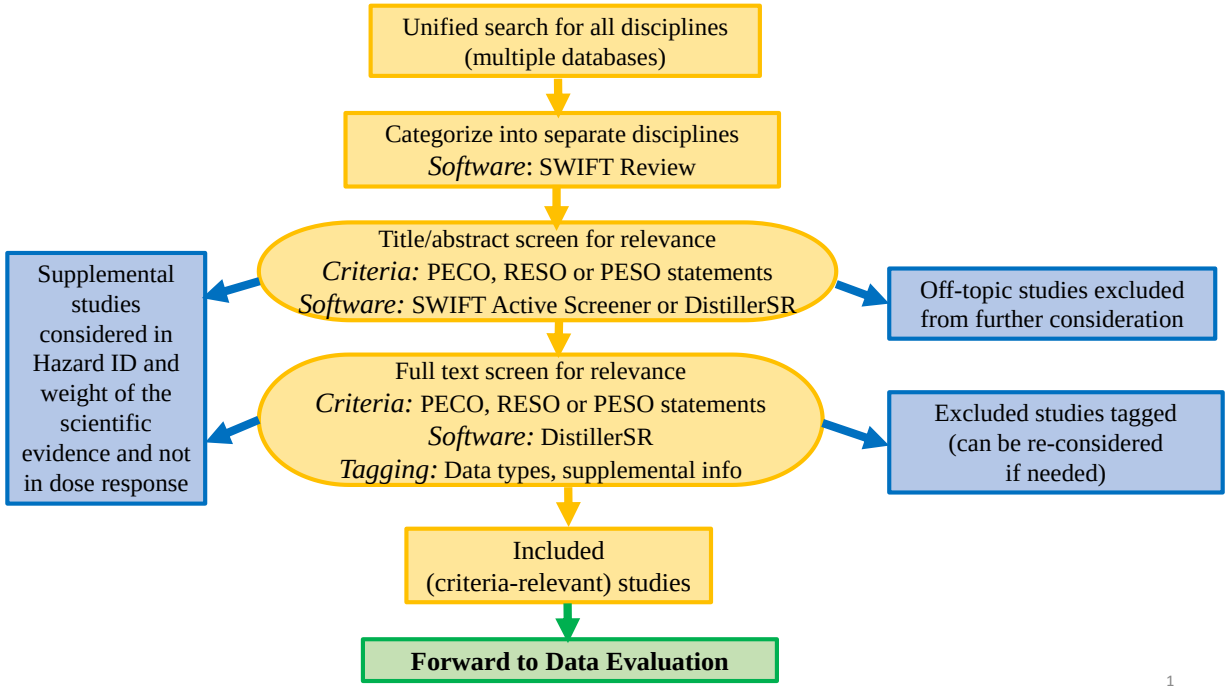

Figure 4-2. Workflow for Searching and Screening Peer-Reviewed Literature

EPA may perform additional supplemental searches for targeted information (*e.g.*, exposure parameters used in exposure models and applicable to multiple chemicals) that may differ in some of the above steps. These supplemental searches are generally performed simultaneously with chemical-specific searches.

4.2.1 Chemical-Specific Initial Searching of Databases for Peer-Reviewed Literature

Database searching is performed by an information specialist. The chemical-specific literature searches focus only on the chemical name (including synonyms and trade names) with no additional search limits. Using this approach and searching multiple databases, the search is designed to be comprehensive, using validated chemical descriptors to generate a wide capture of information and yield information for all disciplines (*i.e.*, physical and chemical properties, fate, engineering, exposure, environmental hazard, and human health hazard). Full details of the search strategies are presented in Appendix B. Chemical descriptors used for the 2019 high priority substances and MRREs are described in Appendix C. Using this strategy, EPA searches the following databases:

- Agricola
- Current Contents Connect
- Dissertation & Theses
- ProQuest
- PubMed
- Scopus
- Toxline – PubMed subset and ProQuest subset
- Web of Science

It should be noted that these sources reflect resource changes that have taken place since initial searches for many of the chemicals in Appendix C. Previous search strategies used Toxline, which has since been

deactivated. References that were stored in the Toxline subsection of ToxNet were divided and redistributed to the ProQuest and PubMed databases. EPA now acquires Toxline references by searching the ProQuest and PubMed subsections. Additionally, Science Direct is no longer searched, but its content is covered by Elsevier's larger and more comprehensive literature database, Scopus. Further, the ECOTOX database has been incorporated into gray literature searching and is not searched for peer-reviewed literature.

Results of the search are stored in EPA's HERO database with each citation being assigned a HERO reference identification number (referred to as HERO ID hereafter). HERO is an evergreen EPA database that hosts scientific studies and other references that are considered during a risk evaluation. Projects in HERO can be made private or public, allowing EPA to provide both a transparent and interactive platform for evaluation stakeholders to view progress.

The chemical-specific literature searches are updated periodically and targeted to identify studies that have been published since the finalization of the initial literature search. Unique references that are new to a chemical project are integrated into the systematic review workflow. EPA maintains literature trees and evidence maps for each chemical and discipline that are evergreen so that the public can access up-to-date versions of these visualizations. Additional information on these visualizations is available in Section 4.7 and links to the literature trees and evidence maps for all 2019 high priority substances and MRREs are presented in Appendix I.[2]

4.2.2 Supplemental Literature Searching to Fill Data Gaps

In addition to the initial chemical-specific literature search, EPA conducts supplemental literature searches to resolve data gaps that are discovered during screening (*e.g.,* Conditions of use or other non chemical-specific information topics that may inform exposure or hazard-related susceptibility). Once the extent of a data gap is determined, a targeted literature search is performed following current protocol guidelines. Unique references that were not captured in the initial search are integrated into the systematic review workflow.

Supplemental searches that consist solely of new chemical-specific keywords (*e.g.,* chemical synonyms) are combined with the initial search for all subsequent updates. Supplemental searches that target a broader topic (*e.g.,* chemical isomers, consumer uses, exposure parameters) remain separate, but are updated on the same schedule as the primary search. One or more of these same databases used for the chemical-specific searches may be used for supplemental searches.

4.2.3 Deduplication of Peer-Reviewed Literature Search Results

The search results from each of the above databases are imported into EPA's HERO database and automatically deduplicated. The deduplication process includes comparisons of

- journal, volume, issue, and page number combination against references already in HERO;
- title, publication year, and first author against references already in HERO; title comparisons ignore punctuation and case; and
- digital object identifier (DOIs), PubMed IDs (PMIDs), or Web of Science IDs (WoSIDs).

A new HERO ID is assigned to each reference determined to be unique following these comparisons. If a reference matches an existing HERO entry, HERO tags the existing reference and does not create a duplicate entry.

[2] Links are also available in the scope documents for the 2019 starts and MRREs.

When importing large numbers of citations from the literature searches into HERO, duplicate references may enter the systematic review workflow when a source database has not provided sufficient identifying information for a given reference, thus making it appear unique. This is generally attributed to differences in indexing practices between source databases, and information that may have changed over time (*e.g.*, journal name, DOI link has changed). When HERO cannot determine that a reference already exists within the database, it defaults to creating a new reference. Thus, additional duplicates may be identified during screening or full-text PDF acquisition steps. At this point, duplicates are manually resolved by redirection—a process in which a group of duplicate references are consolidated, or redirected, to a single HERO ID. The single resulting HERO ID retains all values (*e.g.*, reference information, tag assignments) of each duplicate. This ensures that although a reference's HERO ID may change during its life cycle, no information about the reference is lost.

4.2.4 General Approach for Filtering Search Results of Peer-Reviewed Literature

After deduplication in HERO and prior to title/abstract screening, EPA uses SWIFT-Review to categorize the peer-reviewed literature search results into the various discipline specific data streams. SWIFT-Review is a text-mining and machine learning software tool that can be used for topic modeling,[3] categorization, and prioritization of search results as well as visualization of patterns in literature search results (Howard et al., 2016). It is freely available to the public and used by academia and many government and non-government organizations to support systematic reviews.

Use of SWIFT-Review allows EPA to reduce the screening burden by quickly identifying references most relevant to a particular discipline according to topic-specific key terms using priority-ranking algorithms.

4.2.4.1 Built-in Filtering Strategies in SWIFT-Review for the Physical and Chemical Properties, Environmental Fate, and Hazard Disciplines

As described by Howard et al. (2016), SWIFT-Review[4] uses the Apache Lucene open-source software to provide a search engine and query language that can be used to interactively explore and filter references using both custom and built-in searches.

EPA relies on the built-in search strategies available in SWIFT-Review to tag potentially relevant references for the physical and chemical properties, fate, environmental hazard and human health hazard disciplines.

The software identifies relevant references by automatically scanning for search terms characteristic of each of these disciplines in the title, abstract, and Medical Subject Heading (MeSH) fields of each reference. The search strings for each of these disciplines were developed by EPA's Office of Research and Development (ORD) in collaboration with SWIFT-Review developer, Sciome. The specific physical and chemical property and environmental fate parameter terms are provided in Appendix G. The environmental and human health hazard search strings are provided online.

Only references that include one or more of the search terms in the title, abstract, keyword, or MeSH fields advance to title and abstract screening. References not tagged to these three disciplines using the SWIFT-Review strategies are not screened at the title/abstract stage.

[3] According to Howard et al. (2016), topic modeling is "a statistical method used to automatically cluster related documents in a collection of unlabeled texts and to discover computationally derived themes common among those documents."
[4] See SWIFT-Review Search Strategies – As noted on the website, SWIFT-Review includes detailed search strings to "automatically tag documents in various categories of interest to environmental health researchers." EPA uses these specific search strings to tag the disciplines physical and chemical properties, fate endpoints, and human health.

4.2.4.2 EPA-Generated Filtering Strategies Using SWIFT-Review for the Exposure and Engineering Disciplines

EPA also uses SWIFT-Review to tag potentially relevant references for the engineering and exposure disciplines. However, EPA developed the exposure and engineering categorization processes rather than using pre-established strategies (as was done for physical and chemical and fate properties and human health disciplines). EPA tailored the engineering and exposure strategies to meet the specific requirements of the TSCA risk evaluations instead of relying on the strings available in SWIFT-Review.

As described by Howard (2016), SWIFT-Review has a machine learning model that can be used to priority rank relevant studies in focused areas. EPA used this model to identify on-topic[5] and off-topic[6] engineering and exposure references from the broad search results of the peer-reviewed literature conducted for chemical substances undergoing risk evaluation. This process involved training the machine to recognize positive and negative seed references. A positive seed reference contains text in the title and abstract associated with potentially relevant information for the discipline of interest (*i.e.*, exposure or engineering). In contrast, a negative seed does not contain text in the title and abstract corresponding to potentially relevant information for the risk evaluation. Specifically, the identification of relevant references relied on an algorithm that considers term frequency and latent Dirichlet allocation topic modeling (Howard et al., 2016). A score was then used to evaluate the performance of the priority-ranking method.

For the exposure discipline, EPA identified positive seed references from the TSCA's first 10 chemical risk evaluations initiated in 2016. These seeds were manually classified into one of four exposure data types: consumer (108 seeds), human biomonitoring (49 seeds), environmental release (288 seeds), and dietary (36 seeds). Because these references were used in a previous risk evaluation, the aggregated text in the titles and abstracts provide reasonable exposure-relevant positive seed references for future TSCA risk evaluations. Therefore, a total of 474 negative seeds were chosen from a pool of literature for the 2019 starts that did not include any broad exposure keywords in SWIFT-Review. Examples of subjects identified in these off-topic studies include analytical/organic synthesis/electrochemistry methodology development; structure analysis (experimental or theoretical) of metallic-organic frameworks/disorder carbon networks; and bioremediation studies.

The positive and negative seeds were used to generate the statistical classification model in SWIFT-Review. Each reference was assigned a classification score based on the model. Any reference with a score above a given threshold value[7] was prioritized for further review for the exposure discipline. After developing the classification (*i.e.*, reference prioritization) model, EPA performed a validation step showing that misclassification of references using the model was relatively minor.

For the engineering discipline, EPA assumed that the citations used in the final risk evaluations would be reasonable as positive seeds (similar to the exposure discipline) and identified 50 positive seed references from a representative subset of peer-reviewed engineering references for a subset of TSCA chemicals from 2016. These seeds were manually classified into one of three engineering data types: general facility estimate, occupational exposure, and environmental release (or a combination of the three). To choose the negative seeds, reviewers manually examined titles and abstracts in SWIFT-

[5] *On-topic* references are those that may contain data and/or information relevant to the risk evaluation.
[6] *Off-topic* references are those that do not appear to contain data and/or information relevant to the risk evaluation.
[7] Threshold was defined as (min[positive seed score]) − 2×std(positive seed score) and a value of 0.62 was used.

Review and selected those not relevant to the engineering discipline. EPA used an equal number of negative seeds (50) to provide an unbiased training set for SWIFT-Review.

For engineering, a total of five validation runs were performed. Apart from one data set (1,4-dioxane), all "integrated" peer-reviewed references score above the 80th percentile value of the respective dataset discipline showed that the positive seeds captured occupational exposure. The 1,4-dioxane dataset was found to be a poor test example because the only integrated, peer-reviewed sources were two journal articles that contain process description specific to dioxane conditions of use. These two articles did not receive high scores in SWIFT-Review and would not serve as good seeds, as seeds should cover data elements that are chemical-agnostic. For engineering, peer-reviewed literature typically offers little information related to general facility estimate and environmental release; these data would generally be identified in gray literature and screened manually without being processed in SWIFT-Review.

For any chemical being evaluated, titles and abstracts from the search results of peer-reviewed literature that most closely resemble the positive seed references rank higher and move forward in title and abstract screening process. For exposure, the criterion used was a threshold of 60th percentile, and for engineering, the criterion was that references needed to score above the 80th percentile threshold value.[8] Any titles and abstracts that resemble the negative seed references rank lower and do not move to title and abstract screening process. Refer to Appendix G for additional details on the process used to develop the strategies used to filter peer-reviewed exposure and engineering literature including chemicals used to build the machine learning models, results of classification for the chosen seeds and performance of the models.

4.2.5 Screening of Search Results

After categorization using SWIFT-Review, EPA screens the titles and abstracts using pre-determined criteria to determine whether to include or exclude the reference for further (full-text) screening. These criteria differ by discipline (and may differ by chemical). EPA uses Population, Exposure, Comparator, Outcome (PECO) statements for the exposure and human health/environmental hazard disciplines; Processes, Exposure, Setting or Scenario, and Outcomes (PESO) statements for environmental fate properties; and Receptors, Exposure, Setting or Scenario, and Outcomes (RESO) statements for the engineering discipline. Screening at the title/abstract level is meant to decrease screening burden because reviewing titles and abstracts takes less time than screening full texts and many references can be determined to be off-topic at this stage. The ability to exclude irrelevant studies at the title and abstract level also reduces the cost of purchasing the full reference texts (*i.e.*, PDF).

If a reference is determined to be on-topic during the title/abstract screening step, EPA obtains PDFs of the studies, loads them into the HERO database and the references advance to full text screening. Some disciplines such as exposure and hazard also tag some title/abstract screening results as "unclear" if the screening result is not certain. EPA retrieves PDFs for these "unclear" studies and then screens the full texts. Although EPA may use the same criteria statements at full-text screening, the criteria may be revised as needed based on the screeners' experiences during title/abstract screening. Appendix H presents criteria statements used for the respective disciplines for the chemicals started in 2019, the MRREs, evaluation of Asbestos Part 2 (supplemental evaluation including legacy uses and associated disposal), and 1,4-dioxane supplement. These PESO/RESO statements may be updated in future iterations to better incorporate information relevant for special considerations (*e.g.*, PESS,

[8] The *o*-dichlorobenzene (*o*-DCB), triphenyl phosphate (TPP), and phthalic anhydride literature pools were used as pilots for SWIFT Review reference prioritization and title and abstract screening. These pilots used a 50th percentile (median) score as the threshold value. Results from these pilots showed that this value was overly conservative and included too many off-topic references. Therefore, this threshold value was updated to the 80th percentile for subsequent chemicals.

environmental justice).

The screening process is similar for both the title/abstract and full-text screening phases. Both start with a calibration phase during which a select number of references are screened by all assessors.[9] The screeners then meet to discuss differences in their screening decisions and identify where clarification or refinement of the screening criteria or chemical-specific supplemental material tags might be needed. During this phase, EPA may also develop detailed guidance to assist assessors in the screening process.

After calibration, screeners are assigned a batch of references to review. Each reference is screened by two independent screeners to ensure a more robust result. If the two screeners' responses differ, they may work together to resolve the conflict. If they cannot reach consensus or if they encounter situations that may be common to multiple screeners, they may consult discipline-specific experts or the full screening team. Some disciplines (*e.g.*, engineering) may instead use a third independent reviewer to resolve conflicts.

EPA uses the specialized web-based software programs DistillerSR[10] and SWIFT-Active-Screener,[11] [12] to assist with the screening process. Using these tools, EPA develops electronic forms with questions based on the PECO and other criteria statements. The tools are important to assist with the workflow when assessors need to screen thousands of citations. These tools also ensure transparency in the process by tracking the individuals who screened each study and their screening decisions. DistillerSR and SWIFT Active-Screener also track disagreements in screening decisions among the two screeners of a reference so that they can more easily resolve any disagreements.

EPA may use either SWIFT Active-Screener or DistillerSR to do the initial title/abstract screening. A chemical with a large number of references is screened using SWIFT Active-Screener in order to take advantage of the machine learning aspects of this software that reduce the amount of manual screening required. As the screening proceeds, the machine-learning algorithm in SWIFT Active-Screener automatically computes which of the remaining unscreened documents are most likely to be relevant.[13] The algorithm is constantly updating as the screener makes decisions about including or excluding references and thus it is able to reasonably predict whether to include or exclude a reference. SWIFT Active-Screener also has a statistical model that estimates the number of relevant articles remaining in the pool of references that are waiting to be screened. EPA screens 95 percent of the references predicted by the algorithm to be relevant for the discipline and chemical being screened.

Although several disciplines (*e.g.*, exposure and engineering) used SWIFT Active-Screener exclusively to do the initial screen of titles and abstracts of the 2019 high priority substances and MRREs, the

[9] For hazard, all 2019 high priority substance title and abstract projects included a calibration step, except for *o*- and *p*-dichlorobenzene; these two chemicals were screened together in one project for a pilot screening.
[10] As noted on the DistillerSR web page, this systematic review software "automates the management of literature collection, triage, and assessment using AI and intelligent workflows...to produce transparent, audit ready, and compliant literature reviews." EPA uses DistillerSR to manage the workflow related to screening and evaluating references; the literature search is conducted external to DistillerSR.
[11] SWIFT-Active Screener is another systematic review software that EPA is adopting in the TSCA systematic review process. From Sciome's SWIFT-Active Screener web page: "As screening proceeds, reviewers include or exclude articles while an underlying statistical model in SWIFT-Active Screener automatically computes which of the remaining unscreened documents are most likely to be relevant. This 'Active Learning' model is continuously updated during screening, improving its performance with each reference reviewed. Meanwhile, a separate statistical model estimates the number of relevant articles remaining in the unscreened document list."
[12] 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.
[13] Description comes from the SWIFT-Active Screener web page.

hazard discipline used DistillerSR for chemicals with smaller pools of literature and SWIFT Active Screener for larger datasets (>1,000 references). Appendix F identifies which software tool was used for each of these chemicals for the hazard discipline.

EPA uses two simple screening outcome tags (*i.e.*, relevant or not relevant according to the pre-established criteria) in SWIFT Active-Screener. Unclear references are treated as relevant in this software. Also, for disciplines such as hazard that include supplemental tags (*e.g.*, mechanistic or toxicokinetic data) for references that may be reviewed later, these supplemental tags are also initially identified as relevant in SWIFT Active-Screener. After conflict resolution between these dichotomous (relevant/not-relevant) options is completed in SWIFT Active-Screener, all references are moved to DistillerSR. Disciplines that use the supplemental tags then go through a second conflict resolution in DistillerSR to complete the title/abstract screening phase. This second conflict resolution phase is needed for those references that still show differing results among the clearly "included" citations that proceed immediately to full-text screening and those that are "supplemental" and kept for possible future screening and data evaluation later.

For chemical title and abstract projects screened exclusively in DistillerSR, 100 percent of all references, whether included, supplemental or excluded, are screened manually for relevance and conflicts between criteria-relevant, excluded, and supplemental references are resolved between the screeners.

During the title and abstract and full-text screening, relevant references are tagged for specific data elements and these tags are subsequently used to construct the literature inventory trees. In the case of exposure, these tags are also used for tables. Section 4.7 discusses how the tags of on-topic references for title and abstract and full-text screening are used to construct the inventory trees and evidence tables.

For engineering, on-topic references are tagged for one or more data elements:

- general facility estimate,
- occupational exposure, and
- environmental release.

For exposure, the following tags are assigned during screening to identify specific pathways:

- Ambient Air
- Indoor Air
- Surface Water (includes wastewater)
- Groundwater
- Drinking Water
- Sediment
- Biosolids
- Soil
- Aquatic
- Terrestrial
- Field Aquatic Species
- Field Terrestrial Species

The exposure pathway tags were used to facilitate further consideration of the reference in full-text screening but were not used in prioritization.[14]

[14] For the 2019 high priority substances, one more set of tags was applied to each reference based on the exposure pathways.

For hazard, EPA screens and tags multiple data types:

- Environmental Hazard – Ecological Studies
- Human Health Hazard – Animal Toxicity Studies
- Human Health Hazard – Epidemiology Studies

Hazard studies may also be tagged as supplemental for possible later evaluation. Examples of these supplemental tags include mechanistic (including genotoxicity) studies, toxicokinetic and physiological based pharmacokinetic models, non-English studies, conference abstracts. Supplemental tags used for the 2019 high priority substances, MRREs, Asbestos Part 2, and 1,4-dioxane uses are identified in tables within Appendix H.

Linking and Tagging Epidemiological Cohort Studies

In many epidemiological cohort studies, similar tables may be included to show continuity and context for tracking of the cohort. After epidemiology studies are screened individually in DistillerSR, peer-reviewed studies by the same authors are manually assessed to determine whether the same results tables are duplicated in multiple publications. If it is found that authors conducted one study and published the same results tables in multiple publications, then these studies are linked in DistillerSR. The reference with more detailed information is treated as the parent reference and the associated reference or references with less detailed information are linked as child references. Each set of linked parent and child references is then selected for either independent or non-independent review for data evaluation. Independent review is selected if the child reference provides additional results that are not included in the parent reference. For independent linked references, each of the linked references is reviewed separately but is accompanied by a table indicating the relationship between studies. Non-independent review is selected if the child reference does not provide any additional results that are not included in the parent reference. A non-independent child reference may provide additional details about methods or other aspects of the parent study that are relevant to data quality evaluation. Therefore, each set of non-independent references undergoes review together. For non-independent linked references, reviewers evaluate the parent reference and use information in the linked child reference to support the evaluation.

4.3 Gray Literature Search and Screening Strategies

EPA conducts a gray literature search for available information to support the TSCA risk evaluations. Gray literature is defined as the broad category of data or information sources not found in the standard, peer-reviewed literature databases such as PubMed and Web of Science. It is produced by organizations outside of traditional academic publishing channels. Gray literature includes data/information sources such as white papers, conference proceedings, technical reports, reference books, dissertations, information on various stakeholder websites, and various databases. Given how gray literature is curated, results may not include a bibliographic citation or abstract. Therefore, gray literature is processed using a decision tree logic described in Section 4.3.2 for potential relevance prior to applying a discipline-specific PECO at full-text screening.

Exposure pathways for each chemical were initially denoted as either primary or supplemental based on applicable EPA regulatory rulings by route of exposure/exposure pathway. If the chemical is not currently regulated as a hazardous air pollutant (HAP) or drinking water contaminant, all pathways are considered "primary." If it is regulated as a HAP, the ambient air pathway is considered "supplemental," and all other pathways are considered "primary." Thus, all PECO-relevant studies were categorized as follows:

1. Primary (covers any pathway not currently regulated by EPA)
2. Supplemental (covers only pathways currently regulated by EPA)
3. Unclear (pathways are unclear from title/abstract)

The designation for supplemental studies was later determined as unnecessary and those studies were brought into the data evaluation process as described in Section 5.

Search terms varied depending on source and based discipline-specific knowledge of the utility of a given source to provide potentially relevant information. A summary of sources are provided in are provided in Appendix E, Table_Apx E-1, and Table_Apx E-2. A summary of search terms are provided in Appendix E, Table_Apx E-4 and Table_Apx E-5.

Databases with physical and chemical property information (see Appendix E.1) are searched earlier than the rest of the gray literature because there is a need to identify physical and chemical property endpoints early in the evaluation process to inform scoping activities.[15] Appendix E.1 also provides the list of databases that are regularly searched, a summary of the data and information contained in each, and their curation and quality control processes. Gray literature sources are searched for physical and chemical property information using the corresponding CAS Registry Number (CASRN) and chemical name.

Physical and chemical properties affect several aspects of chemical risk evaluation, including determination of expected environmental concentrations for exposure assessments and possible routes of exposure for human health assessments. The physical and chemical properties to be identified for the risk evaluation are listed in Appendix H.1.

The criteria for determining the potential relevance of documents identified from gray literature sources are described in the following sections.

4.3.1 Gray Literature Search Strategy for Hazard, Fate, Engineering, and Exposure

EPA has curated lists of websites and databases since 2017 to target sources of gray literature that may yield useful primary and secondary data for each discipline. Although these data sources focus on primarily on the fate, engineering and exposure, and hazard disciplines, there may be some information on physical and chemical properties as well. Depending on the source, the search terms used to search for documents related to each chemical may vary. For example, if a site or database provided the ability to search by CAS number, this was used by default. If a chemical name was required for a search, a shortened list (when compared to peer-reviewed literature search strings) of chemical synonyms or chemical group terms were employed for each chemical search. This revision of search terms is necessary because of limitations in the length of search strings supported by gray literature sources (typically fewer than 256 characters). For the chemicals listed in Table 1-1, the gray literature search strings provided in Table_Apx E-4 in Appendix E were developed by librarians and chemists. In addition to recording results by chemical search per databases, EPA also documented whether a database yielded “no results” for an individual chemical.

4.3.2 Screening of Gray Literature

To reduce the overall burden of processing gray literature results, EPA employs a screening process to determine the potential relevance of gray literature sources.
Figure 4-3 describes the decision logic used to screen gray literature search results. Screening is done on gray literature search results rather than gray literature sources, as sources may yield results that meet the decision tree criteria in some cases while also yield some results that do not meet the decision tree criteria in other cases.

[15] For the 2019 starts, the search results from the physical and chemical property databases did not undergo screening under the gray literature decision tree (Section 4.3.2).

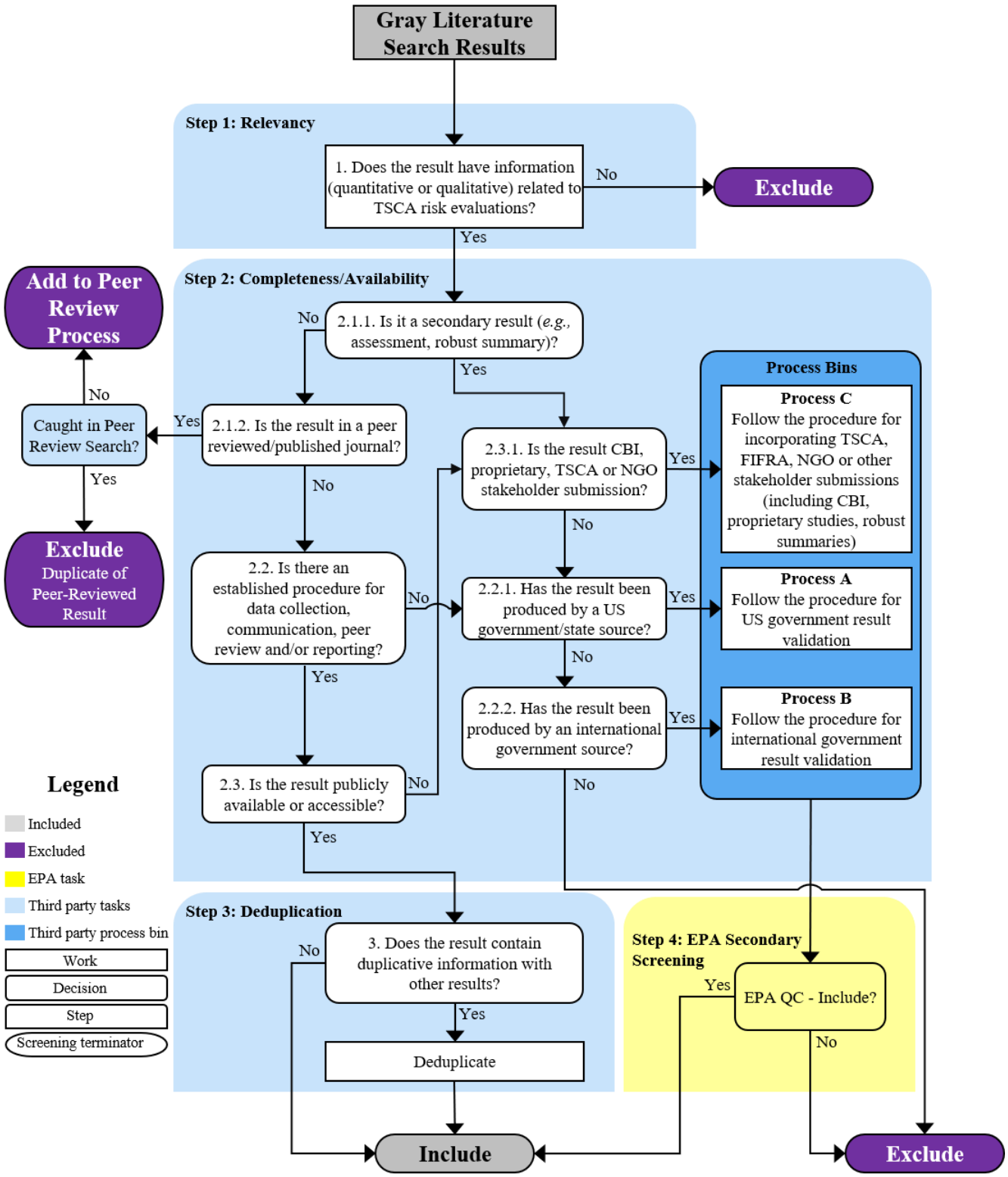

Figure 4-3. Decision Logic Tree Used to Screen Gray Literature Search Results

4.3.2.1 Initial Screening of Sources Using Decision Logic Tree

The purpose of the inclusion/exclusion decision logic tree in Figure 4-3 is to provide a broad, general screening technique to determine whether each gray literature source should be included and further screened or excluded with no additional screening. The rectangular boxes with the rounded edges in the decision tree require analysis and decision by the screener, whereas the boxes with the sharp edges are a straightforward work. Literature screening performed via the gray literature decision logic tree is a manual process. All the questions used in the decision process are provided in Table 4-1.

Table 4-1. Decision Logic Tree Overview

Step	Question	Considerations
1.	Does the result have information (quantitative or qualitative) related to TSCA risk evaluations?	• Does it present information (quantitative or qualitative) that is relevant to TSCA risk evaluations of a chemical of concern? Discipline-specific examples can be found in Section 4.3.2.1.1 below. • At this stage, a gray literature source may be potentially relevant for one discipline but not potentially relevant for another. • This step does not fully consider the PECO or other criteria statement but rather the potential for relevant data. The PECO or other criteria statement is considered during the full-text extraction step.
2.1.1.	Is it a secondary result (*e.g.*, assessment, robust summary)?	• Secondary results include assessments with no original data, TSCA submission databases, or robust summaries that are analyses of data. • If the result contains any primary data, it satisfies the primary result criteria and should not be categorized as a secondary result.
2.1.2.	Is the result in a peer-reviewed/ published journal?	• If the study is published in a peer-reviewed journal it should be excluded in the gray literature decision tree process and move to the peer-reviewed literature process (described previously). In such cases, the decision is to "check in peer."
2.2.	Is there an established procedure for data collection, communication, peer review and/or reporting?	• Does the result include reference to a sampling methodology, reporting rule, or guidance manual that indicates some quality assurance mechanism? If there is no indication that the source was peer-reviewed, are there standardized or published methods implied, or a protocol referenced? • Indications of an established procedure for peer review may be given as a link, page citation, or description of a peer review process found on the result's landing page or within the document. • In some instances, if proof of data collection and reporting procedures are noted then this would satisfy this criterion. The aim is for this to be a soft check and to provide assurance that the data adheres to some type of protocol and/or peer review to provide confidence on how data was collected. • This step is to establish whether the source has been subject to any established procedures for data collection, communication, reporting, and/or peer review. In this step, the reviewer should not evaluate the data quality of the result; the evaluation of the methodology occurs downstream in the data evaluation steps (see Section 5).
2.2.1.	Has the result been produced by a U.S. government/state source?	• Results produced by U.S. government sources that may or may not have established procedures for data collection, communication and/or reporting, or are not publicly available, do move forward. • This includes secondary results such as databases or documents curated by government agencies.

Step	Question	Considerations
		• Examples range from the Water Quality Portal (WQP) database with data on chemical occurrence in water to IRIS assessments. • Further considerations for Process A results are outlined in Section 4.3.2.1.3
2.2.2.	Has the result been produced by an international government source?	• Results produced by international governments move forward regardless of evidence of having been developed using established procedures for data collection, communication and/or reporting, or public availability. • This includes secondary results such as data or documents curated by government agencies. • Further considerations for Process B results are outlined in Section 4.3.2.1.3
2.3.	Is the result publicly available or accessible?	• This step is a check on how accessible the information is to the assessors, reviewers, and the public. • The difference between sources that are publicly available and publicly accessible is that accessible results need search parameters to be found, whereas available results do not require any search parameters. ○ An example of a publicly accessible source is a link to a public database. The gray literature source may be referencing data that is found in the accessible database but does not provide any information on how to retrieve the data contained in the database.
2.3.1.	Is the result CBI, proprietary, TSCA or NGO stakeholder submission?	• Does the result contain any confidential or proprietary information? • This may include results from sources that contain masked information/data that cannot be found elsewhere; for example, the ECHA database. • TSCA submissions that were not found through TSCA database searches should not enter the decision tree process and should be tracked in a separate file which is provided to EPA.
3.	Does the result contain duplicative information with other results?	• Are there any obvious or apparent redundancies in information provided by another result? • If a gray literature result is duplicative with another result, EPA staff uses professional judgment to determine which gray literature result to include and exclude the other result from the downstream full-text, extraction, and evaluation steps.

4.3.2.1.1 Step 1: Relevancy

Relevancy refers to whether the gray literature and its associated data may be related to the risk evaluation of the particular chemical being evaluated. A gray literature result (a study or database value from a gray literature source) is potentially relevant when it presents information (quantitative or qualitative) that is relevant to TSCA risk evaluations. Each result is screened for potential relevance to each discipline and tagged appropriately. An answer of "Yes" to any one of the following discipline-specific criteria results in a gray literature result being tagged as potentially relevant:

- Physical and chemical properties
  - Search result provides physical or chemical property information as outlined in Appendix H.1
- Fate
  - Search result provides information on environmental fate and transport, persistence, bioaccumulation, and waste removal
- Engineering

    - Search result provides information related to manufacturing processes, general facility estimates, occupational/workplace exposure, and environmental releases
- Exposure
    - Search result provides chemical-specific or chemical-non-specific information related to consumer use scenarios
    - Search result reports measured media concentrations that relate to human exposures, including indoor air contaminants, drinking water, and other environmental exposures
    - Search result pertains to human biomonitoring studies
    - Search result contains non-chemical specific exposure factors, such as food or water ingestion rates
- Environmental Hazard
    - Search result provides ecological health endpoints measured at the level of species or lower biological organizations
- Human Health Hazard
    - Search result provides information related to human health endpoints in epidemiological, animal toxicity, and *in vitro* studies

4.3.2.1.2 Step 2: Completeness and Availability

Screening for completeness ensures that gray literature search results and associated data provide documentation of established peer review or quality assurance procedures using a step-wise process, as detailed in Table 4-1. In Step 2.1.1, the screener evaluates whether the result is "secondary," such as assessments with no primary data, TSCA submission databases, or robust summaries of existing data. If the search result is secondary data (*i.e.*, does not contain original data), the screener moves to one of three processes (A, B, or C) in Step 2.3.1. If the result contains primary data, the screener moves to Step 2.1.2 to determine whether the document is published is peer-reviewed. If so, the result is excluded from the gray literature decision tree process and is moved to the peer review literature process; if not, the screener would proceed to Step 2.2.

In Step 2.2, the screener checks whether the search result uses an established procedure for peer review, data collection, communication and/or reporting. A description or reference to a sampling or analytical methodology, a reporting rule, peer review process, or a guidance manual that describes the quality assurance protocol is adequate/sufficient to include the source in further screening. At this stage, the screener does not perform data evaluation. Rather, at this time the screener records the presence or absence of some quality assurance documentation and notes the citation or statement provided by the author. The evaluation of the study methodology occurs at the discipline-specific data evaluation step. If so, the author documented, or cited quality assurance protocols and the screener moves to Step 2.3. If not, the screener moves to Step 2.2.1 and, if necessary, Step 2.2.2 where it is determined whether the source is domestic or international, respectively.

Availability refers to how accessible the information is to assessors, reviewers, and the public. In Step 2.3, screeners verify that the information from the source is publicly available or accessible. The difference between results that are publicly available and publicly accessible is that accessible results need search parameters to be found, whereas available results do not require any search parameters. An example of a publicly accessible source is a link to a public database. The gray literature source may be referencing data that is found in the accessible database but does not provide any information on how to retrieve the data contained in the database. If a screener determines that a result is publicly available or accessible, they move to Step 3 to determine if it is a duplicate result. If a result either does not indicate a quality assurance procedure in Step 2.2 or is not determined to be publicly available in Step 2.3, it is not excluded at the initial screening process. These results would yield to an alternate process by one of

the following steps:

- Process A – The results are produced by primary U.S. governmental sources that do not have established procedures for data collection, communication and/or reporting, are not publicly available or are secondary sources via Step 2.2.1.
- Process B – The results are produced by primary international governmental sources that do not have established procedures for data collection, communication and/or reporting, are not publicly available or are secondary sources via Step 2.2.2.
- Process C – The result is a TSCA, NGO, or other stakeholder submission (including CBI and proprietary studies as well as robust summaries such as FIFRA) via Step 2.3.1.

There are additional considerations for gray literature sources that are proprietary or confidential business information (CBI). It should be noted that the results been produced by the government, or the government literatures, will be defined as the documents or the sources directly and originally produced by a government agency, or produced by the third party whose works are fully under the control of a government agency and the documents or the sources are the property of a government agency. Any documents which are not produced by the government, even they are provided by the government, will be treated as non-government documents.

4.3.2.1.3 References that Require Alternate Processes

Processes A and B: U.S. Government and International Sources

Certain sources go through specific screening processes, Process A is used for U.S. government sources and Process B for international government sources. Many of these sources are previous assessments completed by federal and state agencies that either contain secondary data that could have been missed by peer-reviewed literature database searches or contain primary data, such as modeled media concentrations and dose-response analyses that could be useful for comparisons.

EPA considers Process A and B sources on a case-by-case basis. EPA generally considers several parameters when determining to include or exclude a source. These parameters include whether the source has

- primary or secondary data;
- an established evaluation procedure or has been subject to a procedure for data collection, communication, reporting, and peer review; and
- publicly available or could be made publicly available.

Gray literature sources that meet the conditions of having primary data, having developed using established procedures for peer review, data collection, communication, and/or reporting and are/could be made publicly available move on to full-text screening. EPA may decide to initiate a backwards search as described in Section 4.3.3 on sources that are deemed to have relevant secondary data.

In situations where parameters are unclear, EPA may reach out to the source or agency authors to retrieve information to help gauge whether the source should be included or excluded from further review.

Process C: TSCA and other Stakeholder Submissions

Search of EPA Databases for TSCA Submissions: EPA screens non-CBI and CBI information submitted under TSCA sections 4, 5, 6, 8(d), and 8(e), as well as for your information (FYI) submissions to find data potentially relevant to physical and chemical properties, environmental fate, engineering (including occupational exposure, release, manufacturing, processing, use, and disposal data), exposure, human health hazard, and environmental hazard. EPA considers the databases that contain TSCA submissions

to be secondary sources (Step 1.1 in the Decision Logic Tree) because the metadata in the databases are secondary. Sources identified within these databases (and which often include primary data) advance to Step 2.3.1 and then to Process C. The Process C steps are described here.

EPA generally searches four databases that house TSCA submissions (two are not CBI and two contain CBI data), which are identified in Appendix E.3. Occasionally, information pertinent to one of the TSCA authorities may be submitted through a unique docket or other method. For example, under an enforceable consent agreement pursuant to TSCA section 4 (EPA-HQ-OPPT-2012-0209), signatory companies conducted testing and generated data for octamethylcyclotetra- siloxane (D4) that was subsequently submitted to EPA.

Title Screening: First, title screening of each data source is conducted using two screeners and the inclusion and exclusion criteria within the relevant PECOs, PESOs, or RESOs for each discipline (Appendix H). This title screening step is particularly useful to decrease the number of studies that need to be obtained from microfiche or long-term storage. For example, a study summary may be submitted in one instance, but the full study may be submitted in another case; OPPT prioritizes the full study. Also, OPPT excludes interim reports (*e.g.*, interim sacrifices for toxicity studies) and conducts full-text screening only on final reports. Third, some submitted data may not be relevant for TSCA risk evaluations. If the title is not clear regarding the document's contents, EPA obtains the full-text and advances to full-text screening.

Depending on the needs of the risk evaluation or the availability of data from other sources, EPA may decide not to obtain some studies from microfiche or in long-term storage. For example, acute oral studies may not be needed for a chemical evaluation that assesses only inhalation and dermal routes or environmental media concentration data for non-persistent chemicals that are several decades old and more recent data is available.

Full-Text Screening: After full text PDFs are obtained, EPA considers the same parameters identified in Process A and B, including whether the source has

- primary or secondary data;
- an established procedure for peer review, data collection, communication and/or reporting; and
- is publicly available or could be made publicly available.

Sources that have primary data, an established procedure for peer review, data collection, communication and/or reporting and are/can be made publicly available moves on to full-text screening. Due to the varied nature of data submitted to the agency under sections of TSCA, EPA evaluates these parameters in different ways. For example, adherence to OECD guidelines and good laboratory practices (GLP) may be sufficient for toxicity and environmental fate studies, but exposure monitoring data would require other procedures such as identification of a sampling plan.

In situations where procedures for peer review of the data and data collection processes are unclear, EPA may reach out to the authors to retrieve information to gauge whether the source should be included or excluded.

Sometimes companies submit studies published in peer-reviewed journals. Similar to Step 2.1.2, the study is excluded and moves to the peer review literature screening process. Any studies not already captured through the peer-reviewed literature are then screened and evaluated for data quality if relevant.

EPA may decide to initiate a backwards search, as described in Section 4.3.3 for any individual TSCA submissions that are secondary sources.

EPA conducts full-text screening within DistillerSR using HERO IDs as unique identifiers. EPA generates unique HERO IDs for only one copy of the final report and splits PDFs that contain multiple studies in a single submission into individual study PDFs. Duplicate copies and interim reports are identified in a "comments" field within the HERO entry for the final study. Similar to the title screening step, two screeners screen each full text according to the PECOs, PESOs, and RESOs (see Appendix H).

EPA conducts multiple checks for duplication of TSCA submissions throughout the process. After de-duplication, EPA implements the "Proprietary/CBI Sources" process described in Section 4.3.3 for any remaining CBI sources.

Other Stakeholder Data Submitted to EPA

Additional stakeholder data may be submitted to EPA under other authorities (*e.g.*, Federal Insecticide, Fungicide, and Rodenticide Act [FIFRA]). Also, data may be submitted from non-governmental organizations (NGOs) or academia. Industry may also submit information to EPA in other ways. Sources of other stakeholder data all go through relevant steps identified in Process C described above. For example, a full study skips title screening, and a publicly available study does not need CBI substantiation but goes through other identified steps. Deduplication steps are still important but are likely fewer than the number of TSCA submission deduplication steps.

4.3.2.1.4 Step 3: Screening for Duplicates

The de-duplication step (see Figure 4-3) determines whether a gray literature result is an exact duplicate of another gray literature result or has overlapping information with another result from either the gray literature search or from peer-reviewed journals.

If a gray literature source is duplicative of one or more other sources, EPA uses professional judgment to determine which source to keep, while usually excluding the other source(s) from the downstream full text, extraction, and evaluation steps. Factors include which source contains the most information on a study and the identity of the submitter (*e.g.*, the company that sponsored a study is preferred to an alternate submitter). Sometimes EPA evaluates a gray source along with a duplicative study (*e.g.*, if published in a peer-reviewed journal) because there may be unique information in each source, even if they both report information from the same experiment(s). For transparency and consistency in referencing, EPA retains duplicative studies and links them to each other in HERO and DistillerSR.

Additional considerations in the case of TSCA submissions require EPA to follow multiple de-duplication steps. For example, TSCA submissions are contained in two CBI and two non-CBI databases (Appendix E); information among these databases may be duplicative. Further, studies may have been submitted to the Agency more than once or could have been duplicated as CBI and non-CBI submissions. Submitters may also send EPA both interim and final reports for a given study; EPA prioritizes the final reports and excludes the interim reports. Finally, in addition to these four databases, TSCA submissions are also cited in peer review databases; EPA excludes the latter citations because the above four databases are more comprehensive.

4.3.3 Obtaining Confidential Business Information and Proprietary Data

EPA considers all reasonably available confidential business information (CBI) and proprietary information information as defined in 40 CFR 702.33 during the systematic review process. For these sources, EPA initiates the same systematic review processes used for publicly available gray literuare.

For any CBI or proprietary data that are not reasonably available (*e.g.*, only summaries of the studies are available), EPA uses the guidelines described in Section 4.4.1 to determine whether the source may have information valuable for use in the risk evaluations. During this process, EPA determines whether such studies are duplicated in public databases (*e.g.*, published in a peer-reviewed journal or submitted later without CBI claims) and uses the public versions whenever possible.

Once EPA has generated a list of data sources to obtain, EPA works with industry sources (*e.g.*, company study sponsors or consortia sponsors) to retrieve the data. In certain instances, EPA is limited in its authority and ability to obtain foreign studies that are not publicly available. If EPA is successful in obtaining these data, the data are also screened and evaluated using the same process used for other gray literature.

For any CBI or proprietary studies that are included during the systematic review process (*i.e.*, those that will be included in the risk evaluations), EPA works with the industry sources to start the process to declassify the studies [better language here] and make them public.

4.4 Backward Searches

Backward searches are used as a validation step of the overall peer-reviewed and gray literature search strategy and as a means of obtaining primary data from secondary sources. For example, EPA reviews summaries that may contain proprietary data (*e.g.*, within OECD SIDS documents, EPA hazard characterizations, ECHA REACH registration dossiers, NICNAS, Japanese National Institute of Technology and Evaluation [NITE] reports). Public comments from various assessment efforts—including comments on previous TSCA existing chemicals drafts (*e.g.*, prior to 2017) and the scope documents for ongoing risk evaluations—are also reviewed to identify additional primary data that may have been missed during the initial literature searches.

EPA identifies key secondary references to be used for backwards searching for each chemical. These references may include existing assessments by government agencies, review articles in the published literature, or other authoritative documents deemed of sufficient quality as described in Section 4.3.2.1.

The reference section of each document and screened into one of the following categories:

- Document not relevant to TSCA risk evaluation (*e.g.*, general risk assessment guidance documents for other government agencies, references that provide non-chemical specific information that is not generalizable to the TSCA risk evaluation, etc.)
- Document relevant to TSCA risk evaluation
    - Physical and chemical properties
    - Fate properties
    - Engineering and occupational exposure
    - General population and consumer exposure
    - Environmental and human health hazards

Next, TSCA-relevant documents are compared against the "included" articles for each discipline for a given chemical from both the peer-reviewed and gray literature searches. These references can be used to assess the efficacy of the search, literature prioritization, and screening processes, and missing references can be included in subsequent systematic review steps (*e.g.*, full-text screening and data evaluation).

Available gray literature sources must be manually reviewed at the most detailed level of information initially provided by that source. For example, EPA reviews each of the robust summaries of proprietary

data for ECHA REACH submissions and OECD SIDS reports as well as titles and abstracts (if full text not also provided) for studies identified via public comments. Each discipline reviews their discipline specific data within the overall gray literature source.

4.4.1 Screening, Reviewing, and Obtaining Studies that Are Difficult to Obtain and Not Reasonably Available

If EPA determines that a primary source referenced within a gray literature source or database may contain valuable information that EPA has not already obtained, EPA initiates a process for obtaining the complete study or data source. If that source is not reasonably available (*e.g.*, EPA has only an ECHA REACH summary), EPA uses the following guidelines to decide whether to retrieve proprietary and CBI information: (1) non-CBI database for a chemical is limited; (2) the CBI data for a specific chemical conflicts with or may conflict with other data used in the risk evaluation; and/or (3) data for a chemical is expected to affect the risk evaluation.

The process to obtain the primary study information from unpublished propritery or CBI studies that EPA does not have in its possession can take years to complete. Therefore, EPA reviews these sources in two phases to initiate the study acquisition process as soon as possible. Phase 1 occurs as soon as the gray literature sources are identified and Phase 2 occurs after data evaluation and extraction of the already-obtained studies has been completed.

4.4.1.1 Phase 1

Each disciplinary team reviews their respective section within each robust summary's gray literature source. When a chemical has robust summaries from multiple sources (*e.g.,* OECD SIDS and ECHA REACH summaries), assessors first determine whether certain studies are cited by both sources. The following studies or information sources are flagged for acquisition if the study is unpublished:

A) Studies that contain data needs identified as part of a TSCA section 4 Test Order
B) Studies that contain an endpoint that might be identified as influencing hazard and that differs from an endpoint identified in existing EPA assessment (*e.g.*, IRIS)
    Note that this requires the reviewer to be generally familiar with the existing assessments for a given chemical substance
C) Significant human health studies, which include
    a. Developmental studies
    b. Cancer bioassays
    c. 1-generation reproductive studies
    d. Multigeneration reproductive studies
    e. Neurotoxicity studies
    f. Chronic (>6-month exposure duration) studies
    g. Examination of unique endpoints or PESS groups
D) Significant ecological health studies, which include
    a. Aquatic and terrestrial environmental hazard studies
    b. All relevant toxicological endpoints
E) Significant exposure data, which include
    a. Exposure concentration, duration, frequency
    b. Worker, consumer activity
F) Significant engineering information, which include
    a. General engineering (*e.g.*, market data, production volume (PV), chemical concentration, uses information)
    b. Occupational exposure (*e.g.*, exposure routes, duration, frequency, personal and/or area sampling data)

c. Environmental release (*e.g.*, description of release source, release or emission factors, release quantity, frequency)

After each discipline has flagged studies for retrieval, the gray literature coordinator begins the process to acquire the flagged studies. If a flagged study has previously been captured during other searches, it does not need to be obtained through the process for obtaining studies outlined below.

4.4.1.2 Phase 2

Each discipline conducts a more thorough review of the robust summaries after EPA has evaluated the resulting Phase 1 data sources for data quality. Based on the known available database of acceptable studies, EPA uses the following logic to determine the utility and need for obtaining the study:

1. If other similar studies are available (*e.g.*, the ECHA summary is for a short-term [*e.g.*, 21-day] repeated dose study and there are already similar studies that used the same species and method)
    a. **EPA does not** obtain the original study in the robust summary if results are very similar to existing full studies
    b. **EPA does** obtain the original study if results are not similar to existing full studies
2. If no other similar studies are available
    a. **EPA does not** obtain the original study currently in the robust summary if the study is not deemed essential (*e.g.*, an oral acute toxicity study if the risk evaluation does not contain conditions of use (COUs) with expected oral pathways; a physical and chemical property for a chemical where that physical and chemical property is not deemed appropriate for that chemical COUs)
    b. **EPA does** obtain the original study if the study is "essential" (*e.g.*, a 90-day repeated-dose toxicity study)
3. If a study has conflicting results to those identified as part of evidence integration
    a. **EPA does** obtain the original study

4.5 Data Obtained Using TSCA Authorities and New Test Orders

As described in previous sections, EPA broadly searches for both peer-reviewed and gray literature that already exist. However, EPA may also issue a rule under TSCA section 8d to request that industry submit any data to the agency in their possession.[16] EPA may also develop test orders under TSCA section 4 authority that require industry to conduct new tests (*e.g.*, *in vitro* dermal absorption assays or hazard study generation) or develop new data (*e.g.*, chemical monitoring data at a manufacturing facility) to fill critical data needs. These tests are intended to fill critical data gaps identified after searches provided from prioritization and scoping, and data gaps identified in systematic review evidence tables for each discipline.

EPA reviews and approves test protocols for studies conducted via test orders prior to initiation. Submitted test order study results are reviewed using the same study evaluation criteria for studies found in the peer-reviewed or gray literature and these data evaluation criteria inform and reiterate to test order recipients the nature of data acceptance criteria of test order generated data.

[16] For the 20 2019 high priority substances, EPA issued a rule under TSCA section 8d on June 29, 2021, to require manufacturers and importers to report data that they already have on health and safety, environmental effects and occupational, general population, and consumer exposure data sources.

4.6 Tagging Structure: Linking HERO Tags vs. Discipline Screening Efforts

Developed to complement and reflect the systematic review process, a unified tagging structure in HERO is used. It is designed to facilitate and document the risk evaluation process with full transparency. Within a chemical project, stakeholders should be able to follow the life cycle of a given reference or subset of references, identify areas of overlap within the project, and view progress at a high level. A description of the full tagging structure with defined explanations of each tag is provided in Appendix J.

4.6.1 HERO ID Assignment: Pre-screening Work

HERO IDs are the singular critical elements to the functionality of the tagging structure. A HERO ID is the unique number ID assigned to a reference upon being added to the HERO database. This process can happen manually or automatically via import. Current practice for OPPT systematic review provides for HERO ID assignment upon receipt, meaning that when a reference package is received, it is immediately entered into HERO and every reference is assigned a HERO ID. Exclusions to this practice include rules (published in the Federal Register [FR] and codified in the Code of Federal Regulations [CFR]), and may follow CFR or Federal Register naming conventions), news and trade articles, and items solely expressing opinions that have not been validated with scientific methodology (*i.e.*, blog posts).

Prior to entering systematic review screening, references are tagged by source (peer-reviewed literature, gray literature, etc.) and discipline as determined by SWIFT-Review filtering.

4.6.2 Tagging Procedures during Systematic Review Screening

Tags are applied to a reference based on values determined during systematic review. This is done as early as possible to preserve the accuracy of review decisions. Reasons for tagging include

- advancement to a new screening level in SWIFT-Active or DistillerSR;
- reassignment to different screening criteria (*e.g.*, a TSCA record is discovered in gray literature and reassigned to TSCA Literature); and
- data relevance and evaluation (inclusion/exclusion, acceptable/uninformative, etc.).

4.7 Mapping the Evidence: Creating Literature Inventory Trees and Evidence Tables

EPA uses literature inventory trees to illustrate the flow of data and information sources as they are reviewed through the different stages of the TSCA systematic review. These web-based data visualizations provide transparency of the decisions resulting from the screening process described above. Developed using EPA's HAWC, the web-based literature trees are generated for each TSCA discipline and are evergreen in that they can be updated as new studies are found and screened. These updates are generally derived from data provided through public comment, peer review, or periodic search updates during life span of the chemical assessment.

The characteristics of the data and information sources included in the screening process are tabulated and presented as evidence tables using Tableau visualization software. The enumerated results displayed in the evidence table are derived either from tags added by screeners in the DistillerSR software during screening or are predicted by SWIFT-Review filters based on TIAB keywords and MESH terms, depending upon the discipline.

The initial inventory trees and evidence tables are critical elements of scoping documents and help inform data gaps and additional analysis for critical data needs for possible test orders. As an example, the literature inventory trees at the full-text screening stage for D4 and corresponding evidence tables are provided in Section 4.7.1 through Section 4.7.5. These figures represent static screen captures of the interactive data visualizations, but links to interactive figures are also provided. Appendix I further provides links to the literature inventory trees and evidence tables for the chemicals listed in Table 1-1.

4.7.1 Literature Inventory Tree for Physical and Chemical Properties

An example literature inventory tree for physical and chemical properties for both the title/abstract and full-text review stages is shown in Figure 4-4. Note that the nature of the studies supporting physical and chemical properties are displayed in data visualizations other than evidence tables (*e.g.*, box and whisker and tornado plots).

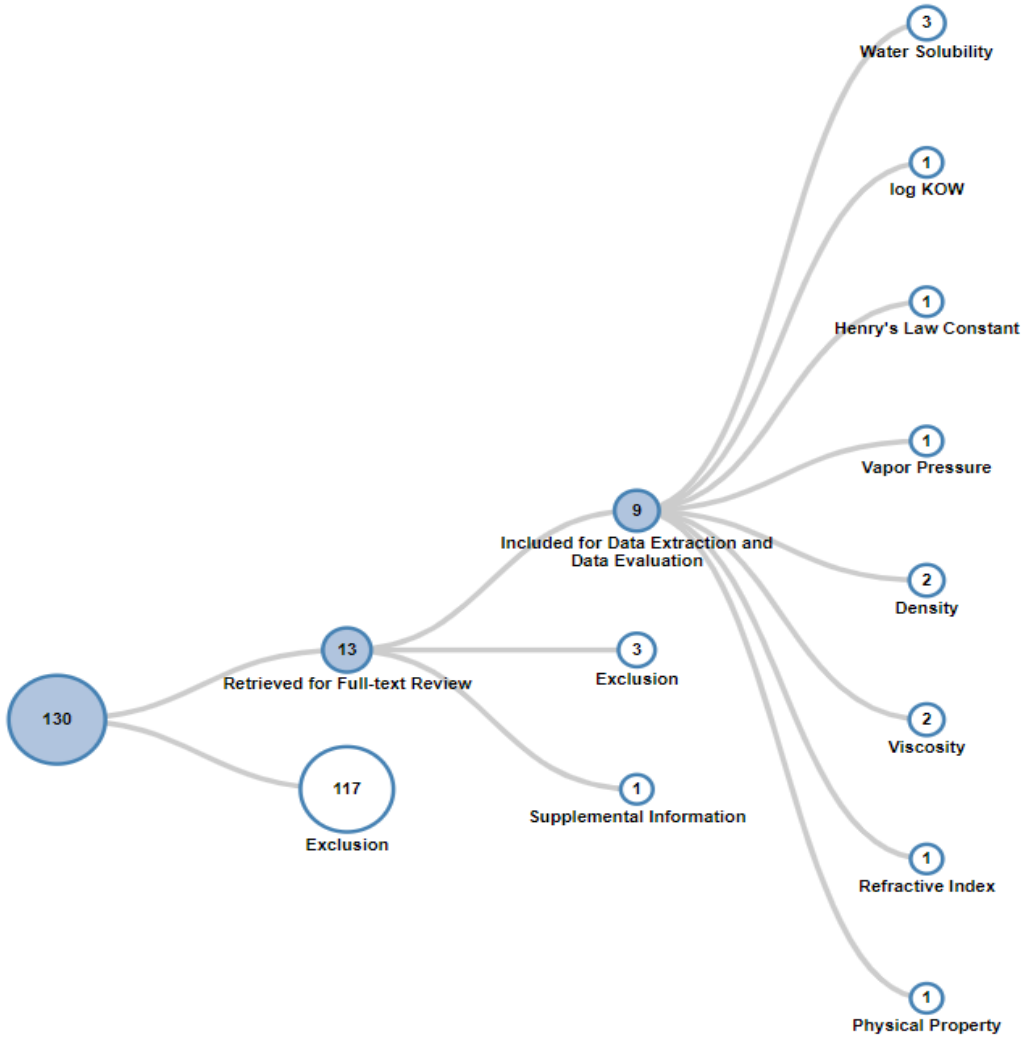

Figure 4-4. Example Literature Inventory Tree for Physical and Chemical Properties for D4
View the interactive literature inventory tree in HAWC. Data in this static figure represent references that were included during full-text screening as of May 6, 2021, which was the cutoff for development of this draft scope. Additional data may be added to the interactive version as they become available.

4.7.2 Literature Inventory Tree and Evidence Table for Fate

An example literature inventory tree for title and abstract screening for the fate discipline is shown in

Figure 4-5. Figure 4-6 presents the proposed layout for the fate evidence table at the title/abstract and full-text screening stages. The fate literature inventory displays the number of included references reporting fate properties or endpoints for various environmental media.

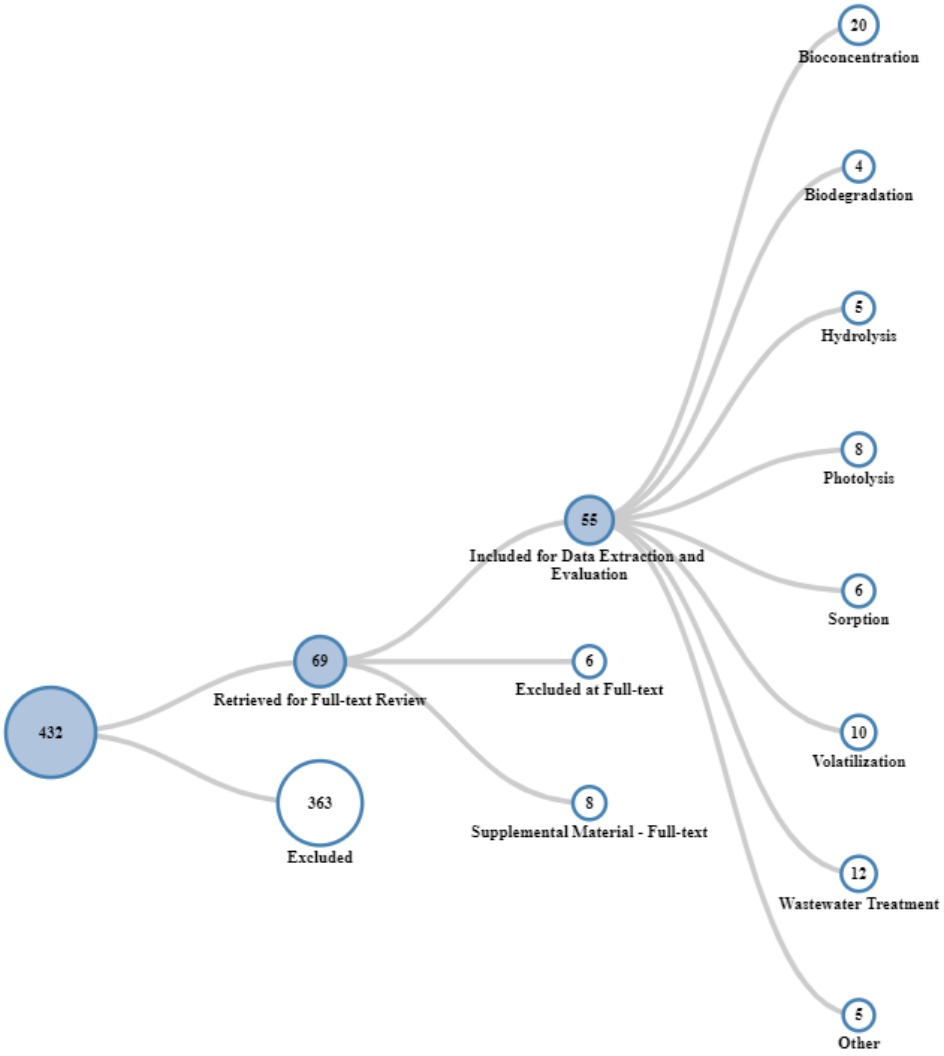

Figure 4-5. Example Literature Inventory Tree for Fate Properties for D4
View the interactive literature inventory tree in HAWC. Data in this figure represent references included during full-text screening as of May 20, 2021. Additional data may be added to the interactive version as they become available.

	Media					
Endpoint	**Air**	**Soil, Sediment**	**Wastewater, Biosolids**	**Water**	**Other**	**Grand Total**
Bioconcentration	1	4	2	19	1	20
Biodegradation		1	1	2		4
Hydrolysis		2	1	2		5
Photolysis	7	2	1	1		8
Sorption		3	1	3		6
Volatilization	4	3	3	6		10
Wastewater Treatment	3	3	11	1		12
Other	2	3	1	4		5
Grand Total	14	15	14	30	1	55

Figure 4-6. Fate Evidence Table for D4
View the interactive version in HAWC for additional study details. The column totals, row totals, and grand totals indicate total numbers of unique references, as some references may be included in multiple cells. The various shades of color visually represent the number of relevant references identified by exposure media or data type. The darker the color, the more references are available for a given exposure media or data type.

4.7.3 Literature Inventory Tree and Evidence Table for Engineering

An example literature inventory tree for title and abstract screening for the engineering and occupational exposure discipline is shown in Figure 4-7. Figure 4-8 presents the proposed layout for the engineering evidence table at the title and abstract screening. It displays the number of included references that report general facility estimates, environmental releases, and occupational exposure information as well as the excluded and supplemental references. EPA further reviews the full texts of included studies and identifies additional categories of information such as the number of facility sites, release quantity, and exposure monitoring data.

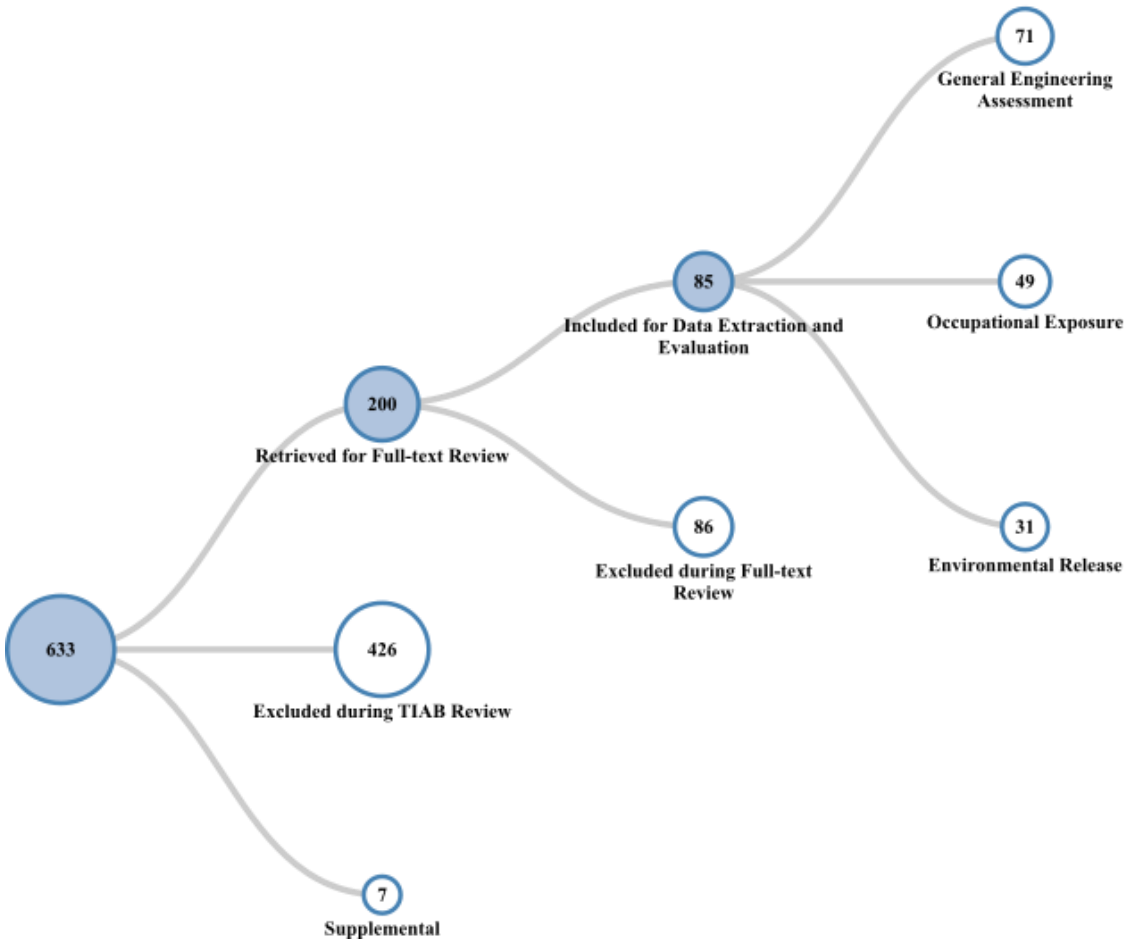

Figure 4-7. Literature Inventory Tree for Engineering and Occupational Exposure Data for D4
View the interactive literature inventory tree in HAWC. Data in this figure represents references included during full-text screening as of May 6, 2021. Numbers for "Included for Data Extraction and Evaluation" plus "Excluded for Data Extraction and Evaluation" may not add up to the number retrieved for full-text review because of ongoing full-text screening, and additional data may be added to the interactive version as they become available.

Data Type	Evidence Tags	
Environmental Releases	Description of release source	25
	No evidence tag	1
	Release frequency	2
	Release or emission factors	17
	Release quantity	8
	Waste treatment methods and pollution control	15
	Total	31
General Engineering Assessment	Chemical concentration	49
	Life cycle description	14
	No evidence tag	5
	Number of sites	7
	Process description	23
	Production, import, or use volume	22
	Throughput	7
	Total	71
Occupational Exposures	Area sampling data	27
	Dermal exposure data	18
	Engineering control	8
	Exposure duration	10
	Exposure frequency	6
	Exposure route	31
	No evidence tag	4
	Number of workers	12
	Particle size characterization	1
	Personal protective equipment	8
	Personal sampling data	7
	Physical form	21
	Worker activity description	14
	Total	49
Grand Total		85

Figure 4-8. Engineering Evidence Table for D4
View the interactive version in HAWC for additional study details. Data in this figure represent references included during full-text screening as of May 6, 2021. The grand total captures the number of unique references. Additional data may be added to the interactive version as they become available.

4.7.4 Literature Inventory Tree and Evidence Table for Exposure

An example literature inventory tree for full-text screening for the exposure discipline is shown in Figure 4-9. Figure 4-10 presents the proposed layout for the exposure evidence table at full-text screening. It displays the number of included references that discuss each exposure pathway as well as the excluded and supplemental references.

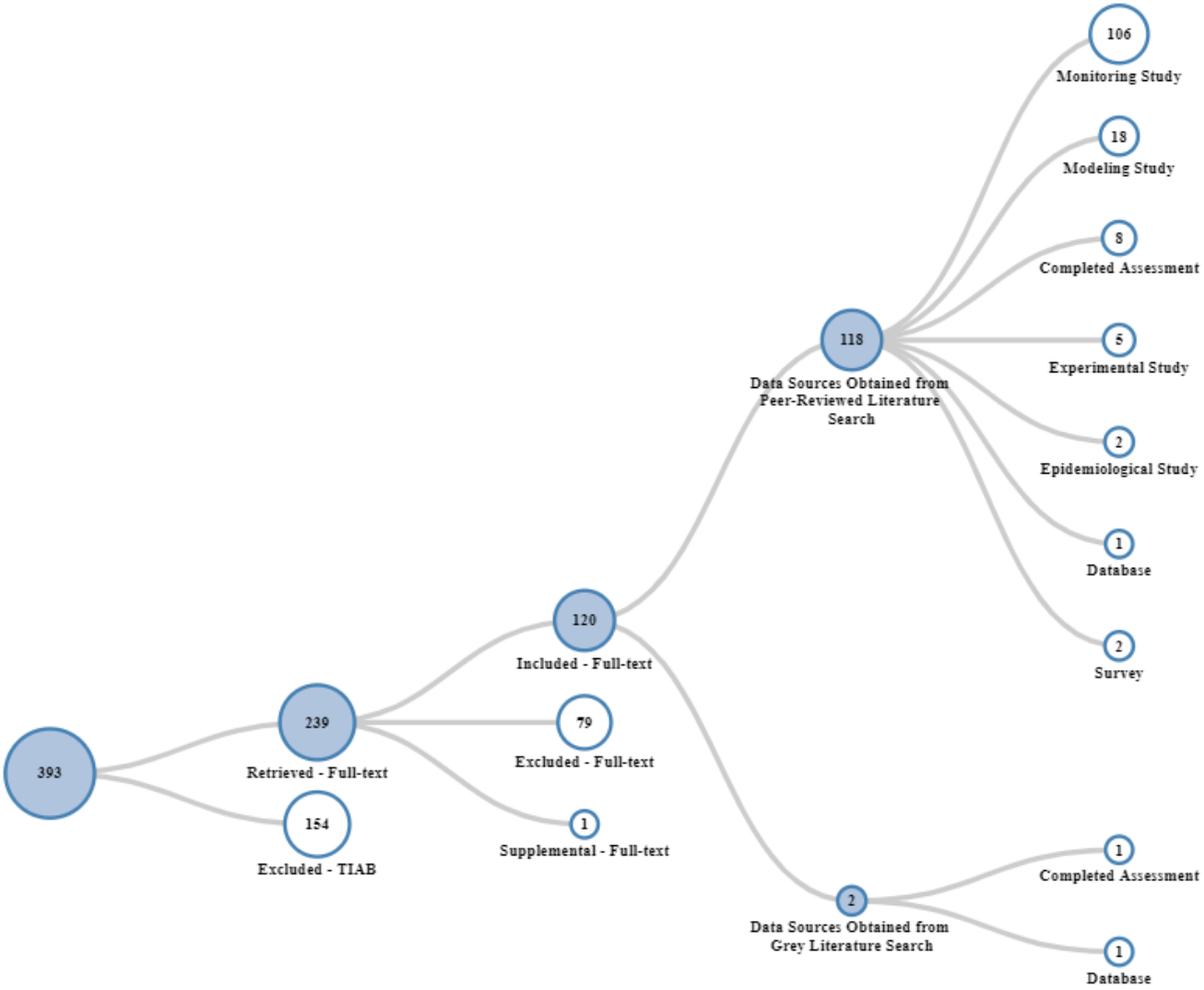

Figure 4-9. Literature Inventory Tree for General Population and Environmental Exposure Data for D4

View the interactive literature inventory tree in HAWC. Data in this figure represents references obtained included during full-text screening as of May 5, 2021. Numbers at the third-level nodes may not total the number retrieved for full-text review because of ongoing full-text screening, and additional data may be added to the interactive version as they become available.

Exposure Heat Map of Octamethylcyclotetrasiloxane (D4)

Media (group)	Data Type: Monitoring Study	Modeling Study	Completed Assessment	Experimental Study	Epidemiological Study	Database	Survey	Grand Total
Ambient Air	29	8	2	2	1			32
Biosolids/Sludge	15	2	4					18
Drinking Water			1					1
Groundwater	1							1
Sediment	28	3	4					29
Soil	14	4	3	1	2		1	17
Surface Water	16	5	4					20
Wastewater	24	3	4					27
Aquatic Species	31		3		1		1	33
Terrestrial Species	5		1		2		1	6
Consumer	10	3	4	5		1		16
Dietary	1		1					2
Dust	7	1	1					8
Exposure Factors			1					1
Exposure Pathway	6	3	1					8
Human Biomonitoring	8	3	1	2				13
Indoor Air	13	2	1	2				15
Isomers	9			1		1	1	9
Use Information			2			1		3
No Evidence Type			1					1
Land Disposal/Landfill	3	1						3
Grand Total	106	18	9	5	2	2	2	120

Figure 4-10. Exposure Literature Inventory Results for D4

View the interactive version in HAWC for additional study details. The column totals, row totals, and grand totals indicate total numbers of unique references only, as some references may be included in multiple cells. The various shades of color visually represent the number of relevant references identified by exposure media or data type. The darker the color, the more references are available for a given exposure media or data type. Data in this figure represent references that were included during full-text screening as of May 5, 2021. Additional data may be added to the interactive version as they become available.

4.7.5 Literature Inventory Tree and Evidence Table for Environmental and Human Health Hazards

An example literature inventory tree for full-text screening for the environmental and human health hazard discipline is shown in Figure 4-11. Figure 4-12 presents the evidence table for plant and animal studies (both human health and environmental models). The following information is summarized: study type (*e.g.*, acute, subchronic, developmental, etc.), route, species, and health system or type of effect assessed. Although certain non-mammalian model systems are increasing used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish) these studies are categorized as ecotoxicological models for scoping and problem formulation purposes, recognizing they may ultimately be considered in human health assessments.

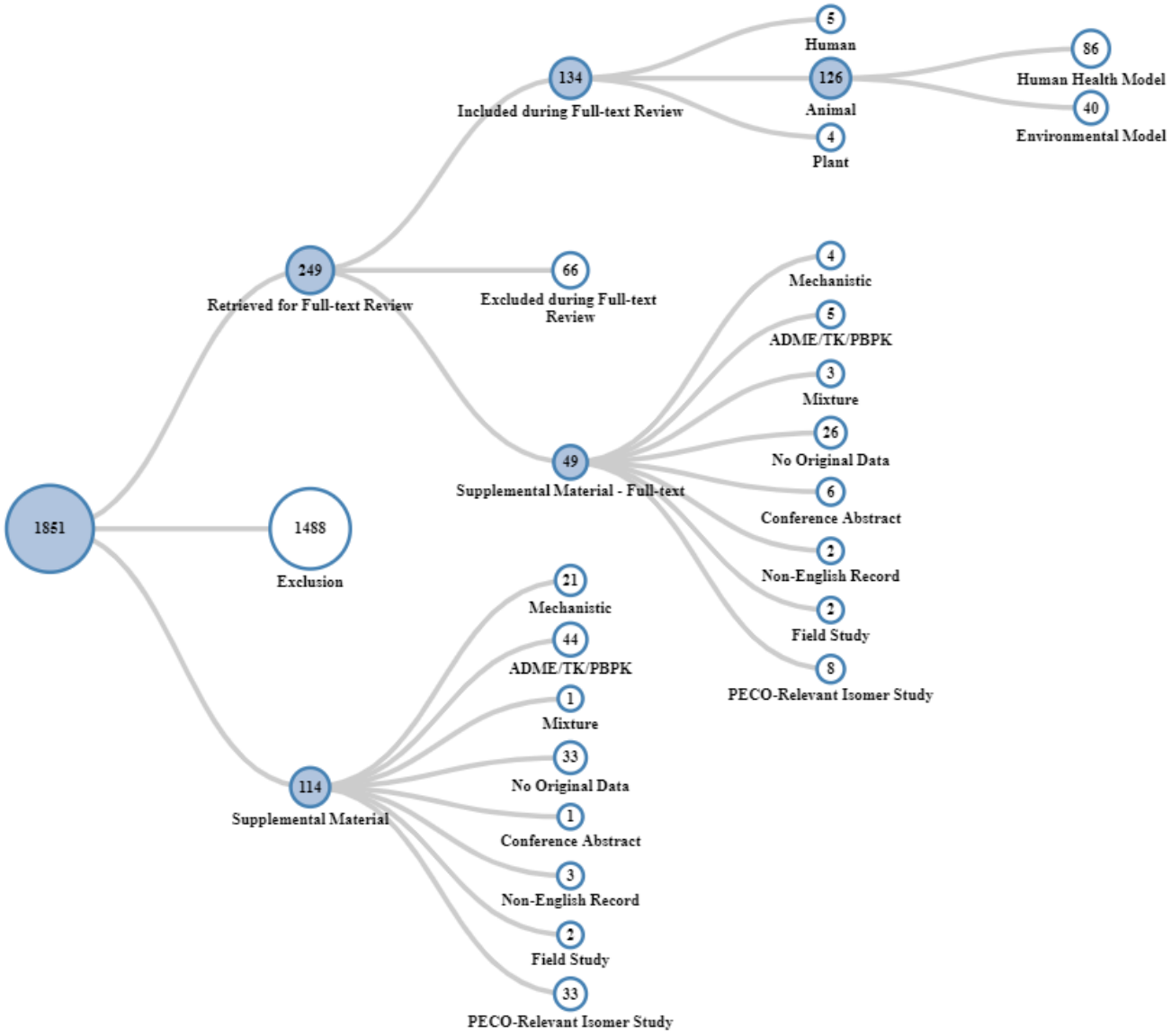

Figure 4-11. Literature Inventory Tree for Environmental and Human Hazard for D4
View the interactive literature inventory tree in HAWC. Data in this figure represent references included during full-text screening as of May 6, 2021. Additional data may be added to the interactive version as they become available.

	Evidence Type				
Health Outcomes	**Human**	**Animal - Human Health Model**	**Animal - Environmental Model**	**Plant**	**Grand Total**
ADME		47	3		50
Cancer		3			3
Cardiovascular					
Developmental		19	4	1	24
Endocrine		13			13
Gastrointestinal	1	2	1		4
Hematological and Immune	2	10			12
Hepatic		15			15
Mortality		3	5		8
Musculoskeletal					
Neurological		5	2		7
Nutritional and Metabolic		6	4		10
Ocular and Sensory	2	5			7
PBPK					
Renal		3			3
Reproductive		22	2		24
Respiratory	1	43	1		45
Skin and Connective Tissue	1	6			7
No Tag	1	21	29	3	53
Grand Total	5	86	40	4	134

Figure 4-12. Human Health and Environmental Hazard Literature Inventory Results for D4
View the interactive version in HAWC for additional study details. The numbers indicate the number of studies with title and abstract keywords related to a particular health outcome, not the number of studies that observed an association with D4. Evidence types were manually extracted, and health systems were determined via machine learning. Therefore, in studies examining multiple health outcomes and evidence types, the connections between health outcome, and evidence type may not be accurately represented. If a study evaluated multiple health outcomes or included multiple populations or study designs, it is shown here multiple times. Data in this figure represent those included during full-text screening as of May 6, 2021.

5 DATA EVALUATION

During data evaluation, EPA assesses the risk of bias, methodological quality, sensitivity and reporting of individual data sources. These sources are used to understand the hazards, exposures, conditions of use, and PESS as required by TSCA. The goal of the method used by EPA is to provide transparency, consistency, and as much objectivity as possible to the evaluation process while meeting the requirements under TSCA section 26(h) and (i) to make decisions based on the best available science and the weight of the scientific evidence.

The evaluation method uses a structured framework to evaluate each data/information source for each discipline used in the risk evaluation. The following sections describe EPA's development of the framework used, a description of the evaluation method, documentation and reviewer evaluation processes, and important caveats about the method. Details related to data evaluation metrics, domains, and criteria are outlined for each of the following disciplines and appendices:

- Physical and chemical properties (Appendix K);
- Environmental fate (Appendix L);
- Occupational exposure and release data (Appendix M);
- Consumer, general population and environmental exposure (Appendix N);
- Exposure Models (Appendix O);
- Environmental hazard studies (Appendix P);
- Animal toxicity and *in vitro* studies (Appendix Q);
- Epidemiological studies (Appendix R); and
- *In vitro* dermal absorption studies (Appendix S).

Appendix T provides a comparison of metrics for hazard data quality criteria (environmental hazard, animal toxicity, *in vitro*, and epidemiological studies).

5.1 Development of the TSCA Systematic Review Evaluation Method to Assess the Quality of Data/Information

To develop the data evaluation strategies, EPA consulted with a broad range of scientists with expertise evaluating a variety of data/information used to inform risk and hazard evaluations and reviewed a variety of evaluation tools and frameworks:

- *Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals (BEES-C) Instrument* (Lakind et al., 2014)
- *Criteria Used in EPA's ECOTOXicology Knowledgebase* (U.S. EPA, 2018b)
- *Criteria for Reporting and Evaluating Ecotoxicity Data (CRED)* (Moermond et al., 2016b)
- Systematic review practices in EPA's Integrated Risk Information System (IRIS) (U.S. EPA, 2018c) as well as the most recent public comment draft of the ORD staff handbook for developing IRIS assessments (IRIS Handbook) (U.S. EPA, 2020)
- EPA's *Guidelines for Human Exposure Assessment* (U.S. EPA, 2019)
- EPA's *Summary of General Assessment Factors for Evaluating the Quality of Scientific and Technical Information* (U.S. EPA, 2003c)
- EPA's *Exposure Factors Handbook* (U.S. EPA, 2011a)
- *Handbook for Conducting a Literature-based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration* (NTP, 2015a)
- *NAS report on Human Biomonitoring for Environmental Chemicals* (NRC, 2006)

- *Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement* (Von Elm et al., 2008)
- ToxRTool (Toxicological data Reliability Assessment Tool) developed by the European Commission (EC, 2018)
- Various guidance documents on exposure, environmental fate and modeling data (see appendices more information) (U.S. EPA, 2019; EC, 2018; OECD, 2017; Cooper et al., 2016; ECHA, 2016; Lynch et al., 2016; Moermond et al., 2016a; Moermond et al., 2016b; Samuel et al., 2016; NTP, 2015a, b; Hooijmans et al., 2014; Koustas et al., 2014; Lakind et al., 2014; NRC, 2014; OECD, 2014; Kushman et al., 2013; Hartling et al., 2012; ECHA, 2011a, c; U.S. EPA, 2011a, b; Hooijmans et al., 2010; U.S. EPA, 2009; Von Elm et al., 2008; OECD, 2007; Barr et al., 2006; FTC, 2006; NRC, 2006; U.S. EPA, 2006; ATSDR, 2005; OECD, 2004a, 2003; U.S. EPA, 2003a, b, c; Bower, 1999; OECD, 1998, 1997, 1995; NRC, 1991)

Of the above references that informed TSCA evaluation method and its evaluation domains, metrics, and criteria for hazard, the IRIS Handbook (U.S. EPA, 2020) was highly influential. Evaluation domains represent general categories of attributes that are evaluated for each study (*e.g.,* test substance, test conditions, reliability, representativeness). Each domain contains a unique set of metrics, or sub-categories of attributes, which are intended to assess an aspect of the methodological quality, sensitivity, risk of bias, or lack of reporting of the study. Bias is a systematic error in which results are consistently over- or underpredicted (*e.g.,* under-estimating exposure). Methodological quality is the extent to which the authors conducted their studies to the highest possible standards (*e.g.,* whether authors properly measured hematology parameters); methodological quality as used here is distinct from the "overall study quality" levels of *high*, *medium*, and *low* that EPA uses to evaluate the studies. Sensitivity relates to whether a study is sensitive enough to observe effects (*e.g.,* whether detection limits are low enough to measure chemical concentrations) (NTP, 2019). Reporting is the completeness in which study methods and/or results are described.

To evaluate each metric, EPA developed criteria based on professional judgment and existing systematic review frameworks. By design, the TSCA systematic review process uses a fit-for-purpose literature search and relevance-driven eligibility criteria (*e.g.,* PECO) during the title/abstract and full-text screening steps described in Section 3 to exclude irrelevant (off topic) studies before they are evaluated for risk of bias, quality, and reporting. However, the data evaluation step may include some measures of applicability/relevance. For example, to conduct human health hazard identification and a comprehensive weight of the scientific evidence analysis, EPA evaluates studies conducted by all routes of exposure, even if some routes may not be used directly in the dose-response assessment for the risk evaluation.

The TSCA evaluation strategies in some cases refer to study guidelines such as OECD test guidelines and Good Laboratory Practices (GLP); therefore, assessors may consult such test guidelines in addition to the TSCA data quality criteria while evaluating studies. Along with professional judgment, such guidelines assist in determining the adequacy or appropriateness of certain study designs or analytical methods. Use of guideline study protocols should not imply that non-guideline studies have lower confidence than guideline studies. EPA considers any and all available, relevant data and information that conform to the requirements under TSCA section 26(h) and (i) to make decisions based on the best available science and the weight of the scientific evidence when developing the risk evaluations, irrespective of whether they were conducted in accordance with standardized protocol methods.

Some data sources may be evaluated under multiple evaluation criteria. For instance, an epidemiological study may be evaluated by the exposure assessment discipline and the epidemiology sub-discipline within the human health hazard assessment discipline. Exposure assessors evaluate the study for

estimating exposure via direct measurements or modeling. Epidemiologists evaluate the same study for associations between the chemical exposure and health outcomes in human populations. Additionally, different data types as reported within a single data source or study may have different metrics that are applicable to them (examples provided below in Section 5.2), therefore potentially resulting in one study having multiple overall study quality rankings.

EPA considers evaluation of information from new approach methodologies or (NAMs), or alternative test methods and strategies, as applicable and available, to support TSCA risk evaluations. This is consistent with EPA's *Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program* to reduce, refine or replace vertebrate animal testing (U.S. EPA, 2018d) and which was developed to meet the requirements of TSCA section 4(h). Because these NAMs may support analyses for the exposure and hazard assessments, the data quality criteria may need to be optimized or new criteria developed as part of evaluating and integrating NAMs in the TSCA risk evaluation process. For example, EPA recently developed criteria tailored to *in vitro* dermal absorption studies from OECD guidance and OPP evaluation guidance to meet the needs of new test orders (see Appendix S).

5.2 Evaluation Method

Based on specific criteria for assessing the strengths, limitations, and deficiencies of each study, the reviewer determines whether the study is *acceptable*, *critically deficient*, or *not rated/not applicable* for each individual metric. For metrics that are designated as *acceptable*, the reviewer assigns quality levels of *high*, *medium*, or *low* for that metric based on defined criteria. Although many metrics have criteria for all four bins (*i.e.*, *high*, *medium*, *low*, and *critically deficient*), there are some metrics with dichotomous or trichotomous criteria to better fit the nature of the metric.

The study quality levels and corresponding rankings at the metric level are defined below:

- *High* – No notable deficiencies or concerns are identified related to the metric that are likely to influence results [ranking of 1].
- *Medium* – Minor uncertainties or limitations are noted related to the metric that are unlikely to have a substantial impact on results [ranking of 2].
- *Low* – Deficiencies or concerns are noted related to the metric that are likely to have a substantial impact on results [ranking of 3].
- *Critically deficient* – Serious flaws are noted related to the metric that consequently make the study unusable for quantitative analyses [ranking of 4].
- *Not rated/not applicable* – Rating of this metric is not applicable to the study or data type being evaluated [no ranking]. Specifically, each data type has different considerations, therefore specific metrics may not apply to all data types. For example, when evaluating environmental release and occupational exposure qualitative information such as process information, sample size is not reported. Therefore the metric in which sample size is evaluated is not appropriate for the quality evaluation of process information. Additionally, the environmental hazard data quality metric that evaluates whether a study has a sufficient number of organisms and replicates per exposure group is given a not applicable rating for limit toxicity tests because these tests often do not utilize the same number of organisms per replicate or exposure treatment group replicates or as other toxicity tests where the derivation of a dose-response is the goal of the study.

The individual metric rankings are based on an ordinal scale and are used to obtain an overall study ranking. All metrics have an equal weight in determining the overall study ranking, and domains within

which the metrics are nested (*e.g.*, test substance) are strictly used to categorize the individual metrics. Therefore, each domain may have different numbers of metrics. The resulting values are converted to an ordinal quality level (*high*, *medium*, *low*, *critically deficient*, or *not rated/not applicable*).

EPA relies more heavily on studies with overall study quality rankings of *high*, *medium*, or *low* to quantitatively or qualitatively support risk evaluations (overall study quality rankings are defined below in Table 5-1). Should any metric be rated as *critically deficient* [ranking of 4], the study will automatically have an overall study ranking of *uninformative.* The quantitative use of an *uninformative* study may be inappropriate (*i.e.*, dose-response for hazard studies), however the information within an *uninformative* study may be used to qualitatively provide contextual or supportive information for the risk evaluation. Specifically, some aspects of *uninformative* studies may inform the hazard identification determination and/or weight of the scientific evidence when evaluating the body of literature for a specific discipline. Therefore, data or information from *uninformative* studies might be useful qualitatively on a case-by-case basis. The terminology of *critically deficient* and *uninformative* was made in collaboration with EPA/ORD and matches the terminology in the IRIS Handbook (U.S. EPA, 2020).

Table 5-1. Definition of Overall Study Quality Rankings

Overall Study Quality Ranking	Definition
High	No notable deficiencies or concerns are identified, and the data therefore could be used in the assessment with a high degree of confidence.
Medium	Possible deficiencies or concerns are noted, and the data therefore could be used in the assessment with a medium degree of confidence.
Low	Deficiencies or concerns are noted, and the data therefore could be used in the assessment with a low degree of confidence.
Uninformative	Serious flaw(s) are identified and therefore, the data cannot be used or have strict limits on use (*e.g.*, it will not be used for dose-response assessment in hazard assessments).

Among the aspects of study quality evaluated by EPA, reporting quality (*i.e.*, how completely an element was reported in a study) is an important consideration. Other frameworks (*e.g.*, the IRIS Program) use a separate reporting quality domain for animal toxicology studies. EPA's TSCA method integrates reporting quality metrics within each domain because reporting contributes to the evaluation of each facet of the data source. If sufficient methodological details are not reported, specific metrics that incorporate reporting quality cannot be rated as *high* because it is not possible to tell whether the methods were appropriate. The challenge, in many cases, is to distinguish a deficit in reporting from a problem in the underlying study methods. Other information sources cited by the study being evaluated, in lieu of providing detailed descriptions (*e.g.*, method details), are also considered when evaluating metrics where this information may be relevant. If the cited information is readily available, the relevant metrics are then re-evaluated using the additional information provided in the cited reference. However, if the cited information is unavailable, then the metric evaluation will reflect the amount of details provided in the original study being evaluated.

After the overall study quality ranking is determined, professional judgment may be used to adjust the

ranking level. This approach has been used in other established tools such as the ToxRTool developed by the European Commission (EC, 2018). The reviewer must have a compelling reason to adjust the overall quality ranking and document reasoning. As stated above, the evaluation of metrics depends highly on what is reported by the author(s), therefore some metrics within the same domain may be able to provide additional confidence regarding an aspect of a study characteristic, potentially increasing the overal study quality ranking. For example, domain one for the data quality criteria of environmental hazard studies (Appendix P) is test substance; this domain contains three individual metrics: test substance identity, test substance source, and test substance purity. If no analytical analysis is provided for the test substance, metric two will get a low ranking. However, metric three involves the evaluation of test substance purity, where often times a study may report the purity of the test substance as provided by the supplier, therefore potentially providing greater confidence that the test substance quality (and reported exposure concentrations) is accurately depicted and quantified by the study methodologies despite the lack of analytical verification of the test substance itself (metric two). When looking at multiple metrics together, greater confidence regarding one or multiple study characteristics or methodologies may provide rationale for adjusting the overall study ranking. Since publication of EPA's *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a), EPA has revised the metric criteria and screener notes for some disciplines to make them more objective and decrease the need for changing the overall study quality ranking. For example, for metric 3 for animal toxicity studies used for human health assessment, the level of purity of a test substance needs to be 70% or greater to be acceptable.

5.3 Documentation and Reviewer Process to Evaluate Data Sources

EPA conducts data quality evaluation using a tool (DistillerSR) that tracks and records the assessors' evaluations for each study. EPA's use of this tool is important to maintain transparency in using EPA's data evaluation framework under TSCA.

First, an assessor conducts an initial review by assigning a ranking for each relevant metric within each domain by following the ranking specifications detailed above in Section 5.2, along with professional judgment. The reviewer assigns the quality level by selecting/checking a box for either "*acceptable*," "*critically deficient*," or "*N/A*" and then for acceptable studies, selecting *high*, *medium*, or *low* from a pull-down menu. For each data source, a second assessor who has reviewed the study also then provides a quality review of the first assessor's initial review. Both reviewer responses are recorded in DistillerSR and EPA uses the second reviewer's responses as the final data quality evaluation for each data source. Should there be conflicting views on a metric or overall study ranking between the primary reviewer and QC reviewer, the reviewers may discuss the differences and use professional judgement to determine the final ranking. All reviewers are trained (*i.e.*, calibration exercises) using the same materials and methodologies, resulting in a consistent and transparent review of all information and data considered for use in TSCA risk evaluations. Professional judgement does incorporate the need for similar expertise to be used when evaluating different types of studies (*i.e.*, epidemiologists review epidemiology studies). Therefore, reviewer guidance for each metric is developed to promote consistency across assessors, and these may evolve over time to incorporate increased experience with different studies and unique scenarios.

During the evaluation of each study, the reviewers document concerns, uncertainties, strengths, and limitations for each metric, when necessary. If a publication reports more than one study or endpoint, each study or endpoint is evaluated separately. This approach results in an individual reference potentially having multiple overall study quality rankings to reflect the differences in quality of a reported endpoint or outcome. The reviewer is strongly encouraged to provide a comment for each metric that is ranked (whether *high, medium, low or critically deficient)* to improve transparency. Also,

the reviewer records any relevancy issues with the data/information source (*e.g.*, study is not useful to answer assessment questions) and provides comments for any data source for which the overall ranking has been changed based on professional judgment and the QC reviewer provides a rationale for changes to the initial review. Ordinal ranking in conjunction with clear evaluation criteria are used to guide evaluation and finalization of both the individual metric and overall study rankings. However, based on the needs of the risk evaluation, the overall study ranking can be updated to a higher or lower ranking to reflect other considerations (*e.g.*, unique study-specific characteristics, risk evaluation-specific data needs). Throughout the process, professional judgment is required when determining ranking.

5.4 Important Notes Regarding the Evaluation Method

Data quality evaluation, the process of considering each metric and assigning descriptors of acceptable (*high/medium/low quality*), *critically deficient*, or *not applicable*, requires some professional judgment. Differences in judgment among reviewers is handled through initial as well as ongoing calibration exercises, written guidance documents that can be updated when clarification is needed, and discussion between initial and QC reviewers. The data quality evaluation metrics (Appendix K through Appendix T) each receive a ranking (1, 2, 3, 4, or 0 for metrics that are N/A). The ordinal ranking of each metric provides consistency and transparency to the evaluation process and is translated to an overall quality rating which informs the characterization of studies during the evidence integration phase. See Appendix Q for an example of how metric rankings are used to obtain the overall study ranking for animal toxicity studies. This categorical ranking of the data evaluation system is not intended to imply a false sense of precision and/or accuracy implicit in other numerical scoring systems previously employed in the first 10 risk evaluations. Therefore, the qualitative study quality rankings are not the numerical scores used in the evidence integration of previous risk evaluations and is a significant change from previous publication in EPA's *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a).

Although the overall data quality level is derived from the summary of individual metric rankings and serves as the baseline for consideration of the study quality, it may not be the final decision. The primary reviewer and QC reviewer may agree to provide an updated ranking; in such cases, they must provide a justification for the ranking adjustment to ensure transparency for the decision.

Domains and metrics used for study quality evaluation reflect the most important qualities standard in the respective scientific fields. The data quality criteria for several disciplines include options for including additional metrics for a given study or study type if important aspects of study quality are not covered by the existing metrics.

6 DATA EXTRACTION

Data extraction is the process in which quantitative and qualitative data/information are identified from each relevant data/information source and extracted using structured forms or templates. When possible, the same reviewers used for data evaluation are used for data extraction, because these reviewers are already familiar with the references. EPA uses various extraction tools to meet the needs of each chemical assessment. These may include specialized web-based software (*e.g.*, DistillerSR, HAWC).

Data extraction occurs for those studies containing relevant data/information for the risk evaluation. EPA may limit extraction of data/information from sources identified as *uninformative* during data evaluation because of serious flaws that would make the study data limited for use in evidence integration.

When applicable and feasible, EPA reaches out to the authors of the data/information source to obtain raw data or missing elements that would be important to support the data evaluation and data integration steps. 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. The following sections provide specific information about the data/information extraction for the various disciplines supporting the risk evaluation, including generic information related to extraction templates. These templates may be modified to fit the data extraction needs for each risk evaluation and serve as the starting point to create other tables presented in the risk evaluation to tabulate data related to the hazard identification and evidence integration.

6.1 Extraction of Physical and Chemical Property and Environmental Fate Data

The bullets below summarize the types of information that are collected for physical and chemical properties and environmental fate characteristics that are presented in the TSCA risk evaluation. Some physical and chemical properties (*e.g.*, auto flammability, viscosity) may be included on a case-by-case basis. Examples of extracted physical and chemical and fate property data that may be included in the TSCA scope and risk evaluation documents are provided below in Section 6.1.1 and Section 6.1.2, respectively.

6.1.1 Physical and Chemical Property Data

- Physical state and properties (for solids include morphology and particle size)
- Melting point, boiling point
    - Substance purity also recorded for each data source
- Viscosity
    - Temperature also recorded for each data source
- Density
- Temperature, reference substance, and dynamic viscosity also recorded for each data source
- Vapor pressure
    - Temperature and substance purity also recorded for each data source
- Vapor density
- Henry's law constant
    - Temperature also recorded for each data source
- Water solubility
    - Temperature and pH also recorded for each data source

- Dissociation constant (pKa)
  - Temperature and substance purity also recorded for each data source
- Octanol-water partition coefficient (log K_{OW})
  - Temperature, pH, and substance purity also recorded for each data source
- Autoflammability/flash point

6.1.2 Fate Property Data

- Biodegradation
  - Initial concentration, inoculum source, (an)aerobic status, and duration also recorded for each data source
- Bioconcentration
  - Initial concentration, species, and duration also recorded for each data source
- Photolysis
  - Wavelength range, species, and duration also recorded for each data source
- Hydrolysis
  - Temperature, pH, and duration also recorded for each data source
- Sorption
  - Sorbent source, sorbent qualities, and duration also recorded for each data source
- Other fate endpoints
  - Study type also recorded for each data source

6.2 Extraction of Environmental Release and Occupational Exposure Data

Essential elements (*i.e.*, data sources and relevant descriptors for the data) of environmental release and occupational exposure data extraction and evaluation are presented in Table 6-1, Table 6-2, and Table 6-3. Based on the data evaluation method and data quality evaluation approach (as described in Section 5 and Appendix M), the reviewer documents relevant metadata in the metadata column and then provides a ranking, or a notation of not applicable, in the ranking column based on the quality criteria of the metrics (described in Appendix M). Here, data extraction and evaluation steps are conducted simultaneously using DistillerSR. The process involves the assessment of a data point from a reference (or source) based on one of the data types (*i.e.*, general engineering, occupational exposure, and environmental release as discussed in the RESO in Appendix H) and the condition of use of the chemical.

After ranking is complete, the reviewer documents the overall data quality ranking (*high, medium, low*, or *uninformative*). Suppose the source contains more than one data or information element. In that case, the reviewer provides a data quality evaluation ranking for each data type or information element found in the source. Therefore, a reference may have more than one data or information set or type and associated overall quality ranking.

Table 6-1. Data Extraction and Evaluation Template for General Life Cycle and Facility Data

Data Source (HERO ID)	Extracted Data
General life cycle and facility data (note: these apply to both occupational exposures and environmental release)	Condition of use
	Life cycle description
	Production, import, or use volume
	Process description

Data Source (HERO ID)	Extracted Data
	Throughput
	Number of sites
	Chemical concentration
Data quality evaluation	High/medium/low/critically deficient

Table 6-2. Data Extraction and Evaluation Template for Occupational Exposure Data

Data Source (HERO ID)	Extracted Data
Occupational exposure data	Condition of use
	Worker activity (or source of exposure if stationary sampling) or Job description
	Route of exposure
	Physical form
	Personal sampling data
	Area sampling data
	Type of measurement (*e.g.*, TWA, STEL) or method (*e.g.*, modeling)
	Bulk and dust particle size distribution
	Dermal exposure data
	Exposure duration
	Exposure frequency
	Number of workers
	Personal protective equipment
	Engineering control and % exposure reduction
Data quality evaluation	High/medium/low/critically deficient

Table 6-3. Data Extraction and Evaluation Template for Environmental Release Data

Data Source (HERO ID)	Extracted Data
Environmental release data	Condition of use
	Description of release source (at the process- or unit-level with the type of waste)
	Release estimation method

Data Source (HERO ID)	Extracted Data	
	Daily and annual release quantity	(kg/day)
		(kg/yr)
	Release days per year	
	Release or emission factor	
	Waste treatment method	
	Pollution prevention/control and percent efficiency	
Data quality evaluation	High/medium/low/critically deficient	

6.3 Extraction of Environmental, General Population, and Consumer Exposure Data

Table 6-4 through Table 6-8 are examples of extraction templates for various types of exposure data/information supporting the characterization of exposures for environmental receptors, the general population, and consumers. Bullets summarizing other types of exposure information that are collected are also presented below.

Table 6-4. Generic Extraction Template for Product Use Directions and Concentration Data

Field in Template	Instructions for Field
HERO ID	HERO ID for the study
Citation	Short citation name (*e.g.*, [author] *et al.* [year])
Chemical	Name of chemical
Product use category/scenario	This is the broad category or scenario. Examples include the OECD Use Category, CEM Generic Use Category, SHEDS HT Use Scenario, CONSEXPO Scenario The category should include the formulation type (liquid, spray, solid, etc., if applicable)
Product name and sampling information	This the name of the product, or other identifying information If product names are not provided, this field may be used to record a description such as “Nine liquid handwashing products sold in the Japan” If product is not sold in the U.S., indicate the country If the date the product analysis differs from the source date, please give indication of currency
Test setting/scenario	
Dilution	This is mainly to record the product dilution requirements or application rate. Record the maximum application rate (*i.e.*, most concentrated end-use dilution)

Field in Template		Instructions for Field
Weight fraction – raw (undiluted, concentrate, ready-to-use)	mg/kg or ppm	This is the weight fraction in the product in an undiluted state. Weight fractions are usually reported in mg/kg or %. Record/convert both. Use the conversion worksheet tab as needed to show conversions. If there are replicates of the same product, or only summary stats are provided for a group of products, include the range and central tendency values.
	%	
Weight fraction – adjusted (diluted)	mg/kg or ppm	This is the weight fraction in the product in the diluted (end-use) state Weight fractions are usually reported in mg/kg or % Record/convert both. Use the conversion worksheet tab as needed to show conversions If there are replicates of the same product, or only summary stats are provided for a group of products, include the range and central tendency values This should reflect the most concentrated end-use concentration if a range of dilutions are provided; may be referred as "heavy-duty" on labels
	%	
Product density (g/cm^3)		Note the product density in g/cm^3 if available.
Other product use information		Include any noteworthy comments and other contextual information that would be useful for the assessment, such as: <u>Product Information</u> Application rate Application amount Container size (weight or volume) Application equipment Product density <u>Supplementary Use Information</u> Application timing Frequency of use Room of use Ventilation requirements Protective equipment Duration of use
Snip 1 and 2		Studies might have pertinent graphs, figure, or tables which are difficult to extract in a spreadsheet format. These cells are available to provide a cut and paste snip.
Reviewer comments		Any comments about the generalizability of the study results or other study details.
Reviewer 1 initials		Initials of the primary data extractor.
QC initials		Initials of the quality assurance extractor.
For a useful reference for the extraction of experimental data, see Indoor Exposure Product Testing Protocols.		

Table 6-5. Generic Extraction Template for Experimental Data from Chamber/Emission, Product Testing/Concentrations and Simulation Studies

Field in Template		Instructions for Field
HERO ID		HERO ID for the study
Citation		Short Citation name (*e.g.*, [author] *et al.* [year])
Chemical		Name of chemical
Product/article description		
Test setting/scenario		
Country of continent		
Comments		
Measured concentrations	Text values	
	Snip 1 and 2	Studies might have pertinent graphs, figure, or tables which are difficult to extract in a spreadsheet format; these cells are available to provide a cut and paste snip
Emission rates	Model fit	
	Text values	
	Snip 1 and 2	Studies might have pertinent graphs, figure, or tables which are difficult to extract in a spreadsheet format; these cells are available to provide a cut and paste snip
Analytical methodology	Analytical method	
	No. of observations	
	Detection frequency	
	Detection limit	
Reviewer comments		Any comments about the generalizability of the study results or other study details
Reviewer 1 initials		Initials of the primary data extractor
QC initials		Initials of the quality assurance extractor

Table 6-6. Generic Extraction Template for Exposure Factors/Survey Data

Field in Template	Instructions for the Field
HERO ID	HERO ID for the study
Citation	Short Citation name (*e.g.*, [author] *et al.* [year])
Chemical	Name of chemical

Field in Template	Instructions for the Field	
Objective/scenario	Description of conditions to which the study results apply (*e.g.*, typical shampoo use, air exchange rate in summer months, etc.)	
Survey tools/method	Analytical method or survey tool (*e.g.*, diary, video) used to collect exposure factor data.	
Survey size	Number of subjects/samples in the study	
Survey date	Date when experiment or survey was conducted	
Geographic location	Location where study was conducted, including the International Organization for Standardization (ISO) country code.	
Metric	Application method	Area treated
	Uses per year	Amount of product used
	Duration of use	Time spent applying
	Time since last use	Air exchange rate
	Frequency of use	Mass of product used per event
Value(s) and limits	Minimums, medians, means, maximums, and detection limits, as applicable	
Snip 1 and 2	Studies might have pertinent graphs, figure, or tables which are difficult to extract in a spreadsheet format; these cells are available to provide a cut and paste snip	
Reviewer comment	Any comments about the generalizability of the study results or other study details	
Reviewer 1 initials	Initials of the primary data extractor	
QC initials	Initials of the quality assurance extractor	

Table 6-7. Generic Extraction Template for Modeled Concentration Data

Data/Information Attribute	Template Instructions
HERO ID	HERO ID for the study
Citation	Short citation name (*e.g.*, [author] *et al.* [year])
Chemical	Name of chemical
Concentration name	Name of concentration in media. Examples include predicted concentration and Predicted Environmental Concentration (PEC) local. PECs are usually from European authoritative sources or European Chemical Safety Reports. Only Predicted Environmental Concentration locals are applicable to TSCA assessments as these are concentrations based on releases from industrial sites. The modeling approach is similar to OPPT's approaches. Predicted Environmental Concentration Regionals are based on fugacity modeling, which OPPT would not use. It is okay

Data/Information Attribute	Template Instructions
	to provide a range of predicted environmental concentrations across scenarios for a given media.
Media	Environmental media in which the concentration is predicted; examples include surface water, marine water, soil, and ambient air
Scenario description	Description of scenario associated with the predicted concentration, typically an industry or activity which was the source of the predicted concentration. Often this is the name and industrial, commercial, or consumer use category of associated with the release.
Country	Include the country associated with the predicted concentration
Representative population/receptor	For concentrations in media such as indoor air, may include the environment in which the person is exposed (office building, single family home, dry cleaning establishment, etc.)
Model name	Optional. Name of model used, such as E-FAST, EUSES. If a model name is not provided and if the model is not readily known, include a screen shot or brief text description of the basic model equation.
Key model inputs	Optional. May include information such as emission rates, flow rates, time, surface area, room volume, air exchange rates, etc.
Value(s)	The predicted concentration(s)
Unit	Units for the predicted concentration
Snip 1 and 2	Studies might have pertinent graphs, figure, or tables which are difficult to extract in a spreadsheet format; these cells are available to provide a cut and paste snip
Reviewer 1 comment	Any comments about the generalizability of the study results or other study details
Reviewer 1 initials	Initials of the primary data extractor
Reviewer 2 initials	Initials of the quality assurance extractor

Table 6-8. Generic Extraction Template for Monitoring Data Compiling All Media Types[a]

HERO ID	HERO ID for the Study
Citation	Short citation name (*e.g.*, [author] *et al.* [year])
Chemical	Name of chemical
Country code	ISO country code for location of sample collection
Year	Year the samples were collected
Representative population/ receptor	Description of population where monitoring data were collected or receptors for which media data were modeled

HERO ID	HERO ID for the Study
Description/phase/type/ duration	The information provided serves as a brief description of the dataset with information like the site description (*e.g.*, "near fenceline of facility"), phase of chemical or type of sample (*e.g.*, "gas phase" or "wet weight"), and duration of the study.
Units	Units in which monitoring metrics are reported
Detection limit	Detection limit as specified in the study for the applicable analytical method, including type of detection limit (MRL, MDL, LOD, etc)
Number of samples	Number of samples collected
Analytical method	Description of method used for sample analysis
Detection frequency	Fraction of samples above the limit of detection (LOD)
Minimum value	Minimum value reported for the population/receptor
Median value	Minimum value reported for the population/receptor
Geometric mean value	Minimum value reported for the population/receptor
Mean value	Minimum value reported for the population/receptor
Maximum value	Minimum value reported for the population/receptor
Variance	Minimum value reported for the population/receptor
Confidence in data source	Study quality evaluation for the study
Snip 1 and 2	Studies might have pertinent graphs, figure, or tables that are difficult to extract in a spreadsheet format; these cells are available to provide a cut and paste snip
Reviewer comments	Any comments about the generalizability of the study results or other study details
Reviewer 1 initials	Initials of the primary data extractor
QC initials	Initials of the quality assurance extractor

[a] Monitoring data are extracted for ambient air, wastewater, surface water, drinking water/finished water, soil, sludge, leachate, sediment, indoor dust, indoor air, biomonitoring (*e.g.*, breast milk, tissue, blood, urine, hair) and personal exposures (handwipe, patch, whole body dosimetry).

6.4 Extraction of Environmental and Human Health Hazard Data

Data extraction and content management are carried out using tables in Excel, Word or HAWC based on information that is entered into DistillerSR forms. If HAWC is used, the risk evaluation provides web links to the chemical page in HAWC containing the extracted data. The bullets below summarize the types of information that are collected during data extraction for environmental and human health hazard data, respectively:

- Environmental hazard studies of aquatic and terrestrial organisms
    - Test organism, exposure media, exposure parameters, dose/concentrations, hazard value,

and effect type
- Human health hazard studies of animal toxicity data
    - Target organ system, species/strain/sex, dose/concentrations, study duration, hazard value, and effect
- Human health hazard studies of epidemiological data
    - Endpoint, study population, exposure, and results specific to individual target organs/systems

Other data types (*e.g.*, mechanistic, non-quantitative PESS information) are extracted as needed, depending on the amount and type of other data that are available for a specific chemical. Additionally, relevant PESS information from extracted studies may also be noted alongside the details listed above.

6.4.1 Data Extraction of Study Methods and Results

When extracting methods and results from a study that has met PECO criteria, all findings are considered for extraction, regardless of statistical significance. However, not all studies that meet the PECO criteria undergo *detailed* data extraction. The level of data extraction for specific outcomes within a study may range from a brief narrative to a full extraction of dose-response effect size information, depending on data quality evaluation (see evaluation criteria in Appendix K through Appendix T) and availability of data. Studies evaluated as *uninformative* are not always extracted in detail. Similarly, data from low quality studies may not always be extracted in detail if enough medium- and high-quality studies (*e.g.*, on an outcome) are available.

For those data extraction results that have been uploaded in HAWC, the included studies are presented in the risk evaluation and made available for download from HAWC in Excel format[17] when the draft risk evaluation is publicly released. For quality control, data extraction is performed by one member of the evaluation team and independently verified by at least one other member. Discrepancies in data extraction are resolved by discussion or consultation with a third member of the evaluation team. Digital rulers, such as WebPlotDigitizer, are used to extract numerical information from figures, and their use is documented in the risk evaluation or supplementary documents.

As previously described, routine attempts are made to obtain missing information from environmental and human health hazard studies, if this information is considered influential during study evaluations (see Section 5 and Appendix O, Appendix Q) or when it can provide information important for dose- or concentration-response analysis or interpretations of significance (*e.g.*, missing group size or variance descriptors such as standard deviation or confidence interval). Missing data from individual mechanistic (*e.g., in vitro*) studies are generally not sought.

For peer-reviewed environmental hazard studies that are included in HAWC and evaluated in DistillerSR, data extraction is conducted outside of DistillerSR. The extracted data reside in the ECOTOXicology Knowledgebase (ECOTOX) database. ECOTOX is a comprehensive, publicly available knowledgebase created, maintained, and updated by EPA ORD. Data that reside in ECOTOX comprise chemical environmental toxicity data on aquatic and terrestrial organisms. As part of the systematic literature review, EPA is working to export data for environmental health hazard studies evaluated at the full-text level in DistillerSR from relevant fields in ECOTOX and import the data into DistillerSR using a JavaScript Object Notation (JSON) file with one-to-one matches for each field question in the DistillerSR data extraction form. The DistillerSR data extraction forms are provided in Excel format in the draft risk evaluations released for the public.

[17] The following browsers are supported for accessing HAWC: Google Chrome (preferred), Mozilla Firefox, and Apple Safari. There are errors in functionality when viewed with Internet Explorer.

6.4.2 Standardizing Reporting of Effect Sizes

When extracting results from epidemiology studies, adjusted statistical estimates are entered into the extraction form when possible rather than unadjusted or raw estimates. The data extraction tables used in risk evaluation indicate when this approach is used for epidemiological evidence. It is important to consider the variability associated with effect size estimates, with better powered studies generally showing more precise estimates. Effect size estimation can be affected, however, by such factors as variances that differ substantially among treatment groups, or by lack of information to characterize variance, especially for animal studies in biomedical research (Vesterinen et al. (2014). The nature of any variance issues and the associated uncertainties are described and accounted for during the evidence integration process.

6.4.3 Standardizing Administered Dose Levels/Concentrations for Human Health Hazard Studies

Exposures are standardized to common units for data extraction tables. Where study authors provide exposure levels in concentrations in the diet or drinking water (*e.g.*, ppm in diet), dose conversions are made using study-specific food or water consumption rates and body weights, when available, to obtain consistent units (*e.g.*, mg/kg-bw/day for oral human health hazard studies). If specific information on food or water consumption is lacking in the study, EPA uses defaults (U.S. EPA, 1988) for the species/strain and sex as well as age of the animal of interest. Where study authors provide inhalation exposures as total, inhalable, and respirable concentrations (or fractions of the total) based on particle size data and/or inhalation dosimetry modeling, this information is captured in the extraction. Exposure levels in inhalation studies are expressed in units of mg/m^3 and exposures used in oral and dermal studies are mg/kg-bw/day. Assumptions and/or models used when performing dose conversions are documented in the data extraction tables used in risk evaluation. In some cases, internal dose metrics may be reported. The data extraction tables capture administered doses and consideration of internal dose metrics occurs at the evidence integration phase, along with other toxicokinetic data.

7 EVIDENCE INTEGRATION

Following scoping, EPA initiates the analysis phase of the risk evaluation, which begins with integration of the reasonably available evidence. Evidence integration refers to the consideration of evidence obtained from systematic review and scientific information obtained from sources beyond systematic review. Integration can be a step-wise or iterative process, depending on the discipline, and may include quantitative analyses and/or qualitative interpretation. The integration of evidence is an important step preceding the characterization of exposure and environmental and human health effects based on the conceptual model and analysis plan as presented in the TSCA scope documents. In this phase, EPA begins analyzing the weight of the scientific evidence for the exposure and hazard assessments.

Within the TSCA context, the weight of the 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 assembling of evidence and evaluation of that data for quality and relevance has been previously described. This section describes the integration of evidence, taking into account the strengths, limitations, and relevance, to support conclusions (U.S. EPA, 2016). This integrative and interpretive process considers both positive and negative data and information, yielding conclusions regarding the strength of the evidence. Professional judgment is used in the integration of evidence and is clearly documented.

The general approaches for integrating evidence for physical and chemical properties, fate, exposure, and hazard are discussed in Sections 7.1, 7.2, 7.3, 7.4, and 7.4.3, respectively. The analyses, approaches, and processes used to integrate different data streams, from systematic review and beyond systematic review, within each discipline can vary based on what is deemed most appropriate, informative, and feasible for each discipline.

7.1 Integration of Physical and Chemical Property Evidence and Information

After physical and chemical property data have been extracted and evaluated, values for the endpoints are selected for use in the risk evaluation. The selected values should always be those rated the highest by the systematic review criteria (high > medium > low; see Figure 7-2 and Appendix K for information on physical and chemical data quality evaluation). However, when several studies with equal rankings are available, the following data hierarchy is used to select a value:

1. Trusted sources
    a. Studies from established physical and chemical property databases, which have been expert- or peer-reviewed (see Table_Apx K-1).
2. Measured data
    a. Studies conducted according to established test guidelines
    b. Non-guideline studies that are conducted according to scientific principles with sufficient documentation highlighting where the study deviated from established test guidelines and the rationale for the deviation
    c. Data derived from experiments with minimal supporting details
3. Estimated values from models (quantitative structure-activity relationships, QSARs) and/or estimated values from read-across and structural analogues, whichever is more appropriate

Physical and chemical property data includes multiple lines of evidence. The accuracy, validity, and

consistency with similar substances are considered. Some endpoint values vary with experimental conditions or are only defined for substances with certain other physical and chemical properties. There are endpoint-specific considerations, including

- Physical state, melting point (MP), and boiling point (BP) should align. Sublimation is also noted and considered when evaluating these endpoints.
    - MP <25 °C assessed as a liquid
    - MP >25 °C assessed as a solid
    - BP <25 °C assessed as a gas
        - Boiling point and vapor pressure are related. If BP is <25 °C consider vapor pressure.
        - Note that boiling point decreases as the vapor pressure increases. The boiling point of a liquid is the temperature at which its vapor pressure is equal to the pressure of the gaseous phase in contact with the liquid.
- If the chemical is a solid, the physical structure and morphology is considered (*e.g.*, crystalline, amorphous, particle size distribution).
- Viscosity should only be assessed if a substance is a liquid.
- Reactivity of the chemical should be noted (*e.g.*, does it hydrolyze, oxidize, photolyze? Is it pyrophoric?) Confirm which substance was measured in the experiment; the parent compound, the degradation product, or a mixture of both; and any special circumstances (*e.g.*, presence of a catalyst, low wavelength light source <290nm, temperature or pressure above or below standard temperature and pressure).
- Dissociation constant (pKa) measurements are for chemicals in aqueous solutions. Chemicals not soluble in water require further consideration.
- Water solubility and octanol-water partition coefficient (log K_{OW}) should align.
    - Log Kow < 1 – highly soluble in water
    - Log Kow > 4 – slightly soluble in water
    - Log Kow > 8 – negligible solubility, difficult to measure water solubility experimentally
- Partition coefficients
    - Henry's law constant, vapor pressure, and water solubility should be in agreement;
    - And are generally expected to vary with temperature.
- Experimental Henry's law constant can be compared to the value calculated from experimental vapor pressure and water solubility.

These physical and chemical property endpoints are then used to inform chemical specific decisions across other disciplines. High quality data is preferred in the selection of physical and chemical properties. When few, or no high-quality studies are identified, a mix of high-medium studies, or medium studies may be used to inform selection.

7.2 Integration of Fate Evidence and Information

Relevant data for environmental fate and transport assessment typically includes physical and chemical properties, biotic and abiotic degradation rates, and environmental partitioning potential of the chemical substance. There is a general data source hierarchy for obtaining reliable data as illustrated in Figure 7-2. Measured data from well-documented experimental studies are preferred. In the absence of experimental data, predictive tools and methods are used to identify appropriate analogues and estimate values for endpoints based on their experimental data (*i.e.*, read-across predictions), QSAR models, and structural alerts.

Any significant issues, strengths, and limitations of the data and the uncertainties that require consideration are presented, and the major points of interpretation are highlighted. Professional

judgment is used at every step of the process and applied transparently, clearly documented, and to the extent possible, follow principles and procedures that are articulated prior to conducting the assessment (U.S. EPA, 2016). It is important to note that the information on environmental fate endpoints collected through systematic review is first considered, then data gaps and uncertainties are addressed through the use of models, read-across, and/or test orders. All data streams, whether resulting from systematic review or not, are considered in the weight of the scientific evidence analysis. Fate endpoints are presented as single values or ranges of applicable values identified within, and outside of systematic review. High-quality fate data points are preferred when presenting ranges for use in the risk evaluation. In the absence of high-quality data points, data deemed to be of lesser quality may be used to formulate the ranges. In the absence of multiple data points to determine a range of viable values for a given fate endpoint, a single value may be stated.

7.2.1 Data Hierarchy in Evidence Integration

High-quality measured data is preferred for fate properties to minimize uncertainty in the assessment. The quality of fate data is evaluated for four different data sources—experimental data, field studies, modeling data, and monitoring data—as described in Section 7.1. Generally, experimental fate data is preferred over modeled data; however, fate data from all data sources may be considered based on a similar data hierarchy structure that is described below. Definitions for these data types are shown in Table 7-1. Because the availability of information varies considerably for different chemicals, it is anticipated that there are cases where some study types are not available and other cases where additional study types may be identified beyond those listed in Table 7-1.

Table 7-1. Types of Fate Data

Type of Data Source	Definition
Experimental data	Data obtained from experimental studies conducted in a controlled environment with pre-defined testing conditions. Examples include data from laboratory tests such as those conducted for ready biodegradation (*e.g.*, MITI test) or hydrolysis (*i.e.*, following Organisation for Economic Cooperation and Development Testing Guideline [OECD TG]) 111, among others.
Field studies	Data collected from incidental sampling of environmental media, especially to provide information on partitioning, bioconcentration, or long-term environmental fate.
Modeling data	Calculated values derived from computational models for estimating environmental fate and property data including degradation, bioconcentration, and partitioning.
Monitoring data	Measured chemical concentration(s) obtained from systematic sampling of environmental media (*e.g.*, air, water, soil, biota) to observe and study the effect of environment conditions on the fate of chemicals. Monitoring data may include studies of chemical(s) after a known exposure/release of test substance as well as measured chemical concentrations over a period of time to provide direct evidence about fate in environment.

7.2.2 Incorporating Evidence Streams from outside of Systematic Review

After systematic review activities conclude, any data gaps that remain are identified and may be filled using a variety of methods that fall under evidence integration in Figure 7-1. These include but are not

limited to, estimated values using methods such as computational estimation techniques (EPI Suite™, NOMO5, OPERA, etc.), read-across from analogous chemical substances, and professional judgment. When evidence streams from outside of systematic review form the basis of conclusions in the risk evaluation, the evidence streams, and any analyses are clearly described and documented.

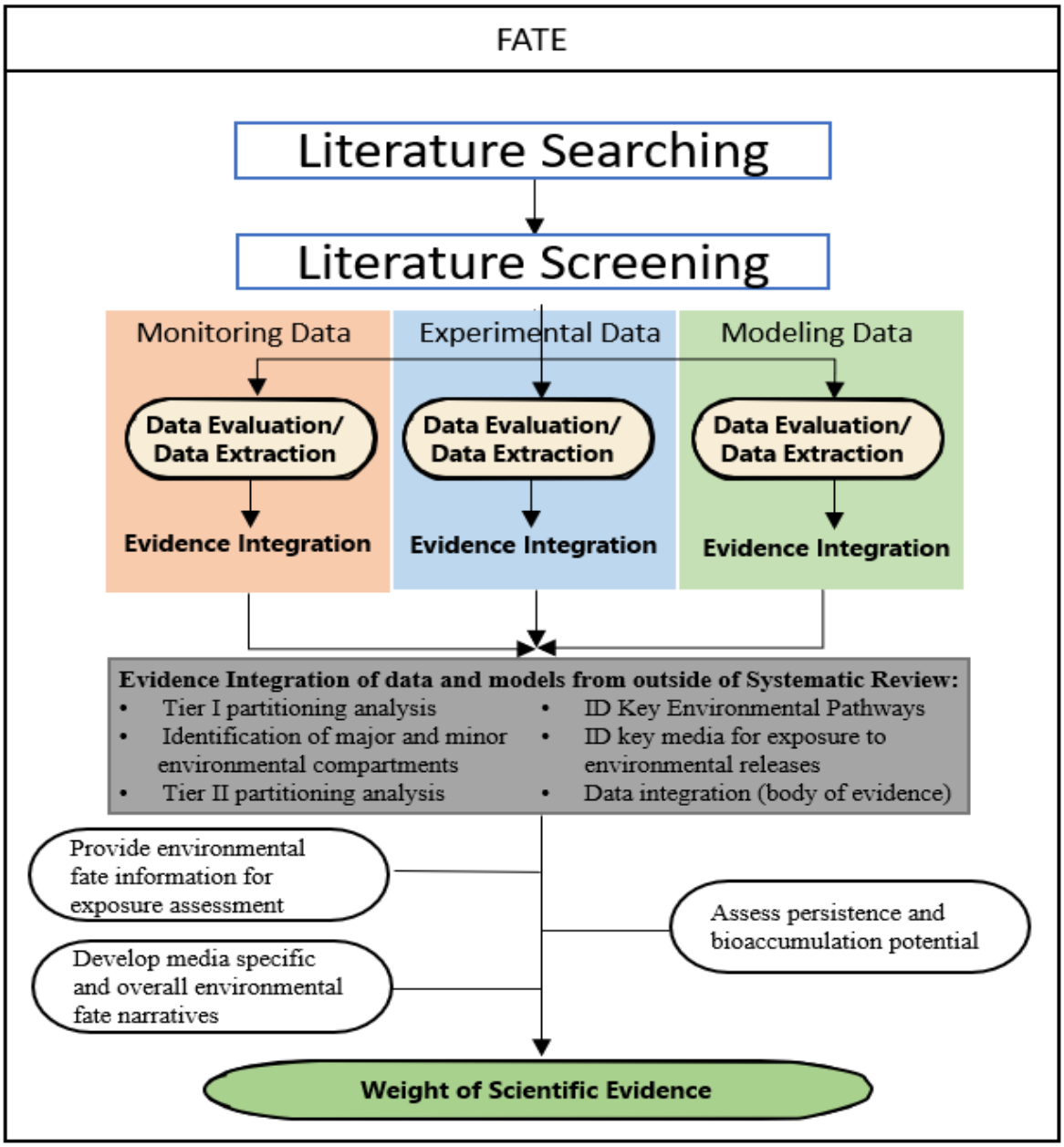

Figure 7-1. Fate Workflow as It Pertains to Both Systematic Review and Evidence Incorporated Outside of Systematic Review

7.2.3 Evaluating the Weight of the Scientific Evidence

The integration of evidence involves narrative summaries that bring together the findings from the analyses of the informative evidence relevant to each potential environmental fate endpoint, including summary judgments regarding the strength of the evidence (*e.g.*, likelihood of persistence and bioconcentration in the environmental) from each fate endpoint. During evidence integration, describing aspects of the evidence (*e.g.*, consistency, study design) is evaluated for each assessed fate endpoint.

During evidence integration, a determination of confidence in the range of fate endpoint(s) are made based on the study quality of contributing data points. The evaluations of the available studies of fate endpoints inform interpretations about the extent to which the data support a judgment that a chemical is potentially persistent and/or bioaccumulative as interpreted from relevant fate and transport parameters determined from systematic review. The interpretations regarding the strength of a study, model, or data point that contributes to a fate endpoint for a chemical are judged and considered together. This culminates in a final judgment about the extent to which the available evidence supports that the chemical's potential persistence and bioaccumulation/bioconcentration in the environment.

Prior to drawing overall judgments about the strength of the evidence and conclusions regarding a chemical's fate and transport in the environment, the reasonably available evidence is evaluated, integrated, and summarized for the subject chemical. For each assessed environmental compartment (*e.g.*, air, water, soil, sediment), the relevancy of available environmental fate data (*i.e.*, biodegradability, POTW removal rate, potential for migration to, and persistence in groundwater) for a specific environmental compartment is evaluated and considered alongside other evidence types that may be available (*e.g.*, internally run models, calculators). As shown in detail in Figure 7-2, the strength of the evidence is based upon considerations of consistency, study design, study conditions, and uncertainty.

In Figure 7-2, the information for a given fate endpoint is first sorted by Tier 1 considerations, which are divided into four categories based on data quality and whether the information is measured or estimated. If there are multiple data sources in the highest category of Tier 1 (*e.g.*, more than one *high* quality, measured data point) then the data points may be further sorted using the Tier 2 considerations. In Tier 2, various factors that may increase or decrease the strength of a study are evaluated and ranked based on data quality evaluation metrics.

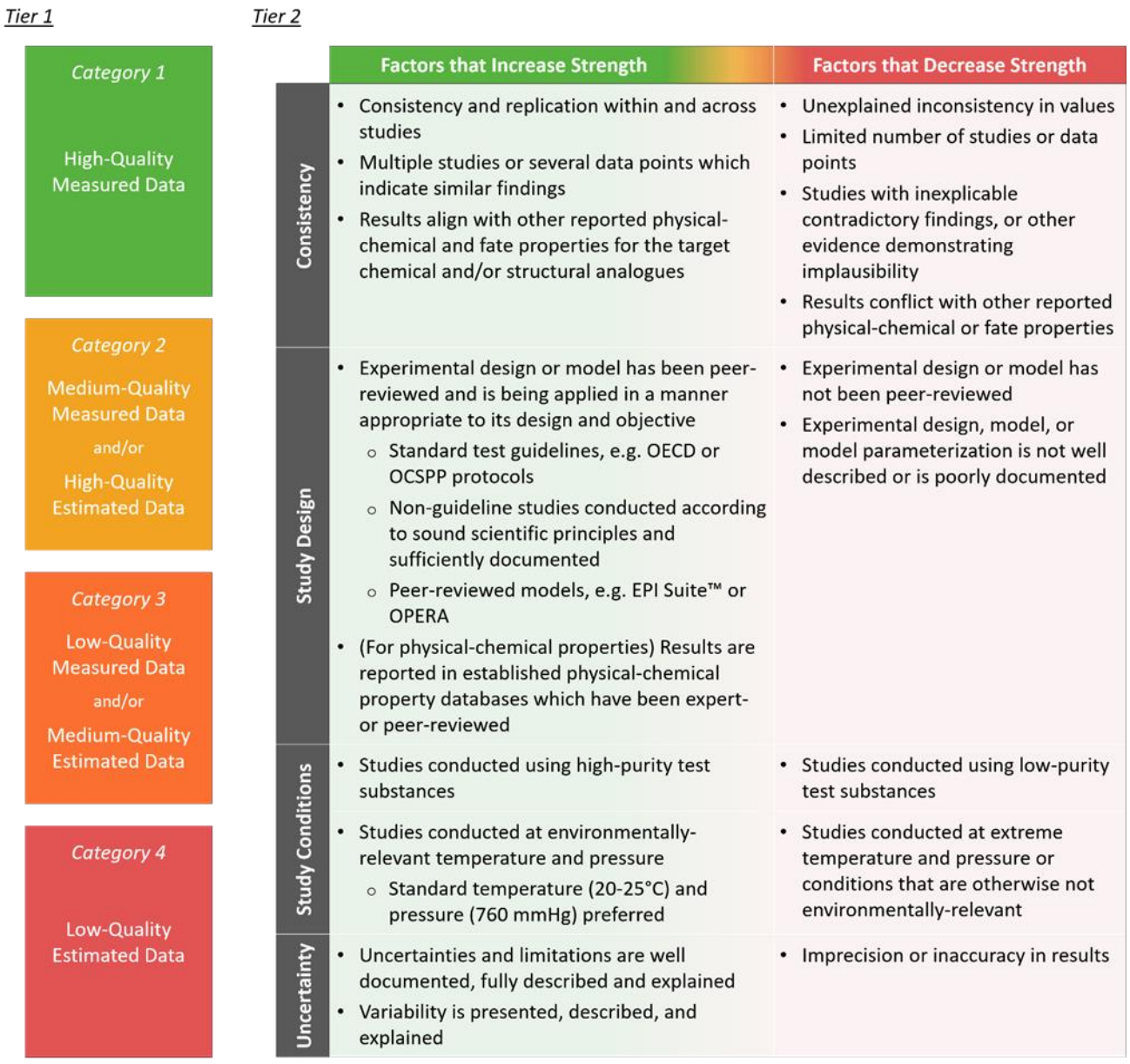

Figure 7-2. Data Hierarchy of Information Sources Used to Inform Risk in the Selection of Physical and Chemical and Environmental Risk Assessment

7.2.3.1 Characterization of Assumptions, Limitations, Variability, and Uncertainty

The scientific defensibility of the environmental fate assessments is presented in risk evaluations based on the integration and evaluation of the strength of the evidence for environmental fate and transport information for the chemical substance under evaluation. Within this context, the underlying assumptions and rationales supporting the environmental fate and transport properties are documented, including science policy assumptions. This includes a discussion of the strengths and limitations of the data sources supporting the environmental fate and transport properties, as well as a characterization of their uncertainties and variability.

For endpoints where there is no measured data of sufficient quality or other uncertainties determined during evidence integration, models or read-across from structural analogues may be relied upon to

resolve the data gap or test orders may be issued under the authority of TSCA section 4 to obtain measured values.

7.3 Integration of Exposure Evidence and Information

Following data extraction and evaluation, the exposure analysis for a chemical begins. This is a complex process that includes multiple levels of evidence integration. In organizing the exposure information to be considered in the risk evaluation, pursuant to TSCA section 6(b)(4)(F)(ii), EPA, "where relevant, will take into account the likely duration, intensity, frequency, and number of exposures under the conditions of use in an exposure assessment." Consistent with TSCA, the exposure assessment evaluates, where relevant, the likely duration, intensity, frequency, and number of exposures to human populations (*e.g.*, general population, consumer, worker)—including PESS and environmental receptors (*e.g.*, aquatic, terrestrial species) for the conditions of use of the chemical substance. TSCA also requires that a risk evaluation describe whether aggregate or sentinel exposures are considered in the exposure assessment and the basis for that consideration.

Because the type of data needed to assess location, duration, intensity, frequency, and number of exposures is so varied, extracted data from the systematic review process is categorized into data types. Integration within data types depends on how comparable and applicable the data sets are for a given exposure scenario and exposure assessment; that is, each data type is measuring the same thing. Each of the possible extracted data types are listed in Table 7-2 along with the corresponding definition and applicable exposure assessment for which the data is integrated.

Data characterization, such as statistical and geospatial analyses and integration, occurs within data types and then is utilized in the following four exposure assessment components:

1. *Environmental release assessment* characterizes the potential environmental releases of the chemical associated with the use of the chemical for the conditions of use. Release quantity, emission factors and other environmental release data types identified through systematic review are used to support this assessment.
2. *Environmental media concentrations* are developed using existing measurements and/or estimating the magnitude or concentration of the chemical substance in environmental media stemming from releases occuring from TSCA COUs. Concentration data for chemical substances in various media are obtained through studies and databases identified through the systematic review process. Estimated or modeled chemical concentrations are developed using environmental release data, fate and transport properties, physical and chemical properties, and characteristics of the environmental media. The integration of data from both actual concentration data and modeling estimates characterizes environmental and human health exposures.
3. *Environmental exposure assessment* employs the environmental media concentrations of the chemical substance to determine the levels at which environmental receptors are exposed to. The dose of the chemical substance that receptors are exposed to is determined by the concentration of the chemical in media and the frequency and duration of the exposure. EPA utilizes existing data and studies identified and reviewed through the systematic review process, as well as estimation (models) in the environmental exposure assessment.
4. *Human health exposure assessment* characterizes the exposure levels of the chemical substance in the environment at which human receptors are exposed to. In the risk evaluation process, EPA assesses exposure to the chemical substance to general population, including PESS such as workers (occupational) and consumers. EPA utilizes existing data and studies identified and reviewed through the systematic review process, as well as estimation (models) in the exposure

assessment. Data from estimation models (*i.e.,* modeled concentration data) is integrated outside of systematic review.

Table 7-2 Types of Exposure Data

Type of Extracted Data	Definition	Exposure Assessment Component
General life cycle and facility data	Life cycle description, production, import or use volume, process description, throughput, number of sites, and chemical concentration	Human health exposures assessment (*e.g.,* worker exposures) Environmental releases and media concentration
Occupational exposure	Worker activity description, route of exposure, physical form, personal sampling data, area sampling data, type of measurement or method, bulk and dust particle size distribution, dermal exposure data, exposure duration, exposure frequency, number of workers, personal protective equipment, and engineering control and percent exposure reduction	Human health exposure assessment (*e.g.,* worker exposures)
Environmental release	Description of the release source, release estimation method, release quantity, release days per year, release emission factor, waste treatment method, and pollution prevention/control and percent efficiency	Environmental release and media concentrations (for assessing ecological exposures, general population, and occupational exposures)
Product use data	Product use and concentration data for consumer products containing the chemical of interest and covered under TSCA	Human health exposure assessment (*e.g.,* consumer exposures)
Experimental chamber, product testing data	Consumer product or article amount and rate of emissions of the chemical of interest	Human health exposure assessment (*e.g.,* consumer exposures)
Modeled concentration data	Predictive modeling of human dose based on other measured exposure data	Human health exposure assessment (*e.g.,* general population exposures)
Monitoring data	Measured chemical concentration(s) obtained from systematic sampling of environmental media (*e.g.,* air, water, soil, biota) to observe and study the effect of environment conditions on the fate of chemicals. Monitoring data may include studies of chemical(s) after a known exposure/release of test substance as well as measured chemical concentrations over a period of time to provide direct evidence about fate in environment.	Environmental media concentrations (for assessing ecological exposures, general population exposures)

The following subsections describe the general framework for evidence integration for the four assessments, including the evidence needed for the assessments and provided by data extracted from the systematic review process or other evidence streams as described in the integration process.

7.3.1 Development of Exposure Scenarios

EPA follows the *Guidelines for Exposure Assessment* (U.S. EPA, 2019) to develop exposure scenarios which details how the receptors may be exposed. Exposure scenarios commonly used in TSCA risk evaluations are tailored to the chemical, the condition of use, relevant exposure sources and pathways, and potential receptors including PESS. Developing the exposure scenario is the first step in evidence integration. The exposure scenarios are used to organize the data and information from data evaluation/extraction in order to derived estimates for a set of circumstances and descriptors.

Human and environmental exposure scenarios include the frequency, duration, and amount of chemical exposure to which human, aquatic or terrestrial receptors could be exposed. The chemical's properties, the location, operating conditions, and human activities that affect exposure to a chemical, or exposure to products containing the chemical, as well as the characterization of the exposed population, are a part of building a human exposure scenario. Data supporting the exposure scenario development is compiled from extracted systematic review data (*e.g.*, fate and transport, environmental release, environmental media concentration analysis) as well as data gathered from outside of systematic review to further support characterization (*e.g.*, economic data, *EPA Exposure Factors Handbook*). Data and information extracted from the literature evaluated as acceptable during the systematic review process is gathered and analyzed according to the appropriate exposure scenario.

7.3.2 Integration of Exposure Information

Information across related but distinct exposure evidence streams (*i.e.*, physical and chemical properties, fate and transport, engineering release, and environmental and human exposure) are identified, considered, and documented—including those factors that increase or decrease the strength of the evidence when analyzing and integrating the data to support conclusions. After these data have been assembled, determinations are made regarding which exposure pathways, routes and receptors have sufficient supporting information of sufficient quality to be considered for deriving estimations of human or environmental exposure for quantitative assessment.

Environmental or human exposure concentrations can be measured directly through media sampling or monitoring, or indirectly estimated using estimation methodologies and/or models. EPA uses various tools and models to assist with exposure estimation used in occupational, consumer, general population, and environmental assessments. Modeling is an analytical assessment activity generally considered outside of systematic review. However, systematic review process may identify data in scientific literature that can be used to parameterize specific estimation approaches, models, and exposure scenarios. Models that estimate chemical substance concentrations in various media based on release assessment inputs are commonly used when suitable and reliable measurement data are limited or not available. In the absence of monitoring data, model use allows EPA to estimate the exposures associated with specific exposure scenarios.

Figure 7-3 presents a graphic representation of the overall framework for the exposure assessment including integration of systematic review data from peer-reviewed and gray literature with other data streams. For example, exposure data is evaluated from various study types including modeling studies, monitoring studies and/or experimental studies (see "Systematic Review" box in Figure 7-3). Inputs from the other data streams such as environmental releases and fate parameters derived from the systematic review process, are integrated into approaches and models used in the risk evaluation's exposure assessment (see "Exposure Assessment" box in Figure 7-3). Further, the extracted data from the systematic review process are integrated with the results from modeled data, which are outside of the systematic review process to provide a weight of the scientific evidence for exposure receptors.

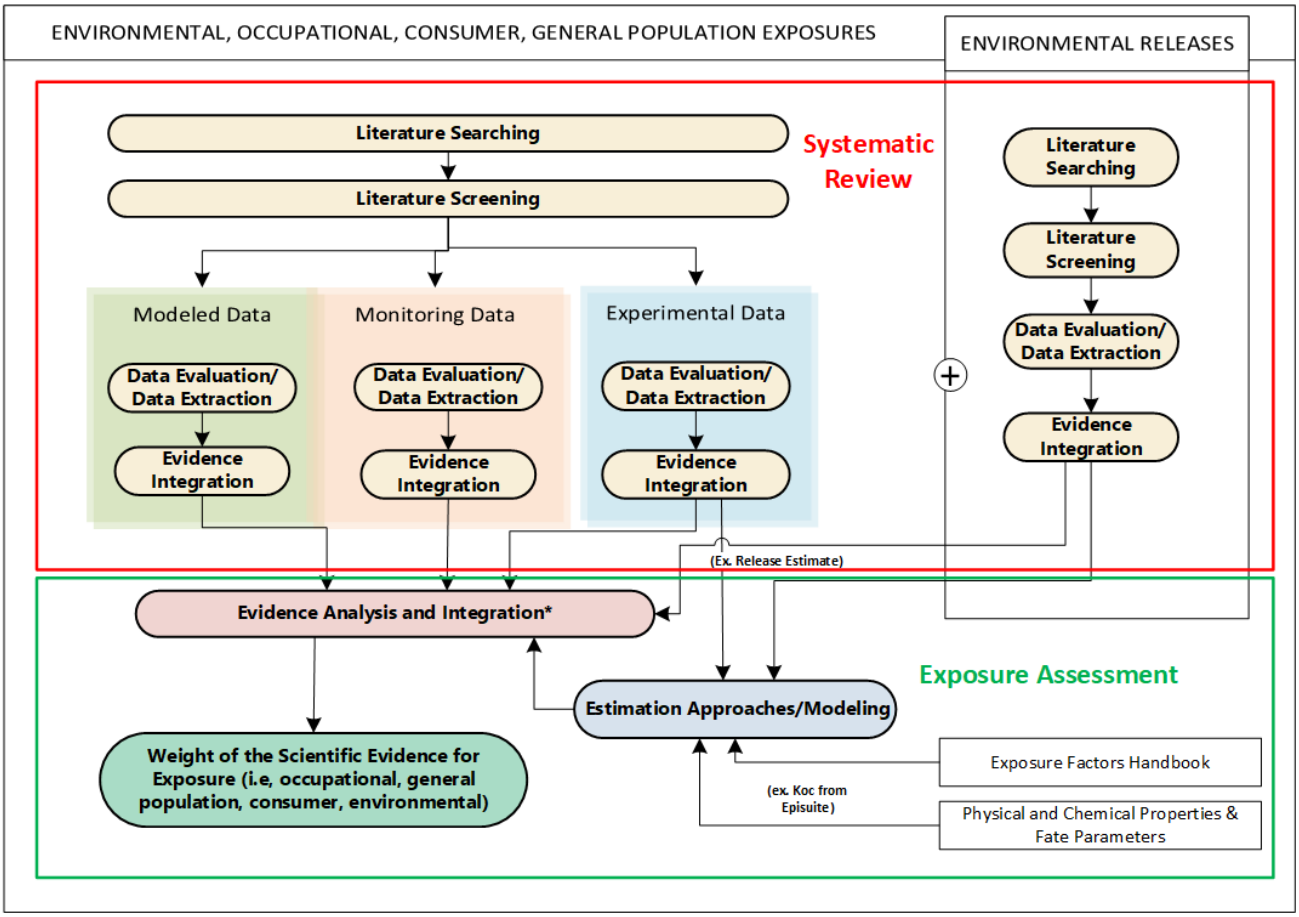

Figure 7-3. Example Integration of Exposure Data and Evidence Streams and Weight of the Scientific Evidence for Chemical Substance Media Concentration Estimates and Analysis
The asterisk in "Evidence Analysis and Integration" denotes the integration of data from systematic review and data outside of systematic review.

Table 7-3, Table 7-4, and Table 7-5 present the hierarchy of preferences guiding the analysis and integration of data and information supporting the assessment of environmental releases, occupational exposures, and exposures to consumers, general population, and environmental receptors, respectively. The preferences within the hierarchy are listed from more preferred to less preferred; however, these preferences reflect an ideal data landscape which may not be frequently realized. The amount, quality and type of information that can be utilized for a specific exposure scenario may vary depending on the chemical, thus the order within the hierarchy may change based on professional judgement and the availability and quality of data and information. Examples of such a change of hierarchy order may include when data are judged to be limited, unreliable or under representative for a particular reason. Some exposure estimates may be derived from a combination of two or more of these methods using a hybrid approach (U.S. EPA, 2015). For example, if there is limited or insufficient high quality measured or monitored data to adequately determine the range of exposure for a specific scenario, EPA may also incorporate predictive (computational modeling) approaches to support, supplement or more fully describe variability or to understand parameter sensitivity as they relate the exposure scenario. The determination of whether and when to incorporate more than one type of approach may be discerned during the earlier stages of systematic review (data evaluation and quality review) of the exposure data such that identification of data gaps can be used to inform the necessity for and identification of

appropriate estimation approaches. Moreover, if warranted, EPA may use data or information of lower rated quality as supportive evidence in the exposure assessments.

Table 7-3. Hierarchy Guiding Integration of Environmental Release Data/Information

For environmental releases, the generic hierarchy of preferences, listed from highest to lowest, is as follows (and may be modified based on the assessment):	
More Preferred  Less Preferred	**Monitoring and measured data:** Releases calculated from site-specific concentration in medium and flow rate data (*e.g.*, concentration in and flow rate of wastewater effluent discharged through outfall) Releases calculated from mass balances or emission factor methods using site-specific measured data (*e.g.*, process flow rates and concentrations)
	Modeling approaches: Surrogate monitoring data: Modeling release for chemical "X" and condition of use "A" based on observed monitoring data for chemical "Y" and condition of use "A," assuming a known relationship (*e.g.*, a linear relationship) between observed release and physical property (*e.g.*, vapor pressure). Fundamental modeling approaches: Modeling release for chemical "X" for condition of use "A" based on fundamental mass transfer, thermodynamic, and kinetic phenomena for chemical "X" and data for condition of use "A" Fundamental modeling approaches (with surrogacy): A modeling approach following the above approach, but using surrogate data in the model, such as data for condition of use "B" judged to be similar to condition of use "A" Statistical regression modeling approaches: Modeling release for chemical "X" in condition of use "A" using a statistical regression model developed based on: Observed monitoring data for chemical "X" statistically correlated with observed data specific for condition of use "B" judged to be similar to condition of use "A" such that replacement of input values in the model can extrapolate exposure results to condition of use "A" Observed monitoring data for chemical "Y" statistically correlated with physical properties and/or molecular structure such that a release prediction for chemical "X" can be made (*e.g.*, QSAR techniques)
	Release limits: Company-specific limits (for site-specific exposure assessments, *e.g.*, there is only one manufacturer who provides to EPA their internal limits (*e.g.*, point-source permits) but does not provide monitoring data) NESHAP or effluent limitations/requirements

Table 7-4. Hierarchy Guiding Integration of Occupational Exposure Data/Information

For occupational exposures, the generic hierarchy of preferences, listed from highest to lowest, is as follows (and may be modified based on the assessment)	
More Preferred ↑ Less Preferred	**Monitoring data:** Personal and directly applicable Area and directly applicable Personal and potentially applicable or similar Area and potentially applicable or similar
	Modeling approaches: Surrogate monitoring data: Modeling exposure for chemical "X" and condition of use "A" based on observed monitoring data for chemical "Y" and condition of use "A," assuming a known relationship (*e.g.,* a linear relationship) between observed exposure and physical property (*e.g.,* vapor pressure). Fundamental modeling approaches: Modeling exposure for chemical "X" for condition of use "A" based on fundamental mass transfer, thermodynamic, and kinetic phenomena for chemical "X" and data for condition of use "A" Fundamental modeling approaches (with surrogacy): A modeling approach following item 2.b, but using surrogate data in the model, such as data for condition of use "B" judged to be similar to condition of use "A" Statistical regression modeling approaches: Modeling exposure for chemical "X" in condition of use "A" using a statistical regression model developed based on: • Observed monitoring data for chemical "X" statistically correlated with observed data specific for condition of use "B" judged to be similar to condition of use "A" such that replacement of input values in the model can extrapolate exposure results to condition of use "A" • Observed monitoring data for chemical "Y" statistically correlated with physical properties and/or molecular structure such that an exposure prediction for chemical "X" can be made (*e.g.,* QSAR techniques)
	Occupational exposure limits (OELs): Company-specific OELs (for site-specific exposure assessments, *e.g.*, there is only one manufacturer who provides to EPA their internal OEL but does not provide monitoring data) OSHA PEL Voluntary limits (ACGIH TLV, NIOSH REL, Occupational Alliance for Risk Science [OARS] workplace environmental exposure level [WEEL; formerly by AIHA])

Table 7-5. Hierarchy Guiding Integration of Consumer, General Population, and Environmental Exposure Data/Information

The generic hierarchy of preferences, listed from highest to lowest levels, is as follows (and may be modified based on the assessment)	
More Preferred ↑ Less Preferred	**Monitoring data:** *Consumer and general population* Personal and directly applicable to exposure scenario and chemical Area and directly applicable to exposure scenario and chemical Personal and potentially applicable or similar Area and potentially applicable or similar Concentration in environmental medium *Environmental* a. Concentration in medium
	Modeling approaches: Consider a specific chemical "X" that has a developed exposure scenario (based on the specific condition of use and the associated exposure pathways) "A." Then, consider there may also be a chemical "Y" that shares some chemical or use properties with chemical "X" and an exposure scenario "B" that covers a separate, but similar, condition of use than scenario "A." Exposure assessment may use surrogate monitoring data, modeling approaches, or modeling inputs based on the available information: Surrogate monitoring data: Modeling exposure for chemical "X" and scenario "A" based on observed monitoring data for chemical "Y" and condition of use "A," assuming a known relationship (*e.g.*, a linear relationship) between observed exposure and physical property (*e.g.*, vapor pressure). Fundamental modeling approaches: Modeling exposure for chemical "X" for scenario "A" based on fundamental mass transfer, thermodynamic, and kinetic phenomena for chemical "X" and data for condition of use "A" Fundamental modeling approaches (with surrogacy): A modeling approach following item 2.b, but using surrogate data in the model, such as data for condition of use "B" judged to be similar to condition of use "A" Statistical regression modeling approaches: Modeling exposure for chemical "X" in scenario "A" using a statistical regression model developed based on: Statistically Correlated Modeling Inputs: Observed monitoring data for chemical "X" statistically correlated with observed data specific for scenario "B" judged to be similar to scenario "A" such that replacement of input values in the model can extrapolate exposure results to scenario "A" Statistically Correlated Monitoring Observations: Observed monitoring data for chemical "Y" statistically correlated with physical properties and/or molecular structure such that an exposure prediction for chemical "X" can be made (*e.g.*, QSAR techniques)

Integration of exposure and release data and information involves the summarization of datasets and selection of key data and information sources that are used to develop exposure estimates that are representative of the conditions of use, with consideration of inherent variability and uncertainties within exposure scenarios. The selection of data and information are informed by the hierarchy of preferences, which considers the use of both measured (monitoring) and estimated (modeled) data. While comprehensive high-quality measured data specific to the exposure scenario being evaluated is generally preferred, EPA recognizes that sufficient monitoring data which specifically align with the exposure scenario are often scarce or may not always adequately represent the exposure scenarios of interest. Thus, modeling in a tiered fashion (simple to complex) is conducted in many cases. Higher level modeling involves the use of numerous chemical-specific and scenario-specific inputs, such as emission

profiles (derived from experimental studies) and habits and practices exhibited by the receptors. Depending on the model, higher level modeling may also allow probabilistic calculations (distributions of data as inputs).

Methodologies (whether incorporating measured or modeled data) for deriving estimates of exposure for workers, consumers, general population, or environmental receptors are not mutually exclusive within the exposure assessment approach hierarchy and can be applied within the systematic review framework to provide more options for conducting the analyses. The choice of whether to use measured data, modeled estimates, or a combination of both approaches, may depend on the size and complexity of the exposure scenario as well as the amount or extent and quality of available information for the specific chemical and scenario. These approaches may include a review of the reasonably available monitoring or measured data, including careful consideration of the factors that may strengthen or weaken the weight of the evidence as well as estimation approaches that rely upon parameterization of a computational model that utilizes default and/or chemical or scenario specific inputs, to arrive at exposure estimates in the media of interest for the receptor of interest.

Specific considerations for integrating exposure data/information are described below.

Data Quality and Reporting Considerations

As previously indicated, EPA only integrates data or information rated as *high*, *medium*, or *low* obtained during the data evaluation phase. Data and information rated as *uninformative* are not used in exposure evidence integration. In general, higher rankings are given preference over lower ratings; however, lower ranked data may be used over higher ranked data when specific aspects of the data are carefully examined and compared. For example, a lower ranked data set that precisely matches the exposure scenario of interest may be used over a higher ranked study that does not as closely match the scenario of interest. The robustness of the reported results is an aspect of data quality. During integration, data sets available to generate central tendency and high-end measurements/estimates are prioritized. Central tendency may include 50th percentile (median), mean (arithmetic or geometric), mode, or midpoint. High-end may include 95th percentile, 90th to 99.9th percentile, maximum, or bounding.

Primary Input Considerations

EPA uses both measured and modeled concentrations to obtain accurate and representative estimates (*e.g.*, central-tendency, high-end) of the population, environmental, consumer or worker exposures resulting directly from a specific source, medium, or product. If available, measured concentrations are given preference over modeled concentrations, with the highest preference given to monitoring data that are both chemical-specific and directly representative of the conditions under which exposure is known or assumed to occur for each situation. The quantitative data or information usually come from primary sources such as monitoring or biomonitoring concentrations, modeled intakes and doses, trends, emission factors, and product formulations. It is anticipated that, in many if not most cases, data satisfying representative exposure conditions are relatively scarce; thus, data reliance needs to be placed on modeling.

In some cases, chemical-specific and/or scenario-specific data may not be available. In these cases, surrogate chemical or scenario data may be used instead. Consumer exposure estimates, for example, are highly dependent on a variety of scenario-specific factors and the data must be carefully evaluated for representativeness. Example factors to be considered for a consumer exposure scenario include (1) type of product or article releasing the chemical; (2) amount, frequency, and duration of use for products or the loading ratio and duration since installation for articles; and (3) ancillary conditions such as ventilation rates and background concentrations.

Ultimately, integration of the exposure evidence combines decisions regarding the strength of the exposure information (including fate and transport, environmental release information, and measured and/or estimated human and environmental exposures), incorporating information on plausibility and coherence across these bodies of evidence.

In summary, EPA interprets the exposure data and information and provides a discussion of the strength and limitations of the exposure evidence, along with a discussion on the uncertainties, variability, and underlying assumptions including science policy assumptions supporting the exposure estimates. EPA describes limitations that may be inherent in any of the underlying key and supporting data/information sources, input parameters, and assumptions supporting the exposure estimates.

7.3.3 Evaluating the Strength of the Evidence and the Weight of the Scientific Evidence for Exposure Assessments

Integration of the exposure evidence streams across systematic review and non-systematic review sources results in an exposure estimate for the chemical of interest. A judgment on the weight of the scientific evidence supporting the exposure estimate is decided based on the strengths, limitations, and uncertainties associated with the exposure estimates. The judgment is summarized using confidence descriptors: robust, moderate, slight, or indeterminate confidence descriptors.

In determining the strength of the overall weight of the scientific evidence, EPA considers factors that increase or decrease the strength of the evidence supporting the exposure estimate (whether measured or estimated), including quality of the data/information, relevance of data to the exposure scenario (including considerations of temporal relevance, spatial relevance), and the use of surrogate data when appropriate. In general, higher rated studies (as determined through Data Evaluation) increase the weight of the scientific evidence when compared to lower rated studies, and chemical- and scenario-specific data are given preference over surrogate data (similar chemical or scenario). General considerations are summarized in Table 7-6.

During review, an assessor may review the strength of each evidence stream to arrive at an overall judgment. An overall judgment may be made for a single exposure scenario or it may be most appropriate for an exposure route in the exposure scenario. Table 7-7 provides example judgments based on the general considerations listed in Table 7-6.

Table 7-6. Considerations that Inform Evaluations of the Strength of the Evidence

Considerations	Factors that Increase Strength	Factors that Decrease Strength
The Overall Weight of the Scientific Evidence Judgment considers the general considerations below as well as chemical-specific considerations to designate each exposure scenario as robust, moderate, slight, or indeterminate. The designation is a measure of the weight of the evidence supporting the representativeness of the exposure estimates toward the true distribution of exposure (and releases) for the scenario.		
Relevance to exposure scenario	• Directly relevant to evaluated exposure scenario	• Data used is for an alternative or surrogate scenario
For modeled estimates	• Model used has been peer-reviewed and is being applied in a manner appropriate to its design and objective	• Evidence demonstrating implausibility • Model has not been peer-reviewed and no ground-truthing has been performed

Considerations	Factors that Increase Strength	Factors that Decrease Strength
		• Parameterization is not well described, documented or is not appropriate to the evaluated scenario
Data quality	• Medium or high data quality ranking (via Data Evaluation)	• Low data quality ranking (via Data Evaluation) • Imprecision or inaccuracy
Data points	• High number of data points	• Low number of data points • High proportion of data sampled prior to changes in industry or other relevant conditions (*e.g.*, OSHA PEL)
Representative of the whole industry (for occupational scenarios)	• Large proportion of sites included within the exposure scenario were measured	• Evidence may not be sufficiently representative of all of the sites for the exposure scenario
Representative of the sub-population	• Applicable to most or all of the different population groups included within the exposure scenario	• Information was not available to sufficiently cover most or all of population groups included within the exposure scenarios
Consistency	• Consistency and replication within a study and across studies	• Inexplicable contradictory findings across studies
Variability	• Variability is accounted in estimates • Full distributions of input parameters	• Variability unaccounted in estimates
Uncertainties	• Uncertainties are low and the uncertainties are unlikely to significantly impact exposure estimates	• Uncertainties that are likely to over- or under-estimate exposure from the actual exposures for the exposure scenario

Table 7-7. Evaluation of the Weight of the Scientific Evidence for Exposure Assessments

Category	Robust	Moderate	Slight	Indeterminate	Overall Weight of the Scientific Evidence
Exposure Scenario Factors (*e.g.*, habits, worker activities, exposure factors)	• Directly relevant to evaluated exposure scenario • Applicable to most or all of the different population groups included within the exposure scenario • Full distributions of input parameters • High or medium quality data rankings • The habits, worker activities, and/or use patterns are accounted for, are current • Uncertainties are low and the uncertainties are unlikely to significantly impact exposure estimates	• Surrogate scenarios from similar chemicals are used to infer similar exposures or emissions. • Some distribution of input parameters • High or medium quality data rankings • There is some, but not complete, documentation or description of assumptions, limitations and uncertainties • Surrogate scenarios from similar uses are used to infer similar use patterns or habits and practices	• Medium or low quality data rankings • Partially supported by assumptions • Uncertainties are not fully known or documented • Habits and practices are not fully known and there is a high degree of uncertainty in defining use patterns	• Qualitative descriptions of exposure without additional context. • No supporting data on habits and practices are available	The consideration factors and the categories to the left result in an overall weight of the scientific evidence judgment as one of the following: • *Robust* • *Moderate* • *Slight* • *Indeterminate*
Measured/Monitored Data	There is measured information and the temporal and spatial aspect of the measurements are well described, relevant and reflect current conditions • Medium or high data quality ranking (via Data Evaluation) • High number of data points • Multiple studies or a large number of data points which indicate similar findings • Large proportion of sites included within the	There is measured information which does not reflect current environmental conditions or does not correspond to current activities but provides evidence of exposure. • Limited number of studies or limited number of data points which indicate similar findings • Information was not available to sufficiently cover most or all of population groups included within the exposure scenarios	There is limited measured information and information and does not reflect exposure conditions and does not correspond to known activities. • Information was not available to sufficiently cover most or all of population groups included within the exposure scenarios • Assumptions and uncertainties are not known or documented	No measured or monitored data are available	

Category	Robust	Moderate	Slight	Indeterminate	Overall Weight of the Scientific Evidence
	exposure scenario were measured • Consistency and replication within a study and across studies • Uncertainties are low and the uncertainties are unlikely to significantly impact exposure estimates • Sensitivity of the exposure estimates has been described and quantified incorporating assumptions, limitations, and uncertainties	• There is some, but not complete, documentation or description of assumptions, limitations and uncertainties			The consideration factors and the categories to the left result in an overall weight of the scientific evidence judgment as one of the following: • *Robust* • *Moderate* • *Slight* • *Indeterminate*
Estimation Methodology/Data	• The methodology for deriving the estimate is well described and the underlying computational and/or scientific basis is robust, has an empirical basis or well documented mathematical basis and considers chemical specificity (*e.g.*, physical and chemical properties and fate) • Applicable to most or all of the different population groups included within the exposure scenario (representative) • Sensitivity of the exposure estimates has been described and quantified incorporating assumptions, limitations, and uncertainties	• The methodology for deriving the estimate is well described and the underlying computational and/or scientific basis is robust, however there is uncertainty in the parameterization or applicability • There is some, but not complete, documentation or description of assumptions, limitations and uncertainties.	• Modeling approach used to estimate exposures is not rooted in scientific rigor or does not mathematically represent the exposure scenario; parameterization is not complete or does not utilize the best available science. • Assumptions and uncertainties are not known or documented	• Modeling approach is not available for the scenario or lack of information on parameters prohibits use of available models.	The consideration factors and the

Category	Robust	Moderate	Slight	Indeterminate	Overall Weight of the Scientific Evidence
Comparison of Estimated and Measured Exposures (*if both estimated and measured estimates are used*)	• There are comparable estimates using alternate approaches • There is concordance between measured and/or reported and modeled estimates/predictions for the same exposure scenario • Sensitivity of the exposure estimates has been described and quantified incorporating assumptions, limitations, and uncertainties	• Modeled estimates and measured exposure values are comparable, however differences in methodology, collection, or context make it difficult to arrive at full concordance • There is some, but not complete, documentation or description of assumptions, limitations and uncertainties	• There is a lack of correspondence between measured exposures and modeled exposure estimates even when uncertainty and variability are accounted for. • Assumptions and uncertainties are not known or documented	• Category does not have indeterminate criterion.	categories to the left results in an overall weight of the scientific evidence judgment as one of the following: • *Robust* • *Moderate* • *Slight* • *Indeterminate*

7.4 Integration of Environmental Hazard Evidence and Information

7.4.1 Integration of Evidence for Relevant Environmental Hazard Effects

The organization and approach to integrating hazard evidence is determined by the reasonably available evidence regarding routes of exposure, exposure media, duration of exposure, taxa, metabolism and distribution, effects evaluated, the number of studies pertaining to each effect, as well as the results of the data quality evaluation.

The environmental hazard integration is organized around effects to aquatic and terrestrial organisms as well as the respective environmental compartments (*e.g.*, pelagic, benthic, soil). Environmental hazard assessment may be complex based on the considerations of the quantity, relevance, and quality of the available evidence.

Typically, environmental hazard data from toxicology studies identified during systematic review have three different streams of evidence: evidence that characterizes apical endpoints; evidence that characterizes cellular, biochemical or molecular mechanism of a toxic effect; and/or evidence of community level effects from field studies. These three streams of evidence can be organized by aquatic and terrestrial organisms for evidence integration. Table 7-8 lists some questions that may be asked of the evidence to assist with this decision. These questions extend from considerations and decisions made during development of the analysis plan to include review of the concerns raised during individual study evaluations as well as the direction and magnitude of the study-specific results. Resolution of these questions inform critical decisions about the organization of the environmental hazard evaluation and help determine what studies may be useful in dose-response analyses.

Table 7-8. Querying the Evidence to Organize Integration for Environmental Data and Information

Evidence Stream	Questions
Apical endpoints	Of the available data, are there endpoints that could have population level effects such as reproduction, growth, and/or mortality?
Mechanistic data	Is the mechanistic endpoint linked to an apical endpoint? Is it part of an AOP? If not, can you instead use it qualitatively? If a transcriptomic point of departure (tPOD) is available, is it appropriate to use quantitatively?
Field studies	Are there any field studies available showing adverse effects? How does exposure to the chemical of interest affect the community of organisms? Are there any co-occurring adverse environmental conditions other than exposure to the chemical of interest that should be taken into consideration?

Additionally, other methods outside of systematic review can be used to supplement this information and address identified data gaps. These methods include the use of read-across to other chemicals with similar chemical structures or hazard profiles as well as *in silico* estimation tools (*e.g.*, the ECOlogical Structure-Activity Relationship Model [ECOSAR] Class Program, the Species Sensitivity Distribution [SSD] Toolbox, Web-based Interspecies Correlation Estimation [WebICE]). These read-across and *in silico* methods – which fall outside of systematic review – may also be used to estimate a hazard threshold based on toxicological data available on various species.

The characterization of environmental hazard effects involves describing the potential adverse effects and dose-response relationships resulting from exposure to a chemical substance. EPA evaluates the quality of the study using the evaluation strategy in Appendix P.3 and Appendix P.4. Briefly, studies are evaluated using 23 metrics and each metric will be binned into a quality level of *high*, *medium*, *low*, or *critically deficient*. The binning of individual metrics is then used to assess the overall quality of the study as *high*, *medium*, *low*, or *uninformative for dose-response*. Individual metrics considered c*ritically deficient* will not be used to inform the environmental hazard assessment. An overall data quality level of *high*, *medium*, or *low* may be used to quantitatively or qualitatively support the environmental hazard assessment while studies ranked as *uninformative for dose-response* may be considered during the hazard assessment and in the weight of the scientific evidence but will not be considered for dose-response.

In addition to the quality of a study, EPA considers the relevance of the data/information. EPA determines if data/information are relevant based on whether they have biological, physical, chemical, and environmental relevance (U.S. EPA, 1998a):

1. Biological relevance – correspondence among the taxa, life stages, and processes measured or observed and the assessment end point;
2. Physical and chemical relevance – correspondence between the chemical or physical agent tested and the chemical or physical agent constituting the stressor of concern; and
3. Environmental relevance – correspondence between test conditions and conditions in the region of concern (U.S. EPA, 1998a).

While integrating environmental hazard evidence to characterize environmental effects, EPA gives precedence to relevant data/information ranked high for quality, as described in the hierarchy of preferences in Table 7-9. This hierarchy, which for least preferred data also includes information outside of systematic review, guides how the data from systematic review and outside of systematic review are analyzed and integrated for environmental hazard in the TSCA risk evaluations. The hierarchy may be modified depending on the specific chemical assessment.

Table 7-9. Hierarchy Guiding Integration of Environmental Hazard Data and Information

For environmental hazard data, the generic hierarchy of preferences, listed from highest to lowest levels, is as follows (and may be modified based on the assessment)	
More Preferred  Less Preferred	1. Quantitative lab or field data with a high-quality ranking and is relevant.
	2. Quantitative lab or field data with a medium quality ranking and is relevant.
	3. Quantitative lab or field data with a low evaluation ranking and is relevant.
	4. Qualitative data/information that is relevant (*e.g.*, descriptive field /mesocosm studies, mechanistic or gene expression studies that do not measure an organism-level toxic effect) OR Quantitative data that is less relevant (*e.g.*, the test does not use the substance of concern [instead uses an analogue, isomer or mixture], or the test includes conditions that would not occur in the environment). [Some of this information might be outside of systematic review.] OR Modeled quantitative data that is relevant (*e.g.*, structure activity relationship [SAR]/QSAR information using ECOSAR, or other predictive tools like WebICE). (Modeled data produced by EPA are outside of systematic review.)

7.4.2 Evaluating the Strength of the Evidence and Weight of the Scientific Evidence for Environmental Hazard Assessments

As discussed above in Section 7.4.1, information obtained through the systematic review process is evaluated for quality and relevance to inform the environmental hazard assessment. Additionally, other methods outside of systematic review can be used to supplement this information and address identified data gaps. Both information obtained through the systematic review process and information obtain outside of systematic review are considered together with integrated evidence when evaluating the overall weight of the scientific evidence for the environmental hazard assessment as described below in Section 7.4.2.1 and Section 7.4.2.2.

7.4.2.1 Evaluating the Strength of the Evidence within Evidence Streams

EPA evaluates and summarizes the strength of the available evidence prior to drawing overall judgment whether the weight of the scientific evidence supports an association between the chemical substance and the environmental health effect(s) in various organisms given relevant exposure circumstances. For each assessed ecosystem (*e.g.*, aquatic, terrestrial), the relevance of available toxicological information (*i.e.*, exposure duration, media, and pathway) for a specific organism or receptor (*i.e.*, different levels of biological organization) is evaluated through the systematic review process and considered alongside similar data/information that fall outside of systematic review and may have been integrated (*e.g.*, read-across, ECOSAR data) (Table 7-12). The evaluation of the strength of the evidence for hazard effects occurs for relevant environmental systems and exposure pathways and media. Furthermore, the interrelatedness of effects is also evaluated to support the environmental hazard threshold used to determine environmental risk.

In the case of environmental hazard, data can either be quantitative or qualitative. EPA uses quantitative and relevant data/information of the highest quality available for each exposure pathway and trophic

level to calculate environmental hazard thresholds (*e.g.*, concentration of concern [COC], hazard value, or Toxicity Reference Value [TRV]).

Additionally, qualitative data/information can be used to supplement and further describe quantitative data. When quantitative data are unavailable, qualitative data can be used on its own to describe environmental hazard with uncertainties noted. Analogue data or SARs may also be used to fill data gaps or support other data/information. Uncertainties, data gaps, and assumptions are described for all above-mentioned approaches in Section 7.4.3.

Table 7-10. Considerations that Inform Evaluations of the Strength of the Evidence within an Evidence Stream (*i.e.*, Apical Endpoints, Mechanistic, or Field Studies)

Consideration	Factors that Increase Evidence Strength (of the Apical Endpoints, Mechanistic, or Field Studies Evidence)	Factors that Decrease Evidence Strength (of the Apical Endpoints, Mechanistic, or Field Studies Evidence)
The structured categories and criteria laid out here guide the application of strength-of-evidence judgments for an outcome or environmental hazard effect within a given evidence stream. Evidence integration or synthesis results that do not warrant an increase or decrease in evidence strength for a given consideration are considered "neutral" and are not described in this table (and, in general, are captured in the assessment-specific evidence profile tables).		
Quality of the database (risk of bias)	A large evidence base of *high*- or *medium*-quality studies increases strength, and in addition, strength increases if relevant species are represented in a database.	An evidence base of mostly *low*-quality studies or other types of data low on the data hierarchy in Table 7-9 (*e.g.*, analogue, modeled data) decreases strength. Strength also decreases if the database has data gaps for relevant species; *i.e.*, a trophic level that is not represented. Decisions to increase strength for other considerations in this table should generally not be made if there are serious concerns for risk of bias; in other words, all the other considerations in this table are dependent upon the quality of the database.
Consistency	Similarity of findings for a given outcome (*e.g.*, of a similar magnitude, direction) across independent studies or experiments increases strength, particularly when consistency is observed across species, life stage, sex, wildlife populations, and across or within aquatic and terrestrial exposure pathways.	Unexplained inconsistency (*i.e.*, conflicting evidence; see (U.S. EPA, 2005a)) decreases strength. Generally, strength should not be decreased if discrepant findings can be reasonably explained by study strength of the evidence conclusions; variation in population or species, sex, or life stage; frequency (*e.g.*, intermittent or continuous); exposure levels (low or high); or exposure duration.
Strength (effect magnitude) and precision	Evidence of a large magnitude effect (considered either within or across studies) can increase strength. Effects of a concerning rarity or severity can also increase strength, even if they are of a small magnitude. Precise results from individual studies or across the set of studies increases strength, noting that biological significance is prioritized over statistical significance.	Strength may be decreased if effect sizes that are small in magnitude are concluded not to be biologically significant, or if there are only a few studies with imprecise results.
Biological gradient/dose-response	Evidence of dose-response increases strength. Dose-response may be demonstrated across studies or within studies and it can be dose- or duration-	A lack of dose-response when expected based on biological understanding and having a wide range of doses/exposures evaluated in the evidence base can decrease strength.

Consideration	Factors that Increase Evidence Strength (of the Apical Endpoints, Mechanistic, or Field Studies Evidence)	Factors that Decrease Evidence Strength (of the Apical Endpoints, Mechanistic, or Field Studies Evidence)
	dependent. It also may not be a monotonic dose-response (monotonicity should not necessarily be expected; *e.g.*, different outcomes may be expected at low vs. high doses due to activation of different mechanistic pathways or induction of systemic toxicity at very high doses). Decreases in a response after cessation of exposure (*e.g.*, return to baseline fecundity) also may increase strength by increasing certainty in a relationship between exposure and outcome (this is particularly applicable to field studies).	In experimental studies, strength may be decreased when effects resolve under certain experimental conditions (*e.g.*, rapid reversibility after removal of exposure). However, many reversible effects are of high concern. Deciding between these situations is informed by factors such as the toxicokinetics of the chemical and the conditions of exposure [see (U.S. EPA, 1998b)], endpoint severity, judgments regarding the potential for delayed or secondary effects, as well as the exposure context focus of the assessment (*e.g.*, addressing intermittent or short-term exposures). In rare cases, and typically only in toxicology studies, the magnitude of effects at a given exposure level might decrease with longer exposures (*e.g.*, due to tolerance or acclimation). Like the discussion of reversibility above, a decision about whether this decreases evidence strength depends on the exposure context focus of the assessment and other factors. If the data are not adequate to evaluate a dose-response pattern, then strength is neither increased or decreased.
Biological relevance	Effects observed in different populations or representative species suggesting that the effect is likely relevant to the population or representative species of interest (*e.g.*, correspondence among the taxa, life stages, and processes measured or observed and the assessment endpoint.)	An effect observed only in a specific population or species without a clear analogy to the population or representative species of interest decreases strength.
Physical and chemical relevance	Correspondence between the substance tested and the substance constituting the stressor of concern.	The substance tested is an analogue of the chemical of interest or a mixture of chemicals which include other chemicals besides the chemical of interest.
Environmental relevance	Correspondence between test conditions and conditions in the region of concern.	The test is conducted using conditions that would not occur in the environment.

7.4.2.2 Evaluating the Weight of the Scientific Evidence across Evidence Streams

While evaluating the weight of the scientific evidence within evidence streams (*e.g.*, apical endpoints, mechanistic, field studies), a judgement of robust, moderate, slight, or indeterminate is made based on considerations outlined in Table 7-11. Next, the evidence is evaluated across evidence streams, and an overall judgment of robust, moderate, slight, or indeterminate is made. Data/information is used across evidence streams to calculate a hazard threshold for environmental hazard characterization.

Table 7-11. Considerations that Inform Evaluations of the Strength of the Evidence across Evidence Streams

Category/ Evidence Stream	Robust	Moderate	Slight	Indeterminate	Overall Judgement
In vivo apical endpoint studies in animals or plants	Relevant *high*- and *medium*-quality studies with quantitative data for most trophic level within the ecosystems (*e.g.*, aquatic or terrestrial) being assessed for a chemical. Ideally, there is enough data to analyze the data using probabilistic methods (*e.g.*, SSDs) to calculate hazard thresholds. However, there may be some trophic levels that require a deterministic method to calculate hazard thresholds (*e.g.*, aquatic plants, or chronic data for other aquatic species).	Relevant *high*- and *medium*-quality studies with quantitative data for multiple trophic levels within the ecosystems (*e.g.*, aquatic or terrestrial) being assessed for a chemical. *Low*-quality data and/or suitable analogue data or SARs are used to fill data gaps or support other data/information. Ideally, there is enough data to analyze the data using probabilistic methods (*e.g.*, SSDs) to calculate hazard thresholds. However, there may be some trophic levels that require a deterministic method to calculate hazard thresholds (*e.g.*, aquatic plants, or chronic data for other aquatic species).	Relevant *high*- and *medium*-quality studies with quantitative data for only some or no trophic levels within the ecosystems (*e.g.*, aquatic or terrestrial) being assessed for a chemical. *Low*-quality data and/or suitable analogue data or SARs are used to fill data gaps. Likely includes a small dataset and requires a deterministic method to calculate hazard thresholds.	No relevant data available on the chemical of interest and very little to no relevant data on close analogues for most trophic levels. Additionally, the chemical is outside the domain of applicability for predictive tools.	Example scenarios: – Robust: For aquatic ecosystems, each trophic level is represented (*e.g.*, at least one aquatic plant, invertebrate and vertebrate species), and for terrestrial ecosystems, at least one invertebrate and vertebrate species is represented. All the data are from *high*- and/or *medium*-quality studies. – Moderate: For aquatic ecosystems, some trophic levels are represented (*e.g.*, aquatic plant, invertebrate or vertebrate species), and for terrestrial ecosystems, only one species is represented. All the data is from *high*- and/or *medium*-quality studies. In addition, mechanistic evidence exists from *medium*- or *high*-quality studies for a trophic level that includes a sub-organism level effect that cannot be tied to an apical endpoint but can be used to describe an effect qualitatively in support of other data.
Mechanistic studies	Evidence includes one or more medium- or high-quality studies for a trophic level that includes a sub-organism level effect that can be tied to an apical	Evidence includes one or more medium- or high-quality studies for a trophic level that includes a sub-organism level effect that cannot be tied to an apical endpoint but can be used to	Evidence includes only low-quality studies with a sub-organism level effect that cannot be tied to an apical endpoint but can be used to describe	No mechanistic studies available	

Category/ Evidence Stream	Robust	Moderate	Slight	Indeterminate	Overall Judgement
	endpoint through an Adverse Outcome Pathway (AOP) or if a transcriptomics Point of Departure (tPOD) is derived and it can be considered biologically significant enough to use.	describe an effect qualitatively in support of other data.	an effect qualitatively in support of other data.		– Slight: Low-quality data and/or suitable analogue data or SARs are used to fill data gaps. In addition, low quality field studies are available to support *in vivo* and/or suitable SAR data. Judgments considering the factors and the categories to the left result in an overall judgment as one of the following: • *Robust* • *Moderate* • *Slight* • *Indeterminate*
Field/mesocosm studies	Evidence includes one or more *medium*- or *high*-quality studies that together examine multiple species across trophic levels from an ecosystem (*e.g.*, aquatic or terrestrial) being assessed with biological, physical, chemical, and environmental relevance.	Evidence includes one or more *medium*- or *high*-quality studies that together examine just one species or one trophic level from an ecosystem (*e.g.*, aquatic or terrestrial) being assessed with biological, physical, chemical, and environmental relevance.	Evidence includes one or more *low* quality studies representing an ecosystem (*e.g.*, aquatic or terrestrial) being assessed. Or Evidence includes one or more *medium*- or *high*-quality studies that include at least one species representing at least one trophic level from an ecosystem (*e.g.*, terrestrial or aquatic) *without* biological, physical, chemical, and environmental relevance.	No field or mesocosm studies available	

7.4.2.1 Overall Weight of the Scientific Evidence Judgments

The overall weight of the scientific evidence judgment combines decisions regarding the strength of the evidence for apical endpoint data, mechanistic data, and field studies. This overall judgment also considers any additional data obtained external to the systematic review process, if applicable. The decision process culminates in a summary of judgments regarding the evidence for each ecosystem (*i.e.*, aquatic and terrestrial). This summary of judgements is used to inform the causal determination or association between chemical exposure and environmental health effects (Table 7-12).

Table 7-12. Classification for Weight of the Scientific Evidence for Causal Determinations for Characterizing Potential Environmental Hazards Evidence

Overall Evidence Integration Judgment in Narrative	Evidence Integration Judgement Level	Description
Evidence demonstrates that there is the environmental health outcome(s) with the relevant chemical exposures.	Evidence demonstrates	The substance has been shown to result in effects in studies in which chance, confounding, and other biases could be ruled out with reasonable weight of the scientific evidence. Controlled exposure studies (laboratory or field studies) provide the strongest evidence for causality, but the scope of inference may be limited. Generally, the determination is based on multiple studies conducted by multiple research groups, and evidence that is considered sufficient to infer a causal relationship is usually obtained from the joint consideration of many types of evidence that reinforce each other.
Evidence is sufficient to conclude that there is likely an association between the environmental health outcome(s) and the relevant chemical exposures.	Evidence indicates likely	An association has been observed between the substance and the outcome in studies in which chance, confounding, and other biases are minimized but cannot be ruled out and uncertainties remain. Example for when biases are minimized, field studies show a relationship, but suspected interacting factors cannot be controlled, and other lines of evidence are limited or inconsistent. Example for when biases are cannot be ruled out, at least one high-quality study shows an effect, but the results of other studies are insufficient. Generally, the determination is based on multiple studies by multiple research groups.
Evidence is inadequate to determine that a relationship exists with relevant substance exposures.	Evidence is inadequate	The available studies are of insufficient quality, consistency, or relevancy to permit a conclusion regarding the presence or absence of an effect.
Evidence is sufficient to conclude that there is likely no association between the environmental health outcome(s) and the relevant chemical exposures.	Strong evidence supports no effect	Evidence indicates there is no causal relationship with relevant substance exposures. Several adequate studies examining relationships with relevant exposures are consistent in failing to show an effect at any level of exposure.

7.4.3 Characterization of Strengths, Limitations, Assumptions, and Key Sources of Uncertainty in the Environmental Hazard Assessments

In determining the strength of the available evidence together with the relevance of available toxicological information [which is in turn based on whether the information is derived from environmental hazard studies of acceptable quality obtain through the systematic review process or estimated through types of data/information that may have been integrated and fall outside of systematic review (*e.g.*, read-across, QSAR data)], a number of assumptions are made for all integrated data that can lead to uncertainties in the hazard characterization. The further down in the hierarchy of preferences in Table 7-9 (*i.e.*, the more evidence from less preferred evidence types), the more uncertainties there are. Assumptions and uncertainties may be related to data used for the characterization of environmental exposure (*e.g.*, inability to directly relate monitoring sites to conditions of use, model input parameters) and environmental hazard (*e.g.*, selection of representative organisms to estimate hazard thresholds for other organisms). These assumptions and uncertainties are taken into consideration in the weight of the scientific evidence for causal determinations for environmental hazard (Table 7-12).

Ultimately, the overall weight if the scientific evidence in environmental hazard information is based on the uncertainties of all evidence streams as a whole. The strength of the evidence for each evidence stream informs the overall weight of the scientific evidence and judgment of the weight of the scientific evidence. That is, consistency, strength, relevance, and reliability on environmental hazard information across evidence supports the conclusion of whether the evidence is robust, moderate, or slight (Table 7-11).

7.5 Integration of Human Health Hazard Evidence and Information

The hazard integration results in conclusions that are drawn based on the combined strength and coherence of inferences appropriately drawn from all of the available information.

Section 7.5.1 discusses the process for identifying relevant human health effects for a particular chemical. Section 7.5.1.1 through Section 7.5.1.3 describe the integration of human health information within the distinct evidence streams of human, animal (both addressed in Section 7.5.1.2), and mechanistic data (Section 7.5.1.3), while Section 7.5.1.4 addresses integration of data obtained from outside the systematic review process. Section 7.5.2 then presents how EPA makes conclusions based on the weight of the scientific evidence (WoSE). Section 7.5.2.4 presents an overview of how risk evaluations consider assumptions, strengths, limitations, and uncertainties. It is important to emphasize that the information presented in this draft protocol is by no means an in-depth discussion of the complexities reviewing and interpreting hazard evidence associated to chemical exposures. EPA considers the following information along with agency guidance documents and accepted risk assessment practices in developing the human health hazard assessment. The majority of the evidence integration process for human health hazard information is adapted from a draft of EPA's ORD Staff Handbook for Developing IRIS Assessments (U.S. EPA, 2020). Minor deviations are present throughout the section based on TSCA-specific needs and interpretations. More prominent instances of these variations will be noted when present.

7.5.1 Integration of Evidence for Relevant Human Health Effects

7.5.1.1 General Considerations for Human Health Hazard Evidence Integration

The integration of separate bodies of evidence (*i.e.*, human, animal, and mechanistic evidence) described in this section directly informs the integration across all evidence to draw an overall judgment for each of the assessed human health effects.

For each potential human health effect (or smaller subset of related effects), EPA integrates separately the available phenotypic human and animal evidence pertaining to that potential health effect. Mechanistic evidence is also considered in targeted analyses conducted prior to, during, and after the integration of phenotypic human and animal evidence. Integration of all relevant data for a particular outcome provides a summary discussion of the available evidence that addresses considerations regarding causation. These considerations are adapted from considerations for causality introduced by Sir Bradford Hill (Hill, 1965): consistency, dose-response relationship, strength of the association, temporal relationship, biological plausibility, coherence, and "natural experiments" in humans (see additional discussion in (U.S. EPA, 2005a) and (U.S. EPA, 1994)). Importantly, the evidence integration process explicitly considers and incorporates the conclusions from the individual study evaluations. Data permitting, the integrations also discuss analyses relating to PESS.

7.5.1.2 Integration of Apical Health Effects Information from Human and Animal Studies

The integrations of the human and animal apical health effects evidence focus on describing aspects of the evidence that best inform causal interpretations, including the exposure context examined in the sets of studies. All study information are considered together for evidence integration; however, studies of *high* and *medium* quality have the greatest influence. Data from *low*-quality studies may be influential if few or no studies with higher quality are available to help evaluate consistency, or if the study designs of the *low*-quality studies address notable uncertainties in the set of *high*- or *medium*-quality studies on a given health effect. When data from *low*-quality or *uninformative for dose-response* studies are used to support the evidence integration, EPA carefully examines and documents how their quality affects the evidence integration conclusions alongside other considerations (Table 7-13).

The number of studies and the differences encompassed by the studies determine the extent to which specific factors can be examined for use in stratifying study results. Additionally, for both the human and animal evidence integration, if supported by the available data, additional analyses across studies (such as meta-analysis) may also be conducted.

7.5.1.3 Integration of Mechanistic Information

The characterization of mechanistic information informs the integration of health effects evidence for both hazard identification (*i.e.*, biological plausibility or coherence of the available human or animal evidence, inferences regarding human relevance, or the identification of susceptible populations and life stages across the human and animal evidence) and dose-response evaluation. As described in Section 4.2.5, these references are included as supplemental references during the screening phase, and a subset is evaluated as needed for any given chemical (Appendix H.5).

Mechanistic evidence includes any experimental measurement related to a health effect that provides information about the biological or chemical events associated with phenotypic effects. These measurements can improve understanding of the mechanisms involved in the toxic effects following exposure to a chemical but are not generally considered adverse effects.

Evaluations of mechanistic information typically differ from evaluations of phenotypic evidence (*e.g.*, from routine toxicology studies). This is primarily because mechanistic data evaluations consider the support for and involvement of specific events or sets of events within the context of a broader research question (*e.g.*, support for a hypothesized mechanism, consistency with known biological processes), rather than evaluations of individual apical endpoints considered in relative isolation. Such analyses are complicated because a chemical may operate through multiple mechanistic pathways, even if one hypothesis dominant in the literature. Similarly, multiple mechanistic pathways might interact to cause

an adverse effect. The format of these characterizations is expected to vary from a short narrative summary of existing knowledge to an in-depth analysis and weighing of the evidence underlying multiple mechanistic events, depending on data availability and the criticality of the assessment-specific uncertainty(ies).

Other analyses of mechanistic information focus on the evidence most useful for informing key uncertainties in the human or animal health effect evidence. This means that, for example, if extensive and consistently *robust* human or animal evidence is available, the need to integrate all relevant mechanistic evidence is likely be diminished. In these cases, the analyses focus on the review and interpretation of smaller sets of mechanistic studies that specifically address controversial or outstanding issues that are anticipated to have a substantial impact on the assessment conclusions. Generally, key uncertainties are addressed in the mechanistic evidence integration by considering the biological understanding of how the effect(s) in question develop or are related. In this way, the analyses can provide information on, for example, (1) potential precursor events when the apical data are uncertain (or unusable for dose-response analyses), (2) the human relevance of animal results when their relevance is unclear or controversial and the human evidence is weak, (3) the shape of the dose-response curve at low exposure levels when this understanding is highly uncertain and data informing this uncertainty are known to exist, or (4) the identification of likely susceptible populations and life stages. Thus, consideration of biological understanding represents an important component of the evidence analysis. However, mechanistic understanding is not a prerequisite for drawing a conclusion that a chemical causes a given health effect (NTP, 2015a; NRC, 2014).

Based on the analyses and considerations described above, the results of the health effect- and assessment-specific mechanistic evidence characterization inform both the weight of the scientific evidence and dose-response analyses. Therefore, while mechanistic data is evaluated on its own, the mechanistic evidence is most useful in demonstrating the relevance and reliability of apical outcome findings in animal and human studies.

7.5.1.4 Data Obtained Outside the Systematic Review Process

For human health, the vast majority of relevant information is expected to be obtained and evaluated through the systematic review process. However, there may be situations where the available literature is insufficient to address all potential health concerns. TSCA-specific needs may require evaluation of health effects in the absence of traditional human health hazard data. Evidence integration therefore will also consider information sources and data types not addressed by the IRIS Handbook (U.S. EPA, 2020).

In cases of data gaps, systematic review outputs may be supplemented by read-across to analogues with additional hazard information. Read-across is especially useful for hazard identification but may introduce significant uncertainty in dose-response analysis unless the analogue is very similar (*e.g.*, an isomer). Manual read-across may also be supplemented by *in silico* estimates from various software. (Q)SAR analysis can estimate the toxicological activity of a chemical based on similarities to other chemicals with known toxicological effects. Examples of software available to EPA that could be useful for (Q)SAR analysis include QSAR Toolbox and Oncologic. Human, animal, and mechanistic data obtained on an analog will be evaluated for quality through the systematic review process similar to any data obtained on the chemical of interest whenever possible. However, certain information (*e.g.*, QSAR data) may not be able to be formally evaluated through existing data evaluation metrics.

Any additional data should be considered together with integrated evidence when evaluating the overall weight of the scientific evidence (see Section 7.5.2 below). Read-across data should be considered

alongside integrated evidence within the same evidence stream (*i.e.*, human, animal, or mechanistic). *In silico* (Q)SAR data should be considered mechanistic when considering the weight of the scientific evidence.

7.5.2 Evaluating the Strength of the Evidence and Weight of the Scientific Evidence for Human Health Hazard Assessments

During evidence integration, a structured and documented process is used (as depicted in Figure 7-4):

1. Building from the evaluation of each evidence stream (animal, human, and mechanistic, see Section 7.5.2.1), the strength of the evidence from the available human, animal, and mechanistic studies is summarized in parallel, but separately, using a structured evaluation of an adapted set of considerations first introduced by Sir Bradford Hill (Hill, 1965). Table 7-13 describes these structured evaluations and the explicit consideration of study quality within each evidence stream.
2. The strength of the evidence for each health effect or endpoint is then considered together in light of inferences across evidence streams (see Section 7.5.2.2). Specifically, this step integrates the strength of the evidence judgment for each individual evidence stream as into an overall conclusion for the health endpoint. Table 7-14 describes how the within-evidence stream conclusions is integrated into an overall WoSE conclusion, resulting in a summary judgment as to whether the available evidence base for each potential human health effect is sufficient (or insufficient) to indicate that the chemical exposure has the potential to be hazardous to humans.

For human, animal, and mechanistic evidence, the analyses of each consideration in Table 7-13 are used to qualitatively summarize the strength of evidence for the separate evidence streams in the evidence integration narrative. Table 7-13 provides the criteria that guide how to draw the judgment for each health effect, and the terms that are used to summarize those evidence integration judgments (across evidence streams). Notably, the considerations in both Table 7-13 and Table 7-14 should be construed as generalized guidance but are not intended to be restrictive or exhaustive. Additional considerations and interpretations may be incorporated on a case-by-case basis.

The decision points within the structured evidence integration process are summarized in an evidence profile table for each health effect category/organ system (see Table 7-15 for a template) in support of the evidence integration narrative. The specific decision frameworks for the structured evaluation of the strength of the human and animal evidence streams as well as for drawing the overall evidence integration judgment are described in Figure 7-4. This process is based on considerations of the approach used by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE; Morgan et al. (2016); Guyatt et al. (2011); (Schünemann et al., 2011)), which arrives at an overall integration conclusion based on consideration of the body of evidence. As described in Figure 7-4, the human, animal, and mechanistic evidence serve as inputs providing a foundation for the evidence integration decisions; thus, the major conclusions from the integration of these analyses are summarized in the evidence profile table (see Table 7-15) for a template version with included guidance) supporting the evidence integration narrative. The evidence profile tables on each potential human health effect evaluated summarize the judgments and their evidence basis for each step of the structured evidence integration process. Separate sections are included for summarizing the human and animal evidence, for the inference drawn across evidence streams, and for the overall evidence integration judgment. The table presents the key information from the different bodies of evidence that informs each decision.

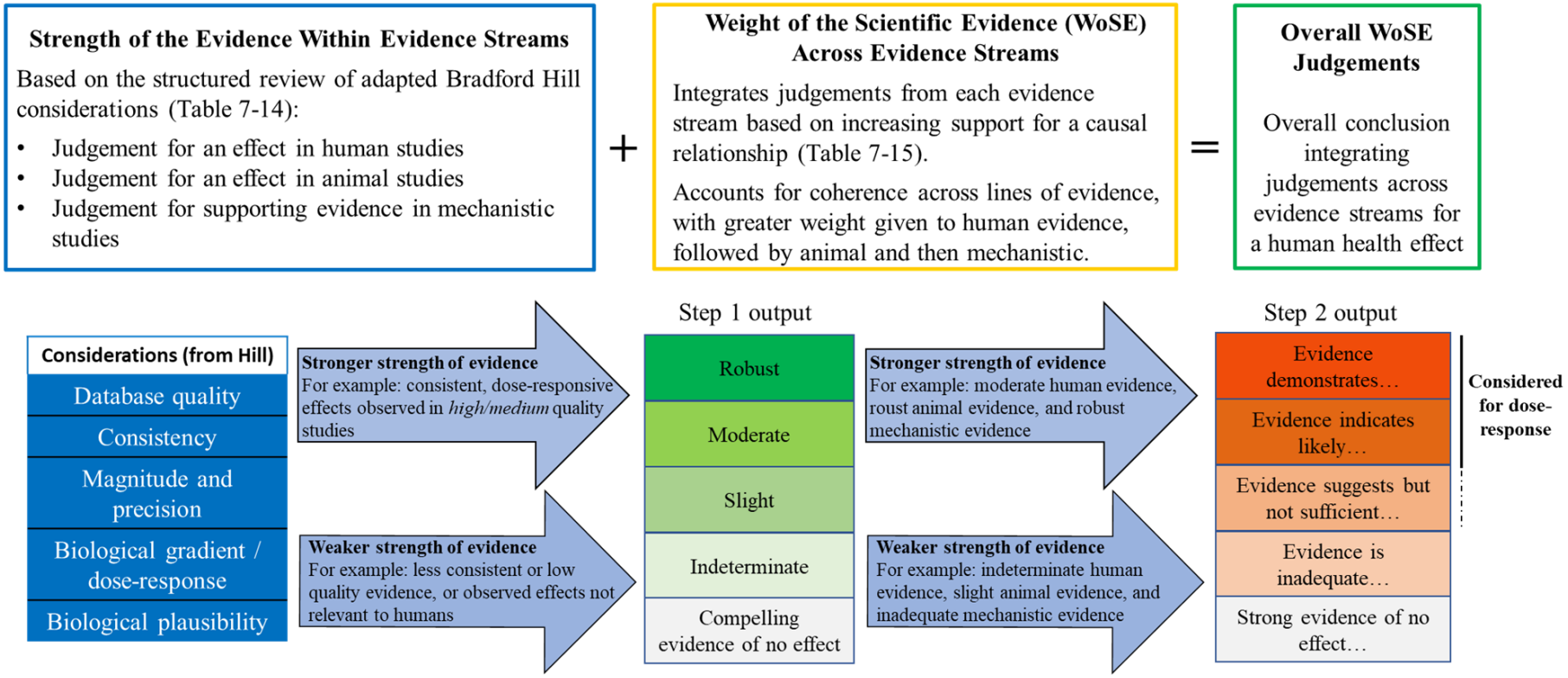

Figure 7-4. Process for Weight of the Scientific Evidence Integration of Human Health Hazard Data
Note that stronger evidence can apply to both a judgment of "evidence demonstrates…" or "strong evidence of no effect," depending on the nature and extent of the available evidence (see also Table 7-14). This figure has been adapted from Table 11-1 in the draft *ORD Staff Handbook for Developing IRIS Assessments* (U.S. EPA, 2020).

7.5.2.1 Evaluating the Strength of the Scientific Evidence within Evidence Streams

EPA evaluates and summarizes the strength of evidence for the available human, animal, and mechanistic evidence prior to drawing overall judgments about whether the weight of the scientific evidence supports the chemical substance causing certain health effect(s) in humans given relevant exposure circumstances. For the purposes of systematic review, these three categories are referred to as "evidence streams" for human health hazard information. For each assessed health effect or health effect grouping, EPA evaluates the relevant mechanistic evidence in exposed humans and animals (or in their cells, relevant NAMs or *in silico* models), which are based on the approaches and considerations described in Section 7.5.1.3 and integrated with the evidence from the available studies of phenotypic effects in humans and animals along with any read-across or QSAR data (Section 7.5.1.4). The considerations described below in Table 7-13 (*i.e.*, the different features of the evidence considered and summarized during evidence integration) are evaluated by the assessment teams within the context of how they affect judgments of the strength of evidence that directly inform the overall evidence integration judgment.

The evaluation of the strength of the human or animal health effects evidence (*i.e.*, based on the considerations in Section 7.5.1.1) preferably occur at the most specific health outcome level possible (*e.g.*, an analysis at the level of decreased pulmonary function is generally preferable to an analysis of respiratory system effects), if there is an adequate set of studies for analyses at this level and considering the interrelatedness of the available outcomes. If studies on a target system are sparse or varied, or if the interpretation of evidence strength relies largely on the consideration of coherence across related outcomes, then the analyses may need to be conducted at a broader health effect level. The factors judged to increase or decrease the strength of the evidence are summarized in tabular format using the evidence profile template in Table 7-15 (or a similar process/template), to transparently convey expert judgments made throughout the evidence integration processes. Evidence profile tables allow for consistent documentation of the supporting rationale for each decision.

Strength of the evidence judgments within evidence streams is characterized as one of the following descriptors, based on the considerations outlined in Table 7-13:

- Robust,
- Moderate,
- Slight,
- Indeterminate, or
- Compelling evidence of no effect.

Selection of the appropriate descriptor is based on the expert judgment of human health assessors when judging the strength of the evidence supporting whether a chemical exposure is associated with an adverse health effect. Expert judgments within evidence streams (*i.e.*, human, animal, or mechanistic) are based on the available information and should account for the relative balance of considerations—such as the quality of the database, consistency, magnitude and precision, dose-response, coherence, and biological significance—which may differ across endpoints and chemical databases, thereby increasing or decreasing the strength of the evidence conclusion (Table 7-13). Expert judgments within each evidence stream may be determined at the level of individual outcomes, specific endpoints, or overall organ systems/hazard domains. These considerations are presented alongside the judgment for each evidence stream in an evidence profile table (Table 7-15). Although a judgement of "compelling evidence of no effect" in human or animal studies will be based on convincing evidence of a null apical outcome, mechanistic data may also achieve that judgement by concluding that any plausible mode of action for the apical outcomes is not applicable to humans under relevant exposure circumstances.

Table 7-13. Considerations that Inform Evaluations of the Strength of the Evidence within an Evidence Stream (*i.e.*, Human, Animal, or Mechanistic)[18]

Consideration	Factors that Increase Strength (of the Human, Animal, or Mechanistic Evidence)	Factors that Decrease Strength (of the Human, Animal, or Mechanistic Evidence)
The structured categories of considerations and criteria for increased or decreased evidence strength described here are meant to help guide the human health assessor apply the strength of evidence judgments for an outcome or health effect within a given evidence stream.		
Quality of the database	• A large evidence base of *high*- or *medium*-quality studies increases strength.	• An evidence base of mostly *low*-quality studies decreases strength. • If the database is of very poor quality without sufficient reliable studies, other considerations in this table are of limited importance and limit the overall judgment for the endpoint. Additionally, a very limited database (*e.g.*, only one relevant study available) would also decrease strength for a given observed outcome.
Consistency	• Similarity of findings for a given outcome (*e.g.*, of a similar magnitude, direction) across independent studies or experiments increases strength, particularly when consistency is observed across populations (*e.g.*, geographical location, sexes, other PESS groups) or exposure scenarios in human studies, and across laboratories, populations (*e.g.*, species, sexes, cell types), or exposure scenarios (*e.g.*, duration; route; timing) in animal and mechanistic studies.	• Any inconsistency across studies (*i.e.*, conflicting evidence; see (U.S. EPA, 2005b)) decreases strength. However, generally strength should not be substantively decreased if inconsistent findings can be reasonably explained by differences in study quality (with higher-quality studies supporting the effect), variation in population or species, sex, or life stage, exposure patterns (*e.g.*, intermittent or continuous), exposure levels (low or high), or exposure duration.
Magnitude and precision	• Evidence of a large magnitude of effect (*e.g.*, a larger percentage change), considered either within or across studies, can increase strength. Effects of a concerning rarity or severity can also increase strength, even if they are of a small magnitude. • Precise results (*i.e.*, small variance) from individual studies or across the set of studies increases strength, noting that biological significance should be considered in addition to merely statistical significance.	• Strength of the evidence may be decreased if effect sizes are small in magnitude and are concluded not to be biologically significant, or if the available studies report imprecise (*i.e.*, large variance) results.

[18] This table has been adapted from Table 11-2 in the IRIS Handbook (U.S. EPA, 2020), with minor variation due to program-specific terminology differences and a more formalized evidence integration process for mechanistic data in this TSCA SR Protocol compared to the IRIS Handbook (U.S. EPA, 2020).

Consideration	Factors that Increase Strength (of the Human, Animal, or Mechanistic Evidence)	Factors that Decrease Strength (of the Human, Animal, or Mechanistic Evidence)
Biological gradient/dose-response	• Evidence of dose-responsive changes increases strength. Dose-response may be demonstrated across studies or within studies and it can be dose- or duration-dependent. A monotonic dose-response is not required (monotonicity should not necessarily be expected, *e.g.*, different outcomes may be expected at low vs. high doses due to activation of different mechanistic pathways or induction of systemic toxicity at very high doses), however alternative dose-responses should be supported by mechanistic information. • In observational epidemiological studies, decreases in a response after cessation of exposure (*e.g.*, symptoms of current asthma) also may increase strength by increasing certainty in a relationship between exposure and outcome.	• A lack of dose-response when expected based on biological understanding and having a wide range of doses/exposures evaluated in the evidence base can decrease strength. • In experimental studies, strength may be decreased when effects resolve under certain experimental conditions (*e.g.*, rapid reversibility after removal of exposure). However, many reversible effects are of high concern. Deciding between these situations is informed by factors such as the toxicokinetics of the chemical and the relevancy of exposure conditions to real-world exposure, endpoint severity, judgments regarding the potential for delayed or secondary effects, as well as the exposure context focus of the assessment (*e.g.*, addressing intermittent or short-term exposures). • In rare cases, and typically only in animal toxicology studies, the magnitude of effects at a given exposure level might decrease with longer exposures (*e.g.*, due to tolerance or acclimation). Similar to the discussion of reversibility above, a decision about whether this decreases evidence strength depends on the relevance of the exposure scenario and other factors. • If the data are not adequate to evaluate a dose-response pattern, then strength is neither increased or decreased.
Biological plausibility and relevance to humans	• A plausible mechanism believed to exist in humans between cause and effect based on experimental evidence which links exposure to outcome. Without evidence to the contrary, the human relevance of animal findings is assumed.	• An effect observed only in a specific animal population, species, or sex (or *in vitro* scenario) without a clear analogy to human biology (*e.g.*, kidney toxicity observed only in male rats with evidence of α-2u globulin involvement).

Because there are numerous permutations of the above considerations that may result in a given judgment, strength of the evidence analyses are conducted using expert judgment on a case-by-case basis. However, assessors should strive for consistency in evaluation of each consideration described in Table 7-13. Below are some examples of datasets to help apply the strength-of-evidence judgments for an outcome or health effect within a given evidence stream:

- An animal dataset for liver toxicity includes six studies covering a similar dose range. Four high-quality studies report 12 to 25 percent dose-responsive increased liver weight in both male and female rats but without any evidence of histopathological effects or increased serum enzyme levels. One medium-quality study demonstrates all three effects but with a less apparent dose-response and small effect size (less than 10 percent change with a statistically significant but plateaued dose-response), however only in female rats. One low-quality study reported no statistically significant change for any liver outcome.
    - *Increased strength* – all medium or high-quality studies demonstrate at least some liver effect and the medium-quality study reported all three liver outcomes typically associated with adverse effects.
    - *Increased strength* – increased liver weight was dose-responsive in high-quality studies, with the 25 percent increase could be considered adverse even in the absence of other indicators of liver toxicity.
    - *Decreased strength* – one study (albeit low quality) did not observe any liver effects.
    - *Decreased strength* – increased liver weight alone is typically not sufficient for indicating adverse liver effects and all three outcomes were observed only in a single sex within one study that did not demonstrate consistent dose-responsiveness.
    - Based on these considerations, this scenario would likely result in a strength of the evidence judgment of "Moderate"—some type of liver effect was consistently observed across studies and at least one study in the database demonstrated either multiple outcomes or dose-responsive increased liver weight up to 25 percent, however the factors in Table 7-13 were not supported in all studies.
- A human dataset for neurotoxicity includes six studies. One medium-quality case study reports both acute and chronic central nervous system depression in exposed workers. Two high-quality yet small cohort studies report dose-responsively increased with exposure intensity but non-statistically significant increased relative risk (RRs) for multiple neurological outcomes. One medium-quality case-control study reports statistically significant odds ratio (OR) = 1.9 for reduced visual acuity among residents exposed to the chemical for medium-duration, non-statistically significant and lower OR = 1.4 for residents exposed for high-duration, and non-statistically significant OR = 1.6 for low-duration exposure. Two medium-quality and one low-quality cross-sectional study did not report any neurotoxicological outcomes, however neurotoxicity was not the focus of those studies.
    - *Increased strength* – observation of statistically-significant association between exposure and a specific neurological outcome in a medium-quality study
    - *Increased strength* – reported acute and chronic neurological outcome in a case study
    - *Decreased strength* – low coherence across studies with four of six studies not identifying any association (although three studies did not focus on neurotoxicity) and the other two reporting different outcomes
    - *Decreased strength* – no statistically-significant association with any neurological outcomes in two high-quality studies (despite a dose-responsive increase in incidence)
    - *Decreased strength* – inconsistent dose-response across exposure duration groups in the case-control study
    - Based on these considerations, this scenario would likely result in a strength of the evidence judgment of "Indeterminate"—some indications of neurological effects,

however among non-case studies only one of five studies demonstrated a statistically-significant association. Some caveats to the negative data influencing the judgment include increases in OR despite lack of statistical significance and potential reduced relevance of some studies to neurotoxicity.

7.5.2.2 Evaluating the Weight of the Scientific Evidence across Evidence Streams

For the analysis of human health effects that might result from chemical exposure, EPA draws integrated judgments across human, animal, and mechanistic evidence for each assessed health effect. As previously discussed in Section 7.5.1.3, the approach to evaluating the mechanistic evidence relevant to each assessed health effect follows a step-wise approach, and is expected to vary depending on the nature and impact of the uncertainties identified within each evidence base, as well as the specific mechanistic information available to address those uncertainties. This includes evaluations of mechanistic evidence relevant to the identified key science issues prior to or in parallel with evaluations of the phenotypic data in human and animal studies, as well as other focused mechanistic analyses identified during draft development to address key assessment uncertainties. For evaluating weight of the scientific evidence (WoSE) across evidence streams, assessors evaluate the coherence of the evidence by considering how observed evidence in epidemiological, animal, and mechanistic studies relate. Plausible biological relationships supporting observed health effects demonstrate coherence and increase the overall strength of the evidence for a given effect.

The overall WoSE narrative presents a qualitative summary of the strength of each evidence stream and an overall judgment across all relevant evidence, with exposure context provided. For each health effect or specific cancer type of potential concern, the first sentence of the narrative should include the summary judgment (see description below for how these judgments help inform selection of a descriptor for carcinogenicity (U.S. EPA, 2005a). Table 7-14 describes the categories of evidence integration judgments that are used in the risk evaluations and provides examples of database scenarios that fit each category of evidence.

These summary judgments provide a succinct and clear representation of the decisions from the more detailed analyses of whether (or not) the evidence indicates that chemical exposure has the potential to cause the human health effect(s) under the necessary conditions of exposure. Consistent with EPA non-cancer (U.S. EPA, 2002b) and cancer (U.S. EPA, 2005a) guidelines (U.S. EPA, 2005b), a judgment that the evidence supports an apparent lack of an effect of chemical exposure on the health effect(s) is only be used when the available data are considered robust for deciding that there is no basis for human hazard concern; lesser levels of evidence suggesting a lack of an effect are characterized as "inadequate."

Table 7-14. Classification for Weight of the Scientific Evidence for Causal Determinations for Characterizing Potential Human Health Hazards[19]

Overall Evidence Integration Judgment[a] in Narrative	Evidence Integration Judgement Level[b]	Guidance and Example Scenario[c]
The currently available **evidence demonstrates** that [chemical] causes [health effect] in humans[d] under relevant exposure circumstances. This conclusion is based on studies of [humans or animals] that assessed [exposure or dose] levels of [range of concentrations or specific cutoff level concentration[e]].	**Evidence demonstrates**	A strong evidence base demonstrating that [chemical] exposure causes [health effect] in humans. • This conclusion level is used if there is either: ○ *Robust* human evidence supporting an effect.[f] • *Moderate* human evidence supporting an effect and *robust* animal evidence if there is also *robust* mechanistic evidence that the findings in animals are anticipated to occur and progress in humans. Most notably, if evidence supports a mode of action (MOA) interpreted with reasonable certainty or aligns with an Adverse Outcome Pathway, alternative explanations could be ruled out.

The currently available **evidence indicates that [chemical] likely** causes [health effect] in humans under relevant exposure circumstances. This conclusion is based on studies of [humans or animals] that assessed [exposure or dose] levels of [range of concentrations or specific cutoff level concentration].	**Evidence indicates likely[f]**	An evidence base that indicates that [chemical] exposure likely causes [health effect] in humans, although there may be outstanding questions or limitations that remain, and the evidence is insufficient for the higher conclusion level.
		• This conclusion level is used if there is either:
		  ○ *Moderate* human evidence supporting an effect and *robust* animal evidence
		  ○ *Moderate* human evidence supporting an effect and *slight* or *indeterminate* animal evidence that is supported by at least *slight* mechanistic evidence
		  ○ *Slight* or *indeterminate* human evidence supporting an effect and *robust* animal evidence
		  ○ *Indeterminate* or *slight* human evidence supporting an effect and *moderate* animal evidence s that is supported by at least *slight* supporting mechanistic evidence.
		• When there is *indeterminate* or *slight* animal or human evidence (a judgment of *slight* is required for at least one evidence stream), mechanistic evidence may increase a judgment level from "*evidence suggests*…" to "*evidence indicates likely*…" based on a judgment of *moderate* or *robust*.

[19] This table has been adapted from Table 11-5 in the draft *ORD Staff Handbook for Developing IRIS Assessments* (U.S. EPA, 2020), with minor variation due to program-specific terminology differences and a more formalized evidence integration process for mechanistic data in this TSCA SR Protocol compared to the IRIS Handbook (U.S. EPA, 2020).

Overall Evidence Integration Judgment[a] in Narrative	Evidence Integration Judgement Level[b]	Guidance and Example Scenario[c]
The currently available **evidence suggests but is not sufficient to conclude** that [chemical] may cause [health effect] in humans under relevant exposure circumstances. This conclusion is based on studies of [humans or animals] that assessed [exposure or dose] levels of [range of concentrations or specific cutoff level concentration].	**Evidence suggests but is not sufficient to conclude**	An evidence base that suggests that [chemical] exposure may cause [health effect] in humans, but there are very few studies that contributed to the evaluation, the evidence is very weak or conflicting, and/or the methodological conduct of the studies is poor. • This conclusion level <u>is</u> used if there is: ○ *Indeterminate* or *slight* human evidence supporting an effect and *moderate* animal evidence combined with *indeterminate* mechanistic evidence. • When there is *indeterminate* or *slight* animal or human evidence (a judgment of *slight* is required for at least one evidence stream), a judgement of "*evidence suggests…"* is applicable when mechanistic evidence is *indeterminate* or *slight.* • In the absence of informative conventional studies in humans or in animals (*i.e.*, *indeterminate* evidence in both, mechanistic evidence, including information obtained outside the systematic review process (*e.g.*, read-across, QSAR, see Section 7.5.1.4), <u>could also be</u> used to conclude *"evidence suggests"* if the mechanistic evidence is sufficient to highlight potential human toxicity[h] (*i.e.*, *moderate* or *robust* evidence).

The currently available evidence is inadequate to assess whether [chemical] exposure may cause [health effect] in humans under relevant exposure circumstances.	**Evidence is inadequate**[i]	This conveys either a lack of information or an inability to interpret the available evidence for [health effect]. On an assessment-specific basis, a single use of this "inadequate" conclusion level might be used to characterize the evidence for multiple health effect categories (*i.e.*, all health effects that were examined and did not support other conclusion levels).
		• This conclusion level <u>is</u> used if there is:
		  ○ *Indeterminate* or *slight* human evidence supporting an effect and *slight* to *robust* animal evidence if mechanistic evidence (*e.g.*, a MOA interpreted with reasonable certainty) indicates the findings in animals are very unlikely to be relevant to humans (*i.e.*, *compelling evidence of no effect*).
		  ○ *Indeterminate* human evidence supporting an effect and *compelling evidence of no effect* animal evidence if the database lacks mechanistic support that the models are relevant to humans for the effect of interest (*i.e.*, *indeterminate*).
		  ○ *Indeterminate* evidence supporting an effect in both humans and animals with *slight* or worse mechanistic evidence.
		  ○ *Indeterminate* human evidence supporting an effect, *compelling evidence of no effect* in animals, and *indeterminate* mechanistic evidence.
		  ○ *Compelling evidence of no effect* human evidence and *slight* animal evidence supported by *slight* or better mechanistic evidence.

Overall Evidence Integration Judgment[a] in Narrative	Evidence Integration Judgement Level[b]	Guidance and Example Scenario[c]
		Importantly, a conclusion of "*evidence is inadequate…*" is not a determination that the agent does not cause the indicated health effect(s). It indicates that the available evidence is insufficient to reach conclusions.

Strong evidence supports no effect in humans from [chemical] exposures under relevant circumstances. This conclusion is based on studies of [humans or animals] that assessed [exposure or dose] levels of [range of concentrations].	**Strong evidence supports no effect**[j]	This represents a situation in which extensive evidence across a range of populations and exposure levels has identified no effects/associations. This scenario requires a high degree of confidence in the conduct of individual studies, including consideration of study sensitivity, and comprehensive assessments of the endpoints and lifestages of exposure relevant to the heath effect of interest.
		• This conclusion level is used if there is:
		  ○ *Compelling evidence of no effect* human evidence and *indeterminate* or *compelling evidence of no effect* evidence in animals.
		  ○ *Indeterminate* human evidence and *compelling evidence of no effect* animal evidence with experimental support that the models are relevant to humans for the effect of interest (*e.g., compelling evidence of no effect*).
		• *Compelling evidence of no effect* human evidence and *moderate-to-robust* animal evidence if strong mechanistic information indicates that the animal evidence is unlikely to be relevant to humans (*i.e., compelling evidence of no effect*).

[a] Evidence integration judgments are typically developed at the level of the health effect when there are sufficient studies on the topic to evaluate the evidence at that level; this should always be the case for evidence demonstrates and strong evidence supports no effect, and typically for evidence indicates (likely). However, some databases only allow for evaluations at the category of health effects examined; this is more frequently the case for conclusion levels of evidence suggests and evidence inadequate. These determinations regarding confidence in the evidence supporting hazard are useful for other assessment decisions, including prioritizing studies and outcomes in quantitative analyses and characterizing assessment uncertainties. Thus, for all evidence scenarios, but particularly for those in the lower end of this range, it is important to characterize the uncertainties in the evidence base within the evidence integration narrative and convey the evidence strength to subsequent steps, including toxicity values developed based on those effects.

[b] Health effects characterized as having "evidence demonstrates," "evidence indicates" (likely), and, in some cases, "evidence suggests" are evaluated for use in dose-response assessment (see Section 7.5.2.3).

[c] Terminology of "is" refers to the default option; terminology of "could also be" refers to situational options dependent on mechanistic understanding.

[d] In some assessments, these conclusions might be based on data specific to a particular lifestage of exposure, sex, or population (or another specific group). In such cases, this would be specified in the narrative conclusion, with additional detail provided in the narrative text. This applies to all conclusion levels.

[e] If concentrations cannot be estimated, an alternative expression of exposure level (*e,g.*, "occupational exposure levels") is provided. This applies to all conclusion levels.

[f] For some applications, such as benefit-cost analysis, to better differentiate the categories of "*evidence demonstrates…*" and "*evidence indicates (likely)…*", the former category should be interpreted as evidence that more strongly supports an exposure-effect linkage that is likely to be causal.

[g] When there is *moderate* or *robust* human evidence, the overall strength of the evidence is neither increased or decreased due to a lack of experimental information on the human relevance of the animal evidence or mechanistic understanding (mechanistic evidence may exist, but it is inconclusive); in these cases, the animal data are judged

Overall Evidence Integration Judgment[a] in Narrative	Evidence Integration Judgement Level[b]	Guidance and Example Scenario[c]
not to conflict with current biological understanding (general knowledge of biological changes associated with the observed effects) and thus are assumed to be relevant, while findings in humans and animals are presumed to be real unless evidence indicates otherwise. [h] This determination is based on expert judgment dependent on the state-of-the-science at the time of review. As previously discussed in Section 7.5.2.1, scientific understanding of toxicity mechanisms and of the human implications of new toxicity testing methods (*e.g.*, from high-throughput screening, from short-term *in vivo* testing of alternative species, or from new *in vitro* and *in silico* testing and other NAMs) will continue to increase. Thus, the sufficiency of mechanistic evidence alone for identifying potential hazards is expected to increase as the science evolves. The understanding of such evidence scenarios at the time of protocol development is consistent with a determination of "*evidence suggests…"* [i] Specific narratives for each of the health effects with an evidence integration judgment of evidence inadequate may be deemed unnecessary. [j] Due to the expected rarity of scenarios where "*strong evidence supports no effect*," this judgment is unlikely to be used in most instances.		

7.5.2.3 Overall Weight of the Scientific Evidence Judgments

The overall weight of the scientific evidence judgment combines decisions regarding the strength of the human, animal, and mechanistic evidence. As explained in Section 7.5.1.3, the mechanistic evidence serves to: inform the human relevance of the animal evidence, inform or justify atypical dose-response relationships in the human or animal data, support coherence across bodies of evidence, and provide information on susceptible populations and life stages, based on the considerations and analyses outlined in Section 7.5.1.1. This overall judgment also considers any additional data obtained external to the systematic review process, if applicable (Section 7.5.1.4). The decision process culminates in a summary of judgments regarding the evidence for each potential health effect/endpoint (*i.e.*, each non-cancer health effect and specific type of cancer or broader grouping of related outcomes). For each health effect, this summary considers the following information:

1. A descriptive summary of the primary judgments about the evidence informing the potential for health effects in exposed humans, based on the following analyses
    - evaluations of the strength of the available human, animal, and mechanistic evidence (see Table 7-15);
    - consideration of the coherence of findings (*i.e.*, the extent to which the evidence for health effects and relevant mechanistic changes are similar) across human and animal studies; and
    - other information on the human relevance of findings in animals; and conclusions drawn based on the predefined mechanistic analyses (see Section 7.5.1.3), as well as those based on analyses identified during step-wise consideration of the health effect-specific evidence during draft development.
2. A summary of key evidence supporting these judgments, highlighting the evidence that was the primary driver of these judgments and any notable issues (*e.g.*, data quality; coherence of the results), and a narrative expression of confidence (a summary of strengths and remaining uncertainties) for these judgments.
3. Information on the general conditions of expression of these health effects (*e.g.*, exposure routes and levels in the studies that were the primary drivers of these judgments), noting that these conditions are clarified during dose-response analysis.
4. Indications of potentially affected susceptible populations or life stages (*i.e.*, an integrated summary of the available evidence on potential susceptible populations and life stages drawn across the human, animal, and mechanistic evidence).
5. A summary of key assumptions used in the analysis, which are generally based on EPA guidelines and which are largely captured in this protocol, as well as strengths and limitations of the weight of the scientific evidence judgments. These should include key uncertainties and data gaps, as well as the limitations of the systematic review.

Assessments include an evidence profile table (Table 7-15 or similar) for each organ system/hazard domain to support the evidence integration narrative by providing the major decisions and supporting rationale. Distinct WoSE judgements will be made for each health effect/endpoint within a particular organ system. Additional narrative may or may not be included as needed.

For evaluations of carcinogenicity, consistent with EPA's Cancer Guidelines (U.S. EPA, 2005b), one of EPA's standardized cancer descriptors are used as a shorthand characterization of the evidence integration narrative, describing the overall potential for human carcinogenicity across all potential cancer types. These are, (1) *carcinogenic to humans*, (2) *likely to be carcinogenic to humans*, (3) *suggestive evidence of carcinogenic potential*, (4) i*nadequate information to assess carcinogenic potential*, or (5) *not likely to be carcinogenic to humans*. More than one descriptor may be used when a

chemical's effects differ by exposure level or route (U.S. EPA, 2005b); if the database supports such an analysis, these decisions are clarified based on a more thorough review of the mechanistic evidence or more detailed dose-response analysis). In some cases, mutagenicity may also be evaluated (*e.g.*, when there is evidence of carcinogenicity) because it influences the approach to dose-response assessment and subsequent application of adjustment factors for exposures early in life (U.S. EPA, 2005a, b).

An evidence integration narrative, evidence profile table, and summary judgment are provided for each cancer subtype, as described above for non-cancer effects. The cancer descriptor considers the interrelatedness of cancer types potentially related to chemical exposure, consistency across the human and animal evidence for any cancer type (noting that site concordance is not required (U.S. EPA, 2005a)), and the uncertainties associated with each assessment-specific conclusion. In general, however, if a systematic review of more than one cancer type was conducted, then the overall judgment and discussion of evidence strength in the evidence integration narrative for the cancer type(s) with the strongest evidence for hazard is used to inform selection of the overall cancer classification descriptor, with each assessment providing a transparent description of the decision rationale. The cancer descriptor and evidence integration narrative for potential carcinogenicity, including application of the MOA framework, consider the conditions of carcinogenicity, such as exposure (*e.g.*, route, level) and susceptibility (*e.g.*, genetics, life stage), as the data allow (Farland, 2005; U.S. EPA, 2005a, b).

Application of Evidence Integration Judgments to Dose-Response Analysis

Selection of specific data sets for dose-response assessment and performance of the dose-response assessment is conducted after evidence integration is complete and involves database- and chemical-specific biological judgments. The latter build from decisions made at earlier stages of assessment development. Several EPA guidance and support documents detail data requirements and other considerations for dose-response modeling, particularly *Benchmark Dose Technical Guidance* (U.S. EPA, 2012), *Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002b), *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), and *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). This section of the draft protocol provides an overview of considerations for conducting the dose-response assessment, particularly statistical considerations specific to dose-response analysis that support quantitative risk assessment. Importantly, these considerations do not supersede existing EPA guidance.

EPA conducts dose-response assessments with a goal of developing both cancer and non-cancer risk estimates based on the available data and judgments during hazard identification as well as the suitability of studies for dose-response analysis. The derivation of points of departure for non-cancer and cancer risk estimates depend on the health hazard conclusions drawn during evaluation of the weight of the scientific evidence (see Section 7.5.2). Specifically, for non-cancer health effects (as indicated in Figure 7-4), these assessments generally include dose-response assessments when the weight of the scientific evidence judgments indicate either "*evidence demonstrates…*" or "*evidence indicates likely…*" When the database includes at least one well-conducted study and one of these twos judgments of *evidence suggests* is drawn, quantitative analyses may still be useful for some purposes (*e.g.*, providing a sense of the magnitude and uncertainty of estimates for health effects of potential concern, ranking potential hazards, or setting research priorities), but not for others (see related discussions in (U.S. EPA, 2005b)). It is critical to transparently convey the extreme uncertainty in any such estimates. Some consideration is also given to health effects with determinations of "*evidence suggests but is not sufficient to conclude…*" on a case-by-case basis, depending on the breadth of the hazard database and sensitivity of the available dose-response information (see below). Quantitative analyses are generally not attempted for "*evidence is inadequate to infer a causal relationship*" conclusions. A parallel approach is used for potential cancer health effects in these assessments. EPA generally conducts dose-

response assessments and derives cancer values for chemicals that are classified as "*carcinogenic"* or "*likely to be carcinogenic"* to humans.

When "*evidence suggests but is not sufficient to conclude…*" a non-cancer effect or there is "*suggestive evidence of carcinogenicity"* to humans, in most instances EPA generally would not conduct a dose-response assessment or derive a cancer value except when the evidence includes a high-quality study and quantitative analyses may be useful for some purposes. For example, quantitative results for endpoints in this category may help for providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities (U.S. EPA, 2005b). It is critical to transparently convey the large uncertainty in any such estimates.

Table 7-15. Evidence Profile Figure Template

<table>
<tr><th>Database Summary</th><th>Factors that Increase Strength</th><th>Factors that Decrease Strength</th><th>Summary of Key Findings and within-Stream Strength of the Evidence Judgement</th><th>Inferences across Evidence Streams and Overall Weight of the Scientific Evidence Judgement</th></tr>
<tr><td colspan="4">[Health effect/endpoint or outcome grouping]</td><td rowspan="3">• Human relevance of findings in animals/ mechanistic data
• Cross-stream coherence
• Summary of potential susceptible populations or lifestages
• Other inferences:
• Information on susceptibility
• MOA analysis inferences
• Relevant information from other sources (e.g., read across)

Describe judgment regarding whether there is sufficient (or insufficient) evidence to identify a potential human health hazard, integrating evidence across streams and including a summary of the models and range of dose levels upon which the judgment is primarily reliant
• Include mechanistic evidence for informing biological plausibility (e.g., precursor events linked to adverse outcomes)
• Mechanistic data may substantiate the extent to which the evidence influences inferences across evidence streams (e.g., establishing a biological linkage between animal findings and outcomes observed in humans).</td></tr>
<tr><td colspan="4">Evidence in studies of exposed humans [may be separated by exposure route or other study design characteristic [a]</td></tr>
<tr><td><u>[May be separate rows by outcome]</u>
• Summary of database
• Study quality summary
• Study design descriptions</td><td>• Consistency
• Dose-response gradient
• Coherence of observed effects
• Effect size
• Mechanistic evidence providing plausibility
• Medium or high quality studies [b]</td><td>• Unexplained inconsistency
• Imprecision
• Low quality studies [b]
• Evidence demonstrating implausibility</td><td>Qualitative summary of the strength of the evidence from human studies based on the factors at left, including the primary evidence basis and considering:
• Results across human epidemiological and controlled exposure studies
• Interpretations regarding any human mechanistic evidence informing biological plausibility (e.g., precursor events linked to adverse outcomes)
Judgments within evidence streams are summarized as one of the following:
• Robust
• Moderate
• Slight
• Indeterminate
• Compelling evidence of no effect</td></tr>
<tr><td colspan="4">Evidence from in vivo mammalian animal studies [may be separated by exposure route or other study design characteristic] [a]</td></tr>
<tr><td><u>[May be separate rows by outcome]</u>
• Summary of database
• Study quality summary
• Study design descriptions</td><td>• Consistency and/or Replication
• Dose-response gradient
• Coherence of observed effects
• Effect size
• Mechanistic evidence providing plausibility</td><td>• Unexplained inconsistency
• Imprecision
• Low quality studies [b]
• Evidence demonstrating implausibility</td><td>Qualitative summary of the strength of the evidence for an effect in animals based on the factors at left, including the primary evidence basis and considering:
• Results across animal toxicological studies
Judgments within evidence streams are summarized as one of the following:
• Robust</td></tr>
</table>

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall Weight of the Scientific Evidence Judgement
	• *Medium* or *high* quality studies [b]		• *Moderate* • *Slight* • *Indeterminate* • *Compelling evidence of no effect*	Select a conclusion among the options below (from Table 7-14): • Evidence demonstrates that [chemical] exposure causes… • Evidence indicates that [chemical] exposure likely causes… • Evidence suggests but is not sufficient to conclude that [chemical] exposure may cause… • The currently available evidence is inadequate to assess whether [chemical] exposure may cause… • Strong evidence supports no effect in humans from [chemical] exposures… All judgements apply to "under relevant exposure circumstances".
Evidence in mechanistic studies and supplemental information [may be separated by exposure route/study type/test system] [a]				
[May be separate rows/sections by outcome or evidence type (*e.g.*, *ex vivo*, in culture, *in silico*, non-mammalian)] [c] • Summary of database • Study quality summary • Study design descriptions	• Consistency and/or Replication • Dose-response gradient • Coherence of observed effects • Effect size • Mechanistic data is supported by available AOP or signaling pathway information • Results are consistent with related apical endpoints • *Medium* or *high* quality studies [b]	• Unexplained inconsistency • Imprecision • Low quality studies [b] • Evidence demonstrating implausibility • Mechanistic data conflicts with known AOP or signaling pathway information • Results are unrelated to or inconsistent with apical endpoints	*Key findings*: Summary of findings in the body of evidence (may focus on or emphasize highly informative study designs, endpoints or findings). • Include range of exposure levels and durations tested • May summarize information that is not chemical-specific (*e.g.*, for use in read-across) • Mechanistic evidence may be related to multiple apical effects and cannot always be parsed to one specifically Judgments within evidence streams are summarized as one of the following: [d] • *Robust* • *Moderate* • *Slight* • *Indeterminate* • *Compelling evidence of no effect*	

[a] In addition to exposure route, the summaries of the strength of each evidence stream may include multiple rows; for example, by study quality, population, or species, if this informed the analysis of results heterogeneity.

[b] Study quality is considered when evaluating each of the other factors that increase or decrease strength (*e.g.*, consistency). Notably, lack of findings in studies deemed insensitive neither increases nor decreases strength.

[c] In many cases, mechanistic evidence will not be specific to any particular endpoint or health outcome within an organ system. In these cases, the mechanistic evidence will be considered as potential support for all relevant endpoints within the organ system.

[d] The inclusion of within-stream strength of the evidence judgements for mechanistic data is a distinction between the TSCA SR Protocol and the IRIS Handbook (U.S. EPA, 2020). The TSCA SR Protocol presents a more formalized evidence integration process for mechanistic data.

7.5.2.4 Characterization of Strengths, Limitations, Assumptions, and Key Sources of Uncertainty in the Human Health Hazard Assessments

EPA presents the most scientifically defensible human health hazard assessment in risk evaluations based on the WoSE of the available information. Within this context, EPA documents underlying assumptions and rationales supporting the human health hazard values, including science policy assumptions. This process includes a discussion of the strengths and limitations of the data sources supporting the human health hazard values, as well as a characterization of their uncertainties and variability.

The assessment should describe how the assessment accounts for primary sources of uncertainty and other considerations, including whether these assumptions/uncertainties are likely to overestimate or underestimate human health risk. These may include (but are not limited to)

- *Consistency of the overall database for estimating the most sensitive endpoint associated with important adverse outcomes* – For each endpoint, the variability among effect levels for the same outcome is evaluated, taking into account potential explanations for differences (*e.g.*, different durations, different species/strains).
- *Potentially Exposed or Susceptible Subpopulations* – Were any identified PESS groups or factors incorporated into evidence integration and dose-response analysis? For any PESS considerations that could not be accounted for quantitatively, how might they qualitatively impact interpretation of the hazard analysis? Are there data gaps related to the extent of certain sensitive endpoints or in accounting for population variability due to genetics/lifestage/pre-existing conditions or other susceptibility factors?
- *Relevance of animal data to humans and human exposure scenarios* – Is there weak epidemiological or mechanistic support for the human relevance or adversity of an apical endpoint observed in animal studies? Are the exposure conditions associated with adverse health outcomes unlikely to be relevant to human exposure scenarios, based on the conditions of use for that chemical?
- *Application to the relevant exposure scenario* – The exposure duration of the study may not easily match one of the assessed exposure scenarios (*i.e.*, acute, short-term, chronic, lifetime). Especially for animal studies, is there uncertainty whether the endpoint observed in the study would present in the assigned human exposure duration/scenario?
- *Other considerations specific to dose-response assessment that are external to the systematic review process* – Uncertainties and assumptions associated with derivation of Points of Departure will be described in the risk evaluation and are outside the scope of this protocol.

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GLOSSARY OF SELECT TERMS

Term	Definition
Best available science	Science that is reliable and unbiased. Use of best available science involves the use of supporting studies conducted in accordance with sound and objective science practices, including, when available, peer-reviewed science and supporting studies and data collected by accepted methods or best available methods (82 FR 33726, July 20, 2017).
Clarity and completeness	The degree of intelligibility and comprehensiveness with which the data, assumptions, methods, quality assurance, and analyses employed to generate information are documented.
Conditions of Use	The circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used or disposed of.
Quality levels	Qualitative judgment describing the certainty of the data quality evaluation: High Quality – No notable deficiencies or concerns were identified in the domain metric that are likely to influence results [raking of 1]; Medium Quality – Minor uncertainties or limitations were noted in the domain metric that are unlikely to have a substantial impact on results [ranking of 2]; Low Quality – Deficiencies or concerns were noted in the domain metric that are likely to have a substantial impact on results [ranking of 3]; Critically deficient – Serious flaws were noted in the domain metric that consequently make the data source unusable or of limited application [ranking of 4]
Confidential Business Information (CBI)	Proprietary information considered confidential to the submitter, the release of which would cause substantial business injury to the owner. Companies generally request CBI designation for confidential proprietary information believed to give other companies an advantage in the marketplace, such as details of their manufacturing processes and formulas. TSCA section 14 broadly defines CBI that may not be disclosed by EPA and the requirements for substantiating a CBI claim.
Criteria	Standards developed by which something may be judged or decided. OPPT uses criteria for study inclusion as well as criteria for each metric for data quality evaluation (high, medium, low, or critically deficient [for individual criteria]/uninformative [for study inclusion]).
Data	Retrieved, collected, or simulated quantitative or qualitative values of variables (*e.g.*, numbers, observations) that are generally attained from a single reference (*e.g.*, peer-reviewed literature) or source (*e.g.*, model, database).
Data evaluation	The evaluation of the quality of the data from individual references searched for and screened using the process outlined in Section 3.
Data extraction	The extraction of data from individual references searched for, screened and evaluated using the process outlined in Section 3 and Section 5.

Data need	Information required for a thorough or robust assessment of chemical hazard or exposure, typically provided by a guideline study. In cases where data needs are traditionally filled using vertebrate animal toxicity tests, TSCA section 4(h) describes additional considerations of alternative, reasonably available existing information, to reduce or replace vertebrate animal testing. EPA considers, as appropriate and to the extent practicable and scientifically justified, toxicity information, computational toxicology and bioinformatics, and high-throughput screening methods and the prediction models of those methods. EPA also encourages and facilitates the use of valid test methods and strategies that reduce or replace the use of vertebrate animals, as well as read-across data from chemical categories where testing of a chemical substance would provide scientifically valid and useful information on another chemical in the category (15 U.S.C. § 2601 et seq., 2016).
Data quality ranking	Quantitative ranking calculated following evaluation of discipline-specific and data type-specific data evaluation domains and metrics according to predefined ranking criteria.
Data streams	Body of discipline specific information derived or relevant to a specific topic area.
Data types	Data or information from specific study types within each discipline for exposure and hazard.
Discipline	Technical areas within EPA OPPT that are responsible for the assessment of information supporting TSCA risk evaluations. The disciplines include: (1) physical and chemical properties, (2) environmental fate, (3) exposure, (4) engineering, (5) human health hazard, and (6) environmental hazard.
Domain	The general categories of data/information attributes intended to assess methodological conduct and/or risk of bias.
Dose-response	The concentration-response relationship between an exposure and a health effect, regardless of the source or route of exposure, including internal dose as it impacts a target tissue.
Evaluation and review	The extent of independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies, or models.
Evaluation domains	The categories of attributes that are evaluated for each data/information source (*e.g.*, test substance, test conditions, reliability, representativeness). Each domain contains a unique set of metrics, or sub-categories of attributes, intended to assess an aspect of the methodological conduct of the data/information source.
Evidence	Useful, contextualized information that may be attained from a single reference or multiple references and used to support a conclusion

Evidence integration	The consideration of evidence obtained from systematic review and scientific information obtained from trusted sources beyond systematic review. Integration can be a step-wise or iterative process and may include quantitative analyses and/or qualitative interpretation.
Evidence table	Visual depiction of potential evidence gaps within a discipline. Evidence table content may reflect predicted evidence based on the presence of data stream key words present in the titles and abstracts of peer-reviewed literature or may reflect results of full-text screening results. Evidence tables do not provide information on the study data quality.
Evidence stream	Sub-categories of the types of information within each discipline. The various evidence streams within a discipline are depicted in the literature inventory trees and evidence maps (*e.g.,* human health hazard includes epidemiological, animal, and mechanistic evidence streams).
Gray literature	The broad category of data or information sources not found in the standard, peer-reviewed literature databases such as PubMed and Web of Science.
For your information	Voluntary submissions by people or organizations not subject to the reporting requirements under TSCA but desire to inform EPA of potential toxic substances that may pose a risk to human health or the environment.
Information	The functional use of data, where data is interpreted with context.
Literature inventory tree	Interactive, visual display showing the inclusion/exclusion of citations within a discipline.
Literature streams	Categories of the sources where potentially relevant literature are found during systematic review. Sources include, but are not limited to, the following: peer-reviewed literature, gray literature, TSCA submissions, manufacturer request risk evaluation submissions, public provided, enforcement consent agreement, and use reports.
Metrics	The sub-categories of domain attributes for which systematic qualitative evaluation of study attributes is assessed.
Not rated/not applicable	Rating of this metric is not applicable to this data source/data set [no ranking; not considered in overall ranking determination].
Office of Pollution Prevention and Toxics	The office within EPA which administers the TSCA, including the existing chemical risk evaluations under TSCA section 6.
Potentially exposed or susceptible subpopulation	A group of individuals within the general population identified by the Agency who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly (15 U.S.C. 2602 or 40 CFR 702.33).

Robustness	Characteristic indicating the result is resilient to small changes in the parameters which determine the result. In the context of evidence integration, robustness refers to having numerous studies with similar outcomes in the same direction. Characterization of a study or body of evidence that indicates the results or judgements are strong and resistant to error.
Scoping	A step also known as problem formulation in EPA's risk paradigm which provides the analytical framework for the systematic review and includes a conceptual model and analysis plan for a risk evaluation.
Sensitivity	Characteristic indicating if the design is sufficient to observe effects (*e.g.*, whether detection limits are low enough to measure chemical concentrations or effect outcomes).
Soundness	The extent to which the scientific information, technical procedures, measures, methods, protocols, methodologies, or models employed to generate the information are reasonable for and consistent with the intended use of the information.
Strength of the evidence	Consideration of the strengths, limitations, and relevance of the evidence and information within a specific evidence stream based primarily on pre-defined, discipline-specific factors (factors that increase or decrease strength).
Systematic approach	Peer-reviewed methods used for gap filling and extrapolation in the absence of reasonable available data or used to complement data from systematic review in evidence integration and weight of the scientific analysis.
Topic area	Sub-categories of discipline-specific information supporting EPA's risk evaluations. OPPT topic areas include (1) physical and chemical properties, (2) environmental fate and transport, (3) occupational exposure, (4) environmental releases, (5) general population exposure, (6) consumer exposure, (7) environmental exposure, (8) human health hazard, and (9) environmental hazard.
Variability	Characterization of consistency, quantified by a distribution of frequencies of multiple instances of the quantity, derived from observed data.
Uncertainty	Characterization of reliability, quantified by a probability distribution which depends upon our state of information about the likelihood of what the single, true value of the uncertain quantity is.
Weight of the scientific evidence (WoSE)	As defined in the risk evaluation rule, "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" (82 FR 33726, July 20, 2017). In the context of this protocol and evidence integration, weight of the scientific evidence refers to a comprehensive evaluation of evidence and

	information, taking into consideration the strengths, limitations, and uncertainties across streams of evidence within a discipline. This yields a qualitative, overall summary of the strength of each evidence stream and an overall judgment across all relevant evidence.
8(e)	Studies submitted under section 8(e) of TSCA as a substantial risk notification. Section 8(e) requires that EPA be immediately notified when substances or mixtures present a substantial risk of injury to health or the environment.

APPENDICES

Appendix A UPDATES TO THE SYSTEMATIC REVIEW PROTOCOL IN RESPONSE TO NASEM, SACC, AND PUBLIC COMMENT RECOMMENDATIONS

The Frank R. Lautenberg Chemical Safety for the 21st Century Act of 2016, which amends the Toxic Substances Control Act (TSCA) requires EPA to evaluate chemicals that already exist in commerce (existing chemicals). TSCA section 6(b)(4)(F) states that EPA shall "integrate and assess available information on hazards and exposures" and "describe the weight of the scientific evidence." Section 26(h) and (i) require that, "[EPA] shall use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science" and shall make decisions "based on the weight of the scientific evidence." EPA interprets that "weight of the scientific evidence" includes integration of a systematic approach utilizing gap filling methodologies and models as well as a systematic review method for existing reasonably available data, applied and integrated in a manner suited to the nature of the evidence or decision context.

In 2018, EPA released the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a), a framework of systematic review approaches under TSCA for searching, screening and data evaluation. In February 2020, the National Academies of Sciences, Engineering, and Medicine (NASEM) began their review of EPA's *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a), which describes an early framework of applying systematic review approaches for TSCA risk evaluations. Further, the Science Advisory Committee on Chemicals (SACC) provided comments on the first 10 TSCA risk evaluations, and additional comments on OPPT's systematic review approaches were garnered during public comment periods. Major comments from NASEM, SACC, and the public received by the Agency, which precede this TSCA Systematic Review protocol, are listed in Table_Apx A-1. As OPPT considered comments and recommendations from the NASEM, SACC and public, gained additional experience in systematic review, and collaborated with other offices within EPA, OPPT incorporated many improvements to the TSCA systematic review process. These improvements are documented in this generic protocol, as well as the chemical specific and discipline specific appendices. Updates from earlier approaches are outlined in Table_Apx A-2. This table also indicates how these updates address the comments enumerated in Table_Apx A-1, above. This is not a point-by-point response to comments. Rather, Table_Apx A-2 outlines how the development of this protocol has been influenced by the early feedback EPA received on its systematic review approaches, and EPA intends to continue to make improvements going forward.

A few overarching comments and specific responses are provided below. Some of these are repeated here from the Introduction and Overview (Section 1). More detailed updates which address other public and peer review comments follow in Table_Apx A-2.

OPPT Should Adopt an Existing Protocol

The TSCA systematic review approaches leverage existing systematic review protocols, expanding and adapting upon these to achieve a fit-for-purpose protocol. Existing protocols focus almost exclusively on human health hazard, whereas TSCA risk evaluation rule requires systematic review approaches for all of the TSCA disciplines that contribute to the exposure and hazard assessments. OPPT is implementing a more streamlined data evaluation approach for human health hazard based on the cross walk listed below that facilitates more direct utilization of recent and future IRIS systematic reviews. This also

allows more seamless updates of literature evaluation into the TSCA SR evaluations based upon interoperability of software platforms being utilized in both IRIS and TSCA SR evaluation programs.

Transparency and Documentation

Previously, EPA did not have a complete clear and documented TSCA systematic review (SR) protocol. EPA is addressing this lack of *a priori* protocol by releasing this TSCA SR Protocol. In its development, EPA considered existing systematic review approaches for hazard/epidemiology data (*e.g.*, Office of Health Assessment and Translation [OHAT], IRIS Handbook, Navigation Guides) and occupational exposure data/studies (*e.g.*, WHO and ILO collaboration). EPA adopted many features of these mostly hazard-only systematic review approaches in developing this TSCA SR Protocol while also customizing the SR approaches to meet TSCA-specific needs, most importantly the systematic review of more than just hazard data (*e.g.*, data streams for fate and transport, exposure, environmental and workplace monitoring, engineering). To transparently show the similarities and adaptations of existing methods to TSCA data streams, this TSCA SR Protocol provides a crosswalk detailing how EPA adopted and incorporated the best practices from other approaches/frameworks into the TSCA SR Protocol (see Appendix A).

The TSCA SR Protocol also includes a glossary of important terms to provide consistency and transparency about how EPA uses terms with TSCA-specific meaning (*e.g.*, Weight of the Scientific Evidence) and terms that are used frequently in the systematic review field in the TSCA SR context (see GLOSSARY OF SELECT TERMS). Including a glossary of terms is consistent with a recent recommendation made by the NASEM regarding the NASEM report on the TSCA SR approach and EPA's IRIS Handbook, a large part of which is dedicated to systematic review.

In response to NASEM's critique that EPA had not previously documented how TSCA prioritization and problem formulation relate to the TSCA SR, this TSCA SR Protocol clearly presents the alignment of the TSCA prioritization and scoping (problem formulation) processes with the steps of the TSCA SR Protocol. The TSCA SR Protocol further shows how EPA's systematic review efforts identify data gaps and data needs related to TSCA chemical risk evaluations. Identifying these data gaps and data needs provides EPA with the information needed to strategically exercise TSCA authorities to require testing or information collection for use in TSCA prioritization and risk evaluation (Section 2).

New Literature Search Process

For the 20 high-priority substances and manufacturer-requested risk evaluations (MRREs) currently undergoing TSCA risk evaluation, EPA implemented a new, unified literature search process, which is described in this TSCA SR Protocol. It uses a comprehensive set of chemical identifiers to capture as much of the literature relevant for all given disciplines, thereby providing consistency and efficiency to the literature search step of systematic review. In addition, EPA's TSCA SR Protocol now leverages additional SR tools (*e.g.*, SWIFT-Review, SWIFT-Active, Health Assessments Workspace Collaborative [HAWC]) to provide structure, documentation, efficiency, and transparency to searching, filtering, and screening (see Sections 3, 4, and 5). The TSCA SR Protocol also includes a description of the use of machine learning to prioritize literature screening and updates to the search and screening approach, including developing Pathways and Processes, Exposure, Setting or Scenario, and Outcomes (PECO) statements before title/abstract screening and improvements to the screening criteria and templates. All of these approaches are in direct response to the NASEM recommendations, particularly those encouraging harmonization with the IRIS Program.

Reducing Bias and Improving Consistency

The TSCA SR Protocol incorporates the use of the interactive HAWC to generate literature inventory trees and evidence maps (see Appendix I). These inventory trees and evidence maps are also linked to Health and Environmental Research Online (HERO) to provide access to specific titles and abstract of sources and pdf if freely available. These visualizations are evergreen in nature and provide greater transparency, access, and utility to the public and peer reviewers. EPA incorporated this technology after close collaboration and technology transfer with EPA's IRIS Program, consistent with NASEM's recommendation. EPA is fully implementing these tools for the 20 high-priority chemical substances and MRRE risk evaluations currently underway, as evidenced by the chemical-specific search terms (Appendix C), PECO statements (Appendix H), and literature trees and evidence maps (Appendix I).

This TSCA SR Protocol also includes new methods to reduce bias and improve evaluation consistency between reviewers and across chemicals, included in response to NASEM recommendations, SACC comments, and public comments. These improvements include coordinated data evaluation training and calibration exercises for reviewers (both contractor support staff and in-house experts), the development of additional internal evaluation guidance, and incorporation of fields for screener notes within in DistillerSR evaluation forms to capture outcomes of the training and calibration testing. To ensure internal consistency and transparency, whenever EPA revises data evaluation criteria for any discipline, EPA will pilot-test their application and undertake multiple rounds of calibration. Further, as recommended by NASEM and SACC, EPA's data quality evaluation now involves two levels of review for each study: a primary review and a secondary quality control review, which may be followed by an explicit conflict resolution step in cases where the two reviewers are not in agreement.

Data Evaluation and Evidence Integration

In response to a variety of commenters, including NASEM and SACC, the TSCA SR Protocol does not include a quantitative/weighted scoring system for data evaluation. Rather, the TSCA SR Protocol applies ordinal rankings to guide the *qualitative* categorization of *high*, *medium*, *low*, or *critically deficient* for each data evaluation metric. The ordinal rankings for individual metrics are used to derive an overall study qualitative ranking of *high, medium, low, or uninformative*. This approach provides for objectivity, consistency, and transparency in comparing studies (Section 5). These updates to the evaluation criteria have been made across all disciplines (*e.g.*, fate, exposure, engineering, environmental, human health hazard).

The TSCA SR Protocol is significantly different in that it includes the Evidence Integration (Section 7), which was not previously included in the 2018 TSCA SR document (U.S. EPA, 2018a). This substantial addition was in direct response to recommendations by the NASEM and the SACC. The Evidence Integration approach included in the TSCA SR Protocol relies on approaches similar to those in EPA's IRIS Handbook but extended to other disciplines, where appropriate, in the TSCA SR Protocol.

In summary, EPA has carefully considered the important peer review recommendations and public comments received on the 2018 TSCA SR document. In close collaboration with colleagues in EPA's IRIS Program, EPA has adopted, to the extent possible and adapted when necessary to meet unique TSCA needs, many of the approaches, procedures, and state-of-the-art technology tools for conducting systematic review of data and information to be used to support risk evaluations under TSCA.

Table_Apx A-1. List of the Major Recommendations and Comments from NASEM, SACC, and the Public

Comment #	Description
Major comments from NASEM	
1	EPA does not have a complete and clear SR protocol. This problem stems from EPA's use a "de novo" approach.
2	EPA should not use a quantitative/weighted scoring system for data evaluations
3	EPA should be using existing frameworks (*e.g.*, Office of Health Assessment and Translation (OHAT), IRIS, Navigation Guides) • European Food Safety Authority, the OHAT of the National Toxicology Program, the Navigation Guide, the Texas Commission on Environmental Quality, the World Health Organization, and the International Labour Organization for occupational exposures. • NASEM did acknowledge that these methods, however, apply systematic review only to the hazard assessment portion of a risk assessment.
4	EPA's SR methods are not well developed for non-hazard endpoints. EPA should leverage the WHO and International Labour organization collaboration's risk- of-bias tool for assessing data on the prevalence of exposure.
5	There is an apparent lack of method for data synthesis and evidence integration.
6	Difficulty understanding definitions of terms – *e.g.*, the weight of the scientific evidence (in Risk eval rule) vs. systematic review.
7	Environmental and human health exposure assessment • No data quality criteria for PBPK models • Exposure models not fully evaluated
8	Evidence synthesis (within data streams – *e.g.*, epidemiology for human health) • Does not contain elements important to answer research question • Not separated from evidence integration (*i.e.*, too much condensing of steps)
9	Evidence integration (across data streams) • Only available for some examples
10	EPA has no defined approach to documenting how problem formulation and protocol are developed.
11	Some inclusion/exclusion criteria are too broad.
12	EPA is using subjective evaluation metrics that are not tested and that can be changed by the assessor.
13	It's problematic to allow one unacceptable metric to cause a full study to be unacceptable.
14	Statistical power and significance should not be used to evaluate studies – stat. significance is not a measure of association or strength of association (*this comment appears to be related specifically to epidemiology studies).
15	No clear questions or protocols have been developed. SR approach was not documented from the beginning

Comment #	Description
16	Not clear regarding identification of evidence – information on the search process scattered across documents.
17	Numerical scoring obscures key study differences and prevents users from making their own determinations.
18	Unclear how discrepancies were handled among the two reviewers for a given study.
19	Combining evidence synthesis/integration decreases transparency.
20	Confusing terminology within/among documents, lack of information to describe process, lack of documentation of deviations from the process.
Major comments from the SACC and public comment recommendations	
General	
21	Unclear SR Protocol
22	Lack of clarity in how regulatory nexus affects the elimination of exposure pathways for SR analysis.
23	Limited by confidential business information (CBI) availability.
24	Need data gathering efforts for chemicals with data needs.
Process	
25	Issues arising from simultaneously conducting SR and TSCA RE.
26	Lack of clarity and transparent rationale for inclusion and exclusion of studies.
27	Inconsistent application of evaluation criteria for different disciplines.
28	Rationale for upgrading and downgrading needs to be clear.
29	Quantitative and weighted scoring system for data evaluation gives a sense of false precision.
30	Deficient discussion and measures of uncertainty and variability as it related to evidence integration.
31	Lack of description of the SR process in the *Application of SR in TSCA RE* document.
32	Difficulty finding references, recommend an indexing system.
33	Need clarity on why some studies were used in data integration and others were not.
34	Consider using previous systematic review assessments.
35	Changes to epidemiology studies data quality criteria.
36	Risk of bias – There is no empirical evidence demonstrating how each risk-of-bias domain should be weighted, and the exclusion of studies based on an arbitrary rating of the evidence is not supported. Suggest presenting all studies and qualitatively discuss the risk of bias using structured approaches, like OHAT and GRADE.

Table_Apx A-2. List of Updates to the Systematic Review Protocol in Response to Comments[a]

Description of the Update to Systematic Review Protocol in Response to Comments	Update to Comment # [b]
Increasing the transparency of the SR protocol by: • Unifying the search strategy used by all disciplines to attain peer and gray literature • Providing additional insight and tagging structures that relay information on the reference source, chemical risk evaluation, and discipline in which the reference is being considered for dramatically increases transparency and traceability. • Creating figures (*e.g.*, literature inventory trees and evidence tables) to visually demonstrate when references are included, excluded or tagged as supplemental information, as applicable. These figures and evidence tables are now being web posted and updated regularly to make information updates evergreen through the evaluation process of multiple data streams from all TSCA disciplines. Adding section to the SR Protocol to describe evidence integration for hazard and exposure. Section 7 of the TSCA protocol describes approaches used to integrate exposure and hazard information. • OPPT has provided a crosswalk of existing frameworks and the Systematic Review Protocol for TSCA Risk Evaluations for hazard (*e.g.*, OHAT, Navigation Guide, IRIS) and occupational exposure (*e.g.*, WHO and ILO collaboration) from which best practices were adopted and incorporated into TSCA methodology. Note these are all mostly human health hazard-based approaches. • Developing confidence statement SOPs to provide more insight on both data quality and relevance for different disciplines before and after evidence integration phases. This is distinct and different than the broader uncertainty sections and confidence statement used in the first 10 risk evaluations. • Describing how proprietary, CBI and FIFRA claims are either maintained or removed are provided in updates of data evaluation. • Describing data gathering efforts, specifically via test orders, in the SR Protocol under the section that describes references coming from "other" reference streams than the original search for peer and gray publicly available literature. • Incorporation of MRREs: • DIDP, DINP, and D4 are incorporated in the systematic review.	1, 2, 3, 4, 5, 10, 16, 21, 22, 23, 24, 26, 31
A glossary of select terms has been incorporated into the systematic review protocol to define terms such strength of the evidence and weight of the scientific evidence. With the addition of a glossary, terms such as evidence integration and data streams are clearer and their used throughout the protocol is more consistent across disciplines. Evidence integration is a separate section for each of the disciplines that includes integration of data obtained through the systematic review process as well as outside of systematic review. The new evidence integration section also provides examples of the confidence and overall judgement.	6, 8, 9, 19, 30
Data quality criteria (metrics used during data evaluation for environmental and human health assessment) presented in Appx. G are relevant and used for PBPK studies and in vitro studies.	7
Data quality evaluation, inclusion, and exclusion criteria updates/changes: • EPA evaluates individual data evaluation metrics using numerical rankings, but these are associated with *qualitative* ratings of *high*, *medium*, *low* or *critically deficient*. EPA will use only the qualitative rankings when reporting data quality and risk of bias results. Although EPA determines an overall rating for a study after evaluating each metric, EPA considers individual aspects of the evaluation when integrating the	17, 29

Description of the Update to Systematic Review Protocol in Response to Comments	Update to Comment # [b]
information and making conclusions about individual studies. When integrating and synthesizing information, EPA considers domain-specific information. *Critically deficient* metric rankings do not automatically disqualify a study from any consideration depending upon which metric is deemed *critically deficient*. In some cases, a metric deemed *critically deficient* may allow the study to be considered in a contextual manner, specifically to qualitatively inform hazard ID and weight of evidence, but would not be used for quantitative applications, such as dose-response determination. • Removing weighting in the ranking of data quality. OPPT will not apply different weights to individual metrics. However, OPPT will continue to use ordinal rankings of high, medium, and low for individual metrics to derive an overall study ranking in order to objectively, consistently, and transparently determine how a study compares to others. This ordinal ranking of high, medium, and low is based on professional judgement. The TSCA framework provides the following additional flexibility when assigning overall study rankings: (1) metrics may be excluded when not applicable, (2) additional domains and metrics may be included for different study types, and (3) reviewers can upgrade or downgrade the resulting study ranking based on professional judgment. • Inclusion and exclusion of studies is described in the discipline-specific appendices where data quality metrics are described. Should reference overall rankings be upgraded or downgraded in study evaluation, this is also explained more clearly. • Discipline crosswalk of metrics has been effectuated to provide more clarity and consistency across Hazard data streams and between hazard and exposure.	
EPA is utilizing an indexing system for visualizations of evaluations. See interactive HAWC trees in scopes of next 20 high priority chemicals. This linkage of literature inventory trees and evidence maps to HERO and evergreen nature of the new platform will provide greater transparency, access and utility to public and peer reviewers (see comments from HBCD RtC)	32
"In response to comments, about transparency of systematic review processes in this protocol will address many concerns about description of systematic review that were previously only described in risk evaluations. (see comments from 1-BP RtC)	25, 33
"EPA relied on previous assessments (*e.g.*, IRIS) for key information but also reviewed relevant literature identified in the literature search that EPA performed for formaldhyde and selected phthalates evaluated by IRIS." (see comments from HBCD RtC) Also: "EPA used previous chemical assessments to quickly identify relevant key and supporting information as a pragmatic approach to expedite the quality evaluation of the data sources; many of those data sources were already captured in the comprehensive literature search performed according to Strategy for Conducting Literature Searches for Cyclic Aliphatic Bromine Cluster (HBCD) and many solvents, phthalates and formaldhyde. EPA has revised its searching and screening procedures to include all studies in the systematic review process (screening, data evaluation) for the next set of TSCA chemical risk evaluations." (see comments HBCD RtC)	34
"The epidemiologic criteria were later revised to more stringently distinguish between High, Medium and Low studies. After additional piloting of the criteria, EPA found that the initial iteration of the epidemiologic data quality criteria (as published in EPA's *Application of*	13, 18, 35

Description of the Update to Systematic Review Protocol in Response to Comments	Update to Comment # [b]
Systematic Review in TSCA Risk Evaluations (U.S. EPA, 2018a) was inadvertently skewing quality scores toward the tail ends of the quality spectrum (High and Unacceptable). In order to have the criteria represent a more accurate depiction of the quality levels in the epidemiologic literature, the criteria were revised using two methods. • The first method was to make the unacceptable (now described as *critically deficient*) metric rankings less stringent. This was accomplished by either rewording the metrics to allow for more professional judgment in the interpretation of the *critically deficient* criterion, or in some cases, completely removing the option to characterize a metric as *critically deficient* (assign a ranking of 4) because EPA determined the metric was not influential enough to completely disqualify a study from consideration (mostly metrics in the Analysis and Biomonitoring domain). EPA found that these changes greatly reduced the type one error in the *Uninformative* study determinations. Acceptable studies were not inaccurately classified as *Uninformative*. • The second method was to reduce the number of studies that received an overall *High* rating. Most of overall scores in EPA's initial evaluations during piloting tended to be *High*. Therefore, EPA strived to revise the criteria to provide more gradation in the study characterization to more accurately and objectively distinguish studies of the highest quality from *medium* and *low*-quality studies. To do this, EPA removed the *High* criterion from some metrics, particularly in dichotomous metrics (*e.g.*, *High/Low*) that were primarily being binned as *High* by reviewers across the majority of the studies. These dichotomous metrics were contributing to the overall quality scores being skewed towards *High*. To address this, EPA shifted some of the dichotomous metrics such that the highest metric ranking possible (for all studies) is a *Medium*. The change led to the dichotomous metrics having less significant impact to the ordinal ranking and the overall quality rating for each study. With the aforementioned changes to the criteria, EPA observed fewer studies with unacceptable (now called *Uninformative*) rankings and more studies shifting from High to Medium, with only the highest quality studies receiving a High overall rating. Out of the ~200 relevant epidemiologic studies and cohorts evaluated for data quality for the first 10 TSCA chemicals, the majority (~80%) still had rankings of *High* or *Medium*. The remaining ~20% of studies had rankings of *Low* or *Uninformative*. EPA is confident that no studies of acceptable quality were inappropriately assigned as *Uninformative*. EPA is also confident that the revised criteria bins the quality levels of these epidemiologic studies more appropriately than the previous iteration. Additional refinements to the epidemiologic data evaluation criteria are likely to occur as EPA's validation and process improvement efforts continue (see comments in 1-BP RtC).	
"Because EPA was developing the systematic review process while simultaneously implementing the process for 10 chemicals, there were some challenges with maintaining consistency. However, EPA did implement several steps to ensure consistency and reduce bias. EPA used calibration steps among multiple screeners during a pilot phase for both the data TIAB and full text screening and data evaluation processes. Furthermore, instructions were prepared for various aspects of the systematic review (*e.g.*, data screening, data evaluation, and data extraction) to guide the reviewers and provide for more consistency across reviews. Finally, most studies received two data quality evaluations with reviewers working together to resolve conflicts, sometimes with a single arbiter across similar types of studies. EPA has implemented additional calibration steps and internal guidance documents for the next 20 chemicals that are now going through the systematic review process.	2, 36

Description of the Update to Systematic Review Protocol in Response to Comments	Update to Comment # [b]
Any single set of data quality criteria, even for a given category of studies (*e.g.*, animal toxicity studies), cannot necessarily address all aspects of quality relevant for an individual study in the category. Thus, EPA allowed reviewers the ability to adjust the final rankings based on professional judgment. A similar approach has been used in other established tools, including the ToxRTool (Toxicological data Reliability Assessment Tool) developed by the European Commission. EPA implemented a unified literature search process that was different from the first 10 chemicals that included a comprehensive set of chemical identifiers to capture as much of the literature relevant for all given disciplines. However, even with a comprehensive literature search, some important studies may be missed. For instance, an abstract may not identify the chemical of interest by name (*e.g.*, if a genotoxicity test was conducted on many chemicals) and thus might be screened out from further consideration. In addition, some targeted searching for topics not included because of chemical specificity are also being employed and backwards searching of other assessments and sources submitted during public comment periods not anticipated at the beginning of the systematic review scoping might be needed and are described in protocol. Therefore, such backwards searching (or snowballing) and targeted searching remain important aspects of the systematic review process. EPA is publishing this updated protocol document for the next group of TSCA risk evaluations.	
Section 4.1.5[c] General Approach for Screening Peer-Reviewed Search Results: Adding SWIFT-Review to EPA's list of systematic review tools is part of the innovations adopted in the TSCA systematic review process since the development of the first 10 risk evaluations (*i.e.*, the 2016 starts). Use of SWIFT-Review allows EPA to reduce the screening burden by quickly identifying references most relevant to a discipline according to topic-specific key terms using priority-ranking algorithms.	1, 15, 20, 21
Section 4.3.3[c] Obtaining CBI and Proprietary Data and Section 4.4.1 Review Logic for Backward Searching of Gray Literature: EPA considers all reasonably available CBI and proprietary data as defined in 40 CFR 702.33 and has added details to the above sections of the protocol regarding reviewing and obtaining the data.	1, 21, 23
Section 6.4.1 Data Extraction of Study Methods and Results: For environmental health hazards studies, which are included in HAWC and evaluated in DistillerSR, data extraction is conducted outside of DistillerSR. The extracted data reside in the ECOTOXicology Knowledgebase (ECOTOX) database. The ECOTOX database is a comprehensive, publicly available Knowledgebase created, maintained, and updated by EPA. Data that reside in the ECOTOX database comprise of chemical environmental toxicity data on aquatic life, terrestrial plants and wildlife, and other relevant environmental health endpoints. As part of the systematic literature review, EPA is working to export data of environmental health hazard studies evaluated in DistillerSR from the ECOTOX database and import the data into DistillerSR using a JSON file with one-to-one matches for each field question in the DistillerSR data extraction form. The data extraction form will be downloaded from DistillerSR and made available in Excel format when the draft risk evaluation is publicly released.	N/A
Section 7.5.1 Strategy for Initial Database Searches for Literature Searches: The databases listed below are searched for literature containing the chemical search terms. The strategy has been updated to reflect significant resource changes that have taken place since	1, 11, 12, 21

Description of the Update to Systematic Review Protocol in Response to Comments	Update to Comment # [b]
the initial 2019 searches. The first significant change came in response to the ToxNet database being taken offline. References that were stored in the Toxline subsection of ToxNet were divided and redistributed to the ProQuest and PubMed databases. EPA now acquires Toxline references by searching the ProQuest and PubMed subsections. The second significant change is the switch from Science Direct to Elsevier's larger and more comprehensive literature database, Scopus. Additionally, the ECOTOX database has been incorporated into gray literature searching and will not be searched for peer-reviewed literature.	
Appendix L, M, N, R[c]: Although the data quality criteria for several disciplines are the same in this generic protocol as in EPA's *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a) document, the human health and environmental hazard criteria were updated to address SACC, NASEM and public comments. One of the most important updates from *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a) is that EPA added more details to the metric criteria for analyzing the studies; this update is expected to increase objectivity during data evaluation and decrease the percent of overall study ratings that need to be changed (upgraded or downgraded) by professional judgment. EPA also revised criteria to address potential bias towards higher ratings for animal toxicity studies compared with epidemiological studies. For the update, EPA also ensured that criteria for data relevant to environmental hazards (plant, animal, *in vitro*) and human health hazards (animal, epidemiological, *in vitro*) were as consistent as possible. Appendix T presents a crosswalk of the similarities among these data types.	14, 17, 27, 28, 29, 35
[a] The list of updates goes beyond addressing comments and includes improvements identified by EPA. [b] Comment # refers to the comment number by NASEM, SACC, and/or public comment enumerated in Table_Apx A-1. [c] Section or appendix designation has been revised since early feedback was received.	

A.1 Crosswalk of Other Systematic Review Methodologies

As stated above, NASEM recommended the consideration of methodologies developed by the European Food Safety Authority, the National Toxicology Program's (NTP's) Office of Health Assessment and Translation (OHAT), the Navigation Guide, and the Texas Commission on Environmental Quality to evaluate hazard information. Furthermore, the NASEM also recommended EPA consider methodologies used by the World Health Organization, and the International Labour Organization to evaluate occupational exposures. Therefore, crosswalk comparisons between these approaches and TSCA assessments, including EPA's IRIS assessments, are provided below.

A.1.1 Hazard Evaluation

A.1.1.1 OHAT Approach for Systematic Review and Evidence Integration

The OHAT approach was developed by the NTP's OHAT (NTP, 2019). Table_Apx A-3 through Table_Apx A-9 below compare the TSCA approach with the OHAT approach. Blue, bolded text identifies close similarity among the approaches, whereas red, italicized text identifies areas where the two approaches do not align closely. Because the OHAT questions/domains are less specific than the TSCA metrics, some of these apparent areas of difference, particularly for the animal toxicity data, may not be true differences but illustrate more granular questions addressed in TSCA metrics.

Table_Apx A-3. Crosswalk of the Human Health Animal Toxicology Data Qualtiy Metrics for TSCA and OHAT

TSCA Domain	TSCA Metrics	OHAT Domain (RoB or Data Quality Questions)[a]
Test substance	*Identity*, *source*, **purity**	Exposure assessment (question about **purity**) Other sources of bias (because identity, source not addressed specifically)
Test design	**Randomized allocation,** *negative/vehicle controls*, *positive controls*	**Selection bias (randomization**, allocation concealment) Other sources of bias (for TSCA metrics on negative and positive controls)
Exposure characterization	**Preparation/storage of test substance**, consistency of exposure administration, *reporting of doses*, *exposure frequency/duration*, *number of exposure groups/dose spacing*, *exposure route/method*	Detection bias (confidence in the exposure characterization) Exposure assessment (data quality questions including **stability/homogeneity of the test substance**) Performance bias (whether experimental conditions were identical across study groups)
Test organism	*Test animal characteristics*, **adequacy/consistency of animal husbandry conditions**, *number/group*	Performance bias **(consistency of experimental conditions)**
Outcome assessment	Outcome assessment methodology, **consistency of outcome assessment, blinding of assessors**, sampling adequacy, negative control response	**Performance bias (blinding of research personnel)** Detection bias (confidence in the outcome assessment)
Confounding/ variable control	Confounding variables in test design/procedures, health outcomes unrelated to exposure	Attrition/exclusion bias Other sources of bias (Note: OHAT domain regarding confounding is specific to observational studies)
Data presentation and analysis	**Statistical methods, reporting of data**	**Selective reporting bias (whether all outcomes were reported)** **Other sources of bias (*e.g.*, appropriateness of statistical methods)**

Blue, bolded text identifies close similarity among the TSCA and NTP's OHAT (NTP, 2019) approaches, whereas red italicized text identifies areas where the two approaches do not align closely.

[a] See Table 5 of NTP (2019) for OHAT RoB tool; see also text of NTP (2019) for additional data quality questions.

Table_Apx A-4. Crosswalk of the Human Health Epidemiology Data Qualtiy Metrics for TSCA and OHAT

TSCA Domain	TSCA Metric	OHAT Domain (RoB or Data Quality Questions)[a]
Study participation	**Participant selection, attrition, comparison group**	**Selection bias (selection of participants/appropriate comparison groups)** **Attrition/exclusion bias** Performance bias (whether experimental conditions were identical across study groups)
Exposure characterization	**Measurement of exposure**, **exposure levels**, *temporality*	**Detection bias** (**confidence in the exposure characterization)** **Exposure assessment (ability to distinguish different exposure concentrations**, exposure misclassification, *contamination*)
Outcome assessment	Outcome measurement or characterization, **reporting bias**	Detection bias (confidence in outcome assessment) **Selective reporting bias (reporting all measured outcomes)**
Potential confounding	Covariate adjustment, covariate characterization, co-exposure	Confounding bias (accounting for confounding/modifying variables)
Analysis	Study design and methods, statistical power, reproducibility of analyses, **statistical models**	**Confounding bias** Other sources of bias (*e.g.*, **appropriateness of statistical methods**)
Other	**Use of biomarker of exposure**, effect biomarker, **method sensitivity**, biomarker stability, sample contamination, method requirements, matrix adjustment	**Exposure assessment (*e.g.*, specificity of biomarker, method sensitivity, biomarker stability, sample contamination, method requirements, matrix adjustment)**
Blue, bolded text identifies close similarity among the TSCA and NTP's OHAT (NTP, 2019) approaches, whereas *red italicized text* identifies areas where the two approaches do not align closely. [a] See Table 5 of NTP (2019) for OHAT RoB tool; see also text of NTP (2019) for additional data quality questions.		

A.1.1.2 Navigation Guide

The Navigation Guide was developed by researchers at the University of California, San Francisco (Woodruff and Sutton, 2014).

Table_Apx A-5. Crosswalk of the Human Health Animal Toxicology Data Quality Metrics for TSCA and the Navigation Guide

TSCA Domain	TSCA Metric	Navigation Guide Domain
Test substance	Identity, source, purity	Other threats to validity
Test design	**Randomized allocation**, negative/vehicle controls, positive controls	**Sequence generation**, allocation concealment, other threats to validity
Exposure characterization	Preparation/storage of test substance, consistency of exposure administration, reporting of doses, exposure frequency/duration, number of exposure groups/dose spacing, exposure route/method	Other threats to validity (*e.g.*, atypical deviation from methods)
Test organism	Test animal characteristics, adequacy/consistency of animal husbandry conditions, number/group	Other threats to validity (*e.g.*, atypical deviation from methods)
Outcome assessment	Outcome assessment methodology, consistency of outcome assessment, **blinding of assessors**, sampling adequacy, negative control response	**Blinding of personnel/ outcome assessors**, selective outcome reporting, other threats to validity
Confounding/ variable control	Confounding variables in test design/procedures, health outcomes unrelated to exposure	Other threats to validity
Data presentation and analysis	Statistical methods, **reporting of data**	**Selective outcome reporting**
Blue, bolded text identifies close similarity among the TSCA and NTP's OHAT (NTP, 2019) approaches.		

Table_Apx A-6. Crosswalk of the Human Health Epidemiology Data Quality Metrics for TSCA and the Navigation Guide

TSCA Domain	TSCA Metric	Navigation Guide Domain
Study participation	Participant selection, attrition, comparison group	**Recruitment strategy**
Exposure characterization	Measurement of exposure, exposure levels, temporality	**Exposure assessment**
Outcome assessment	Outcome measurement or characterization, reporting bias	**Incomplete outcome data** **Selective outcome reporting**
Potential confounding	Covariate adjustment, covariate characterization, co-exposure	**Confounding**
Analysis	Study design and methods, statistical power, reproducibility of analyses, statistical models	

TSCA Domain	TSCA Metric	Navigation Guide Domain
Other/ Consideration for biomarker selection and measurement	Use of biomarker of exposure, effect biomarker, method sensitivity, biomarker stability, sample contamination, method requirements, matrix adjustment	**Other threats to validity**
Blue, bolded text identifies close similarity among the TSCA and NTP's OHAT (NTP, 2019) approaches.		

A.1.1.3 IRIS Assessments

IRIS assessments conducted by EPA's ORD include systematic reviews of epidemiology and animal toxicology studies. Table_Apx A-7 and
Table_Apx **A-8** align TSCA study evaluation domains and metrics for animal toxicology and epidemiology, respectively, with the most closely corresponding IRIS domains (and corresponding IRIS metrics in parentheses) from the draft IRIS Handbook (U.S. EPA, 2020) and IRIS assessments. In these tables, blue text denotes comparisons that are more direct, with close similarity between corresponding TSCA and IRIS domains or metrics.

Crosswalks and discussions with IRIS staff indicated that nearly all of the information assessed under each TSCA domain is also assessed under an IRIS domain in current and recent IRIS assessments, including the IRIS phthalates assessment. Older IRIS assessments, particularly the IRIS formaldehyde assessment, differ in some metrics and reporting methods. Generally, IRIS domains are more collapsed, whereas TSCA domains are more expansive—a TSCA domain consisting of several metrics might be collapsed into one IRIS metric.

Chemical-specific modifications to the DistillerSR forms for TSCA assessments are being developed to facilitate the use of IRIS systematic review data for phthalates and formaldehyde.

Table_Apx A-7. Crosswalk of Human Health Animal Toxicology Data Qualtiy Domains and Metrics for TSCA and IRIS Assessments

TSCA Domain	TSCA Metric	IRIS Domain (and metric)
Test substance	**Identity**, **source**, **purity**	Exposure Methods (**identity, source, and purity**)
Test design	**Randomized allocation**, negative/vehicle controls, positive controls	Confounding/variable control (negative/positive controls not specifically mentioned; vehicles are), risk of bias (**randomized allocation**)
Exposure characterization	Preparation/storage of test substance, **consistency of exposure administration, reporting of doses, exposure frequency/duration, number of exposure groups/dose spacing, exposure route/method**	Exposure methods (**exposure administration**, **reporting of doses**), exposure timing, frequency, and duration (**exposure frequency**), reporting quality (**number of exposure groups**), chemical administration and characterization (**consistency of**

TSCA Domain	TSCA Metric	IRIS Domain (and metric)
		exposure administration, exposure route/method)
Test organism	**Test animal characteristics, adequacy/ consistency of animal husbandry conditions, number/group**	Reporting quality (**test animal characteristics, animal husbandry procedures**), Sensitivity-outcomes measures and results display domain (**sample size**)
Outcome assessment	Outcome assessment methodology, consistency of outcome assessment, **blinding of assessors**, sampling adequacy, negative control response	Sensitivity-Outcomes measures and results display domain (**methods sensitive to evaluate endpoints of interest**), results presentation (data presented appropriately), reporting quality (**results for at least one endpoint of interest and evaluation methods**), selective reporting and attrition (**all results presented**), endpoint sensitivity (procedures relevant to endpoint of interest, sample size concerns), observational bias/blinding (**reduce observational bias**)
Confounding/ variable control	Confounding variables in test design/procedures, health outcomes unrelated to exposure	Confounding/variable control, Selective reporting and attrition (all outcomes reported, discrepancies explained)
Data presentation and analysis	Statistical methods, **reporting of data**	Results presentation (all results presented appropriately), selective reporting and attrition (**all results for all outcomes**)
Blue, bolded text identifies close similarity among the TSCA and NTP's OHAT (NTP, 2019) approaches.		

Table_Apx A-8. Crosswalk of Human Health Epidemiology Data Qualtiy Domains and Metrics for TSCA and IRIS Assessments

TSCA Domain	TSCA Metric	IRIS Domain (and Metric)
Study participation	**Participant selection**, attrition, comparison group	**Participant selection**
Exposure characterization	**Measurement of exposure**, exposure levels, temporality	Exposure measurement (**exposure measures**)
Outcome assessment	**Outcome measurement or characterization, reporting bias**	**Outcome ascertainment (outcome measures), selective reporting**

TSCA Domain	TSCA Metric	IRIS Domain (and Metric)
Potential confounding	Covariate adjustment, covariate characterization, co-exposure confounding	Confounding
Analysis	Study design and methods, statistical power, reproducibility of analyses, statistical models	Analysis, sensitivity
Other/ consideration for biomarker selection and measurement	Use of biomarker of exposure, effect biomarker, method sensitivity, biomarker stability, sample contamination, method requirements, matrix adjustment	Exposures measurement (exposure measures), outcome ascertainment (outcome measures), analysis
Blue, bolded text identifies close similarity among the TSCA and NTP's OHAT (NTP, 2019) approaches.		

A.1.2 Occupational Exposure

WHO and International Labour Organization collaborated to develop a risk-of-bias tool for assessing data on the prevalence of occupational exposure (see Table_Apx A-9).

Table_Apx A-9. Comparison of TSCA Systematic Review Process vs. WHO/IOL Systematic Review Process

Overview	TSCA Process	WHO/IOL
Systematic review	**Occupational exposure and environmental release**	*Occupational health:* • Occupational *exposure to dust and/or fibers* • Effect *of occupational exposure to dust and/or fibers on pneumoconiosis*
Eligibility criteria	RESO: *Receptor* (human and/or environment), **Exposure**, *Setting or Scenario*, **Outcome**	**PECO:** *Population*, **Exposure**, *Comparator*, Outcome
Information source and search	• **Databases containing publicly available, peer-reviewed literature (*e.g.*, PubMed, Web of Science, ProQuest, Science Direct, TOXNET)** • **Gray literature includes data/information sources such as white papers, conference proceedings, technical reports, reference books, dissertations, information on various stakeholder websites and other databases (*e.g.*, U.S. EPA, California EPA, CDC, FDA, NISOH, NTP, NLM, OSHA, US BLS, ECHA, Environment Canada, OECD)** • **Data/information sources generated from backward searches**	• **Electronic and Academic databases: Ovid Medline with Daily Update, PubMed, EMASE, Web of Science, OSH Update, WHO, OSHA, EUROPA, Eurostat, CNKI, CDC, NIOSH** • **Open gray literature, internet searches, organizational websites, hand-searching and expert consultation**

Overview	TSCA Process	WHO/IOL
	of existing documents containing data/information likely to be relevant to the risk evaluation • *Data and information submitted under TSCA sections 4, 5, [add 6 here], 8(e), and 8(d), as well as for your information (FYI) submissions* • *Public comments that EPA receives during the risk evaluation process* • *Data and information submitted by industry stakeholders as relevant for Manufacturer-Requested Risk Evaluations (hereafter "MRRE literature")*	
Study Selection	**DistillerSR**	*Rayyan Systematic Review Web App* or **DistillerSR**
Title and abstract screening	**Two reviewers and a third reviewer resolves conflicts**	**Two reviewers and a third reviewer resolves conflicts**
Full-text screening	**Two reviewers and a third reviewer resolves conflicts**	**Two reviewers and a third reviewer resolves conflicts**
Extraction	**At minimum one screener extracts and second screener QC**	*At a minimum 2 review authors independently extract; third reviewer will resolve conflicts*
Data Quality/Risk of Bias	Data Quality: *one reviewer evaluated data and second reviewer QC*	*Two reviewers assess risk of bias and quality of evidence; third screeners resolve conflicts*
Blue, bolded text identifies close similarity among the TSCA and NTP's OHAT (NTP, 2019) approaches, whereas *red italicized text* identifies areas where the two approaches do not align closely.		

Appendix B SOURCE OF VERIFICATION FOR CHEMICAL NAMES AND STRUCTURES

B.1 Search Term Genesis and Chemical Verification

B.1.1 Search Term Genesis and Chemical Verification for 2019 Literature Searches

Several online sources are queried to develop the chemical terms to be used in subsequent literature searches. This appendix presents the complete list of sources for chemical verification. From these sources, all chemical names, synonyms, CAS number(s), and trade names are documented and used to generate terms for the database searches. Prior to inclusion in the search string (see Appendix C.1) all forms of chemical names are subject to verification from several potential sources (*e.g.*, CompTox Chemicals Dashboard, STN International-CAS).

- California Department of Pesticide Regulation
- CompTox Chemicals Dashboard
- Pesticide Properties DataBase (PPDB)
- Reregistration Eligibility Decision (RED) documents
- Office of Pesticide Programs Pesticide Chemical Search
- Food and Agriculture Organization of the United Nations
- Pesticide Info Database

This strategy was applied to all chemical literature searches, excluding D4, and phthalic anhydride.

B.1.2 Search Term Genesis and Chemical Verification for Literature Searches Dated 2020 and Newer

Search term development has been updated to reflect a greater range of consideration, and now includes additional verified sources. From these sources, all validated chemical names, synonyms, CAS number(s), and trade names are documented and used to generate terms for the database searches. Prior to inclusion in the search string (see Appendix C.1) all search terms are subjected to verification from multiple potential sources (*e.g.*, CompTox Chemicals Dashboard, PubMed). Search term resources include

- ChemSpider
- ChemID*plus*
- FDA Substance Registration System
- European Chemicals Agency (ECHA)
- CompTox Chemicals Dashboard
- Pesticide Info Database
- Pesticide Properties DataBase (PPDB)
- OPP Pesticide Chemical Search

This strategy was applied to the chemical literature searches for D4 and phthalic anhydride. This is the primary strategy for all search term genesis moving forward.

Table_Apx B-1. Sources for Chemical Names and Structures Used by EPA

Chemical Source	Contents
ChemSpider	CAS RNs, chemical name, synonyms, targets, toxicity data, related chemicals, and regulatory information; International chemical data
ChemID*plus*	CAS RNs, chemical name, synonyms, targets, toxicity data, related chemicals, and regulatory information; International chemical data
FDA Substance Registration System	CAS RNs, chemical name, synonyms
European Chemicals Agency (ECHA)	CAS RNs, chemical name, synonyms, targets, toxicity data, related chemicals, and regulatory information; International chemical data
CompTox Chemicals Dashboard	CAS RNs, synonyms, structures, properties, environmental fate and transport
Pesticide Info Database	CAS RNs, chemical name, synonyms, targets, toxicity data, related chemicals, and regulatory information
Pesticide Properties DataBase (PPDB)	Pesticide information, CAS RNs, synonyms, structure data
U.S. EPA Office of Pesticide Programs Pesticide Fate Database	Multiple databases containing chemicals, pesticides, companies, products, etc.

Table_Apx B-2. Sources for Chemical Names and Structures Used by GDIT

Chemical Source	Contents
CompTox Chemicals Dashboard	CAS RNs, synonyms, structures, properties, environmental fate and transport
Dictionary of Chemical Names and Synonyms	Wide assortment of chemical compounds by chemical name and synonym, has CAS index and some structure data
Farm Chemicals Handbook-1992	Pesticide information, CAS RNs, synonyms, structure data[a]
OPPT SMILES Verification Source	Structure data
RTECS (1983–84 ed.)	Chemical names, synonyms, and CAS RNs
Sigma – Aldrich website	Organic and inorganic compounds by chemical name, has CAS index and some structure and physical property data
STN International (CAS) 1994	Most complete source of chemical name, synonym, and structure information
The Pesticide Manual 10th edition, 1994	Pesticide compounds by chemical name, synonym, product code, has CAS index and some structure and physical property data
TSCA Chemical Substance Inventory (1985 ed.)	Chemical names, synonyms, and CAS RNs

Chemical Source	Contents
World Wide Web (misc. web sources)	Chemical names, synonyms, and CAS RNs
California Department of Pesticide Regulation	Multiple databases containing chemicals, pesticides, companies, and products
Pesticide Info Database	CAS RNs, chemical name, synonyms, targets, toxicity data, related chemicals, and regulatory information
U.S. EPA Office of Pesticide Programs Pesticide Fate Database	Multiple databases containing chemicals, pesticides, companies, products, etc.
[a] Sometimes CAS RN presented for a compound is for the main constituent only.	

Appendix C LITERATURE SEARCH STRATEGIES

C.1 Peer-Reviewed Literature Database Searches

For the 2019 starts and MRREs, public database searches were conducted for all available years at the time of the search. The search date (located below each source name in the summary tables) indicates the earliest date for which literature was available to be searched within the database. Search strings were constructed using syntax provided in their respective online search manuals.

C.1.1 Query Strings for the Peer-Reviewed Literature Database Searches on *o*-Dichlorobenzene

These are the search terms compiled from the Chemical Report for *o*-dichlorobenzene used in the initial search strategies for each of the databases listed below.

"1,2-Dichlorbenzene" OR "1,2-Dichlorbenzol" OR "1,2-Dichlorobenzene" OR "1,3-Dichlorbenzol" OR "1,3-Dichlorobenzene" OR "1,3-diclorobenceno" OR "1,4-Chlorobenzene" OR "1,4-Dichlorbenzol" OR "1,4-Dichlorobenzene" OR "1,4-Dichloro-Benzene" OR "12dichlorobenzene" OR "13Dichlorobenzene" OR "2,4-Dichlorobenzene" OR "2,6-Dichlorobenzene" OR "Amisia-mottenschutz" OR "Caswell No. 301" OR "Caswell No. 632" OR "Chloroben" OR "Cloroben" OR "Di-chloricide" OR "Dichlorobenzene" OR "Dichlorobenzene" OR "Dichlorobenzene (Mixed isomers)" OR "Dichlorobenzene, p" OR "Dichlorobenzene, p-" OR "Dichlorobenzene, para" OR "Dichlorobenzene, para-" OR "Dichlorocide" OR "Dilantin DB" OR "Dilatin DB" OR "Dilatin DBI" OR "Dowtherm E" OR "Kaydox" OR "m-Dichlorbenzol" OR "m-Dichlorobenzene" OR "m-Dichlorobenzol" OR "metadichlorobenzene" OR "meta-Dichlorobenzene" OR "Mottenschutzmittel Evau P" OR "Mott-Ex" OR "m-Phenylene dichloride" OR "m-Phenylenedichloride" OR "NCI-C54944" OR "NCI-C54955" OR "NSC 36935" OR "NSC 60644" OR "NSC 8754" OR "o/mDichlorobenzene" OR "o/m-Dichlorobenzene" OR "o-Dichlor benzol" OR "o-Dichlorbenzol" OR "o-Dichlorobenzene" OR "o-Dichlorobenzol" OR "Orthodichlorobenzene" OR "ortho-Dichlorobenzene" OR "Orthodichlorobenzol" OR "Para crystals" OR "Paradichlorbenzol" OR "Para-dichloro benzene" OR "Paradichlorobenzene" OR "para-Dichlorobenzene" OR "Paradichlorobenzol" OR "Paradow" OR "Paramoth" OR "Paranuggets" OR "Parazene" OR "p-Chlorophenyl chloride" OR "p-Dichlorbenzene" OR "p-Dichlorobenzene" OR "p-Dichloro-Benzene" OR "p-Dichlorobenzol" OR "Persia-Perazol" OR "Rotamott" OR "Santochlor" OR "Special termite fluid" OR "Termitkil" OR "UN 1591" OR "UNII-6PJ93I88XL" OR "UNII-75W0WNE5FP"

Table_Apx C-1. Peer-Reviewed Literature Search Strategy for *o*-Dichlorobenzene

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 5/6/2019	1. 1,2-Dichlorbenzene; 1,2-Dichlorbenzol; 1,2-Dichlorobenzene; 1,3-Dichlorbenzol; 1,3-Dichlorobenzene; 1,3-diclorobenceno; 1,4-Chlorobenzene; 1,4-Dichlorbenzol; 1,4-Dichlorobenzene; 1,4-Dichloro-Benzene 2. 12dichlorobenzene; 13Dichlorobenzene; 2,4-Dichlorobenzene; 2,6-Dichlorobenzene; Amisia-mottenschutz; Caswell No. 301; Caswell No. 632; Chloroben; Cloroben; Di-chloricide 3. Dichlorobenzene; Dichlorobenzene; Dichlorobenzene (Mixed isomers); Dichlorobenzene, p; Dichlorobenzene, p-; Dichlorobenzene, para; Dichlorobenzene, para-; Dichlorocide; Dilantin DB; Dilatin DB	336

Source	Source-Specific Search Strategy	Results
	4. Dilatin DBI; Dowtherm E; Kaydox; m-Dichlorbenzol; m-Dichlorobenzene; m-Dichlorobenzol; metadichlorobenzene; meta-Dichlorobenzene; Mottenschutzmittel Evau P; Mott-Ex 5. m-Phenylene dichloride; m-Phenylenedichloride; NCI-C54944; NCI-C54955; NSC 36935; NSC 60644; NSC 8754; o/mDichlorobenzene; o/m-Dichlorobenzene; o-Dichlor benzol 6. o-Dichlorbenzol; o-Dichlorobenzene; o-Dichlorobenzol; Orthodichlorobenzene; ortho-Dichlorobenzene; Orthodichlorobenzol; Para crystals; Paradichlorbenzol; Para-dichloro benzene; Paradichlorobenzene 7. para-Dichlorobenzene; Paradichlorobenzol; Paradow; Paramoth; Paranuggets; Parazene; p-Chlorophenyl chloride; p-Dichlorbenzene; p-Dichlorobenzene; p-Dichloro-Benzene 8. p-Dichlorobenzol; Persia-Perazol; Rotamott; Santochlor; Special termite fluid; Termitkil; UN 1591; UNII-6PJ93I88XL; UNII-75W0WNE5FP	
Current Contents Search Date: 5/6/2019	TS=("1,2-Dichlorbenzene" OR "1,2-Dichlorbenzol" OR "1,2-Dichlorobenzene" OR "1,3-Dichlorbenzol" OR "1,3-Dichlorobenzene" OR "1,3-diclorobenceno" OR "1,4-Chlorobenzene" OR "1,4-Dichlorbenzol" OR "1,4-Dichlorobenzene" OR "1,4-Dichloro-Benzene" OR "12dichlorobenzene" OR "13Dichlorobenzene" OR "2,4-Dichlorobenzene" OR "2,6-Dichlorobenzene" OR "Amisia-mottenschutz" OR "Caswell No. 301" OR "Caswell No. 632" OR "Chloroben" OR "Cloroben" OR "Di-chloricide" OR "Dichlorobenzene" OR "Dichlorobenzene" OR "Dichlorobenzene (Mixed isomers)" OR "Dichlorobenzene, p" OR "Dichlorobenzene, p-" OR "Dichlorobenzene, para" OR "Dichlorobenzene, para-" OR "Dichlorocide" OR "Dilantin DB" OR "Dilatin DB" OR "Dilatin DBI" OR "Dowtherm E" OR "Kaydox" OR "m-Dichlorbenzol" OR "m-Dichlorobenzene" OR "m-Dichlorobenzol" OR "metadichlorobenzene" OR "meta-Dichlorobenzene" OR "Mottenschutzmittel Evau P" OR "Mott-Ex" OR "m-Phenylene dichloride" OR "m-Phenylenedichloride" OR "NCI-C54944" OR "NCI-C54955" OR "NSC 36935" OR "NSC 60644" OR "NSC 8754" OR "o/mDichlorobenzene" OR "o/m-Dichlorobenzene" OR "o-Dichlor benzol" OR "o-Dichlorbenzol" OR "o-Dichlorobenzene" OR "o-Dichlorobenzol" OR "Orthodichlorobenzene" OR "ortho-Dichlorobenzene" OR "Orthodichlorobenzol" OR "Para crystals" OR "Paradichlorbenzol" OR "Para-dichloro benzene" OR "Paradichlorobenzene" OR "para-Dichlorobenzene" OR "Paradichlorobenzol" OR "Paradow" OR "Paramoth" OR "Paranuggets" OR "Parazene" OR "p-Chlorophenyl chloride" OR "p-Dichlorbenzene" OR "p-Dichlorobenzene" OR "p-Dichloro-Benzene" OR "p-Dichlorobenzol" OR "Persia-Perazol" OR "Rotamott" OR "Santochlor" OR "Special termite fluid" OR "Termitkil" OR "UN 1591" OR "UNII-6PJ93I88XL" OR "UNII-75W0WNE5FP")	2,571
ProQuest Dissertations & Theses Search Date: 5/6/2019	ALL("1,2-Dichlorbenzene" OR "1,2-Dichlorbenzol" OR "1,2-Dichlorobenzene" OR "1,3-Dichlorbenzol" OR "1,3-Dichlorobenzene" OR "1,3-diclorobenceno" OR "1,4-Chlorobenzene" OR "1,4-Dichlorbenzol" OR "1,4-Dichlorobenzene" OR "1,4-Dichloro-Benzene" OR "12dichlorobenzene" OR "13Dichlorobenzene" OR "2,4-Dichlorobenzene" OR "2,6-Dichlorobenzene" OR "Amisia-mottenschutz" OR "Caswell No. 301" OR "Caswell No. 632" OR "Chloroben" OR "Cloroben" OR "Di-chloricide" OR "Dichlorobenzene" OR "Dichlorobenzene" OR "Dichlorobenzene (Mixed isomers)" OR "Dichlorobenzene, p" OR "Dichlorobenzene, p-" OR "Dichlorobenzene, para" OR "Dichlorobenzene, para-" OR "Dichlorocide" OR "Dilantin DB" OR "Dilatin DB" OR "Dilatin DBI" OR "Dowtherm E" OR "Kaydox" OR "m-Dichlorbenzol" OR "m-Dichlorobenzene" OR "m-Dichlorobenzol" OR "metadichlorobenzene" OR "meta-Dichlorobenzene" OR "Mottenschutzmittel Evau P" OR "Mott-Ex" OR "m-Phenylene dichloride" OR "m-Phenylenedichloride" OR "NCI-C54944" OR "NCI-C54955" OR "NSC 36935" OR "NSC 60644" OR "NSC 8754" OR "o/mDichlorobenzene" OR "o/m-Dichlorobenzene" OR "o-Dichlor benzol" OR "o-Dichlorbenzol" OR "o-Dichlorobenzene" OR "o-Dichlorobenzol" OR	30

Source	Source-Specific Search Strategy	Results
	"Orthodichlorobenzene" OR "ortho-Dichlorobenzene" OR "Orthodichlorobenzol" OR "Para crystals" OR "Paradichlorbenzol" OR "Para-dichloro benzene" OR "Paradichlorobenzene" OR "para-Dichlorobenzene" OR "Paradichlorobenzol" OR "Paradow" OR "Paramoth" OR "Paranuggets" OR "Parazene" OR "p-Chlorophenyl chloride" OR "p-Dichlorbenzene" OR "p-Dichlorobenzene" OR "p-Dichloro-Benzene" OR "p-Dichlorobenzol" OR "Persia-Perazol" OR "Rotamott" OR "Santochlor" OR "Special termite fluid" OR "Termitkil" OR "UN 1591" OR "UNII-6PJ93I88XL" OR "UNII-75W0WNE5FP") AND LA(ENG)	
ProQuest Agricultural & Scientific Database Search Date: 5/6/2019	ALL("1,2-Dichlorbenzene" OR "1,2-Dichlorbenzol" OR "1,2-Dichlorobenzene" OR "1,3-Dichlorbenzol" OR "1,3-Dichlorobenzene" OR "1,3-diclorobenceno" OR "1,4-Chlorobenzene" OR "1,4-Dichlorbenzol" OR "1,4-Dichlorobenzene" OR "1,4-Dichloro-Benzene" OR "12dichlorobenzene" OR "13Dichlorobenzene" OR "2,4-Dichlorobenzene" OR "2,6-Dichlorobenzene" OR "Amisia-mottenschutz" OR "Caswell No. 301" OR "Caswell No. 632" OR "Chloroben" OR "Cloroben" OR "Di-chloricide" OR "Dichlorobenzene" OR "Dichlorobenzene" OR "Dichlorobenzene (Mixed isomers)" OR "Dichlorobenzene, p" OR "Dichlorobenzene, p-" OR "Dichlorobenzene, para" OR "Dichlorobenzene, para-" OR "Dichlorocide" OR "Dilantin DB" OR "Dilatin DB" OR "Dilatin DBI" OR "Dowtherm E" OR "Kaydox" OR "m-Dichlorbenzol" OR "m-Dichlorobenzene" OR "m-Dichlorobenzol" OR "metadichlorobenzene" OR "meta-Dichlorobenzene" OR "Mottenschutzmittel Evau P" OR "Mott-Ex" OR "m-Phenylene dichloride" OR "m-Phenylenedichloride" OR "NCI-C54944" OR "NCI-C54955" OR "NSC 36935" OR "NSC 60644" OR "NSC 8754" OR "o/mDichlorobenzene" OR "o/m-Dichlorobenzene" OR "o-Dichlor benzol" OR "o-Dichlorbenzol" OR "o-Dichlorobenzene" OR "o-Dichlorobenzol" OR "Orthodichlorobenzene" OR "ortho-Dichlorobenzene" OR "Orthodichlorobenzol" OR "Para crystals" OR "Paradichlorbenzol" OR "Para-dichloro benzene" OR "Paradichlorobenzene" OR "para-Dichlorobenzene" OR "Paradichlorobenzol" OR "Paradow" OR "Paramoth" OR "Paranuggets" OR "Parazene" OR "p-Chlorophenyl chloride" OR "p-Dichlorbenzene" OR "p-Dichlorobenzene" OR "p-Dichloro-Benzene" OR "p-Dichlorobenzol" OR "Persia-Perazol" OR "Rotamott" OR "Santochlor" OR "Special termite fluid" OR "Termitkil" OR "UN 1591" OR "UNII-6PJ93I88XL" OR "UNII-75W0WNE5FP") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	1,132
PubMed Search Date: 5/30/2019	"1,2-Dichlorbenzene" OR "1,2-Dichlorbenzol" OR "1,2-Dichlorobenzene" OR "1,3-Dichlorbenzol" OR "1,3-Dichlorobenzene" OR "1,3-diclorobenceno" OR "1,4-Chlorobenzene" OR "1,4-Dichlorbenzol" OR "1,4-Dichlorobenzene" OR "1,4-Dichloro-Benzene" OR "12dichlorobenzene" OR "13Dichlorobenzene" OR "2,4-Dichlorobenzene" OR "2,6-Dichlorobenzene" OR "Amisia-mottenschutz" OR "Caswell No. 301" OR "Caswell No. 632" OR "Chloroben" OR "Cloroben" OR "Di-chloricide" OR "Dichlorobenzene" OR "Dichlorobenzene" OR "Dichlorobenzene (Mixed isomers)" OR "Dichlorobenzene, p" OR "Dichlorobenzene, p-" OR "Dichlorobenzene, para" OR "Dichlorobenzene, para-" OR "Dichlorocide" OR "Dilantin DB" OR "Dilatin DB" OR "Dilatin DBI" OR "Dowtherm E" OR "Kaydox" OR "m-Dichlorbenzol" OR "m-Dichlorobenzene" OR "m-Dichlorobenzol" OR "metadichlorobenzene" OR "meta-Dichlorobenzene" OR "Mottenschutzmittel Evau P" OR "Mott-Ex" OR "m-Phenylene dichloride" OR "m-Phenylenedichloride" OR "NCI-C54944" OR "NCI-C54955" OR "NSC 36935" OR "NSC 60644" OR "NSC 8754" OR "o/mDichlorobenzene" OR "o/m-Dichlorobenzene" OR "o-Dichlor benzol" OR "o-Dichlorbenzol" OR "o-Dichlorobenzene" OR "o-Dichlorobenzol" OR "Orthodichlorobenzene" OR "ortho-Dichlorobenzene" OR "Orthodichlorobenzol" OR "Para crystals" OR "Paradichlorbenzol" OR "Para-dichloro benzene" OR "Paradichlorobenzene" OR "para-Dichlorobenzene" OR "Paradichlorobenzol" OR "Paradow" OR "Paramoth" OR "Paranuggets" OR "Parazene" OR "p-Chlorophenyl chloride" OR "p-Dichlorbenzene" OR "p-	1,549

Source	Source-Specific Search Strategy	Results
	Dichlorobenzene" OR "p-Dichloro-Benzene" OR "p-Dichlorobenzol" OR "Persia-Perazol" OR "Rotamott" OR "Santochlor" OR "Special termite fluid" OR "Termitkil" OR "UN 1591" OR "UNII-6PJ93I88XL" OR "UNII-75W0WNE5FP"	
Science Direct Search Date: 5/6/2019	1. "1,2-Dichlorbenzene" OR "1,2-Dichlorbenzol" OR "1,2-Dichlorobenzene" OR "1,3-Dichlorbenzol" OR "1,3-Dichlorobenzene" OR "1,3-diclorobenceno" OR "1,4-Chlorobenzene" OR "1,4-Dichlorbenzol" OR "1,4-Dichlorobenzene" 2. "1,4-Dichloro-Benzene" OR "12dichlorobenzene" OR "13Dichlorobenzene" OR "2,4-Dichlorobenzene" OR "2,6-Dichlorobenzene" OR "Amisia-mottenschutz" OR "Caswell No. 301" OR "Caswell No. 632" OR "Chloroben" 3. "Cloroben" OR "Di-chloricide" OR "Dichlorobenzene" OR "Dichlorobenzene" OR "Dichlorobenzene (Mixed isomers)" OR "Dichlorobenzene, p" OR "Dichlorobenzene, p-" OR "Dichlorobenzene, para" OR "Dichlorobenzene, para-" 4. "Dichlorocide" OR "Dilantin DB" OR "Dilatin DB" OR "Dilatin DBI" OR "Dowtherm E" OR "Kaydox" OR "m-Dichlorbenzol" OR "m-Dichlorobenzene" OR "m-Dichlorobenzol" 5. "metadichlorobenzene" OR "meta-Dichlorobenzene" OR "Mottenschutzmittel Evau P" OR "Mott-Ex" OR "m-Phenylene dichloride" OR "m-Phenylenedichloride" OR "NCI-C54944" OR "NCI-C54955" OR "NSC 36935" 6. "NSC 60644" OR "NSC 8754" OR "o/mDichlorobenzene" OR "o/m-Dichlorobenzene" OR "o-Dichlor benzol" 7. "o-Dichlorbenzol" OR "o-Dichlorobenzene" OR "o-Dichlorobenzol" OR "Orthodichlorobenzene" OR "ortho-Dichlorobenzene" OR "Orthodichlorobenzol" OR "Para crystals" OR "Paradichlorbenzol" OR "Para-dichloro benzene" 8. "Paradichlorobenzene" OR "para-Dichlorobenzene" OR "Paradichlorobenzol" OR "Paradow" OR "Paramoth" OR "Paranuggets" OR "Parazene" OR "p-Chlorophenyl chloride" OR "p-Dichlorbenzene" 9. "p-Dichlorobenzene" OR "p-Dichloro-Benzene" OR "p-Dichlorobenzol" OR "Persia-Perazol" OR "Rotamott" OR "Santochlor" OR "Special termite fluid" OR "Termitkil" OR "UN 1591" 10. "UNII-6PJ93I88XL" OR "UNII-75W0WNE5FP"	1,191
ToxNet Search Date: 5/6/2019	95-50-1 OR 106-46-7 OR 541-73-1 OR 25321-22-6	2,200
WoS Search Date: 5/6/2019	TS=("1,2-Dichlorbenzene" OR "1,2-Dichlorbenzol" OR "1,2-Dichlorobenzene" OR "1,3-Dichlorbenzol" OR "1,3-Dichlorobenzene" OR "1,3-diclorobenceno" OR "1,4-Chlorobenzene" OR "1,4-Dichlorbenzol" OR "1,4-Dichlorobenzene" OR "1,4-Dichloro-Benzene" OR "12dichlorobenzene" OR "13Dichlorobenzene" OR "2,4-Dichlorobenzene" OR "2,6-Dichlorobenzene" OR "Amisia-mottenschutz" OR "Caswell No. 301" OR "Caswell No. 632" OR "Chloroben" OR "Cloroben" OR "Di-chloricide" OR "Dichlorobenzene" OR "Dichlorobenzene" OR "Dichlorobenzene (Mixed isomers)" OR "Dichlorobenzene, p" OR "Dichlorobenzene, p-" OR "Dichlorobenzene, para" OR "Dichlorobenzene, para-" OR "Dichlorocide" OR "Dilantin DB" OR "Dilatin DB" OR "Dilatin DBI" OR "Dowtherm E" OR "Kaydox" OR "m-Dichlorbenzol" OR "m-Dichlorobenzene" OR "m-Dichlorobenzol" OR "metadichlorobenzene" OR "meta-Dichlorobenzene" OR "Mottenschutzmittel Evau P" OR "Mott-Ex" OR "m-Phenylene dichloride" OR "m-Phenylenedichloride" OR "NCI-C54944" OR "NCI-C54955" OR "NSC 36935" OR "NSC 60644" OR "NSC 8754" OR "o/mDichlorobenzene" OR "o/m-Dichlorobenzene" OR "o-Dichlor benzol" OR "o-Dichlorbenzol" OR "o-Dichlorobenzene" OR "o-Dichlorobenzol" OR "Orthodichlorobenzene" OR "ortho-Dichlorobenzene" OR "Orthodichlorobenzol" OR "Para crystals" OR "Paradichlorbenzol" OR "Para-dichloro benzene" OR "Paradichlorobenzene" OR "para-Dichlorobenzene" OR "Paradichlorobenzol" OR "Paradow"	3,972

Source	Source-Specific Search Strategy	Results
	OR “Paramoth” OR “Paranuggets” OR “Parazene” OR “p-Chlorophenyl chloride” OR “p-Dichlorbenzene” OR “p-Dichlorobenzene” OR “p-Dichloro-Benzene” OR “p-Dichlorobenzol” OR “Persia-Perazol” OR “Rotamott” OR “Santochlor” OR “Special termite fluid” OR “Termitkil” OR “UN 1591” OR “UNII-6PJ93I88XL” OR “UNII-75W0WNE5FP”)	
Unify[a] Search Date: 5/7/2019	1,2-Dichlorbenzene|1,2-Dichlorbenzol|1,2-Dichlorobenzene|1,3-Dichlorbenzol|1,3-Dichlorobenzene|1,3-diclorobenceno|1,4-Chlorobenzene|1,4-Dichlorbenzol|1,4-Dichlorobenzene|1,4-Dichloro-Benzene|12dichlorobenzene|13Dichlorobenzene|2,4-Dichlorobenzene|2,6-Dichlorobenzene|Amisia-mottenschutz|Caswell No. 301|Caswell No. 632|Chloroben|Cloroben|Di-chloricide|Dichlorobenzene|Dichlorobenzene|Dichlorobenzene (Mixed isomers)|Dichlorobenzene, p|Dichlorobenzene, p-|Dichlorobenzene, para|Dichlorobenzene, para-|Dichlorocide|Dilantin DB|Dilatin DB|Dilatin DBI|Dowtherm E|Kaydox|m-Dichlorbenzol|m-Dichlorobenzene|m-Dichlorobenzol|metadichlorobenzene|meta-Dichlorobenzene|Mottenschutzmittel Evau P|Mott-Ex|m-Phenylene dichloride|m-Phenylenedichloride|NCI-C54944|NCI-C54955|NSC 36935|NSC 60644|NSC 8754|o/mDichlorobenzene|o/m-Dichlorobenzene|o-Dichlor benzol	366
Total	**Represents total across all databases after deduplication**	**4,756**
[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.		

C.1.2 Query Strings for the Peer-Reviewed Literature Database Searches on *p*-Dichlorobenzene

These are the search terms compiled from the Chemical Report for *p*-dichlorobenzene used in the initial search strategies for each of the databases listed below:

“1, 4-Dichlorobenzene” OR “1,4-Chlorobenzene” OR “1,4-Dichlorbenzol” OR “1,4-Dichlorobenzene” OR “1,4-Dichloro-Benzene” OR “Benzene, 1,4-dichloro-“ OR “BENZENE, P-DICHLORO” OR “Benzene, p-dichloro-“ OR “Caswell No. 632” OR “DICHLORICIDE” OR “Di-chloricide” OR “Dichlorobenzene, p” OR “Dichlorobenzene, p-“ OR “Dichlorobenzene, para” OR “Dichlorobenzene, para-“ OR “Dichlorocide” OR “Di-Choricide” OR “Evola” OR “Globol” OR “Kaydox” OR “NCI-C54955” OR “NSC 36935” OR “Para crystals” OR “Paracide” OR “Paradichlorbenzol” OR “Para-dichloro benzene” OR “Paradichlorobenzene” OR “para-Dichlorobenzene” OR “Paradichlorobenzol” OR “Paradow” OR “Paramoth” OR “Paranuggets” OR “Parazene” OR “p-Chlorophenyl chloride” OR “PDCB” OR “P-DCB” OR “p-Dichlorbenzene” OR “p-Dichlorobenzene” OR “p-Dichloro-Benzene” OR “p-Dichlorobenzol” OR “Persia-Perazol” OR “Santochlor”

Table_Apx C-2. Peer-Reviewed Literature Search Strategy for *p*-Dichlorobenzene

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 4/23/2019	1. 1, 4-Dichlorobenzene; 1,4-Chlorobenzene; 1,4-Dichlorbenzol; 1,4-Dichlorobenzene; 1,4-Dichloro-Benzene; Benzene, 1,4-dichloro-; BENZENE, P-DICHLORO; Benzene, p-dichloro-; Caswell No. 632; DICHLORICIDE 2. Di-chloricide; Dichlorobenzene, p; Dichlorobenzene, p-; Dichlorobenzene, para; Dichlorobenzene, para-; Dichlorocide; Di-Choricide; Evola; Globol; Kaydox	591

Source	Source-Specific Search Strategy	Results
	3. NCI-C54955; NSC 36935; Para crystals; Paracide; Paradichlorbenzol; Para-dichloro benzene; Paradichlorobenzene; para-Dichlorobenzene; Paradichlorobenzol; Paradow 4. Paramoth; Paranuggets; Parazene; p-Chlorophenyl chloride; PDCB; P-DCB; p-Dichlorbenzene; p-Dichlorobenzene; p-Dichloro-Benzene; p-Dichlorobenzol 5. Persia-Perazol; Santochlor	
Current Contents Search Date: 4/23/2019	TS=("1, 4-Dichlorobenzene" OR "1,4-Chlorobenzene" OR "1,4-Dichlorbenzol" OR "1,4-Dichlorobenzene" OR "1,4-Dichloro-Benzene" OR "Benzene, 1,4-dichloro-" OR "BENZENE, P-DICHLORO" OR "Benzene, p-dichloro-" OR "Caswell No. 632" OR "DICHLORICIDE" OR "Di-chloricide" OR "Dichlorobenzene, p" OR "Dichlorobenzene, p-" OR "Dichlorobenzene, para" OR "Dichlorobenzene, para-" OR "Dichlorocide" OR "Di-Choricide" OR "Evola" OR "Globol" OR "Kaydox" OR "NCI-C54955" OR "NSC 36935" OR "Para crystals" OR "Paracide" OR "Paradichlorbenzol" OR "Para-dichloro benzene" OR "Paradichlorobenzene" OR "para-Dichlorobenzene" OR "Paradichlorobenzol" OR "Paradow" OR "Paramoth" OR "Paranuggets" OR "Parazene" OR "p-Chlorophenyl chloride" OR "PDCB" OR "P-DCB" OR "p-Dichlorbenzene" OR "p-Dichlorobenzene" OR "p-Dichloro-Benzene" OR "p-Dichlorobenzol" OR "Persia-Perazol" OR "Santochlor")	362
ProQuest Dissertations & Theses Search Date: 4/23/2019	ALL("1, 4-Dichlorobenzene" OR "1,4-Chlorobenzene" OR "1,4-Dichlorbenzol" OR "1,4-Dichlorobenzene" OR "1,4-Dichloro-Benzene" OR "Benzene, 1,4-dichloro-" OR "BENZENE, P-DICHLORO" OR "Benzene, p-dichloro-" OR "Caswell No. 632" OR "DICHLORICIDE" OR "Di-chloricide" OR "Dichlorobenzene, p" OR "Dichlorobenzene, p-" OR "Dichlorobenzene, para" OR "Dichlorobenzene, para-" OR "Dichlorocide" OR "Di-Choricide" OR "Evola" OR "Globol" OR "Kaydox" OR "NCI-C54955" OR "NSC 36935" OR "Para crystals" OR "Paracide" OR "Paradichlorbenzol" OR "Para-dichloro benzene" OR "Paradichlorobenzene" OR "para-Dichlorobenzene" OR "Paradichlorobenzol" OR "Paradow" OR "Paramoth" OR "Paranuggets" OR "Parazene" OR "p-Chlorophenyl chloride" OR "PDCB" OR "P-DCB" OR "p-Dichlorbenzene" OR "p-Dichlorobenzene" OR "p-Dichloro-Benzene" OR "p-Dichlorobenzol" OR "Persia-Perazol" OR "Santochlor") AND LA(ENG)	11
ProQuest Agricultural & Scientific Database Search Date: 4/23/2019	ALL("1, 4-Dichlorobenzene" OR "1,4-Chlorobenzene" OR "1,4-Dichlorbenzol" OR "1,4-Dichlorobenzene" OR "1,4-Dichloro-Benzene" OR "Benzene, 1,4-dichloro-" OR "BENZENE, P-DICHLORO" OR "Benzene, p-dichloro-" OR "Caswell No. 632" OR "DICHLORICIDE" OR "Di-chloricide" OR "Dichlorobenzene, p" OR "Dichlorobenzene, p-" OR "Dichlorobenzene, para" OR "Dichlorobenzene, para-" OR "Dichlorocide" OR "Di-Choricide" OR "Evola" OR "Globol" OR "Kaydox" OR "NCI-C54955" OR "NSC 36935" OR "Para crystals" OR "Paracide" OR "Paradichlorbenzol" OR "Para-dichloro benzene" OR "Paradichlorobenzene" OR "para-Dichlorobenzene" OR "Paradichlorobenzol" OR "Paradow" OR "Paramoth" OR "Paranuggets" OR "Parazene" OR "p-Chlorophenyl chloride" OR "PDCB" OR "P-DCB" OR "p-Dichlorbenzene" OR "p-Dichlorobenzene" OR "p-Dichloro-Benzene" OR "p-Dichlorobenzol" OR "Persia-Perazol" OR "Santochlor") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	1,415
PubMed Search Date: 5/30/2019	"1, 4-Dichlorobenzene" OR "1,4-Chlorobenzene" OR "1,4-Dichlorbenzol" OR "1,4-Dichlorobenzene" OR "1,4-Dichloro-Benzene" OR "Benzene, 1,4-dichloro-" OR "BENZENE, P-DICHLORO" OR "Benzene, p-dichloro-" OR "Caswell No. 632" OR "DICHLORICIDE" OR "Di-chloricide" OR "Dichlorobenzene, p" OR "Dichlorobenzene, p-" OR "Dichlorobenzene, para" OR "Dichlorobenzene, para-" OR "Dichlorocide" OR "Di-Choricide" OR "Evola" OR "Globol" OR "Kaydox" OR "NCI-C54955" OR "NSC 36935" OR "Para crystals" OR "Paracide" OR "Paradichlorbenzol" OR "Para-dichloro benzene" OR "Paradichlorobenzene" OR "para-Dichlorobenzene" OR "Paradichlorobenzol" OR "Paradow" OR "Paramoth" OR "Paranuggets"	1,172

Source	Source-Specific Search Strategy	Results
	OR “Parazene” OR “p-Chlorophenyl chloride” OR “PDCB” OR “P-DCB” OR “p-Dichlorbenzene” OR “p-Dichlorobenzene” OR “p-Dichloro-Benzene” OR “p-Dichlorobenzol” OR “Persia-Perazol” OR “Santochlor”	
Science Direct Search Date: 4/23/2019	1. “1, 4-Dichlorobenzene” OR “1,4-Chlorobenzene” OR “1,4-Dichlorbenzol” OR “1,4-Dichlorobenzene” OR “1,4-Dichloro-Benzene” OR “Benzene, 1,4-dichloro-“ OR “BENZENE, P-DICHLORO” OR “Benzene, p-dichloro-“ OR “Caswell No. 632” 2. “DICHLORICIDE” OR “Di-chloricide” OR “Dichlorobenzene, p” OR “Dichlorobenzene, p-“ OR “Dichlorobenzene, para” OR “Dichlorobenzene, para-“ OR “Dichlorocide” OR “Di-Choricide” OR “Evola” 3. “Globol” OR “Kaydox” OR “NCI-C54955” OR “NSC 36935” OR “Para crystals” OR “Paracide” OR “Paradichlorbenzol” OR “Para-dichloro benzene” OR “Paradichlorobenzene” 4. “para-Dichlorobenzene” OR “Paradichlorobenzol” OR “Paradow” OR “Paramoth” OR “Paranuggets” OR “Parazene” OR “p-Chlorophenyl chloride” OR “PDCB” OR “P-DCB” 5. “p-Dichlorbenzene” OR “p-Dichlorobenzene” OR “p-Dichloro-Benzene” OR “p-Dichlorobenzol” OR “Persia-Perazol” OR “Santochlor”	478
ToxNet Search Date: 4/23/2019	106-46-7	1,315
WoS Search Date: 9/13/2019	TS=(“1, 4-Dichlorobenzene” OR “1,4-Chlorobenzene” OR “1,4-Dichlorbenzol” OR “1,4-Dichlorobenzene” OR “1,4-Dichloro-Benzene” OR “Benzene, 1,4-dichloro-“ OR “BENZENE, P-DICHLORO” OR “Benzene, p-dichloro-“ OR “Caswell No. 632” OR “DICHLORICIDE” OR “Di-chloricide” OR “Dichlorobenzene, p” OR “Dichlorobenzene, p-“ OR “Dichlorobenzene, para” OR “Dichlorobenzene, para-“ OR “Dichlorocide” OR “Di-Choricide” OR “Evola” OR “Globol” OR “Kaydox” OR “NCI-C54955” OR “NSC 36935” OR “Para crystals” OR “Paracide” OR “Paradichlorbenzol” OR “Para-dichloro benzene” OR “Paradichlorobenzene” OR “para-Dichlorobenzene” OR “Paradichlorobenzol” OR “Paradow” OR “Paramoth” OR “Paranuggets” OR “Parazene” OR “p-Chlorophenyl chloride” OR “PDCB” OR “P-DCB” OR “p-Dichlorbenzene” OR “p-Dichlorobenzene” OR “p-Dichloro-Benzene” OR “p-Dichlorobenzol” OR “Persia-Perazol” OR “Santochlor”)	1,179
Unify[a] Search Date: 4/24/2019	1, 4-Dichlorobenzene|1,4-Chlorobenzene|1,4-Dichlorbenzol|1,4-Dichlorobenzene|1,4-Dichloro-Benzene|Benzene, 1,4-dichloro-|BENZENE, P-DICHLORO|Benzene, p-dichloro-|Caswell No. 632|DICHLORICIDE|Di-chloricide|Dichlorobenzene, p|Dichlorobenzene, p-|Dichlorobenzene, para|Dichlorobenzene, para-|Dichlorocide|Di-Choricide|Evola|Globol|Kaydox|NCI-C54955|NSC 36935|Para crystals|Paracide|Paradichlorbenzol|Para-dichloro benzene|Paradichlorobenzene|para-Dichlorobenzene|Paradichlorobenzol|Paradow|Paramoth|Paranuggets|Parazene|p-Chlorophenyl chloride|PDCB|P-DCB|p-Dichlorbenzene|p-Dichlorobenzene|p-Dichloro-Benzene|p-Dichlorobenzol|Persia-Perazol|Santochlor	216
Total	**Represents total across all databases after deduplication**	**4,365**

[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.

C.1.3 Query Strings for the Peer-Reviewed Literature Database Searches on 1,2-Dichloroethane

These are the search terms compiled from the Chemical Report for 1,2-dichloroethane used in the initial search strategies for each of the databases listed below:

"1,2-Ethylidene dichloride" OR "1, 2-Dichloroethan" OR "1,2-Bichloroethane" OR "1,2-DCA" OR "1,2-DCE" OR "1,2-Dichlorethane" OR "1,2-dichloroetan" OR "1,2-Dichloroethane" OR "1,2-Dichloroethane" OR "1,2-Ethylene dichloride" OR "1,2-Ethylene dichloride" OR "1,2-Ethylidene dichloride" OR "Aethylendichlorid" OR "alpha, beta-dichloride" OR "alpha, beta-dichloroethane" OR "alpha,beta-dichloroethane" OR "alpha,beta-Dichloroethane" OR "Borer sol" OR "Brocide" OR "Caswell No. 440" OR "CCRIS 225" OR "Destruxol borer-sol" OR "dichlor-1,2-ethane" OR "Dichloremulsion" OR "Dichloretan" OR "Dichlor-Mulsion" OR "Di-chlor-mulsion" OR "Dichloroethane, 1,2-" OR "Dutch liquid" OR "Dutch oil" OR "ENT 1,656" OR "ENT 1656" OR "ENT-1656" OR "Ethane dichloride" OR "Ethylene chloride" OR "Ethylene Dichlorine" OR "Ethylenedichloride" OR "Freon 150" OR "Glycol dichloride" OR "HCC 150" OR "HSDB 65" OR "NCI-C00511" OR "RY Dichloro-1,2-ethane" OR "sym-Dichloroethane" OR "UN 1184"

Table_Apx C-3. Peer-Reviewed Literature Search Strategy for 1,2-Dichloroethane

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 4/26/2019	1. 1,2-Ethylidene dichloride; 1, 2-Dichloroethan; 1,2-Bichloroethane; 1,2-DCA; 1,2-DCE; 1,2-Dichlorethane; 1,2-dichloroetan; 1,2-Dichloroethane; 1,2-Dichloroethane; 1,2-Ethylene dichloride 2. 1,2-Ethylene dichloride; 1,2-Ethylidene dichloride; Aethylendichlorid; alpha, beta-dichloride; alpha, beta-dichloroethane; alpha,beta-dichloroethane; alpha,beta-Dichloroethane; Borer sol; Brocide; Caswell No. 440 3. CCRIS 225; Destruxol borer-sol; dichlor-1,2-ethane; Dichloremulsion; Dichloretan; Dichlor-Mulsion; Di-chlor-mulsion; Dichloroethane, 1,2-; Dutch liquid; Dutch oil 4. ENT 1,656; ENT 1656; ENT-1656; Ethane dichloride; Ethylene chloride; Ethylene Dichlorine; Ethylenedichloride; Freon 150; Glycol dichloride; HCC 150 5. HSDB 65; NCI-C00511; RY Dichloro-1,2-ethane; sym-Dichloroethane; UN 1184	371
Current Contents Search Date: 4/24/2019	TS=("1,2-Ethylidene dichloride" OR "1, 2-Dichloroethan" OR "1,2-Bichloroethane" OR "1,2-DCA" OR "1,2-DCE" OR "1,2-Dichlorethane" OR "1,2-dichloroetan" OR "1,2-Dichloroethane" OR "1,2-Dichloroethane" OR "1,2-Ethylene dichloride" OR "1,2-Ethylene dichloride" OR "1,2-Ethylidene dichloride" OR "Aethylendichlorid" OR "alpha, beta-dichloride" OR "alpha, beta-dichloroethane" OR "alpha,beta-dichloroethane" OR "alpha,beta-Dichloroethane" OR "Borer sol" OR "Brocide" OR "Caswell No. 440" OR "CCRIS 225" OR "Destruxol borer-sol" OR "dichlor-1,2-ethane" OR "Dichloremulsion" OR "Dichloretan" OR "Dichlor-Mulsion" OR "Di-chlor-mulsion" OR "Dichloroethane, 1,2-" OR "Dutch liquid" OR "Dutch oil" OR "ENT 1,656" OR "ENT 1656" OR "ENT-1656" OR "Ethane dichloride" OR "Ethylene chloride" OR "Ethylene Dichlorine" OR "Ethylenedichloride" OR "Freon 150" OR "Glycol dichloride" OR "HCC 150" OR "HSDB 65" OR "NCI-C00511" OR "RY Dichloro-1,2-ethane" OR "sym-Dichloroethane" OR "UN 1184")	3,569
ProQuest Dissertations & Theses Search Date:	ALL("1,2-Ethylidene dichloride" OR "1, 2-Dichloroethan" OR "1,2-Bichloroethane" OR "1,2-DCA" OR "1,2-DCE" OR "1,2-Dichlorethane" OR "1,2-dichloroetan" OR "1,2-Dichloroethane" OR "1,2-Dichloroethane" OR "1,2-Ethylene dichloride" OR "1,2-Ethylene dichloride" OR "1,2-Ethylidene dichloride" OR "Aethylendichlorid" OR "alpha, beta-dichloride" OR "alpha, beta-dichloroethane" OR "alpha,beta-dichloroethane" OR "alpha,beta-Dichloroethane" OR "Borer sol" OR "Brocide" OR "Caswell	47

Source	Source-Specific Search Strategy	Results
4/26/2019	No. 440" OR "CCRIS 225" OR "Destruxol borer-sol" OR "dichlor-1,2-ethane" OR "Dichloremulsion" OR "Dichloretan" OR "Dichlor-Mulsion" OR "Di-chlor-mulsion" OR "Dichloroethane, 1,2-" OR "Dutch liquid" OR "Dutch oil" OR "ENT 1,656" OR "ENT 1656" OR "ENT-1656" OR "Ethane dichloride" OR "Ethylene chloride" OR "Ethylene Dichlorine" OR "Ethylenedichloride" OR "Freon 150" OR "Glycol dichloride" OR "HCC 150" OR "HSDB 65" OR "NCI-C00511" OR "RY Dichloro-1,2-ethane" OR "sym-Dichloroethane" OR "UN 1184") AND LA(ENG)	
ProQuest Agricultural & Scientific Database Search Date: 4/24/2019	ALL("1,2-Ethylidene dichloride" OR "1, 2-Dichloroethan" OR "1,2-Bichloroethane" OR "1,2-DCA" OR "1,2-DCE" OR "1,2-Dichlorethane" OR "1,2-dichloroetan" OR "1,2-Dichloroethane" OR "1,2-Dichloroethane" OR "1,2-Ethylene dichloride" OR "1,2-Ethylene dichloride" OR "1,2-Ethylidene dichloride" OR "Aethylendichlorid" OR "alpha, beta-dichloride" OR "alpha, beta-dichloroethane" OR "alpha,beta-dichloroethane" OR "alpha,beta-Dichloroethane" OR "Borer sol" OR "Brocide" OR "Caswell No. 440" OR "CCRIS 225" OR "Destruxol borer-sol" OR "dichlor-1,2-ethane" OR "Dichloremulsion" OR "Dichloretan" OR "Dichlor-Mulsion" OR "Di-chlor-mulsion" OR "Dichloroethane, 1,2-" OR "Dutch liquid" OR "Dutch oil" OR "ENT 1,656" OR "ENT 1656" OR "ENT-1656" OR "Ethane dichloride" OR "Ethylene chloride" OR "Ethylene Dichlorine" OR "Ethylenedichloride" OR "Freon 150" OR "Glycol dichloride" OR "HCC 150" OR "HSDB 65" OR "NCI-C00511" OR "RY Dichloro-1,2-ethane" OR "sym-Dichloroethane" OR "UN 1184") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	2,247
PubMed Search Date: 7/02/2019	"1,2-Ethylidene dichloride" OR "1, 2-Dichloroethan" OR "1,2-Bichloroethane" OR "1,2-DCA" OR "1,2-DCE" OR "1,2-Dichlorethane" OR "1,2-dichloroetan" OR "1,2-Dichloroethane" OR "1,2-Dichloroethane" OR "1,2-Ethylene dichloride" OR "1,2-Ethylene dichloride" OR "1,2-Ethylidene dichloride" OR "Aethylendichlorid" OR "alpha, beta-dichloride" OR "alpha, beta-dichloroethane" OR "alpha,beta-dichloroethane" OR "alpha,beta-Dichloroethane" OR "Borer sol" OR "Brocide" OR "Caswell No. 440" OR "CCRIS 225" OR "Destruxol borer-sol" OR "dichlor-1,2-ethane" OR "Dichloremulsion" OR "Dichloretan" OR "Dichlor-Mulsion" OR "Di-chlor-mulsion" OR "Dichloroethane, 1,2-" OR "Dutch liquid" OR "Dutch oil" OR "ENT 1,656" OR "ENT 1656" OR "ENT-1656" OR "Ethane dichloride" OR "Ethylene chloride" OR "Ethylene Dichlorine" OR "Ethylenedichloride" OR "Freon 150" OR "Glycol dichloride" OR "HCC 150" OR "HSDB 65" OR "NCI-C00511" OR "RY Dichloro-1,2-ethane" OR "sym-Dichloroethane" OR "UN 1184"	1,360
Science Direct Search Date: 4/24/2019	1. "1,2-Ethylidene dichloride" OR "1, 2-Dichloroethan" OR "1,2-Bichloroethane" OR "1,2-DCA" OR "1,2-DCE" OR "1,2-Dichlorethane" OR "1,2-dichloroetan" OR "1,2-Dichloroethane" OR "1,2-Dichloroethane" 2. "1,2-Ethylene dichloride" OR "1,2-Ethylene dichloride" OR "1,2-Ethylidene dichloride" OR "Aethylendichlorid" OR "alpha, beta-dichloride" OR "alpha, beta-dichloroethane" OR "alpha,beta-dichloroethane" OR "alpha,beta-Dichloroethane" OR "Borer sol" 3. "Brocide" OR "Caswell No. 440" OR "CCRIS 225" OR "Destruxol borer-sol" OR "dichlor-1,2-ethane" OR "Dichloremulsion" OR "Dichloretan" OR "Dichlor-Mulsion" OR "Di-chlor-mulsion" 4. "Dichloroethane, 1,2-" OR "Dutch liquid" OR "Dutch oil" OR "ENT 1,656" OR "ENT 1656" OR "ENT-1656" OR "Ethane dichloride" OR "Ethylene chloride" OR "Ethylene Dichlorine" 5. "Ethylenedichloride" OR "Freon 150" OR "Glycol dichloride" OR "HCC 150" OR "HSDB 65" OR "NCI-C00511" OR "RY Dichloro-1,2-ethane" OR "sym-Dichloroethane" OR "UN 1184"	1,989
ToxNet Search Date:	1. 107-06-2 OR 52399-93-6	1,841

Source	Source-Specific Search Strategy	Results
4/24/2019	2. ((“ethylene dichloride” OR “1 2 dichloroethane” OR “glycol dichloride” OR “ethylene chloride” OR “172itamol172dichloride dutch “ OR “ethane dichloride” OR “dutch oil” OR “dutch liquid” OR dichloremulsion OR “destruxol borer sol” OR brocide OR “borer sol” OR “aethylenchlorid german “ OR “1 2 ethylene dichloride” OR “1 2 dicloroetano 172itamol “ OR “1 2 dichlorethane” OR “1 2 dichlor aethan german “ OR “1 2 dichloorethaan dutch “ OR 107-06-2 [rn]) OR 52399-93-6 [rn]) AND 1900:2018 [yr] AND (eng [la]) AND (BIOSIS [org] OR NTIS [org] OR PESTAB [org] OR PubMed [org] OR TSCATS [org])	
WoS Search Date: 9/10/2019	TS=(“1,2-Ethylidene dichloride” OR “1, 2-Dichloroethan” OR “1,2-Bichloroethane” OR “1,2-DCA” OR “1,2-DCE” OR “1,2-Dichlorethane” OR “1,2-dichloroetan” OR “1,2-Dichloroethane” OR “1,2-Dichloroethane” OR “1,2-Ethylene dichloride” OR “1,2-Ethylene dichloride” OR “1,2-Ethylidene dichloride” OR “Aethylendichlorid” OR “alpha, beta-dichloride” OR “alpha, beta-dichloroethane” OR “alpha,beta-dichloroethane” OR “alpha,beta-Dichloroethane” OR “Borer sol” OR “Brocide” OR “Caswell No. 440” OR “CCRIS 225” OR “Destruxol borer-sol” OR “dichlor-1,2-ethane” OR “Dichloremulsion” OR “Dichloretan” OR “Dichlor-Mulsion” OR “Di-chlor-mulsion” OR “Dichloroethane, 1,2-“ OR “Dutch liquid” OR “Dutch oil” OR “ENT 1,656” OR “ENT 1656” OR “ENT-1656” OR “Ethane dichloride” OR “Ethylene chloride” OR “Ethylene Dichlorine” OR “Ethylenedichloride” OR “Freon 150” OR “Glycol dichloride” OR “HCC 150” OR “HSDB 65” OR “NCI-C00511” OR “RY Dichloro-1,2-ethane” OR “sym-Dichloroethane” OR “UN 1184”)	5,112
Unify[a] Search Date: 4/24/2019	1,2-Ethylidene dichloride|1, 2-Dichloroethan|1,2-Bichloroethane|1,2-DCA|1,2-DCE|1,2-Dichlorethane|1,2-dichloroetan|1,2-Dichloroethane|1,2-Dichloroethane|1,2-Ethylene dichloride|1,2-Ethylene dichloride|1,2-Ethylidene dichloride|Aethylendichlorid|alpha, beta-dichloride|alpha, beta-dichloroethane|alpha,beta-dichloroethane|alpha,beta-Dichloroethane|Borer sol|Brocide|Caswell No. 440|CCRIS 225|Destruxol borer-sol|dichlor-1,2-ethane|Dichloremulsion|Dichloretan|Dichlor-Mulsion|Di-chlor-mulsion|Dichloroethane, 1,2-|Dutch liquid|Dutch oil|ENT 1,656|ENT 1656|ENT-1656|Ethane dichloride|Ethylene chloride|Ethylene Dichlorine|Ethylenedichloride|Freon 150|Glycol dichloride|HCC 150|HSDB 65|NCI-C00511|RY Dichloro-1,2-ethane|sym-Dichloroethane|UN 1184	184
Total	**Represents total across all databases after deduplication**	**7,952**

[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.

C.1.4 Query Strings for the Peer-Reviewed Literature Database Searches on *Trans*-1,2-Dichloroethylene

These are the search terms compiled from the Chemical Report for *trans*-1,2-dichloroethylene used in the initial search strategies for each of the databases listed below:

“(1E)-1,2-Dichloroethene” OR “(1Z)-1,2-Dichloroethene” OR “I-1,2-Dichloroethene” OR “I-1,2-Dichloroethylene” OR “(Z)-1,2-Dichloroethene” OR “(Z)-1,2-Dichloroethylene” OR “1,2-cis-Dichloroethene” OR “1,2-cis-Dichloroethylene” OR “1,2-DICHLORAETHEN” OR “1,2-Dichlor-aethen” OR “1,2-Dichlorethylen” OR “1,2-Dichloroethene” OR “1,2-Dichloroethylene” OR “1,2-trans-Dichloroethene” OR “1,2-trans-Dichloroethylene” OR “Acetalyne dichloride” OR “Acetylene dichloride” OR “Acetylene dichloride, cis-“ OR “BRN 1420761” OR “cis-1,2-Dichlorethylene” OR “cis-1,2-Dichloroethene” OR “cis-1,2-Dichloroethylene” OR “cis-

Dichlorethylen" OR "cis-Dichloroethene" OR "cis-Dichloroethylene" OR "Dichloro-1,2-ethylene" OR "EINECS 205-860-2" OR "HCC 1130c" OR "HCC 1130t" OR "NCI-C56031" OR "NSC 60512" OR "NSC 6149" OR "R 1130t" OR "sym-Dichloroethylene" OR "trans-1,2-Dichloroethene" OR "trans-1,2-Dichloroethene radical cation" OR "trans-1,2-Dichloroethylene" OR "trans-Acetylene dichloride" OR "trans-Dichloroethene" OR "trans-dichloroethylene" OR "trans-Dichloroethylene radical cation" OR "UNII-FYO9G15JYD" OR "UNII-XU9RUA6YUT" OR "Vertrel CCA"

Table_Apx C-4. Peer-Reviewed Literature Search Strategy for *Trans*-1,2-Dichloroethylene

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 5/9/2019	1. (1E)-1,2-Dichloroethene; (1Z)-1,2-Dichloroethene; I-1,2-Dichloroethene; I-1,2-Dichloroethylene; (Z)-1,2-Dichloroethene; (Z); 1,2-Dichloroethylene; 1,2-cis-Dichloroethene; 1,2-cis-Dichloroethylene; 1,2-DICHLORAETHEN; 1,2-Dichlor-aethen 2. 1,2-Dichlorethylen; 1,2-Dichloroethene; 1,2-Dichloroethylene; 1,2-trans-Dichloroethene; 1,2-trans-Dichloroethylene; Acetalyne dichloride; Acetylene dichloride; Acetylene dichloride, cis-; BRN 1420761; cis-1,2-Dichlorethylene 3. cis-1,2-Dichloroethene; cis-1,2-Dichloroethylene; cis-Dichlorethylen; cis-Dichloroethene; cis-Dichloroethylene; Dichloro-1,2-ethylene; EINECS 205-860-2; HCC 1130c; HCC 1130t; NCI-C56031 4. NSC 60512; NSC 6149; R 1130t; sym-Dichloroethylene; trans-1,2-Dichloroethene; trans-1,2-Dichloroethene radical cation; trans-1,2-Dichloroethylene; trans-Acetylene dichloride; trans-Dichloroethene; trans-dichloroethylene 5. trans-Dichloroethylene radical cation; UNII-FYO9G15JYD; UNII-XU9RUA6YUT; Vertrel CCA	351
Current Contents Search Date: 5/9/2019	TS=("(1E)-1,2-Dichloroethene" OR "(1Z)-1,2-Dichloroethene" OR "I-1,2-Dichloroethene" OR "I-1,2-Dichloroethylene" OR "(Z)-1,2-Dichloroethene" OR "(Z)-1,2-Dichloroethylene" OR "1,2-cis-Dichloroethene" OR "1,2-cis-Dichloroethylene" OR "1,2-DICHLORAETHEN" OR "1,2-Dichlor-aethen" OR "1,2-Dichlorethylen" OR "1,2-Dichloroethene" OR "1,2-Dichloroethylene" OR "1,2-trans-Dichloroethene" OR "1,2-trans-Dichloroethylene" OR "Acetalyne dichloride" OR "Acetylene dichloride" OR "Acetylene dichloride, cis-" OR "BRN 1420761" OR "cis-1,2-Dichlorethylene" OR "cis-1,2-Dichloroethene" OR "cis-1,2-Dichloroethylene" OR "cis-Dichlorethylen" OR "cis-Dichloroethene" OR "cis-Dichloroethylene" OR "Dichloro-1,2-ethylene" OR "EINECS 205-860-2" OR "HCC 1130c" OR "HCC 1130t" OR "NCI-C56031" OR "NSC 60512" OR "NSC 6149" OR "R 1130t" OR "sym-Dichloroethylene" OR "trans-1,2-Dichloroethene" OR "trans-1,2-Dichloroethene radical cation" OR "trans-1,2-Dichloroethylene" OR "trans-Acetylene dichloride" OR "trans-Dichloroethene" OR "trans-dichloroethylene" OR "trans-Dichloroethylene radical cation" OR "UNII-FYO9G15JYD" OR "UNII-XU9RUA6YUT" OR "Vertrel CCA")	838
ProQuest Dissertations & Theses Search Date: 5/9/2019	ALL("(1E)-1,2-Dichloroethene" OR "(1Z)-1,2-Dichloroethene" OR "I-1,2-Dichloroethene" OR "I-1,2-Dichloroethylene" OR "(Z)-1,2-Dichloroethene" OR "(Z)-1,2-Dichloroethylene" OR "1,2-cis-Dichloroethene" OR "1,2-cis-Dichloroethylene" OR "1,2-DICHLORAETHEN" OR "1,2-Dichlor-aethen" OR "1,2-Dichlorethylen" OR "1,2-Dichloroethene" OR "1,2-Dichloroethylene" OR "1,2-trans-Dichloroethene" OR "1,2-trans-Dichloroethylene" OR "Acetalyne dichloride" OR "Acetylene dichloride" OR "Acetylene dichloride, cis-" OR "BRN 1420761" OR "cis-1,2-Dichlorethylene" OR "cis-1,2-Dichloroethene" OR "cis-1,2-Dichloroethylene" OR "cis-Dichlorethylen" OR "cis-Dichloroethene" OR "cis-Dichloroethylene" OR "Dichloro-1,2-ethylene" OR "EINECS 205-860-2" OR "HCC 1130c" OR "HCC 1130t" OR "NCI-C56031" OR "NSC 60512" OR "NSC 6149" OR "R 1130t" OR "sym-Dichloroethylene" OR "trans-1,2-Dichloroethene" OR "trans-1,2-Dichloroethene radical cation" OR "trans-1,2-Dichloroethylene" OR "trans-Acetylene dichloride" OR "trans-Dichloroethene" OR "trans-dichloroethylene" OR "trans-Dichloroethylene radical cation" OR "UNII-FYO9G15JYD" OR "UNII-XU9RUA6YUT" OR "Vertrel CCA") AND LA(ENG)	0

Source	Source-Specific Search Strategy	Results
ProQuest Agricultural & Scientific Database Search Date: 5/9/2019	ALL("(1E)-1,2-Dichloroethene" OR "(1Z)-1,2-Dichloroethene" OR "I-1,2-Dichloroethene" OR "I-1,2-Dichloroethylene" OR "(Z)-1,2-Dichloroethene" OR "(Z)-1,2-Dichloroethylene" OR "1,2-cis-Dichloroethene" OR "1,2-cis-Dichloroethylene" OR "1,2-DICHLORAETHEN" OR "1,2-Dichlor-aethen" OR "1,2-Dichlorethylen" OR "1,2-Dichloroethene" OR "1,2-Dichloroethylene" OR "1,2-trans-Dichloroethene" OR "1,2-trans-Dichloroethylene" OR "Acetalyne dichloride" OR "Acetylene dichloride" OR "Acetylene dichloride, cis-" OR "BRN 1420761" OR "cis-1,2-Dichlorethylene" OR "cis-1,2-Dichloroethene" OR "cis-1,2-Dichloroethylene" OR "cis-Dichlorethylen" OR "cis-Dichloroethene" OR "cis-Dichloroethylene" OR "Dichloro-1,2-ethylene" OR "EINECS 205-860-2" OR "HCC 1130c" OR "HCC 1130t" OR "NCI-C56031" OR "NSC 60512" OR "NSC 6149" OR "R 1130t" OR "sym-Dichloroethylene" OR "trans-1,2-Dichloroethene" OR "trans-1,2-Dichloroethene radical cation" OR "trans-1,2-Dichloroethylene" OR "trans-Acetylene dichloride" OR "trans-Dichloroethene" OR "trans-dichloroethylene" OR "trans-Dichloroethylene radical cation" OR "UNII-FYO9G15JYD" OR "UNII-XU9RUA6YUT" OR "Vertrel CCA") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	1,913
PubMed Search Date: 7/3/2019	"(1E)-1,2-Dichloroethene" OR "(1Z)-1,2-Dichloroethene" OR "I-1,2-Dichloroethene" OR "I-1,2-Dichloroethylene" OR "(Z)-1,2-Dichloroethene" OR "(Z)-1,2-Dichloroethylene" OR "1,2-cis-Dichloroethene" OR "1,2-cis-Dichloroethylene" OR "1,2-DICHLORAETHEN" OR "1,2-Dichlor-aethen" OR "1,2-Dichlorethylen" OR "1,2-Dichloroethene" OR "1,2-Dichloroethylene" OR "1,2-trans-Dichloroethene" OR "1,2-trans-Dichloroethylene" OR "Acetalyne dichloride" OR "Acetylene dichloride" OR "Acetylene dichloride, cis-" OR "BRN 1420761" OR "cis-1,2-Dichlorethylene" OR "cis-1,2-Dichloroethene" OR "cis-1,2-Dichloroethylene" OR "cis-Dichlorethylen" OR "cis-Dichloroethene" OR "cis-Dichloroethylene" OR "Dichloro-1,2-ethylene" OR "EINECS 205-860-2" OR "HCC 1130c" OR "HCC 1130t" OR "NCI-C56031" OR "NSC 60512" OR "NSC 6149" OR "R 1130t" OR "sym-Dichloroethylene" OR "trans-1,2-Dichloroethene" OR "trans-1,2-Dichloroethene radical cation" OR "trans-1,2-Dichloroethylene" OR "trans-Acetylene dichloride" OR "trans-Dichloroethene" OR "trans-dichloroethylene" OR "trans-Dichloroethylene radical cation" OR "UNII-FYO9G15JYD" OR "UNII-XU9RUA6YUT" OR "Vertrel CCA"	597
Science Direct Search Date: 5/9/2019	1. "(1E)-1,2-Dichloroethene" OR "(1Z)-1,2-Dichloroethene" OR "I-1,2-Dichloroethene" OR "I-1,2-Dichloroethylene" OR "(Z)-1,2-Dichloroethene" OR "(Z)-1,2-Dichloroethylene" OR "1,2-cis-Dichloroethene" OR "1,2-cis-Dichloroethylene" OR "1,2-DICHLORAETHEN" 2. "1,2-Dichlor-aethen" OR "1,2-Dichlorethylen" OR "1,2-Dichloroethene" OR "1,2-Dichloroethylene" OR "1,2-trans-Dichloroethene" OR "1,2-trans-Dichloroethylene" OR "Acetalyne dichloride" OR "Acetylene dichloride" OR "Acetylene dichloride, cis-" 3. "BRN 1420761" OR "cis-1,2-Dichlorethylene" OR "cis-1,2-Dichloroethene" OR "cis-1,2-Dichloroethylene" OR "cis-Dichlorethylen" OR "cis-Dichloroethene" OR "cis-Dichloroethylene" OR "Dichloro-1,2-ethylene" OR "EINECS 205-860-2" 4. "HCC 1130c" OR "HCC 1130t" OR "NCI-C56031" OR "NSC 60512" OR "NSC 6149" OR "R 1130t" OR "sym-Dichloroethylene" OR "trans-1,2-Dichloroethene" OR "trans-1,2-Dichloroethene radical cation" 5. "trans-1,2-Dichloroethylene" OR "trans-Acetylene dichloride" OR "trans-Dichloroethene" OR "trans-dichloroethylene" OR "trans-Dichloroethylene radical cation" OR "UNII-FYO9G15JYD" OR "UNII-XU9RUA6YUT" OR "Vertrel CCA"	578
ToxNet Search Date: 5/9/2019	1. 156-60-5 OR 73245-64-4 OR 156-59-2 OR 540-59-0 OR 43695-79-0 2. 1438395-68-6	979

Source	Source-Specific Search Strategy	Results
WoS Search Date: 9/12/2019	TS=("(1E)-1,2-Dichloroethene" OR "(1Z)-1,2-Dichloroethene" OR "I-1,2-Dichloroethene" OR "I-1,2-Dichloroethylene" OR "(Z)-1,2-Dichloroethene" OR "(Z)-1,2-Dichloroethylene" OR "1,2-cis-Dichloroethene" OR "1,2-cis-Dichloroethylene" OR "1,2-DICHLORAETHEN" OR "1,2-Dichlor-aethen" OR "1,2-Dichlorethylen" OR "1,2-Dichloroethene" OR "1,2-Dichloroethylene" OR "1,2-trans-Dichloroethene" OR "1,2-trans-Dichloroethylene" OR "Acetalyne dichloride" OR "Acetylene dichloride" OR "Acetylene dichloride, cis-" OR "BRN 1420761" OR "cis-1,2-Dichlorethylene" OR "cis-1,2-Dichloroethene" OR "cis-1,2-Dichloroethylene" OR "cis-Dichlorethylen" OR "cis-Dichloroethene" OR "cis-Dichloroethylene" OR "Dichloro-1,2-ethylene" OR "EINECS 205-860-2" OR "HCC 1130c" OR "HCC 1130t" OR "NCI-C56031" OR "NSC 60512" OR "NSC 6149" OR "R 1130t" OR "sym-Dichloroethylene" OR "trans-1,2-Dichloroethene" OR "trans-1,2-Dichloroethene radical cation" OR "trans-1,2-Dichloroethylene" OR "trans-Acetylene dichloride" OR "trans-Dichloroethene" OR "trans-dichloroethylene" OR "trans-Dichloroethylene radical cation" OR "UNII-FYO9G15JYD" OR "UNII-XU9RUA6YUT" OR "Vertrel CCA")	1,250
Unify[a] Search Date: 5/9/2019	(1E)-1,2-Dichloroethene|(1Z)-1,2-Dichloroethene|I-1,2-Dichloroethene|I-1,2-Dichloroethylene|(Z)-1,2-Dichloroethene|(Z)-1,2-Dichloroethylene|1,2-cis-Dichloroethene|1,2-cis-Dichloroethylene|1,2-DICHLORAETHEN|1,2-Dichlor-aethen|1,2-Dichlorethylen|1,2-Dichloroethene|1,2-Dichloroethylene|1,2-trans-Dichloroethene|1,2-trans-Dichloroethylene|Acetalyne dichloride|Acetylene dichloride|Acetylene dichloride, cis-|BRN 1420761|cis-1,2-Dichlorethylene|cis-1,2-Dichloroethene|cis-1,2-Dichloroethylene|cis-Dichlorethylen|cis-Dichloroethene|cis-Dichloroethylene|Dichloro-1,2-ethylene|EINECS 205-860-2|HCC 1130c|HCC 1130t|NCI-C56031|NSC 60512|NSC 6149|R 1130t|sym-Dichloroethylene|trans-1,2-Dichloroethene|trans-1,2-Dichloroethene radical cation|trans-1,2-Dichloroethylene|trans-Acetylene dichloride|trans-Dichloroethene|trans-dichloroethylene|trans-Dichloroethylene radical cation|UNII-FYO9G15JYD|UNII-XU9RUA6YUT|Vertrel CCA	35
Total	**Represents total across all databases after deduplication**	**2,293**

[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.

C.1.5 Query Strings for the Peer-Reviewed Literature Database Searches on 1,1,2-Trichloroethane

These are the search terms compiled from the Chemical Report for 1,1,2-trichloroethane used in the initial search strategies for each of the databases listed below:

"1,1,1-Trichloraethan" OR "1,1,1-Trichlorethan" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichloroethane" OR "1,1,2-TRICHLORAETHAN" OR "1,1,2-Trichlorethan" OR "1,1,2-trichlorethane" OR "1,1,2-Trichloroethane" OR "1,2,2-Trichloroethane" OR "111trichloroethane" OR "112trichloroethane" OR "Aerothene TT" OR "alpha-Trichloroethane" OR "Baltana" OR "beta-trichloroethane" OR "Caswell No. 875" OR "Caswell No. 875A" OR "Chlorotene" OR "Chlorothene" OR "Chlorothene NU" OR "Chlorothene SM" OR "Chlorothene VG" OR "Chlorten" OR "Cleanite" OR "Dowclene LS" OR "Ethana NU" OR "Genklene LB" OR "HCC 140a" OR "ICI-CF 2" OR "Inhibisol" OR "Methyl chloroform" OR "Methylchloroform" OR "Methyltrichloromethane" OR "NCI-C04579" OR "NCI-C04626" OR "NSC 405074" OR "NSC 9367" OR "Solvent 111" OR "Tafclean" OR "Three One A" OR "Three One S" OR "trichloro-1,1,1-ethane" OR "Trichloroethane" OR "Trichloromethylmethane" OR "Tricloroethane" OR "UN 2831" OR "UNII-113C650IR1" OR "UNII-28E9ERN9WU" OR "Used" OR "Vinyl trichloride" OR "Vinyltrichloride"

Table_Apx C-5. Peer-Reviewed Literature Search Strategy for 1,1,2-Trichloroethane

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 5/10/2019	1. 1,1,1-Trichloraethan; 1,1,1-Trichlorethan; 1,1,1-Trichlorethane; 1,1,1-Trichlorethane; 1,1,1-Trichloroethane; 1,1,2-TRICHLORAETHAN; 1,1,2-Trichlorethan; 1,1,2-trichlorethane; 1,1,2-Trichloroethane; 1,2,2-Trichloroethane 2. 111trichloroethane; 112trichloroethane; Aerothene TT; alpha-Trichloroethane; Baltana; beta-trichloroethane; Caswell No. 875; Caswell No. 875A; Chlorotenel; Chlorothene 3. Chlorothene NU; Chlorothene SM; Chlorothene VG; Chlorten; Cleanite; Dowclene LS; Ethana NU; Genklene LB; HCC 140a; ICI-CF 2 4. Inhibisol; Methyl chloroform; Methylchloroform; Methyltrichloromethane; NCI-C04579; NCI-C04626; NSC 405074; NSC 9367; Solvent 111; Tafclean 5. Three One A; Three One S; trichloro-1,1,1-ethane; Trichloroethane; Trichloromethylmethane; Tricloroethane; UN 2831; UNII-113C650IR1; UNII-28E9ERN9WU 6. Vinyl trichloride; Vinyltrichloride	509
Current Contents Search Date: 5/09/2019	TS=("1,1,1-Trichloraethan" OR "1,1,1-Trichlorethan" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichloroethane" OR "1,1,2-TRICHLORAETHAN" OR "1,1,2-Trichlorethan" OR "1,1,2-trichlorethane" OR "1,1,2-Trichloroethane" OR "1,2,2-Trichloroethane" OR "111trichloroethane" OR "112trichloroethane" OR "Aerothene TT" OR "alpha-Trichloroethane" OR "Baltana" OR "beta-trichloroethane" OR "Caswell No. 875" OR "Caswell No. 875A" OR "Chlorotene" OR "Chlorothene" OR "Chlorothene NU" OR "Chlorothene SM" OR "Chlorothene VG" OR "Chlorten" OR "Cleanite" OR "Dowclene LS" OR "Ethana NU" OR "Genklene LB" OR "HCC 140a" OR "ICI-CF 2" OR "Inhibisol" OR "Methyl chloroform" OR "Methylchloroform" OR "Methyltrichloromethane" OR "NCI-C04579" OR "NCI-C04626" OR "NSC 405074" OR "NSC 9367" OR "Solvent 111" OR "Tafclean" OR "Three One A" OR "Three One S" OR "trichloro-1,1,1-ethane" OR "Trichloroethane" OR "Trichloromethylmethane" OR "Tricloroethane" OR "UN 2831" OR "UNII-113C650IR1" OR "UNII-28E9ERN9WU" OR "Vinyl trichloride" OR "Vinyltrichloride")	1,576
ProQuest Dissertations & Theses Search Date: 5/10/2019	ALL("1,1,1-Trichloraethan" OR "1,1,1-Trichlorethan" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichloroethane" OR "1,1,2-TRICHLORAETHAN" OR "1,1,2-Trichlorethan" OR "1,1,2-trichlorethane" OR "1,1,2-Trichloroethane" OR "1,2,2-Trichloroethane" OR "111trichloroethane" OR "112trichloroethane" OR "Aerothene TT" OR "alpha-Trichloroethane" OR "Baltana" OR "beta-trichloroethane" OR "Caswell No. 875" OR "Caswell No. 875A" OR "Chlorotene" OR "Chlorothene" OR "Chlorothene NU" OR "Chlorothene SM" OR "Chlorothene VG" OR "Chlorten" OR "Cleanite" OR "Dowclene LS" OR "Ethana NU" OR "Genklene LB" OR "HCC 140a" OR "ICI-CF 2" OR "Inhibisol" OR "Methyl chloroform" OR "Methylchloroform" OR "Methyltrichloromethane" OR "NCI-C04579" OR "NCI-C04626" OR "NSC 405074" OR "NSC 9367" OR "Solvent 111" OR "Tafclean" OR "Three One A" OR "Three One S" OR "trichloro-1,1,1-ethane" OR "Trichloroethane" OR "Trichloromethylmethane" OR "Tricloroethane" OR "UN 2831" OR "UNII-113C650IR1" OR "UNII-28E9ERN9WU" OR "Vinyl trichloride" OR "Vinyltrichloride") AND LA(ENG)	39
ProQuest Agricultural & Scientific Database Search Date:	ALL("1,1,1-Trichloraethan" OR "1,1,1-Trichlorethan" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichloroethane" OR "1,1,2-TRICHLORAETHAN" OR "1,1,2-Trichlorethan" OR "1,1,2-trichlorethane" OR "1,1,2-Trichloroethane" OR "1,2,2-Trichloroethane" OR "111trichloroethane" OR "112trichloroethane" OR "Aerothene TT" OR "alpha-Trichloroethane" OR "Baltana" OR "beta-trichloroethane" OR "Caswell No. 875" OR "Caswell No. 875A" OR "Chlorotene" OR "Chlorothene" OR "Chlorothene NU" OR "Chlorothene SM" OR "Chlorothene VG" OR "Chlorten" OR "Cleanite" OR	3,874

Source	Source-Specific Search Strategy	Results
5/09/2019	"Dowclene LS" OR "Ethana NU" OR "Genklene LB" OR "HCC 140a" OR "ICI-CF 2" OR "Inhibisol" OR "Methyl chloroform" OR "Methylchloroform" OR "Methyltrichloromethane" OR "NCI-C04579" OR "NCI-C04626" OR "NSC 405074" OR "NSC 9367" OR "Solvent 111" OR "Tafclean" OR "Three One A" OR "Three One S" OR "trichloro-1,1,1-ethane" OR "Trichloroethane" OR "Trichloromethylmethane" OR "Tricloroethane" OR "UN 2831" OR "UNII-113C650IR1" OR "UNII-28E9ERN9WU" OR Vinyl trichloride" OR "Vinyltrichloride") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	
PubMed Search Date: 7/02/2019	"1,1,1-Trichloraethan" OR "1,1,1-Trichlorethan" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichloroethane" OR "1,1,2-TRICHLORAETHAN" OR "1,1,2-Trichlorethan" OR "1,1,2-trichlorethane" OR "1,1,2-Trichloroethane" OR "1,2,2-Trichloroethane" OR "111trichloroethane" OR "112trichloroethane" OR "Aerothene TT" OR "alpha-Trichloroethane" OR "Baltana" OR "beta-trichloroethane" OR "Caswell No. 875" OR "Caswell No. 875A" OR "Chlorotene" OR "Chlorothene" OR "Chlorothene NU" OR "Chlorothene SM" OR "Chlorothene VG" OR "Chlorten" OR "Cleanite" OR "Dowclene LS" OR "Ethana NU" OR "Genklene LB" OR "HCC 140a" OR "ICI-CF 2" OR "Inhibisol" OR "Methyl chloroform" OR "Methylchloroform" OR "Methyltrichloromethane" OR "NCI-C04579" OR "NCI-C04626" OR "NSC 405074" OR "NSC 9367" OR "Solvent 111" OR "Tafclean" OR "Three One A" OR "Three One S" OR "trichloro-1,1,1-ethane" OR "Trichloroethane" OR "Trichloromethylmethane" OR "Tricloroethane" OR "UN 2831" OR "UNII-113C650IR1" OR "UNII-28E9ERN9WU" OR "Used" OR "Vinyl trichloride" OR "Vinyltrichloride"	1,489
Science Direct Search Date: 5/09/2019	1. "1,1,1-Trichloraethan" OR "1,1,1-Trichlorethan" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichloroethane" OR "1,1,2-TRICHLORAETHAN" OR "1,1,2-Trichlorethan" OR "1,1,2-trichlorethane" OR "1,1,2-Trichloroethane" 2. "1,2,2-Trichloroethane" OR "111trichloroethane" OR "112trichloroethane" OR "Aerothene TT" OR "alpha-Trichloroethane" OR "Baltana" OR "beta-trichloroethane" OR "Caswell No. 875" OR "Caswell No. 875A" 3. "Chlorotene" OR "Chlorothene" OR "Chlorothene NU" OR "Chlorothene SM" OR "Chlorothene VG" OR "Chlorten" OR "Cleanite" OR "Dowclene LS" OR "Ethana NU" 4. "Genklene LB" OR "HCC 140a" OR "ICI-CF 2" OR "Inhibisol" OR "Methyl chloroform" OR "Methylchloroform" OR "Methyltrichloromethane" OR "NCI-C04579" OR "NCI-C04626" 5. "NSC 405074" OR "NSC 9367" OR "Solvent 111" OR "Tafclean" OR "Three One A" OR "Three One S" OR "trichloro-1,1,1-ethane" OR "Trichloroethane" OR "Trichloromethylmethane" 6. "Tricloroethane" OR "UN 2831" OR "UNII-113C650IR1" OR "UNII-28E9ERN9WU" 7. "Vinyl trichloride" OR "Vinyltrichloride"	2,156
ToxNet Search Date: 5/09/2019	79-00-5 OR 71-55-6 OR 25323-89-1 OR 1299-89-4 OR 74552-83-3	3,635
WoS Search Date: 9/10/2019	TS=("1,1,1-Trichloraethan" OR "1,1,1-Trichlorethan" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichloroethane" OR "1,1,2-TRICHLORAETHAN" OR "1,1,2-Trichlorethan" OR "1,1,2-trichlorethane" OR "1,1,2-Trichloroethane" OR "1,2,2-Trichloroethane" OR "111trichloroethane" OR "112trichloroethane" OR "Aerothene TT" OR "alpha-Trichloroethane" OR "Baltana" OR "beta-trichloroethane" OR "Caswell No. 875" OR "Caswell No. 875A" OR "Chlorotene" OR "Chlorothene" OR "Chlorothene NU" OR "Chlorothene SM" OR "Chlorothene VG" OR "Chlorten" OR "Cleanite" OR	2,809

Source	Source-Specific Search Strategy	Results
	"Dowclene LS" OR "Ethana NU" OR "Genklene LB" OR "HCC 140a" OR "ICI-CF 2" OR "Inhibisol" OR "Methyl chloroform" OR "Methylchloroform" OR "Methyltrichloromethane" OR "NCI-C04579" OR "NCI-C04626" OR "NSC 405074" OR "NSC 9367" OR "Solvent 111" OR "Tafclean" OR "Three One A" OR "Three One S" OR "trichloro-1,1,1-ethane" OR "Trichloroethane" OR "Trichloromethylmethane" OR "Tricloroethane" OR "UN 2831" OR "UNII-113C650IR1" OR "UNII-28E9ERN9WU" OR "Vinyl trichloride" OR "Vinyltrichloride")	
Unify[a] Search Date: 5/09/2019	1,1,1-Trichloraethan|1,1,1-Trichlorethan|1,1,1-Trichlorethane|1,1,1-Trichlorethane|1,1,1-Trichloroethane|1,1,2-TRICHLORAETHAN|1,1,2-Trichlorethan|1,1,2-trichlorethane|1,1,2-Trichloroethane|1,2,2-Trichloroethane|111trichloroethane|112trichloroethane|Aerothene TT|alpha-Trichloroethane|Baltana|beta-trichloroethane|Caswell No. 875|Caswell No. 875A|Chlorotene|Chlorothene|Chlorothene NU|Chlorothene SM|Chlorothene VG|Chlorten|Cleanite|Dowclene LS|Ethana NU|Genklene LB|HCC 140a|ICI-CF 2|Inhibisol|Methyl chloroform|Methylchloroform|Methyltrichloromethane|NCI-C04579|NCI-C04626|NSC 405074|NSC 9367|Solvent 111|Tafclean|Three One A|Three One S|trichloro-1,1,1-ethane|Trichloroethane|Trichloromethylmethane|Tricloroethane|UN 2831|UNII-113C650IR1|UNII-28E9ERN9WU|Used|Vinyl trichloride|Vinyltrichloride	183
Total	**Represents total across all databases after deduplication**	**7,082**
[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.		

C.1.6 Query Strings for the Peer-Reviewed Literature Database Searches on 1,2-Dichloropropane

These are the search terms compiled from the Chemical Report for 1,2-dichloropropane used in the initial search strategies for each of the databases listed below:

"1,1-Dichloropropane" OR "1,2-Dichloropropane" OR "1,3-Dichloropropane" OR "11Dichloropropane" OR "12dichloropropane" OR "13Dichloropropane" OR "2,2-Dichloropropane" OR "22Dichloropropane" OR "alpha,alpha-Dichloropropane" OR "alpha,alpha-Propylene dichloride" OR "alpha,beta-Dichloropropane" OR "alpha,beta-Propylene dichloride" OR "BRN 1718880" OR "BRN 1731152" OR "Caswell No. 324" OR "Dichloro-1,2 propane" OR "Dichlorodimethylmethane" OR "Dicoloropropane" OR "Dimethyldichloromethane" OR "NCI-C55141" OR "NSC 1237" OR "NSC 6204" OR "Propylene chloride" OR "Propylene dichloride" OR "Propylidene chloride" OR "Trimethylene chloride" OR "Trimethylene dichloride" OR "UNII-AJ1HQ2GUCP" OR "UNII-C5V432N6XB" OR "UNII-RRZ023OFWL" OR "UNII-SR71OVZ2OZ"

Table_Apx C-6. Peer-Reviewed Literature Search Strategy for 1,2-Dichloropropane

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 5/17/2019	1. 1,1-Dichloropropane; 1,2-Dichloropropane; 1,3-Dichloropropane; 11Dichloropropane; 12dichloropropane; 13Dichloropropane; 2,2-Dichloropropane; 22Dichloropropane; alpha,alpha-Dichloropropane; alpha,alpha-Propylene dichloride	47

Source	Source-Specific Search Strategy	Results
	2. alpha,beta-Dichloropropane; alpha,beta-Propylene dichloride; BRN 1718880; BRN 1731152; Caswell No. 324; Dichloro-1,2 propane; Dichlorodimethylmethane; Dicoloropropane; Dimethyldichloromethane; NCI-C55141 3. NSC 1237; NSC 6204; Propylene chloride; Propylene dichloride; Propylidene chloride; Trimethylene chloride; Trimethylene dichloride; UNII-AJ1HQ2GUCP; UNII-C5V432N6XB; UNII-RRZ023OFWL 4. UNII-SR71OVZ2OZ	
Current Contents Search Date: 5/16/19	TS=("1,1-Dichloropropane" OR "1,2-Dichloropropane" OR "1,3-Dichloropropane" OR "11Dichloropropane" OR "12dichloropropane" OR "13Dichloropropane" OR "2,2-Dichloropropane" OR "22Dichloropropane" OR "alpha,alpha-Dichloropropane" OR "alpha,alpha-Propylene dichloride" OR "alpha,beta-Dichloropropane" OR "alpha,beta-Propylene dichloride" OR "BRN 1718880" OR "BRN 1731152" OR "Caswell No. 324" OR "Dichloro-1,2 propane" OR "Dichlorodimethylmethane" OR "Dicoloropropane" OR "Dimethyldichloromethane" OR "NCI-C55141" OR "NSC 1237" OR "NSC 6204" OR "Propylene chloride" OR "Propylene dichloride" OR "Propylidene chloride" OR "Trimethylene chloride" OR "Trimethylene dichloride" OR "UNII-AJ1HQ2GUCP" OR "UNII-C5V432N6XB" OR "UNII-RRZ023OFWL" OR "UNII-SR71OVZ2OZ")	242
ProQuest Dissertations & Theses Search Date: 5/17/2019	ALL("1,1-Dichloropropane" OR "1,2-Dichloropropane" OR "1,3-Dichloropropane" OR "11Dichloropropane" OR "12dichloropropane" OR "13Dichloropropane" OR "2,2-Dichloropropane" OR "22Dichloropropane" OR "alpha,alpha-Dichloropropane" OR "alpha,alpha-Propylene dichloride" OR "alpha,beta-Dichloropropane" OR "alpha,beta-Propylene dichloride" OR "BRN 1718880" OR "BRN 1731152" OR "Caswell No. 324" OR "Dichloro-1,2 propane" OR "Dichlorodimethylmethane" OR "Dicoloropropane" OR "Dimethyldichloromethane" OR "NCI-C55141" OR "NSC 1237" OR "NSC 6204" OR "Propylene chloride" OR "Propylene dichloride" OR "Propylidene chloride" OR "Trimethylene chloride" OR "Trimethylene dichloride" OR "UNII-AJ1HQ2GUCP" OR "UNII-C5V432N6XB" OR "UNII-RRZ023OFWL" OR "UNII-SR71OVZ2OZ") AND LA(ENG)	5
ProQuest Agricultural & Scientific Database Search Date: 5/16/2019	ALL("1,1-Dichloropropane" OR "1,2-Dichloropropane" OR "1,3-Dichloropropane" OR "11Dichloropropane" OR "12dichloropropane" OR "13Dichloropropane" OR "2,2-Dichloropropane" OR "22Dichloropropane" OR "alpha,alpha-Dichloropropane" OR "alpha,alpha-Propylene dichloride" OR "alpha,beta-Dichloropropane" OR "alpha,beta-Propylene dichloride" OR "BRN 1718880" OR "BRN 1731152" OR "Caswell No. 324" OR "Dichloro-1,2 propane" OR "Dichlorodimethylmethane" OR "Dicoloropropane" OR "Dimethyldichloromethane" OR "NCI-C55141" OR "NSC 1237" OR "NSC 6204" OR "Propylene chloride" OR "Propylene dichloride" OR "Propylidene chloride" OR "Trimethylene chloride" OR "Trimethylene dichloride" OR "UNII-AJ1HQ2GUCP" OR "UNII-C5V432N6XB" OR "UNII-RRZ023OFWL" OR "UNII-SR71OVZ2OZ") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	411
PubMed Search Date: 7/2/2019	"1,1-Dichloropropane" OR "1,2-Dichloropropane" OR "1,3-Dichloropropane" OR "11Dichloropropane" OR "12dichloropropane" OR "13Dichloropropane" OR "2,2-Dichloropropane" OR "22Dichloropropane" OR "alpha,alpha-Dichloropropane" OR "alpha,alpha-Propylene dichloride" OR "alpha,beta-Dichloropropane" OR "alpha,beta-Propylene dichloride" OR "BRN 1718880" OR "BRN 1731152" OR "Caswell No. 324" OR "Dichloro-1,2 propane" OR "Dichlorodimethylmethane" OR "Dicoloropropane" OR "Dimethyldichloromethane" OR "NCI-C55141" OR "NSC 1237" OR "NSC 6204" OR "Propylene chloride" OR "Propylene dichloride" OR "Propylidene chloride" OR "Trimethylene	182

Source	Source-Specific Search Strategy	Results
	chloride" OR "Trimethylene dichloride" OR "UNII-AJ1HQ2GUCP" OR "UNII-C5V432N6XB" OR "UNII-RRZ023OFWL" OR "UNII-SR71OVZ2OZ"	
Science Direct Search Date: 5/20/2019	1. "1,1-Dichloropropane" OR "1,2-Dichloropropane" OR "1,3-Dichloropropane" OR "11Dichloropropane" OR "12dichloropropane" OR "13Dichloropropane" OR "2,2-Dichloropropane" OR "22Dichloropropane" OR "alpha,alpha-Dichloropropane" 2. "alpha,alpha-Propylene dichloride" OR "alpha,beta-Dichloropropane" OR "alpha,beta-Propylene dichloride" OR "BRN 1718880" OR "BRN 1731152" OR "Caswell No. 324" OR "Dichloro-1,2 propane" OR "Dichlorodimethylmethane" OR "Dicoloropropane" 3. "Dimethyldichloromethane" OR "NCI-C55141" OR "NSC 1237" OR "NSC 6204" OR "Propylene chloride" OR "Propylene dichloride" OR "Propylidene chloride" OR "Trimethylene chloride" OR "Trimethylene dichloride" 4. "UNII-AJ1HQ2GUCP" OR "UNII-C5V432N6XB" OR "UNII-RRZ023OFWL" OR "UNII-SR71OVZ2OZ"	134
ToxNet Search Date: 5/20/2019	78-87-5 OR 78-99-9 OR 142-28-9 OR 594-20-7 OR 26198-63-0	684
WoS Search Date: 9/10/2019	TS=("1,1-Dichloropropane" OR "1,2-Dichloropropane" OR "1,3-Dichloropropane" OR "11Dichloropropane" OR "12dichloropropane" OR "13Dichloropropane" OR "2,2-Dichloropropane" OR "22Dichloropropane" OR "alpha,alpha-Dichloropropane" OR "alpha,alpha-Propylene dichloride" OR "alpha,beta-Dichloropropane" OR "alpha,beta-Propylene dichloride" OR "BRN 1718880" OR "BRN 1731152" OR "Caswell No. 324" OR "Dichloro-1,2 propane" OR "Dichlorodimethylmethane" OR "Dicoloropropane" OR "Dimethyldichloromethane" OR "NCI-C55141" OR "NSC 1237" OR "NSC 6204" OR "Propylene chloride" OR "Propylene dichloride" OR "Propylidene chloride" OR "Trimethylene chloride" OR "Trimethylene dichloride" OR "UNII-AJ1HQ2GUCP" OR "UNII-C5V432N6XB" OR "UNII-RRZ023OFWL" OR "UNII-SR71OVZ2OZ")	417
Unify[a] Search Date: 5/20/2019	1,1-Dichloropropane|1,2-Dichloropropane|1,3-Dichloropropane|11Dichloropropane|12dichloropropane|13Dichloropropane|2,2-Dichloropropane|22Dichloropropane|alpha,alpha-Dichloropropane|alpha,alpha-Propylene dichloride|alpha,beta-Dichloropropane|alpha,beta-Propylene dichloride|BRN 1718880|BRN 1731152|Caswell No. 324|Dichloro-1,2 propane|Dichlorodimethylmethane|Dicoloropropane|Dimethyldichloromethane|NCI-C55141|NSC 1237|NSC 6204|Propylene chloride|Propylene dichloride|Propylidene chloride|Trimethylene chloride|Trimethylene dichloride|UNII-AJ1HQ2GUCP|UNII-C5V432N6XB|UNII-RRZ023OFWL|UNII-SR71OVZ2OZ	144
Total	**Represents total across all databases after deduplication**	**1,114**

[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.

C.1.7 Query Strings for the Peer-Reviewed Literature Database Searches on 1,1-Dichloroethane

These are the search terms compiled from the Chemical Report for 1,1-dichloroethane used in the initial search strategies for each of the databases listed below:

"1,1-Dichlorethan" OR "1,1-Dichlorethane" OR "1,1-Dichloroethane" OR "1,1-Ethylene dichloride" OR "1,1-Ethylidene dichloride" OR "1,2 -Dichloroethane" OR "1,2-Bichloroethane" OR "1,2-DICHLORAETHAN" OR "1,2-Dichlor-aethan" OR "1,2-Dichlorethan" OR "1,2-Dichlorethane" OR "1,2-Dichloroethane" OR "11Dichloroethane" OR "Aethylenchlorid" OR "Aethylendichlorid" OR "alpha,alpha-Dichloroethane" OR "alpha,beta-dichloroethane" OR "Borer sol" OR "BRN 0605264" OR "Brocide" OR "Caswell No. 440" OR "Chlorinated hydrochloric ether" OR "Destruxol borer-sol" OR "Dichloremulsion" OR "Dichlorethan" OR "Dichlor-Mulsion" OR "Di-chlor-mulsion" OR "Dichloro-1,2-ethane" OR "Dichloroethane" OR "DICHLOROETHANES" OR "Dichloroethylene" OR "Dichloromethylmethane" OR "Dutch liquid" OR "Dutch oil" OR "ENT-1656" OR "Ethane dichloride" OR "Ethylene chloride" OR "Ethylene chloride" OR "Ethylene Dichloride" OR "Ethylene Dichloride" OR "Ethylene DI-Chloride" OR "Ethylenedichloride" OR "Ethylidene chloride" OR "Ethylidene dichloride" OR "Freon 150" OR "Glycol dichloride" OR "NCI-C00511" OR "NCI-C04535" OR "RY Dichloro-1,2-ethane" OR "sym-Dichloroethane" OR "UN 1184" OR "UN 2362" OR "UNII-0S989LNA44" OR "UNII-55163IJI47" OR "UNII-9D6S017631"

Table_Apx C-7. Peer-Reviewed Literature Search Strategy for 1,1-Dichloroethane

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 5/17/2019	1. 1,1-Dichlorethan; 1,1-Dichlorethane; 1,1-Dichloroethane; 1,1-Ethylene dichloride; 1,1-Ethylidene dichloride; 1,2 -Dichloroethane; 1,2-Bichloroethane; 1,2-DICHLORAETHAN; 1,2-Dichlor-aethan; 1,2-Dichlorethan 2. 1,2-Dichlorethane; 1,2-Dichloroethane; 11Dichloroethane; Aethylenchlorid; Aethylendichlorid; alpha,alpha-Dichloroethane; alpha,beta-dichloroethane; Borer sol; BRN 0605264; Brocide 3. Caswell No. 440; Chlorinated hydrochloric ether; Destruxol borer-sol; Dichloremulsion; Dichlorethan; Dichlor-Mulsion; Di-chlor-mulsion; Dichloro-1,2-ethane; Dichloroethane; DICHLOROETHANES 4. Dichloroethylene; Dichloromethylmethane; Dutch liquid; Dutch oil; ENT-1656; Ethane dichloride; Ethylene chloride; Ethylene chloride; Ethylene Dichloride; Ethylene Dichloride 5. Ethylene DI-Chloride; Ethylenedichloride; Ethylidene chloride; Ethylidene dichloride; Freon 150; Glycol dichloride; NCI-C00511; NCI-C04535; RY Dichloro-1,2-ethane; sym-Dichloroethane 6. UN 1184; UN 2362; UNII-0S989LNA44; UNII-55163IJI47; UNII-9D6S017631	1,462
Current Contents Search Date: 5/14/2019	TS=("1,1-Dichlorethan" OR "1,1-Dichlorethane" OR "1,1-Dichloroethane" OR "1,1-Ethylene dichloride" OR "1,1-Ethylidene dichloride" OR "1,2 -Dichloroethane" OR "1,2-Bichloroethane" OR "1,2-DICHLORAETHAN" OR "1,2-Dichlor-aethan" OR "1,2-Dichlorethan" OR "1,2-Dichlorethane" OR "1,2-Dichloroethane" OR "11Dichloroethane" OR "Aethylenchlorid" OR "Aethylendichlorid" OR "alpha,alpha-Dichloroethane" OR "alpha,beta-dichloroethane" OR "Borer sol" OR "BRN 0605264" OR "Brocide" OR "Caswell No. 440" OR "Chlorinated hydrochloric ether" OR "Destruxol borer-sol" OR "Dichloremulsion" OR "Dichlorethan" OR "Dichlor-Mulsion" OR "Di-chlor-mulsion" OR "Dichloro-1,2-ethane" OR "Dichloroethane" OR "DICHLOROETHANES" OR "Dichloroethylene" OR "Dichloromethylmethane" OR "Dutch liquid" OR "Dutch oil" OR "ENT-1656" OR "Ethane dichloride" OR "Ethylene chloride" OR "Ethylene chloride" OR "Ethylene Dichloride" OR	4,956

Source	Source-Specific Search Strategy	Results
	"Ethylene Dichloride" OR "Ethylene DI-Chloride" OR "Ethylenedichloride" OR "Ethylidene chloride" OR "Ethylidene dichloride" OR "Freon 150" OR "Glycol dichloride" OR "NCI-C00511" OR "NCI-C04535" OR "RY Dichloro-1,2-ethane" OR "sym-Dichloroethane" OR "UN 1184" OR "UN 2362" OR "UNII-0S989LNA44" OR "UNII-55163IJI47" OR "UNII-9D6S017631")	
ProQuest Dissertations & Theses Search Date: 5/17/19	ALL("1,1-Dichlorethan" OR "1,1-Dichlorethane" OR "1,1-Dichloroethane" OR "1,1-Ethylene dichloride" OR "1,1-Ethylidene dichloride" OR "1,2 -Dichloroethane" OR "1,2-Bichloroethane" OR "1,2-DICHLORAETHAN" OR "1,2-Dichlor-aethan" OR "1,2-Dichlorethan" OR "1,2-Dichlorethane" OR "1,2-Dichloroethane" OR "11Dichloroethane" OR "Aethylenchlorid" OR "Aethylendichlorid" OR "alpha,alpha-Dichloroethane" OR "alpha,beta-dichloroethane" OR "Borer sol" OR "BRN 0605264" OR "Brocide" OR "Caswell No. 440" OR "Chlorinated hydrochloric ether" OR "Destruxol borer-sol" OR "Dichloremulsion" OR "Dichlorethan" OR "Dichlor-Mulsion" OR "Di-chlor-mulsion" OR "Dichloro-1,2-ethane" OR "Dichloroethane" OR "DICHLOROETHANES" OR "Dichloroethylene" OR "Dichloromethylmethane" OR "Dutch liquid" OR "Dutch oil" OR "ENT-1656" OR "Ethane dichloride" OR "Ethylene chloride" OR "Ethylene chloride" OR "Ethylene Dichloride" OR "Ethylene Dichloride" OR "Ethylene DI-Chloride" OR "Ethylenedichloride" OR "Ethylidene chloride" OR "Ethylidene dichloride" OR "Freon 150" OR "Glycol dichloride" OR "NCI-C00511" OR "NCI-C04535" OR "RY Dichloro-1,2-ethane" OR "sym-Dichloroethane" OR "UN 1184" OR "UN 2362" OR "UNII-0S989LNA44" OR "UNII-55163IJI47" OR "UNII-9D6S017631") AND LA(ENG)	84
ProQuest Agricultural & Scientific Database Search Date: 5/14/2019	ALL("1,1-Dichlorethan" OR "1,1-Dichlorethane" OR "1,1-Dichloroethane" OR "1,1-Ethylene dichloride" OR "1,1-Ethylidene dichloride" OR "1,2 -Dichloroethane" OR "1,2-Bichloroethane" OR "1,2-DICHLORAETHAN" OR "1,2-Dichlor-aethan" OR "1,2-Dichlorethan" OR "1,2-Dichlorethane" OR "1,2-Dichloroethane" OR "11Dichloroethane" OR "Aethylenchlorid" OR "Aethylendichlorid" OR "alpha,alpha-Dichloroethane" OR "alpha,beta-dichloroethane" OR "Borer sol" OR "BRN 0605264" OR "Brocide" OR "Caswell No. 440" OR "Chlorinated hydrochloric ether" OR "Destruxol borer-sol" OR "Dichloremulsion" OR "Dichlorethan" OR "Dichlor-Mulsion" OR "Di-chlor-mulsion" OR "Dichloro-1,2-ethane" OR "Dichloroethane" OR "DICHLOROETHANES" OR "Dichloroethylene" OR "Dichloromethylmethane" OR "Dutch liquid" OR "Dutch oil" OR "ENT-1656" OR "Ethane dichloride" OR "Ethylene chloride" OR "Ethylene chloride" OR "Ethylene Dichloride" OR "Ethylene Dichloride" OR "Ethylene DI-Chloride" OR "Ethylenedichloride" OR "Ethylidene chloride" OR "Ethylidene dichloride" OR "Freon 150" OR "Glycol dichloride" OR "NCI-C00511" OR "NCI-C04535" OR "RY Dichloro-1,2-ethane" OR "sym-Dichloroethane" OR "UN 1184" OR "UN 2362" OR "UNII-0S989LNA44" OR "UNII-55163IJI47" OR "UNII-9D6S017631") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	6,417
PubMed Search Date: 7/02/2019	"1,1-Dichlorethan" OR "1,1-Dichlorethane" OR "1,1-Dichloroethane" OR "1,1-Ethylene dichloride" OR "1,1-Ethylidene dichloride" OR "1,2 -Dichloroethane" OR "1,2-Bichloroethane" OR "1,2-DICHLORAETHAN" OR "1,2-Dichlor-aethan" OR "1,2-Dichlorethan" OR "1,2-Dichlorethane" OR "1,2-Dichloroethane" OR "11Dichloroethane" OR "Aethylenchlorid" OR "Aethylendichlorid" OR "alpha,alpha-Dichloroethane" OR "alpha,beta-dichloroethane" OR "Borer sol" OR "BRN 0605264" OR "Brocide" OR "Caswell No. 440" OR "Chlorinated hydrochloric ether" OR "Destruxol borer-sol" OR "Dichloremulsion" OR "Dichlorethan" OR "Dichlor-Mulsion" OR "Di-chlor-mulsion" OR "Dichloro-1,2-ethane" OR "Dichloroethane" OR "DICHLOROETHANES" OR "Dichloroethylene" OR "Dichloromethylmethane" OR "Dutch liquid" OR "Dutch oil" OR "ENT-1656" OR "Ethane dichloride" OR "Ethylene chloride" OR "Ethylene chloride" OR "Ethylene Dichloride" OR "Ethylene Dichloride" OR "Ethylene DI-Chloride" OR "Ethylenedichloride" OR "Ethylidene chloride" OR "Ethylidene	2,525

Source	Source-Specific Search Strategy	Results
	dichloride" OR "Freon 150" OR "Glycol dichloride" OR "NCI-C00511" OR "NCI-C04535" OR "RY Dichloro-1,2-ethane" OR "sym-Dichloroethane"	
Science Direct Search Date: 5/15/2019	1. "1,1-Dichlorethan" OR "1,1-Dichlorethane" OR "1,1-Dichloroethane" OR "1,1-Ethylene dichloride" OR "1,1-Ethylidene dichloride" OR "1,2 -Dichloroethane" OR "1,2-Bichloroethane" OR "1,2-DICHLORAETHAN" OR "1,2-Dichlor-aethan" 2. "1,2-Dichlorethan" OR "1,2-Dichlorethane" OR "1,2-Dichloroethane" OR "11Dichloroethane" OR "Aethylenchlorid" OR "Aethylendichlorid" OR "alpha,alpha-Dichloroethane" OR "alpha,beta-dichloroethane" OR "Borer sol" 3. "BRN 0605264" OR "Brocide" OR "Caswell No. 440" OR "Chlorinated hydrochloric ether" OR "Destruxol borer-sol" OR "Dichloremulsion" OR "Dichlorethan" OR "Dichlor-Mulsion" OR "Di-chlor-mulsion" 4. "Dichloro-1,2-ethane" OR "Dichloroethane" OR "DICHLOROETHANES" OR "Dichloroethylene" OR "Dichloromethylmethane" OR "Dutch liquid" OR "Dutch oil" OR "ENT-1656" OR "Ethane dichloride" 5. "Ethylene chloride" OR "Ethylene chloride" OR "Ethylene Dichloride" OR "Ethylene Dichloride" OR "Ethylene DI-Chloride" OR "Ethylenedichloride" OR "Ethylidene chloride" OR "Ethylidene dichloride" OR "Freon 150" 6. "Glycol dichloride" OR "NCI-C00511" OR "NCI-C04535" OR "RY Dichloro-1,2-ethane" OR "sym-Dichloroethane" 7. "UN 1184" OR "UN 2362" OR "UNII-0S989LNA44" OR "UNII-55163IJI47" OR "UNII-9D6S017631"	6,570
ToxNet Search Date: 5/15/2019	75-34-3 OR 107-06-2 OR 1300-21-6 OR 52399-93-6	2,204
WoS Search Date: 9/10/2019	TS=("1,1-Dichlorethan" OR "1,1-Dichlorethane" OR "1,1-Dichloroethane" OR "1,1-Ethylene dichloride" OR "1,1-Ethylidene dichloride" OR "1,2 -Dichloroethane" OR "1,2-Bichloroethane" OR "1,2-DICHLORAETHAN" OR "1,2-Dichlor-aethan" OR "1,2-Dichlorethan" OR "1,2-Dichlorethane" OR "1,2-Dichloroethane" OR "11Dichloroethane" OR "Aethylenchlorid" OR "Aethylendichlorid" OR "alpha,alpha-Dichloroethane" OR "alpha,beta-dichloroethane" OR "Borer sol" OR "BRN 0605264" OR "Brocide" OR "Caswell No. 440" OR "Chlorinated hydrochloric ether" OR "Destruxol borer-sol" OR "Dichloremulsion" OR "Dichlorethan" OR "Dichlor-Mulsion" OR "Di-chlor-mulsion" OR "Dichloro-1,2-ethane" OR "Dichloroethane" OR "DICHLOROETHANES" OR "Dichloroethylene" OR "Dichloromethylmethane" OR "Dutch liquid" OR "Dutch oil" OR "ENT-1656" OR "Ethane dichloride" OR "Ethylene chloride" OR "Ethylene chloride" OR "Ethylene Dichloride" OR "Ethylene Dichloride" OR "Ethylene DI-Chloride" OR "Ethylenedichloride" OR "Ethylidene chloride" OR "Ethylidene dichloride" OR "Freon 150" OR "Glycol dichloride" OR "NCI-C00511" OR "NCI-C04535" OR "RY Dichloro-1,2-ethane" OR "sym-Dichloroethane" OR "UN 1184" OR "UN 2362" OR "UNII-0S989LNA44" OR "UNII-55163IJI47" OR "UNII-9D6S017631")	7,390
Unify[a] Search Date: 5/15/2019	1,1-Dichlorethan|1,1-Dichlorethane|1,1-Dichloroethane|1,1-Ethylene dichloride|1,1-Ethylidene dichloride|1,2 -Dichloroethane|1,2-Bichloroethane|1,2-DICHLORAETHAN|1,2-Dichlor-aethan|1,2-Dichlorethan|1,2-Dichlorethane|1,2-Dichloroethane|11Dichloroethane|Aethylenchlorid|Aethylendichlorid|alpha,alpha-Dichloroethane|alpha,beta-dichloroethane|Borer sol|BRN 0605264|Brocide|Caswell No. 440|Chlorinated hydrochloric ether|Destruxol borer-sol|Dichloremulsion|Dichlorethan|Dichlor-Mulsion|Di-chlor-mulsion|Dichloro-1,2-ethane|Dichloroethane|DICHLOROETHANES|Dichloroethylene|Dichloromethylmethane|Dutch liquid|Dutch oil|ENT-1656|Ethane dichloride|Ethylene chloride|Ethylene chloride|Ethylene Dichloride|Ethylene Dichloride|Ethylene DI-	208

Source	Source-Specific Search Strategy	Results
	Chloride|Ethylenedichloride|Ethylidene chloride|Ethylidene dichloride|Freon 150|Glycol dichloride|NCI-C00511|NCI-C04535|RY Dichloro-1,2-ethane|sym-Dichloroethane|UN 1184|UN 2362|UNII-0S989LNA44|UNII-55163IJI47|UNII-9D6S017631	
Total	**Represents total across all databases after deduplication**	**12,823**
[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.		

C.1.8 Query Strings for the Peer-Reviewed Literature Database Searches on Ethylene Dibromide

These are the search terms compiled from the Chemical Report for ethylene dibromide used in the initial search strategies for each of the databases listed below:

"1,1-Dibromoethane" OR "1,2-Dibromaethan" OR "1,2-Dibromethan" OR "1,2-dibromoetano" OR "1,2-Dibromoethane" OR "1,2-Dibroomethaan" OR "1,2-Ethylene dibromide" OR "Aadibroom" OR "Aethylenbromid" OR "alpha, beta-Dibromoethane" OR "alpha, omega-Dibromoethane" OR "BRN 0605266" OR "Bromofume" OR "Caswell No. 439" OR "Celmide" OR "Dayfum W-85" OR "Dibromoethane" OR "11edbDowfume 40" OR "Dowfume EDB" OR "Dowfume W 15" OR "Dowfume W 8" OR "Dowfume W 85" OR "Dowfume W-100" OR "Dowfume W-40" OR "Dowfume W-8" OR "Dowfume W-85" OR "Dowfume W-90" OR "Dwubromoetan" OR "Edabrom" OR "E-D-Bee" OR "Ethane, 1,1-dibromo-" OR "Ethane, 1,2-dibromo-" OR "Ethane, dibromo-" OR "Ethylene bromide" OR "Ethylene dibromide" OR "Ethylidene bromide" OR "Ethylidene dibromide" OR "Ethylidine bromide" OR "Fumo-gas" OR "Glycol dibromide" OR "Iscobrome D" OR "Kopfume" OR "Pestmaster edb-85" OR "Sanhyuum" OR "Soilbrom" OR "Soilbrom 85" OR "Soilbrom 90" OR "Soilbrom-100" OR "Soilbrom-40"OR "Soilbrom-85" OR "Soilbrom-90" OR "Soilbrom-90EC" OR "Soilfume" OR "sym-Dibromoethane" OR "UN 1605" OR "Unifume" OR "UNII-1N41638RNO" OR "UNII-KJ8ZJY72QQ"

Table_Apx C-8. Peer-Reviewed Literature Search Strategy for Ethylene Dibromide

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 5/24/2019	1. 1,1-Dibromoethane; 1,2-Dibromaethan; 1,2-Dibromethan; 1,2-dibromoetano; 1,2-Dibromoethane; 1,2-Dibroomethaan; 1,2-Ethylene dibromide; Aadibroom; Aethylenbromid; alpha, beta-Dibromoethane 2. alpha, omega-Dibromoethane; BRN 0605266; Bromofume; Caswell No. 439; Celmide; Dayfum W-85; Dibromoethane; 11edbDowfume 40; Dowfume EDB; Dowfume W 15 3. Dowfume W 8; Dowfume W 85; Dowfume W-100; Dowfume W-40; Dowfume W-8; Dowfume W-85; Dowfume W-90; Dwubromoetan; Edabrom; E-D-Bee 4. Ethane, 1,1-dibromo-; Ethane, 1,2-dibromo-; Ethane, dibromo-; Ethylene bromide; Ethylene dibromide; Ethylidene bromide; Ethylidene dibromide; Ethylidine bromide; Fumo-gas; Glycol dibromide 5. Iscobrome D; Kopfume; NCI-C00522; Pestmaster edb-85; Sanhyuum; Soilbrom; Soilbrom 85; Soilbrom 90; Soilbrom-100; Soilbrom-40	463

Source	Source-Specific Search Strategy	Results
	6. Soilbrom-85; Soilbrom-90; Soilbrom-90EC; Soilfume; sym-Dibromoethane; UN 1605; Unifume; UNII-1N41638RNO; UNII-KJ8ZJY72QQ	
Current Contents Search Date: 5/22/2019	TS=("1,1-Dibromoethane" OR "1,2-Dibromaethan" OR "1,2-Dibromethan" OR "1,2-dibromoetano" OR "1,2-Dibromoethane" OR "1,2-Dibroomethaan" OR "1,2-Ethylene dibromide" OR "Aadibroom" OR "Aethylenbromid" OR "alpha, beta-Dibromoethane" OR "alpha, omega-Dibromoethane" OR "BRN 0605266" OR "Bromofume" OR "Caswell No. 439" OR "Celmide" OR "Dayfum W-85" OR "Dibromoethane" OR "11edbDowfume 40" OR "Dowfume EDB" OR "Dowfume W 15" OR "Dowfume W 8" OR "Dowfume W 85" OR "Dowfume W-100" OR "Dowfume W-40" OR "Dowfume W-8" OR "Dowfume W-85" OR "Dowfume W-90" OR "Dwubromoetan" OR "Edabrom" OR "E-D-Bee" OR "Ethane, 1,1-dibromo-" OR "Ethane, 1,2-dibromo-" OR "Ethane, dibromo-" OR "Ethylene bromide" OR "Ethylene dibromide" OR "Ethylidene bromide" OR "Ethylidene dibromide" OR "Ethylidine bromide" OR "Fumo-gas" OR "Glycol dibromide" OR "Iscobrome D" OR "Kopfume" OR "Pestmaster edb-85" OR "Sanhyuum" OR "Soilbrom" OR "Soilbrom 85" OR "Soilbrom 90" OR "Soilbrom-100" OR "Soilbrom-40" OR "Soilbrom-85" OR "Soilbrom-90" OR "Soilbrom-90EC" OR "Soilfume" OR "sym-Dibromoethane" OR "UN 1605" OR "Unifume" OR "UNII-1N41638RNO" OR "UNII-KJ8ZJY72QQ")	261
ProQuest Dissertations & Theses Search Date: 5/23/2019	ALL("1,1-Dibromoethane" OR "1,2-Dibromaethan" OR "1,2-Dibromethan" OR "1,2-dibromoetano" OR "1,2-Dibromoethane" OR "1,2-Dibroomethaan" OR "1,2-Ethylene dibromide" OR "Aadibroom" OR "Aethylenbromid" OR "alpha, beta-Dibromoethane" OR "alpha, omega-Dibromoethane" OR "BRN 0605266" OR "Bromofume" OR "Caswell No. 439" OR "Celmide" OR "Dayfum W-85" OR "Dibromoethane" OR "11edbDowfume 40" OR "Dowfume EDB" OR "Dowfume W 15" OR "Dowfume W 8" OR "Dowfume W 85" OR "Dowfume W-100" OR "Dowfume W-40" OR "Dowfume W-8" OR "Dowfume W-85" OR "Dowfume W-90" OR "Dwubromoetan" OR "Edabrom" OR "E-D-Bee" OR "Ethane, 1,1-dibromo-" OR "Ethane, 1,2-dibromo-" OR "Ethane, dibromo-" OR "Ethylene bromide" OR "Ethylene dibromide" OR "Ethylidene bromide" OR "Ethylidene dibromide" OR "Ethylidine bromide" OR "Fumo-gas" OR "Glycol dibromide" OR "Iscobrome D" OR "Kopfume" OR OR "Pestmaster edb-85" OR "Sanhyuum" OR "Soilbrom" OR "Soilbrom 85" OR "Soilbrom 90" OR "Soilbrom-100" OR "Soilbrom-40") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents" OR "Soilbrom-85" OR "Soilbrom-90" OR "Soilbrom-90EC" OR "Soilfume" OR "sym-Dibromoethane" OR "UN 1605" OR "Unifume" OR "UNII-1N41638RNO" OR "UNII-KJ8ZJY72QQ") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	14
ProQuest Agricultural & Scientific Database Search Date: 5/22/2019	ALL("1,1-Dibromoethane" OR "1,2-Dibromaethan" OR "1,2-Dibromethan" OR "1,2-dibromoetano" OR "1,2-Dibromoethane" OR "1,2-Dibroomethaan" OR "1,2-Ethylene dibromide" OR "Aadibroom" OR "Aethylenbromid" OR "alpha, beta-Dibromoethane" OR "alpha, omega-Dibromoethane" OR "BRN 0605266" OR "Bromofume" OR "Caswell No. 439" OR "Celmide" OR "Dayfum W-85" OR "Dibromoethane" OR "11edbDowfume 40" OR "Dowfume EDB" OR "Dowfume W 15" OR "Dowfume W 8" OR "Dowfume W 85" OR "Dowfume W-100" OR "Dowfume W-40" OR "Dowfume W-8" OR "Dowfume W-85" OR "Dowfume W-90" OR "Dwubromoetan" OR "Edabrom" OR "E-D-Bee" OR "Ethane, 1,1-dibromo-" OR "Ethane, 1,2-dibromo-" OR "Ethane, dibromo-" OR "Ethylene bromide" OR "Ethylene dibromide" OR "Ethylidene bromide" OR "Ethylidene dibromide" OR "Ethylidine bromide" OR "Fumo-gas" OR "Glycol dibromide" OR "Iscobrome D" OR "Kopfume" OR OR "Pestmaster edb-85" OR "Sanhyuum" OR "Soilbrom" OR "Soilbrom 85" OR "Soilbrom 90" OR "Soilbrom-100" OR "Soilbrom-40") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents" OR "Soilbrom-85" OR "Soilbrom-90" OR "Soilbrom-90EC" OR "Soilfume" OR "sym-Dibromoethane" OR "UN 1605" OR	1,502

Source	Source-Specific Search Strategy	Results
	"Unifume" OR "UNII-1N41638RNO" OR "UNII-KJ8ZJY72QQ") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	
PubMed Search Date: 7/2/2019	"1,1-Dibromoethane" OR "1,2-Dibromaethan" OR "1,2-Dibromethan" OR "1,2-dibromoetano" OR "1,2-Dibromoethane" OR "1,2-Dibroomethaan" OR "1,2-Ethylene dibromide" OR "Aadibroom" OR "Aethylenbromid" OR "alpha, beta-Dibromoethane" OR "alpha, omega-Dibromoethane" OR "BRN 0605266" OR "Bromofume" OR "Caswell No. 439" OR "Celmide" OR "Dayfum W-85" OR "Dibromoethane" OR "11edbDowfume 40" OR "Dowfume EDB" OR "Dowfume W 15" OR "Dowfume W 8" OR "Dowfume W 85" OR "Dowfume W-100" OR "Dowfume W-40" OR "Dowfume W-8" OR "Dowfume W-85" OR "Dowfume W-90" OR "Dwubromoetan" OR "Edabrom" OR "E-D-Bee" OR "Ethane, 1,1-dibromo-" OR "Ethane, 1,2-dibromo-" OR "Ethane, dibromo-" OR "Ethylene bromide" OR "Ethylene dibromide" OR "Ethylidene bromide" OR "Ethylidene dibromide" OR "Ethylidine bromide" OR "Fumo-gas" OR "Glycol dibromide" OR "Iscobrome D" OR "Kopfume" OR "Pestmaster edb-85" OR "Sanhyuum" OR "Soilbrom" OR "Soilbrom 85" OR "Soilbrom 90" OR "Soilbrom-100" OR "Soilbrom-40" OR "Soilbrom-85" OR "Soilbrom-90" OR "Soilbrom-90EC" OR "Soilfume" OR "sym-Dibromoethane" OR "UN 1605" OR "Unifume" OR "UNII-1N41638RNO" OR "UNII-KJ8ZJY72QQ"	671
Science Direct Search Date: 5/22/2019	1. "1,1-Dibromoethane" OR "1,2-Dibromaethan" OR "1,2-Dibromethan" OR "1,2-dibromoetano" OR "1,2-Dibromoethane" OR "1,2-Dibroomethaan" OR "1,2-Ethylene dibromide" OR "Aadibroom" OR "Aethylenbromid" 2. "alpha, beta-Dibromoethane" OR "alpha, omega-Dibromoethane" OR "BRN 0605266" OR "Bromofume" OR "Caswell No. 439" OR "Celmide" OR "Dayfum W-85" OR "Dibromoethane" OR "11edbDowfume 40" 3. "Dowfume EDB" OR "Dowfume W 15" OR "Dowfume W 8" OR "Dowfume W 85" OR "Dowfume W-100" OR "Dowfume W-40" OR "Dowfume W-8" OR "Dowfume W-85" OR "Dowfume W-90" 4. "Dwubromoetan" OR "Edabrom" OR "E-D-Bee" OR "Ethane, 1,1-dibromo-" OR "Ethane, 1,2-dibromo-" OR "Ethane, dibromo-" OR "Ethylene bromide" OR "Ethylene dibromide" OR "Ethylidene bromide" 5. "Ethylidene dibromide" OR "Ethylidine bromide" OR "Fumo-gas" OR "Glycol dibromide" OR "Iscobrome D" OR "Kopfume" OR "NCI-C00522" OR "Pestmaster edb-85" OR "Sanhyuum" 6. "Soilbrom" OR "Soilbrom 85" OR "Soilbrom 90" OR "Soilbrom-100" OR "Soilbrom-40" 7. "Soilbrom-85" OR "Soilbrom-90" OR "Soilbrom-90EC" OR "Soilfume" OR "sym-Dibromoethane" OR "UN 1605" OR "Unifume" OR "UNII-1N41638RNO" OR "UNII-KJ8ZJY72QQ"	824
ToxNet Search Date: 5/22/2019	1. 106-93-4 OR 557-91-5 OR 25620-62-6 OR 8003-07-4 OR 56729-21-6 2. 625084-37-9	1,574
WoS Search Date: 9/12/2019	TS=("1,1-Dibromoethane" OR "1,2-Dibromaethan" OR "1,2-Dibromethan" OR "1,2-dibromoetano" OR "1,2-Dibromoethane" OR "1,2-Dibroomethaan" OR "1,2-Ethylene dibromide" OR "Aadibroom" OR "Aethylenbromid" OR "alpha, beta-Dibromoethane" OR "alpha, omega-Dibromoethane" OR "BRN 0605266" OR "Bromofume" OR "Caswell No. 439" OR "Celmide" OR "Dayfum W-85" OR "Dibromoethane" OR "11edbDowfume 40" OR "Dowfume EDB" OR "Dowfume W 15" OR "Dowfume W 8" OR "Dowfume W 85" OR "Dowfume W-100" OR "Dowfume W-40" OR "Dowfume W-8" OR "Dowfume W-85" OR "Dowfume W-90" OR "Dwubromoetan" OR "Edabrom" OR "E-D-Bee" OR "Ethane, 1,1-dibromo-" OR "Ethane, 1,2-dibromo-" OR "Ethane, dibromo-" OR "Ethylene bromide" OR "Ethylene dibromide" OR "Ethylidene bromide" OR "Ethylidene dibromide" OR "Ethylidine bromide" OR "Fumo-gas" OR "Glycol dibromide" OR "Iscobrome D" OR	1,386

Source	Source-Specific Search Strategy	Results
	"Kopfume" OR "Pestmaster edb-85" OR "Sanhyuum" OR "Soilbrom" OR "Soilbrom 85" OR "Soilbrom 90" OR "Soilbrom-100" OR "Soilbrom-40" OR "Soilbrom-85" OR "Soilbrom-90" OR "Soilbrom-90EC" OR "Soilfume" OR "sym-Dibromoethane" OR "UN 1605" OR "Unifume" OR "UNII-1N41638RNO" OR "UNII-KJ8ZJY72QQ")	
Unify[a] Search Date: 6/6/2019	1,1-Dibromoethane|1,2-Dibromaethan|1,2-Dibromethan|1,2-dibromoetano|1,2-Dibromoethane|1,2-Dibroomethaan|1,2-Ethylene dibromide|Aadibroom|Aethylenbromid|alpha, beta-Dibromoethane|alpha, omega-Dibromoethane|BRN 0605266|Bromofume|Caswell No. 439|Celmide|Dayfum W-85|Dibromoethane|11edbDowfume 40|Dowfume EDB|Dowfume W 15|Dowfume W 8|Dowfume W 85|Dowfume W-100|Dowfume W-40|Dowfume W-8|Dowfume W-85|Dowfume W-90|Dwubromoetan|Edabrom|E-D-Bee|Ethane, 1,1-dibromo-|Ethane, 1,2-dibromo-|Ethane, dibromo-|Ethylene bromide|Ethylene dibromide|Ethylidene bromide|Ethylidene dibromide|Ethylidine bromide|Fumo-gas|Glycol dibromide|Iscobrome D|Kopfume|Pestmaster edb-85|Sanhyuum|Soilbrom|Soilbrom 85|Soilbrom 90|Soilbrom-100|Soilbrom-40"OR "Soilbrom-85|Soilbrom-90|Soilbrom-90EC|Soilfume|sym-Dibromoethane|UN 1605|Unifume|UNII-1N41638RNO|UNII-KJ8ZJY72QQ	371
Total	**Represents total across all databases after deduplication**	**3,149**
[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.		

C.1.9 Query Strings for the Peer-Reviewed Literature Database Searches on 1,3-Butadiene

These are the search terms compiled from the Chemical Report for 1,3-butadiene used in the initial search strategies for each of the databases listed below:

"1,2-Butadien" OR "1,2-Butadiene" OR "1,3-BUTADIEN" OR "1,3-Butadiene" OR "1-Methylallene" OR "2-Butene-1,4-diyl" OR "Allene, methyl-" OR "alpha,gamma-Butadiene" OR "Biethylene" OR "Bivinyl" OR "Buta-1,2-dien" OR "Buta-1,2-diene" OR "Buta-1,3-dien" OR "Buta-1,3-diene" OR "Butadien" OR "Butadiene" OR "Butadiene" OR "Butadiene monomer" OR "Butadiene-1,2" OR "Butadiene-1,3" OR "Divinyl" OR "Erythrene" OR "Methylallene" OR "NCI-C50602" OR "UN 1010" OR "UNII-2AZI943A8R" OR "UNII-JSD5FGP5VD" OR "Vinylethylene"

Table_Apx C-9. Peer-Reviewed Literature Search Strategy for 1,3-Butadiene

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 5/24/2019	1. 1,2-Butadien; 1,2-Butadiene; 1,3-BUTADIEN; 1,3-Butadiene; 1-Methylallene; 2-Butene-1,4-diyl; Allene, methyl-; alpha,gamma-Butadiene; Biethylene; Bivinyl 2. Buta-1,2-dien; Buta-1,2-diene; Buta-1,3-dien; Buta-1,3-diene; Butadien; Butadiene; Butadiene; Butadiene monomer; Butadiene-1,2; Butadiene-1,3 3. Divinyl; Erythrene; Methylallene; NCI-C50602; UN 1010; UNII-2AZI943A8R; UNII-JSD5FGP5VD; Vinylethylene	688

Source	Source-Specific Search Strategy	Results
Current Contents Search Date: 5/23/2019	TS=("1,2-Butadien" OR "1,2-Butadiene" OR "1,3-BUTADIEN" OR "1,3-Butadiene" OR "1-Methylallene" OR "2-Butene-1,4-diyl" OR "Allene, methyl-" OR "alpha,gamma-Butadiene" OR "Biethylene" OR "Bivinyl" OR "Buta-1,2-dien" OR "Buta-1,2-diene" OR "Buta-1,3-dien" OR "Buta-1,3-diene" OR "Butadien" OR "Butadiene" OR "Butadiene" OR "Butadiene monomer" OR "Butadiene-1,2" OR "Butadiene-1,3" OR "Divinyl" OR "Erythrene" OR "Methylallene" OR "NCI-C50602" OR "UN 1010" OR "UNII-2AZI943A8R" OR "UNII-JSD5FGP5VD" OR "Vinylethylene")	3,405
ProQuest Dissertations & Theses Search Date: 5/30/2019	ALL("1,2-Butadien" OR "1,2-Butadiene" OR "1,3-BUTADIEN" OR "1,3-Butadiene" OR "1-Methylallene" OR "2-Butene-1,4-diyl" OR "Allene, methyl-" OR "alpha,gamma-Butadiene" OR "Biethylene" OR "Bivinyl" OR "Buta-1,2-dien" OR "Buta-1,2-diene" OR "Buta-1,3-dien" OR "Buta-1,3-diene" OR "Butadien" OR "Butadiene" OR "Butadiene" OR "Butadiene monomer" OR "Butadiene-1,2" OR "Butadiene-1,3" OR "Divinyl" OR "Erythrene" OR "Methylallene" OR "NCI-C50602" OR "UN 1010" OR "UNII-2AZI943A8R" OR "UNII-JSD5FGP5VD" OR "Vinylethylene") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	305
ProQuest Agricultural & Scientific Database Search Date: 5/23/2019	ALL("1,2-Butadien" OR "1,2-Butadiene" OR "1,3-BUTADIEN" OR "1,3-Butadiene" OR "1-Methylallene" OR "2-Butene-1,4-diyl" OR "Allene, methyl-" OR "alpha,gamma-Butadiene" OR "Biethylene" OR "Bivinyl" OR "Buta-1,2-dien" OR "Buta-1,2-diene" OR "Buta-1,3-dien" OR "Buta-1,3-diene" OR "Butadien" OR "Butadiene" OR "Butadiene" OR "Butadiene monomer" OR "Butadiene-1,2" OR "Butadiene-1,3" OR "Divinyl" OR "Erythrene" OR "Methylallene" OR "NCI-C50602" OR "UN 1010" OR "UNII-2AZI943A8R" OR "UNII-JSD5FGP5VD" OR "Vinylethylene") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	6,542
PubMed Search Date: 5/28/2019	"1,2-Butadien" OR "1,2-Butadiene" OR "1,3-BUTADIEN" OR "1,3-Butadiene" OR "1-Methylallene" OR "2-Butene-1,4-diyl" OR "Allene, methyl-" OR "alpha,gamma-Butadiene" OR "Biethylene" OR "Bivinyl" OR "Buta-1,2-dien" OR "Buta-1,2-diene" OR "Buta-1,3-dien" OR "Buta-1,3-diene" OR "Butadien" OR "Butadiene" OR "Butadiene" OR "Butadiene monomer" OR "Butadiene-1,2" OR "Butadiene-1,3" OR "Divinyl" OR "Erythrene" OR "Methylallene" OR "NCI-C50602" OR "UN 1010" OR "UNII-2AZI943A8R" OR "UNII-JSD5FGP5VD" OR "Vinylethylene"	5,330
Science Direct Search Date: 5/23/2019	1. "1,2-Butadien" OR "1,2-Butadiene" OR "1,3-BUTADIEN" OR "1,3-Butadiene" OR "1-Methylallene" OR "2-Butene-1,4-diyl" OR "Allene, methyl-" OR "alpha,gamma-Butadiene" OR "Biethylene" 2. "Bivinyl" OR "Buta-1,2-dien" OR "Buta-1,2-diene" OR "Buta-1,3-dien" OR "Buta-1,3-diene" OR "Butadien" OR "Butadiene" OR "Butadiene" OR "Butadiene monomer" 3. "Butadiene-1,2" OR "Butadiene-1,3" OR "Divinyl" OR "Erythrene" OR "Methylallene" OR "NCI-C50602" OR "UN 1010" OR "UNII-2AZI943A8R" OR "UNII-JSD5FGP5VD" 4. "Vinylethylene"	11,792
ToxNet Search Date: 5/24/2019	1. 106-99-0 OR 590-19-2 OR 1213224-27-1 OR 130983-70-9 OR 183592-61-2 2. 25339-57-5	6,302
WoS Search Date: 9/10/2019	TS=("1,2-Butadien" OR "1,2-Butadiene" OR "1,3-BUTADIEN" OR "1,3-Butadiene" OR "1-Methylallene" OR "2-Butene-1,4-diyl" OR "Allene, methyl-" OR "alpha,gamma-Butadiene" OR "Biethylene" OR "Bivinyl" OR "Buta-1,2-dien" OR "Buta-1,2-diene" OR "Buta-1,3-dien" OR "Buta-1,3-diene" OR "Butadien" OR "Butadiene" OR "Butadiene" OR "Butadiene monomer"	29,744

Source	Source-Specific Search Strategy	Results
	OR "Butadiene-1,2" OR "Butadiene-1,3" OR "Divinyl" OR "Erythrene" OR "Methylallene" OR "NCI-C50602" OR "UN 1010" OR "UNII-2AZI943A8R" OR "UNII-JSD5FGP5VD" OR "Vinylethylene")	
Unify[a] Search Date: 6/6/2019	1,2-Butadien|1,2-Butadiene|1,3-BUTADIEN|1,3-Butadiene|1-Methylallene|2-Butene-1,4-diyl|Allene, methyl-|alpha,gamma-Butadiene|Biethylene|Bivinyl|Buta-1,2-dien|Buta-1,2-diene|Buta-1,3-dien|Buta-1,3-diene|Butadien|Butadiene|Butadiene|Butadiene monomer|Butadiene-1,2|Butadiene-1,3|Divinyl|Erythrene|Methylallene|NCI-C50602|UN 1010|UNII-2AZI943A8R|UNII-JSD5FGP5VD|Vinylethylene	22
Total	**Represents total across all databases after deduplication**	**36,777**
[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.		

C.1.10 Query Strings for the Peer-Reviewed Literature Database Searches on HHCB

These are the search terms compiled from the Chemical Report for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (HHCB) used in the initial search strategies for each of the databases listed below:

"(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7R)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-Galaxolide" OR "(4R,7S)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "4,6,6,7,8,8-Hexamethyl" OR "6-Ethyl-1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethylcyclopenta[g]-2-benzopyran" OR "6-Ethyl-4,6,8,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "8-Ethyl-1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethylcyclopenta[g]-2-benzopyran" OR "8-Ethyl-4,6,6,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "Abbalide" OR "Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-" OR "Cyclopenta[g]-" OR "Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-" OR "EINECS 214-946-9" OR "Galaxolide" OR "Galaxolide 50" OR "Galaxolide 50BB" OR "Galaxolide 50IPM" OR "Galaxolide White" OR "Galoxolide" OR "Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran" OR "Hexahydrohexamethyl cyclopentabenzopyran" OR "Hexahydrohexamethylcyclopentabenzopyran" OR "Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-" OR "Pearlide" OR "rel-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "rel-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "UNII-14170060AT"

Table_Apx C-10. Peer-Reviewed Literature Search Strategy for HHCB

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 6/20/2019	1. (4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran; (4R,7R)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran; (4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran 2. (4R,7S)-Galaxolide; (4R,7S)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran; (4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran; (4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran; (4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran; 1,2,4,7,8,9-Hexahydro; 1,3,4,6,7,8-hexahidro 3. 1,3,4,6,7,8-Hexahydro; 1,3,4,6,7,8-HEXAHYDRO; 1,3,4,7,8,9-Hexahydro; 2,3,4,6,7,8-Hexahydro; 4,6,6,7,8,8-Hexamethyl; 6-Ethyl-1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethylcyclopenta[g]-2-benzopyran; 6-Ethyl-4,6,8,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran; 8-Ethyl-1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethylcyclopenta[g]-2-benzopyran; 8-Ethyl-4,6,6,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran; Abbalide 4. Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-; Cyclopenta[g]-; Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-; EINECS 214-946-9; Galaxolide; Galaxolide 50; Galaxolide 50BB; Galaxolide 50IPM; Galaxolide White; Galoxolide 5. Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran; Hexahydrohexamethyl cyclopentabenzopyran; Hexahydrohexamethylcyclopentabenzopyran; Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-; Pearlide; rel-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran; rel-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran; UNII-14170060AT	145
Current Contents Search Date: 6/19/2019	TS=("(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7R)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-Galaxolide" OR "(4R,7S)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "1,2,4,7,8,9-Hexahydro" OR "1,3,4,6,7,8-hexahidro" OR "1,3,4,6,7,8-Hexahydro" OR "1,3,4,6,7,8-HEXAHYDRO" OR "1,3,4,7,8,9-Hexahydro" OR "2,3,4,6,7,8-Hexahydro" OR "4,6,6,7,8,8-Hexamethyl" OR "6-Ethyl-1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethylcyclopenta[g]-2-benzopyran" OR "6-Ethyl-4,6,8,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "8-Ethyl-1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethylcyclopenta[g]-2-benzopyran" OR "8-Ethyl-4,6,6,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "Abbalide" OR "Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-" OR "Cyclopenta[g]-" OR "Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-" OR "EINECS 214-946-9" OR "Galaxolide" OR "Galaxolide 50" OR "Galaxolide 50BB" OR "Galaxolide 50IPM" OR "Galaxolide White" OR "Galoxolide" OR "Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran" OR "Hexahydrohexamethyl cyclopentabenzopyran" OR "Hexahydrohexamethylcyclopentabenzopyran" OR "Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-" OR "Pearlide" OR "rel-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "rel-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "UNII-14170060AT")	518

Source	Source-Specific Search Strategy	Results
ProQuest Dissertations & Theses Search Date: 6/20/2019	ALL("(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7R)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-Galaxolide" OR "(4R,7S)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "1,2,4,7,8,9-Hexahydro" OR "1,3,4,6,7,8-hexahidro" OR "1,3,4,6,7,8-Hexahydro" OR "1,3,4,6,7,8-HEXAHYDRO" OR "1,3,4,7,8,9-Hexahydro" OR "2,3,4,6,7,8-Hexahydro" OR "4,6,6,7,8,8-Hexamethyl" OR "6-Ethyl-1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethylcyclopenta[g]-2-benzopyran" OR "6-Ethyl-4,6,8,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "8-Ethyl-1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethylcyclopenta[g]-2-benzopyran" OR "8-Ethyl-4,6,6,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "Abbalide" OR "Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-" OR "Cyclopenta[g]-" OR "Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-" OR "EINECS 214-946-9" OR "Galaxolide" OR "Galaxolide 50" OR "Galaxolide 50BB" OR "Galaxolide 50IPM" OR "Galaxolide White" OR "Galoxolide" OR "Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran" OR "Hexahydrohexamethyl cyclopentabenzopyran" OR "Hexahydrohexamethylcyclopentabenzopyran" OR "Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-" OR "Pearlide" OR "rel-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "rel-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "UNII-14170060AT") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	1
ProQuest Agricultural & Scientific Database Search Date: 6/19/2019	ALL("(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7R)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-Galaxolide" OR "(4R,7S)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "1,2,4,7,8,9-Hexahydro" OR "1,3,4,6,7,8-hexahidro" OR "1,3,4,6,7,8-Hexahydro" OR "1,3,4,6,7,8-HEXAHYDRO" OR "1,3,4,7,8,9-Hexahydro" OR "2,3,4,6,7,8-Hexahydro" OR "4,6,6,7,8,8-Hexamethyl" OR "6-Ethyl-1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethylcyclopenta[g]-2-benzopyran" OR "6-Ethyl-4,6,8,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "8-Ethyl-1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethylcyclopenta[g]-2-benzopyran" OR "8-Ethyl-4,6,6,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "Abbalide" OR "Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-" OR "Cyclopenta[g]-" OR "Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-" OR "EINECS 214-946-9" OR "Galaxolide" OR "Galaxolide 50" OR "Galaxolide 50BB" OR "Galaxolide 50IPM" OR "Galaxolide White" OR "Galoxolide" OR "Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran" OR "Hexahydrohexamethyl cyclopentabenzopyran" OR "Hexahydrohexamethylcyclopentabenzopyran" OR "Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-" OR "Pearlide" OR "rel-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "rel-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "UNII-14170060AT") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	832
PubMed Search Date:	"(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7R)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-	309

Source	Source-Specific Search Strategy	Results
7/3/2019	benzopyran" OR "(4R,7S)-Galaxolide" OR "(4R,7S)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "4,6,6,7,8,8-Hexamethyl" OR "6-Ethyl-1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethylcyclopenta[g]-2-benzopyran" OR "6-Ethyl-4,6,8,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "8-Ethyl-1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethylcyclopenta[g]-2-benzopyran" OR "8-Ethyl-4,6,6,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "Abbalide" OR "Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-" OR "Cyclopenta[g]-" OR "Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-" OR "EINECS 214-946-9" OR "Galaxolide" OR "Galaxolide 50" OR "Galaxolide 50BB" OR "Galaxolide 50IPM" OR "Galaxolide White" OR "Galoxolide" OR "Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran" OR "Hexahydrohexamethyl cyclopentabenzopyran" OR "Hexahydrohexamethylcyclopentabenzopyran" OR "Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-" OR "Pearlide" OR "rel-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "rel-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "UNII-14170060AT"	
Science Direct Search Date: 6/20/2019	1. "(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7R)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-Galaxolide" OR "(4R,7S)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "1,2,4,7,8,9-Hexahydro" 2. "1,3,4,6,7,8-hexahidro" OR "1,3,4,6,7,8-Hexahydro" OR "1,3,4,6,7,8-HEXAHYDRO" OR "1,3,4,7,8,9-Hexahydro" OR "2,3,4,6,7,8-Hexahydro" OR "4,6,6,7,8,8-Hexamethyl" OR "6-Ethyl-1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethylcyclopenta[g]-2-benzopyran" OR "6-Ethyl-4,6,8,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "8-Ethyl-1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethylcyclopenta[g]-2-benzopyran" 3. "8-Ethyl-4,6,6,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "Abbalide" OR "Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-" OR "Cyclopenta[g]-" OR "Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-" OR "EINECS 214-946-9" OR "Galaxolide" OR "Galaxolide 50" OR "Galaxolide 50BB" 4. "Galaxolide 50IPM" OR "Galaxolide White" OR "Galoxolide" OR "Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran" OR "Hexahydrohexamethyl cyclopentabenzopyran" OR "Hexahydrohexamethylcyclopentabenzopyran" OR "Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-" OR "Pearlide" OR "rel-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" 5. "rel-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "UNII-14170060AT"	102
ToxNet Search Date: 6/20/2019	1. 1222-05-5 OR 172339-62-7 OR 172339-63-8 OR 252332-95-9 OR 252332-96-0 2. 252933-48-5 OR 252933-49-6 OR 1222-06-6 OR 857091-61-3 OR 102296-64-0 3. 135546-43-9 OR 135546-42-8 OR 114109-63-6 OR 114109-62-5 OR 78448-48-3 4. 78448-49-4 OR 80450-66-4	250
WoS Search Date:	TS=("(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7R)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-	567

Source	Source-Specific Search Strategy	Results
9/13/2019	hexamethylcyclopenta[g]-2-benzopyran" OR "(4R,7S)-Galaxolide" OR "(4R,7S)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran" OR "(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "(4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "1,2,4,7,8,9-Hexahydro" OR "1,3,4,6,7,8-hexahidro" OR "1,3,4,6,7,8-Hexahydro" OR "1,3,4,6,7,8-HEXAHYDRO" OR "1,3,4,7,8,9-Hexahydro" OR "2,3,4,6,7,8-Hexahydro" OR "4,6,6,7,8,8-Hexamethyl" OR "6-Ethyl-1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethylcyclopenta[g]-2-benzopyran" OR "6-Ethyl-4,6,8,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "8-Ethyl-1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethylcyclopenta[g]-2-benzopyran" OR "8-Ethyl-4,6,6,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran" OR "Abbalide" OR "Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-" OR "Cyclopenta[g]-" OR "Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-" OR "EINECS 214-946-9" OR "Galaxolide" OR "Galaxolide 50" OR "Galaxolide 50BB" OR "Galaxolide 50IPM" OR "Galaxolide White" OR "Galoxolide" OR "Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran" OR "Hexahydrohexamethyl cyclopentabenzopyran" OR "Hexahydrohexamethylcyclopentabenzopyran" OR "Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-" OR "Pearlide" OR "rel-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "rel-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran" OR "UNII-14170060AT")	
Unify[a] Search Date: 6/20/2019	(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran|(4R,7R)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran|(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran|(4R,7S)-Galaxolide|(4R,7S)-rel-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran|(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-cyclopenta[g]-2-benzopyran|(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran|(4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran|4,6,6,7,8,8-Hexamethyl|6-Ethyl-1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethylcyclopenta[g]-2-benzopyran|6-Ethyl-4,6,8,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran|8-Ethyl-1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethylcyclopenta[g]-2-benzopyran|8-Ethyl-4,6,6,8-tetramethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran|Abbalide|Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-|Cyclopenta[g]-|Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-|EINECS 214-946-9|Galaxolide|Galaxolide 50|Galaxolide 50BB|Galaxolide 50IPM|Galaxolide White|Galoxolide|Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran|Hexahydrohexamethyl cyclopentabenzopyran|Hexahydrohexamethylcyclopentabenzopyran|Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-|Pearlide|rel-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran|rel-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran|UNII-14170060AT	56
Total	**Represents total across all databases after deduplication**	**670**

[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.

C.1.11 Query Strings for the Peer-Reviewed Literature Database Searches on TBBPA

These are the search terms compiled from the Chemical Report for 4,4'-(1-Methylethylidene)bis[2, 6-dibromophenol] (TBBPA) used in the initial search strategies for each of the databases listed below:

"2, 2-Bis (4'-hydroxy-3',-5'-dibromophenyl) propane" OR "2,2',6,6'-Tetrabrom-4,4'-isopropylidendiphenol" OR "2,2',6,6'-tetrabromo-4,4'-isopropilidendifenol" OR "2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol" OR "2,2',6,6'-Tetrabromobisphenol A" OR "2,2-Bis(3,5-dibromo-4-hydroxyphenyl)propane" OR "2,2-Bis(4-hydroxy-3,5-dibromophenyl) propane" OR "2,2-Bis(4-hydroxy-3,5-dibromophenyl)propane" OR "3,3,5,5-Tetrabromobisphenol A" OR "3,3',5,5'-Tetrabromobisphenol A" OR "3,5,3',5'-Tetrabromobisphenol A" OR "4,4'-(1-Methylethylidene)bis(2,6-dibromophenol)" OR "4,4'-(1-Methylethylidene)bis[2,6-dibromophenol]" OR "4,4'-(2,2-propanediyl) bis[2,6-dibromo]phenol" OR "4,4'-(Methylethylidene)bis[2,6-dibromophenol]" OR "4,4'-(Propane-2,2-diyl)bis(2,6-dibromophenol)" OR "4,4'-Isopropylidenebis(2,6-dibromophenol)" OR "4,4'-Isopropylidenebis[2,6-dibromophenol]" OR "4,4'-Isopropylylidenebis(2,6-dibromophenol)" OR "BA 59" OR "BA 59BP" OR "BA 59P" OR "BIS(PHENOL, 2,6-DIBROMO), 4,4'-(1-METHYLETHYLIDENE)" OR "BISPHENOL A, TETRABROMO-" OR "BISPHENOL, 4,4'-(1-METHYLETHYLIDENE)TETRABROMO-" OR "Bromdian" OR "CP 2000" OR "FCP 2010" OR "FG 2000" OR "Fire Guard 2000" OR "Firemaster BP 4A" OR "Flame Cut 120G" OR "Flame Cut 120R" OR "FR 1524" OR "FR 1525" OR "GLCBA 59P" OR "Great Lakes BA-59P" OR "NSC 59775" OR "PB 100" OR "RB 100" OR "Saytex CP 2000" OR "Saytex RB 100" OR "Saytex RB 100PC" OR "T 0032" OR "TBBPA" OR "Tetrabromo-4,4'-isopropylidenediphenol" OR "Tetrabromobisphenol A" OR "TETRABROMOBISPHENOL-A" OR "Tetrabromodian" OR "Tetrabromodiphenylolpropane" OR "Tetrabromodiphenylopropane" OR "UNII-FQI02RFC3A"

Table_Apx C-11. Peer-Reviewed Literature Search Strategy for TBBPA

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 6/7/2019	1. 2, 2-Bis (4'-hydroxy-3',-5'-dibromophenyl) propane; 2,2',6,6'-Tetrabrom-4,4'-isopropylidendiphenol; 2,2',6,6'-tetrabromo-4,4'-isopropilidendifenol; 2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol; 2,2',6,6'-Tetrabromobisphenol A; 2,2-Bis(3,5-dibromo-4-hydroxyphenyl)propane; 2,2-Bis(4-hydroxy-3,5-dibromophenyl) propane; 2,2-Bis(4-hydroxy-3,5-dibromophenyl)propane; 3,3,5,5-Tetrabromobisphenol A; 3,3',5,5'-Tetrabromobisphenol A 2. 3,5,3',5'-Tetrabromobisphenol A; 4,4'-(1-Methylethylidene)bis(2,6-dibromophenol); 4,4'-(1-Methylethylidene)bis[2,6-dibromophenol]; 4,4'-(2,2-propanediyl) bis[2,6-dibromo]phenol; 4,4'-(Methylethylidene)bis[2,6-dibromophenol]; 4,4'-(Propane-2,2-diyl)bis(2,6-dibromophenol); 4,4'-Isopropylidenebis(2,6-dibromophenol); 4,4'-Isopropylidenebis[2,6-dibromophenol]; 4,4'-Isopropylylidenebis(2,6-dibromophenol); BA 59 3. BA 59BP; BA 59P; BIS(PHENOL, 2,6-DIBROMO), 4,4'-(1-METHYLETHYLIDENE); BISPHENOL A, TETRABROMO-; BISPHENOL, 4,4'-(1-METHYLETHYLIDENE)TETRABROMO- 4. Bromdian; CP 2000; FCP 2010; FG 2000; Fire Guard 2000; Firemaster BP 4A; Flame Cut 120G; Flame Cut 120R; FR 1524; FR 1525 5. GLCBA 59P; Great Lakes BA-59P; NSC 59775; PB 100; RB 100; Saytex CP 2000; Saytex RB 100; Saytex RB 100PC; T 0032; TBBPA 6. Tetrabromo-4,4'-isopropylidenediphenol; Tetrabromobisphenol A; TETRABROMOBISPHENOL-A; Tetrabromodian; Tetrabromodiphenylolpropane	417
Current Contents Search Date: 6/10/2019	TS=("2, 2-Bis (4'-hydroxy-3',-5'-dibromophenyl) propane" OR "2,2',6,6'-Tetrabrom-4,4'-isopropylidendiphenol" OR "2,2',6,6'-tetrabromo-4,4'-isopropilidendifenol" OR "2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol" OR "2,2',6,6'-Tetrabromobisphenol A" OR "2,2-Bis(3,5-dibromo-4-hydroxyphenyl)propane" OR "2,2-Bis(4-hydroxy-3,5-dibromophenyl) propane" OR "2,2-Bis(4-hydroxy-3,5-dibromophenyl)propane" OR "3,3,5,5-Tetrabromobisphenol A" OR "3,3',5,5'-Tetrabromobisphenol A" OR	1,375

Source	Source-Specific Search Strategy	Results
	"3,5,3',5'-Tetrabromobisphenol A" OR "4,4'-(1-Methylethylidene)bis(2,6-dibromophenol)" OR "4,4'-(1-Methylethylidene)bis[2,6-dibromophenol]" OR "4,4'-(2,2-propanediyl) bis[2,6-dibromo]phenol" OR "4,4'-(Methylethylidene)bis[2,6-dibromophenol]" OR "4,4'-(Propane-2,2-diyl)bis(2,6-dibromophenol)" OR "4,4'-Isopropylidenebis(2,6-dibromophenol)" OR "4,4'-Isopropylidenebis[2,6-dibromophenol]" OR "4,4'-Isopropylylidenebis(2,6-dibromophenol)" OR "BA 59" OR "BA 59BP" OR "BA 59P" OR "BIS(PHENOL, 2,6-DIBROMO), 4,4'-(1-METHYLETHYLIDENE)" OR "BISPHENOL A, TETRABROMO-" OR "BISPHENOL, 4,4'-(1-METHYLETHYLIDENE)TETRABROMO-" OR "Bromdian" OR "CP 2000" OR "FCP 2010" OR "FG 2000" OR "Fire Guard 2000" OR "Firemaster BP 4A" OR "Flame Cut 120G" OR "Flame Cut 120R" OR "FR 1524" OR "FR 1525" OR "GLCBA 59P" OR "Great Lakes BA-59P" OR "NSC 59775" OR "PB 100" OR "RB 100" OR "Saytex CP 2000" OR "Saytex RB 100" OR "Saytex RB 100PC" OR "T 0032" OR "TBBPA" OR "Tetrabromo-4,4'-isopropylidenediphenol" OR "Tetrabromobisphenol A" OR "TETRABROMOBISPHENOL-A" OR "Tetrabromodian" OR "Tetrabromodiphenylolpropane" OR "Tetrabromodiphenylopropane" OR "UNII-FQI02RFC3A")	
ProQuest Dissertations & Theses Search Date: 6/7/2019	ALL("2, 2-Bis (4'-hydroxy-3',-5'-dibromophenyl) propane" OR "2,2',6,6'-Tetrabrom-4,4'-isopropylidendiphenol" OR "2,2',6,6'-tetrabromo-4,4'-isopropilidendifenol" OR "2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol" OR "2,2',6,6'-Tetrabromobisphenol A" OR "2,2-Bis(3,5-dibromo-4-hydroxyphenyl)propane" OR "2,2-Bis(4-hydroxy-3,5-dibromophenyl) propane" OR "2,2-Bis(4-hydroxy-3,5-dibromophenyl)propane" OR "3,3,5,5-Tetrabromobisphenol A" OR "3,3',5,5'-Tetrabromobisphenol A" OR "3,5,3',5'-Tetrabromobisphenol A" OR "4,4'-(1-Methylethylidene)bis(2,6-dibromophenol)" OR "4,4'-(1-Methylethylidene)bis[2,6-dibromophenol]" OR "4,4'-(2,2-propanediyl) bis[2,6-dibromo]phenol" OR "4,4'-(Methylethylidene)bis[2,6-dibromophenol]" OR "4,4'-(Propane-2,2-diyl)bis(2,6-dibromophenol)" OR "4,4'-Isopropylidenebis(2,6-dibromophenol)" OR "4,4'-Isopropylidenebis[2,6-dibromophenol]" OR "4,4'-Isopropylylidenebis(2,6-dibromophenol)" OR "BA 59" OR "BA 59BP" OR "BA 59P" OR "BIS(PHENOL, 2,6-DIBROMO), 4,4'-(1-METHYLETHYLIDENE)" OR "BISPHENOL A, TETRABROMO-" OR "BISPHENOL, 4,4'-(1-METHYLETHYLIDENE)TETRABROMO-" OR "Bromdian" OR "CP 2000" OR "FCP 2010" OR "FG 2000" OR "Fire Guard 2000" OR "Firemaster BP 4A" OR "Flame Cut 120G" OR "Flame Cut 120R" OR "FR 1524" OR "FR 1525" OR "GLCBA 59P" OR "Great Lakes BA-59P" OR "NSC 59775" OR "PB 100" OR "RB 100" OR "Saytex CP 2000" OR "Saytex RB 100" OR "Saytex RB 100PC" OR "T 0032" OR "TBBPA" OR "Tetrabromo-4,4'-isopropylidenediphenol" OR "Tetrabromobisphenol A" OR "TETRABROMOBISPHENOL-A" OR "Tetrabromodian" OR "Tetrabromodiphenylolpropane") AND LA(ENG)	7
ProQuest Agricultural & Scientific Database Search Date: 6/11/2019	ALL("2, 2-Bis (4'-hydroxy-3',-5'-dibromophenyl) propane" OR "2,2',6,6'-Tetrabrom-4,4'-isopropylidendiphenol" OR "2,2',6,6'-tetrabromo-4,4'-isopropilidendifenol" OR "2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol" OR "2,2',6,6'-Tetrabromobisphenol A" OR "2,2-Bis(3,5-dibromo-4-hydroxyphenyl)propane" OR "2,2-Bis(4-hydroxy-3,5-dibromophenyl) propane" OR "2,2-Bis(4-hydroxy-3,5-dibromophenyl)propane" OR "3,3,5,5-Tetrabromobisphenol A" OR "3,3',5,5'-Tetrabromobisphenol A" OR "3,5,3',5'-Tetrabromobisphenol A" OR "4,4'-(1-Methylethylidene)bis(2,6-dibromophenol)" OR "4,4'-(1-Methylethylidene)bis[2,6-dibromophenol]" OR "4,4'-(2,2-propanediyl) bis[2,6-dibromo]phenol" OR "4,4'-(Methylethylidene)bis[2,6-dibromophenol]" OR "4,4'-(Propane-2,2-diyl)bis(2,6-dibromophenol)" OR "4,4'-Isopropylidenebis(2,6-dibromophenol)" OR "4,4'-Isopropylidenebis[2,6-dibromophenol]" OR "4,4'-Isopropylylidenebis(2,6-dibromophenol)" OR "BA 59" OR "BA 59BP" OR "BA 59P" OR "BIS(PHENOL, 2,6-DIBROMO), 4,4'-(1-METHYLETHYLIDENE)" OR "BISPHENOL A, TETRABROMO-" OR "BISPHENOL, 4,4'-(1-METHYLETHYLIDENE)TETRABROMO-" OR "Bromdian" OR "CP 2000" OR "FCP 2010" OR "FG 2000" OR "Fire Guard 2000" OR "Firemaster BP 4A" OR "Flame Cut 120G" OR "Flame Cut 120R" OR "FR 1524" OR "FR 1525" OR "GLCBA 59P" OR "Great Lakes BA-59P" OR "NSC 59775" OR "PB 100" OR "RB 100" OR "Saytex CP 2000" OR	1,967

Source	Source-Specific Search Strategy	Results
	"Saytex RB 100" OR "Saytex RB 100PC" OR "T 0032" OR "TBBPA" OR "Tetrabromo-4,4'-isopropylidenediphenol" OR "Tetrabromobisphenol A" OR "TETRABROMOBISPHENOL-A" OR "Tetrabromodian" OR "Tetrabromodiphenylolpropane" OR "Tetrabromodiphenylopropane" OR "UNII-FQI02RFC3A") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	
PubMed Search Date: 7/2/2019	"2, 2-Bis (4'-hydroxy-3',-5'-dibromophenyl) propane" OR "2,2',6,6'-Tetrabrom-4,4'-isopropylidendiphenol" OR "2,2',6,6'-tetrabromo-4,4'-isopropilidendifenol" OR "2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol" OR "2,2',6,6'-Tetrabromobisphenol A" OR "2,2-Bis(3,5-dibromo-4-hydroxyphenyl)propane" OR "2,2-Bis(4-hydroxy-3,5-dibromophenyl) propane" OR "2,2-Bis(4-hydroxy-3,5-dibromophenyl)propane" OR "3,3,5,5-Tetrabromobisphenol A" OR "3,3',5,5'-Tetrabromobisphenol A" OR "3,5,3',5'-Tetrabromobisphenol A" OR "4,4'-(1-Methylethylidene)bis(2,6-dibromophenol)" OR "4,4'-(1-Methylethylidene)bis[2,6-dibromophenol]" OR "4,4'-(2,2-propanediyl) bis[2,6-dibromo]phenol" OR "4,4'-(Methylethylidene)bis[2,6-dibromophenol]" OR "4,4'-(Propane-2,2-diyl)bis(2,6-dibromophenol)" OR "4,4'-Isopropylidenebis(2,6-dibromophenol)" OR "4,4'-Isopropylidenebis[2,6-dibromophenol]" OR "4,4'-Isopropylylidenebis(2,6-dibromophenol)" OR "BA 59" OR "BA 59BP" OR "BA 59P" OR "BIS(PHENOL, 2,6-DIBROMO), 4,4'-(1-METHYLETHYLIDENE)" OR "BISPHENOL A, TETRABROMO-" OR "BISPHENOL, 4,4'-(1-METHYLETHYLIDENE)TETRABROMO-" OR "Bromdian" OR "CP 2000" OR "FCP 2010" OR "FG 2000" OR "Fire Guard 2000" OR "Firemaster BP 4A" OR "Flame Cut 120G" OR "Flame Cut 120R" OR "FR 1524" OR "FR 1525" OR "GLCBA 59P" OR "Great Lakes BA-59P" OR "NSC 59775" OR "PB 100" OR "RB 100" OR "Saytex CP 2000" OR "Saytex RB 100" OR "Saytex RB 100PC" OR "T 0032" OR "TBBPA" OR "Tetrabromo-4,4'-isopropylidenediphenol" OR "Tetrabromobisphenol A" OR "TETRABROMOBISPHENOL-A" OR "Tetrabromodian" OR "Tetrabromodiphenylolpropane" OR "Tetrabromodiphenylopropane" OR "UNII-FQI02RFC3A"	1,070
Science Direct Search Date: 6/11/2019	1. "2, 2-Bis (4'-hydroxy-3',-5'-dibromophenyl) propane" OR "2,2',6,6'-Tetrabrom-4,4'-isopropylidendiphenol" OR "2,2',6,6'-tetrabromo-4,4'-isopropilidendifenol" OR "2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol" OR "2,2',6,6'-Tetrabromobisphenol A" OR "2,2-Bis(3,5-dibromo-4-hydroxyphenyl)propane" OR "2,2-Bis(4-hydroxy-3,5-dibromophenyl) propane" OR "2,2-Bis(4-hydroxy-3,5-dibromophenyl)propane" OR "3,3,5,5-Tetrabromobisphenol A" 2. "3,3',5,5'-Tetrabromobisphenol A" OR "3,5,3',5'-Tetrabromobisphenol A" OR "4,4'-(1-Methylethylidene)bis(2,6-dibromophenol)" OR "4,4'-(1-Methylethylidene)bis[2,6-dibromophenol]" OR "4,4'-(2,2-propanediyl) bis[2,6-dibromo]phenol" OR "4,4'-(Methylethylidene)bis[2,6-dibromophenol]" OR "4,4'-(Propane-2,2-diyl)bis(2,6-dibromophenol)" OR "4,4'-Isopropylidenebis(2,6-dibromophenol)" OR "4,4'-Isopropylidenebis[2,6-dibromophenol]" 3. "4,4'-Isopropylylidenebis(2,6-dibromophenol)" OR "BA 59" OR "BA 59BP" OR "BA 59P" OR "BIS(PHENOL, 2,6-DIBROMO), 4,4'-(1-METHYLETHYLIDENE)" OR "BISPHENOL A, TETRABROMO-" OR "BISPHENOL, 4,4'-(1-METHYLETHYLIDENE)TETRABROMO-" OR "Bromdian" OR "CP 2000" 4. "FCP 2010" OR "FG 2000" OR "Fire Guard 2000" OR "Firemaster BP 4A" OR "Flame Cut 120G" OR "Flame Cut 120R" OR "FR 1524" OR "FR 1525" OR "GLCBA 59P" 5. "Great Lakes BA-59P" OR "NSC 59775" OR "PB 100" OR "RB 100" OR "Saytex CP 2000" OR "Saytex RB 100" OR "Saytex RB 100PC" OR "T 0032" OR "TBBPA" 6. "Tetrabromo-4,4'-isopropylidenediphenol" OR "Tetrabromobisphenol A" OR "TETRABROMOBISPHENOL-A" OR "Tetrabromodian" OR "Tetrabromodiphenylolpropane" 7. "Tetrabromodiphenylopropane" OR "UNII-FQI02RFC3A"	1,228

Source	Source-Specific Search Strategy	Results
ToxNet Search Date: 6/11/2019	1. 79-94-7 OR 107719-55-1 OR 108608-60-2 OR 110670-65-0 OR 121839-52-9 2. 124779-54-0 OR 131891-38-8 OR 186673-39-2 OR 224951-26-2 OR 25639-54-7 3. 26446-62-8 OR 30496-13-0 OR 51253-31-7 OR 7300-23-4 OR 76341-26-9	784
WoS Search Date: 9/13/2019	TS=("2, 2-Bis (4'-hydroxy-3',-5'-dibromophenyl) propane" OR "2,2',6,6'-Tetrabrom-4,4'-isopropylidendiphenol" OR "2,2',6,6'-tetrabromo-4,4'-isopropilidendifenol" OR "2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol" OR "2,2',6,6'-Tetrabromobisphenol A" OR "2,2-Bis(3,5-dibromo-4-hydroxyphenyl)propane" OR "2,2-Bis(4-hydroxy-3,5-dibromophenyl) propane" OR "2,2-Bis(4-hydroxy-3,5-dibromophenyl)propane" OR "3,3,5,5-Tetrabromobisphenol A" OR "3,3',5,5'-Tetrabromobisphenol A" OR "3,5,3',5'-Tetrabromobisphenol A" OR "4,4'-(1-Methylethylidene)bis(2,6-dibromophenol)" OR "4,4'-(1-Methylethylidene)bis[2,6-dibromophenol]" OR "4,4'-(2,2-propanediyl) bis[2,6-dibromo]phenol" OR "4,4'-(Methylethylidene)bis[2,6-dibromophenol]" OR "4,4'-(Propane-2,2-diyl)bis(2,6-dibromophenol)" OR "4,4'-Isopropylidenebis(2,6-dibromophenol)" OR "4,4'-Isopropylidenebis[2,6-dibromophenol]" OR "4,4'-Isopropylylidenebis(2,6-dibromophenol)" OR "BA 59" OR "BA 59BP" OR "BA 59P" OR "BIS(PHENOL, 2,6-DIBROMO), 4,4'-(1-METHYLETHYLIDENE)" OR "BISPHENOL A, TETRABROMO-" OR "BISPHENOL, 4,4'-(1-METHYLETHYLIDENE)TETRABROMO-" OR "Bromdian" OR "CP 2000" OR "FCP 2010" OR "FG 2000" OR "Fire Guard 2000" OR "Firemaster BP 4A" OR "Flame Cut 120G" OR "Flame Cut 120R" OR "FR 1524" OR "FR 1525" OR "GLCBA 59P" OR "Great Lakes BA-59P" OR "NSC 59775" OR "PB 100" OR "RB 100" OR "Saytex CP 2000" OR "Saytex RB 100" OR "Saytex RB 100PC" OR "T 0032" OR "TBBPA" OR "Tetrabromo-4,4'-isopropylidenediphenol" OR "Tetrabromobisphenol A" OR "TETRABROMOBISPHENOL-A" OR "Tetrabromodian" OR "Tetrabromodiphenylolpropane" OR "Tetrabromodiphenylopropane" OR "UNII-FQI02RFC3A")	1,631
Unify[a] Search Date: 6/11/2019	2, 2-Bis (4'-hydroxy-3',-5'-dibromophenyl) propane|2,2',6,6'-Tetrabrom-4,4'-isopropylidendiphenol|2,2',6,6'-tetrabromo-4,4'-isopropilidendifenol|2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol|2,2',6,6'-Tetrabromobisphenol A|2,2-Bis(3,5-dibromo-4-hydroxyphenyl)propane|2,2-Bis(4-hydroxy-3,5-dibromophenyl) propane|2,2-Bis(4-hydroxy-3,5-dibromophenyl)propane|3,3,5,5-Tetrabromobisphenol A|3,3',5,5'-Tetrabromobisphenol A|3,5,3',5'-Tetrabromobisphenol A|4,4'-(1-Methylethylidene)bis(2,6-dibromophenol)|4,4'-(1-Methylethylidene)bis[2,6-dibromophenol]|4,4'-(2,2-propanediyl) bis[2,6-dibromo]phenol|4,4'-(Methylethylidene)bis[2,6-dibromophenol]|4,4'-(Propane-2,2-diyl)bis(2,6-dibromophenol)|4,4'-Isopropylidenebis(2,6-dibromophenol)|4,4'-Isopropylidenebis[2,6-dibromophenol]|4,4'-Isopropylylidenebis(2,6-dibromophenol)|BA 59|BA 59BP|BA 59P|BIS(PHENOL, 2,6-DIBROMO), 4,4'-(1-METHYLETHYLIDENE)|BISPHENOL A, TETRABROMO-|BISPHENOL, 4,4'-(1-METHYLETHYLIDENE)TETRABROMO-|Bromdian|CP 2000|FCP 2010|FG 2000|Fire Guard 2000|Firemaster BP 4A|Flame Cut 120G|Flame Cut 120R|FR 1524|FR 1525|GLCBA 59P|Great Lakes BA-59P|NSC 59775|PB 100|RB 100|Saytex CP 2000|Saytex RB 100|Saytex RB 100PC|T 0032|TBBPA|Tetrabromo-4,4'-isopropylidenediphenol|Tetrabromobisphenol A|TETRABROMOBISPHENOL-A|Tetrabromodian|Tetrabromodiphenylolpropane|Tetrabromodiphenylopropane|UNII-FQI02RFC3A	134
Total	**Represents total across all databases after deduplication**	**2,177**

[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.

C.1.12 Query Strings for the Peer-Reviewed Literature Database Searches on TCEP

These are the search terms compiled from the Chemical Report for tris(2-chloroethyl) phosphate (TCEP) used in the initial search strategies for each of the databases listed below:

"2-Chloroethanol phosphate" OR "Amgard TCEP" OR "Antiblaze 100" OR "BRN 1710938" OR "Celluflex" OR "Celluflex CEF" OR "Disflamoll TCA" OR "Ethanol, 2-chloro-, 1,1',1''-phosphate" OR "ETHANOL, 2-CHLORO-, PHOSPHATE" OR "Ethanol, 2-chloro-, phosphate (3:1)" OR "Fyrol CEF" OR "Fyrol CF" OR "Genomoll P" OR "NCI-C60128" OR "Niax 3CF" OR "Niax Flame Retardant 3CF" OR "NSC 3213" OR "Phosphoric acid tris(2-chloroethyl) ester" OR "Phosphoric acid, tris(2-chloroethyl)ester" OR "Roflam E" OR "Tri(2-chloroethyl) phosphate" OR "Tri(2-chloroethyl)phosphate" OR "Tri(beta-chloroethyl) phosphate" OR "Tri(chloroethyl) phosphate" OR "Tri-beta-chloroethyl phosphate" OR "Tris (2-chloroethyl) phosphate" OR "TRIS-(2-CHLORAETHYL)-PHOSPHAT" OR "Tris(2-chlorethyl)phosphat" OR "Tris(2-chloroethyl) orthophosphate" OR "Tris(2-chloroethyl) phosphate" OR "Tris(2-chloroethyl) phosphate (TCEP)" OR "Tris(2-chloroethyl)phosphate" OR "Tris(beta-chloroethyl) phosphate" OR "Tris(beta-chloroethyl) phosphate" OR "Tris(beta-chloroethylphosphate)" OR "Tris(chloroethyl) phosphate" OR "Tris(chloroethyl)phosphate" OR "Tris-2-chloroethyl phosphate" OR "UNII-32IVO568B0"

Table_Apx C-12. Peer-Reviewed Literature Search Strategy for TCEP

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 6/11/2019	1. 2-Chloroethanol phosphate; Amgard TCEP; Antiblaze 100; BRN 1710938; Celluflex; Celluflex CEF; Disflamoll TCA; Ethanol, 2-chloro-, 1,1',1''-phosphate; ETHANOL, 2-CHLORO-, PHOSPHATE; Ethanol, 2-chloro-, phosphate (3:1) 2. Fyrol CEF; Fyrol CF; Genomoll P; NCI-C60128; Niax 3CF; Niax Flame Retardant 3CF; NSC 3213; Phosphoric acid tris(2-chloroethyl) ester; Phosphoric acid, tris(2-chloroethyl)ester; Roflam E 3. Tri(2-chloroethyl) phosphate; Tri(2-chloroethyl)phosphate; Tri(beta-chloroethyl) phosphate; Tri(chloroethyl) phosphate; Tri-beta-chloroethyl phosphate; Tris (2-chloroethyl) phosphate; TRIS-(2-CHLORAETHYL)-PHOSPHAT; Tris(2-chlorethyl)phosphat; Tris(2-chloroethyl) orthophosphate; Tris(2-chloroethyl) phosphate 4. Tris(2-chloroethyl) phosphate (TCEP); Tris(2-chloroethyl)phosphate; Tris(beta-chloroethyl) phosphate; Tris(beta-chloroethyl) phosphate; Tris(beta-chloroethylphosphate); Tris(chloroethyl) phosphate; Tris(chloroethyl)phosphate; Tris-2-chloroethyl phosphate; UNII-32IVO568B0	244
Current Contents Search Date: 6/11/2019	TS=("2-Chloroethanol phosphate" OR "Amgard TCEP" OR "Antiblaze 100" OR "BRN 1710938" OR "Celluflex" OR "Celluflex CEF" OR "Disflamoll TCA" OR "Ethanol, 2-chloro-, 1,1',1''-phosphate" OR "ETHANOL, 2-CHLORO-, PHOSPHATE" OR "Ethanol, 2-chloro-, phosphate (3:1)" OR "Fyrol CEF" OR "Fyrol CF" OR "Genomoll P" OR "NCI-C60128" OR "Niax 3CF" OR "Niax Flame Retardant 3CF" OR "NSC 3213" OR "Phosphoric acid tris(2-chloroethyl) ester" OR "Phosphoric acid, tris(2-chloroethyl)ester" OR "Roflam E" OR "Tri(2-chloroethyl) phosphate" OR "Tri(2-chloroethyl)phosphate" OR "Tri(beta-chloroethyl) phosphate" OR "Tri(chloroethyl) phosphate" OR "Tri-beta-chloroethyl phosphate" OR "Tris (2-chloroethyl) phosphate" OR "TRIS-(2-CHLORAETHYL)-PHOSPHAT" OR "Tris(2-chlorethyl)phosphat" OR "Tris(2-chloroethyl) orthophosphate" OR "Tris(2-chloroethyl) phosphate" OR "Tris(2-chloroethyl) phosphate (TCEP)" OR "Tris(2-chloroethyl)phosphate" OR "Tris(beta-chloroethyl) phosphate" OR "Tris(beta-chloroethyl)	313

Source	Source-Specific Search Strategy	Results
	phosphate" OR "Tris(beta-chloroethylphosphate)" OR "Tris(chloroethyl) phosphate" OR "Tris(chloroethyl)phosphate" OR "Tris-2-chloroethyl phosphate" OR "UNII-32IVO568B0")	
ProQuest Dissertations & Theses Search Date: 6/11/2019	ALL("2-Chloroethanol phosphate" OR "Amgard TCEP" OR "Antiblaze 100" OR "BRN 1710938" OR "Celluflex" OR "Celluflex CEF" OR "Disflamoll TCA" OR "Ethanol, 2-chloro-, 1,1',1''-phosphate" OR "ETHANOL, 2-CHLORO-, PHOSPHATE" OR "Ethanol, 2-chloro-, phosphate (3:1)" OR "Fyrol CEF" OR "Fyrol CF" OR "Genomoll P" OR "NCI-C60128" OR "Niax 3CF" OR "Niax Flame Retardant 3CF" OR "NSC 3213" OR "Phosphoric acid tris(2-chloroethyl) ester" OR "Phosphoric acid, tris(2-chloroethyl)ester" OR "Roflam E" OR "Tri(2-chloroethyl) phosphate" OR "Tri(2-chloroethyl)phosphate" OR "Tri(beta-chloroethyl) phosphate" OR "Tri(chloroethyl) phosphate" OR "Tri-beta-chloroethyl phosphate" OR "Tris (2-chloroethyl) phosphate" OR "TRIS-(2-CHLORAETHYL)-PHOSPHAT" OR "Tris(2-chlorethyl)phosphat" OR "Tris(2-chloroethyl) orthophosphate" OR "Tris(2-chloroethyl) phosphate" OR "Tris(2-chloroethyl) phosphate (TCEP)" OR "Tris(2-chloroethyl)phosphate" OR "Tris(beta-chloroethyl) phosphate" OR "Tris(beta-chloroethyl) phosphate" OR "Tris(beta-chloroethylphosphate)" OR "Tris(chloroethyl) phosphate" OR "Tris(chloroethyl)phosphate" OR "Tris-2-chloroethyl phosphate" OR "UNII-32IVO568B0") AND LA(ENG)	0
ProQuest Agricultural & Scientific Database Search Date: 6/11/2019	ALL("2-Chloroethanol phosphate" OR "Amgard TCEP" OR "Antiblaze 100" OR "BRN 1710938" OR "Celluflex" OR "Celluflex CEF" OR "Disflamoll TCA" OR "Ethanol, 2-chloro-, 1,1',1''-phosphate" OR "ETHANOL, 2-CHLORO-, PHOSPHATE" OR "Ethanol, 2-chloro-, phosphate (3:1)" OR "Fyrol CEF" OR "Fyrol CF" OR "Genomoll P" OR "NCI-C60128" OR "Niax 3CF" OR "Niax Flame Retardant 3CF" OR "NSC 3213" OR "Phosphoric acid tris(2-chloroethyl) ester" OR "Phosphoric acid, tris(2-chloroethyl)ester" OR "Roflam E" OR "Tri(2-chloroethyl) phosphate" OR "Tri(2-chloroethyl)phosphate" OR "Tri(beta-chloroethyl) phosphate" OR "Tri(chloroethyl) phosphate" OR "Tri-beta-chloroethyl phosphate" OR "Tris (2-chloroethyl) phosphate" OR "TRIS-(2-CHLORAETHYL)-PHOSPHAT" OR "Tris(2-chlorethyl)phosphat" OR "Tris(2-chloroethyl) orthophosphate" OR "Tris(2-chloroethyl) phosphate" OR "Tris(2-chloroethyl) phosphate (TCEP)" OR "Tris(2-chloroethyl)phosphate" OR "Tris(beta-chloroethyl) phosphate" OR "Tris(beta-chloroethyl) phosphate" OR "Tris(beta-chloroethylphosphate)" OR "Tris(chloroethyl) phosphate" OR "Tris(chloroethyl)phosphate" OR "Tris-2-chloroethyl phosphate" OR "UNII-32IVO568B0") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	599
PubMed Search Date: 7/03/2019	"2-Chloroethanol phosphate" OR "Amgard TCEP" OR "Antiblaze 100" OR "BRN 1710938" OR "Celluflex" OR "Celluflex CEF" OR "Disflamoll TCA" OR "Ethanol, 2-chloro-, 1,1',1''-phosphate" OR "ETHANOL, 2-CHLORO-, PHOSPHATE" OR "Ethanol, 2-chloro-, phosphate (3:1)" OR "Fyrol CEF" OR "Fyrol CF" OR "Genomoll P" OR "NCI-C60128" OR "Niax 3CF" OR "Niax Flame Retardant 3CF" OR "NSC 3213" OR "Phosphoric acid tris(2-chloroethyl) ester" OR "Phosphoric acid, tris(2-chloroethyl)ester" OR "Roflam E" OR "Tri(2-chloroethyl) phosphate" OR "Tri(2-chloroethyl)phosphate" OR "Tri(beta-chloroethyl) phosphate" OR "Tri(chloroethyl) phosphate" OR "Tri-beta-chloroethyl phosphate" OR "Tris (2-chloroethyl) phosphate" OR "TRIS-(2-CHLORAETHYL)-PHOSPHAT" OR "Tris(2-chlorethyl)phosphat" OR "Tris(2-chloroethyl) orthophosphate" OR "Tris(2-chloroethyl) phosphate" OR "Tris(2-chloroethyl) phosphate (TCEP)" OR "Tris(2-chloroethyl)phosphate" OR "Tris(beta-chloroethyl) phosphate" OR "Tris(beta-chloroethyl) phosphate" OR "Tris(beta-chloroethylphosphate)" OR "Tris(chloroethyl) phosphate" OR "Tris(chloroethyl)phosphate" OR "Tris-2-chloroethyl phosphate" OR "UNII-32IVO568B0"	274

Source	Source-Specific Search Strategy	Results
Science Direct Search Date: 6/11/2019	1. "2-Chloroethanol phosphate" OR "Amgard TCEP" OR "Antiblaze 100" OR "BRN 1710938" OR "Celluflex" OR "Celluflex CEF" OR "Disflamoll TCA" OR "Ethanol, 2-chloro-, 1,1',1''-phosphate" OR "ETHANOL, 2-CHLORO-, PHOSPHATE" 2. "Ethanol, 2-chloro-, phosphate (3:1)" OR "Fyrol CEF" OR "Fyrol CF" OR "Genomoll P" OR "NCI-C60128" OR "Niax 3CF" OR "Niax Flame Retardant 3CF" OR "NSC 3213" OR "Phosphoric acid tris(2-chloroethyl) ester" 3. "Phosphoric acid, tris(2-chloroethyl)ester" OR "Roflam E" OR "Tri(2-chloroethyl) phosphate" OR "Tri(2-chloroethyl)phosphate" OR "Tri(beta-chloroethyl) phosphate" OR "Tri(chloroethyl) phosphate" OR "Tri-beta-chloroethyl phosphate" OR "Tris (2-chloroethyl) phosphate" OR "TRIS-(2-CHLORAETHYL)-PHOSPHAT" 4. "Tris(2-chlorethyl)phosphat" OR "Tris(2-chloroethyl) orthophosphate" OR "Tris(2-chloroethyl) phosphate" OR "Tris(2-chloroethyl) phosphate (TCEP)" OR "Tris(2-chloroethyl)phosphate" OR "Tris(beta-chloroethyl) phosphate" OR "Tris(beta-chloroethyl) phosphate" OR "Tris(beta-chloroethylphosphate)" OR "Tris(chloroethyl) phosphate" 5. "Tris(chloroethyl)phosphate" OR "Tris-2-chloroethyl phosphate" OR "UNII-32IVO568B0"	805
ToxNet Search Date: 6/11/2019	115-86-6 OR 21343-84-0	632
WoS Search Date: 9/13/2019	TS=("2-Chloroethanol phosphate" OR "Amgard TCEP" OR "Antiblaze 100" OR "BRN 1710938" OR "Celluflex" OR "Celluflex CEF" OR "Disflamoll TCA" OR "Ethanol, 2-chloro-, 1,1',1''-phosphate" OR "ETHANOL, 2-CHLORO-, PHOSPHATE" OR "Ethanol, 2-chloro-, phosphate (3:1)" OR "Fyrol CEF" OR "Fyrol CF" OR "Genomoll P" OR "NCI-C60128" OR "Niax 3CF" OR "Niax Flame Retardant 3CF" OR "NSC 3213" OR "Phosphoric acid tris(2-chloroethyl) ester" OR "Phosphoric acid, tris(2-chloroethyl)ester" OR "Roflam E" OR "Tri(2-chloroethyl) phosphate" OR "Tri(2-chloroethyl)phosphate" OR "Tri(beta-chloroethyl) phosphate" OR "Tri(chloroethyl) phosphate" OR "Tri-beta-chloroethyl phosphate" OR "Tris (2-chloroethyl) phosphate" OR "TRIS-(2-CHLORAETHYL)-PHOSPHAT" OR "Tris(2-chlorethyl)phosphat" OR "Tris(2-chloroethyl) orthophosphate" OR "Tris(2-chloroethyl) phosphate" OR "Tris(2-chloroethyl) phosphate (TCEP)" OR "Tris(2-chloroethyl)phosphate" OR "Tris(beta-chloroethyl) phosphate" OR "Tris(beta-chloroethyl) phosphate" OR "Tris(beta-chloroethylphosphate)" OR "Tris(chloroethyl) phosphate" OR "Tris(chloroethyl)phosphate" OR "Tris-2-chloroethyl phosphate" OR "UNII-32IVO568B0")	361
Unify[a] Search Date: 6/11/2019	2-Chloroethanol phosphate|Amgard TCEP|Antiblaze 100|BRN 1710938|Celluflex|Celluflex CEF|Disflamoll TCA|Ethanol, 2-chloro-, 1,1',1''-phosphate|ETHANOL, 2-CHLORO-, PHOSPHATE|Ethanol, 2-chloro-, phosphate (3:1)|Fyrol CEF|Fyrol CF|Genomoll P|NCI-C60128|Niax 3CF|Niax Flame Retardant 3CF|NSC 3213|Phosphoric acid tris(2-chloroethyl) ester|Phosphoric acid, tris(2-chloroethyl)ester|Roflam E|Tri(2-chloroethyl) phosphate|Tri(2-chloroethyl)phosphate|Tri(beta-chloroethyl) phosphate|Tri(chloroethyl) phosphate|Tri-beta-chloroethyl phosphate|Tris (2-chloroethyl) phosphate|TRIS-(2-CHLORAETHYL)-PHOSPHAT|Tris(2-chlorethyl)phosphat|Tris(2-chloroethyl) orthophosphate|Tris(2-chloroethyl) phosphate|Tris(2-chloroethyl) phosphate (TCEP)|Tris(2-chloroethyl)phosphate|Tris(beta-chloroethyl) phosphate|Tris(beta-chloroethyl) phosphate|Tris(beta-chloroethylphosphate)|Tris(chloroethyl) phosphate|Tris(chloroethyl)phosphate|Tris-2-chloroethyl phosphate|UNII-32IVO568B0	32
Total	**Represents total across all databases after deduplication**	**955**

Source	Source-Specific Search Strategy	Results
[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.		

C.1.13 Query Strings for the Peer-Reviewed Literature Database Searches on TPP

These are the search terms compiled from the Chemical Report for Phosphoric acid, triphenyl ester (TPP) used in the initial search strategies for each of the databases listed below:

"Antioxidant TTP" OR "BRN 1888236" OR "Celluflex TPP" OR "DHPF 005" OR "Disflamoll TP" OR "NSC 57868" OR "O,O,O-Triphenyl phosphate" OR "Phenyl phosphate" OR "Phoscon FR 903N" OR "Phosflex TPP" OR "Phosphoric acid, triphenyl ester" OR "Phosphoric acid, triphenyl ester radical ion(1+)" OR "Reofos TPP" OR "Sumilizer TPP" OR "Triphenol phosphate" OR "Triphenoxyphosphine oxide" OR "Triphenyl phosphate" OR "Triphenylphosphat" OR "Triphenylphosphate" OR "UN 3077" OR "UNII-YZE19Z66EA" OR "Wako TPP" OR "WSFR-TPP"

Table_Apx C-13. Peer-Reviewed Literature Search Strategy for TPP

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 5/2/2019	1. Antioxidant TTP; BRN 1888236; Celluflex TPP; DHPF 005; Disflamoll TP; NSC 57868; O,O,O-Triphenyl phosphate; Phenyl phosphate; Phoscon FR 903N; Phosflex TPP 2. Phosphoric acid, triphenyl ester; Phosphoric acid, triphenyl ester radical ion(1+); Reofos TPP; Sumilizer TPP; Triphenol phosphate; Triphenoxyphosphine oxide; Triphenyl phosphate; Triphenylphosphat; Triphenylphosphate; UN 3077 3. UNII-YZE19Z66EA; Wako TPP; WSFR-TPP	270
Current Contents Search Date: 5/2/2019	TS=("Antioxidant TTP" OR "BRN 1888236" OR "Celluflex TPP" OR "DHPF 005" OR "Disflamoll TP" OR "NSC 57868" OR "O,O,O-Triphenyl phosphate" OR "Phenyl phosphate" OR "Phoscon FR 903N" OR "Phosflex TPP" OR "Phosphoric acid, triphenyl ester" OR "Phosphoric acid, triphenyl ester radical ion(1+)" OR "Reofos TPP" OR "Sumilizer TPP" OR "Triphenol phosphate" OR "Triphenoxyphosphine oxide" OR "Triphenyl phosphate" OR "Triphenylphosphat" OR "Triphenylphosphate" OR "UN 3077" OR "UNII-YZE19Z66EA" OR "Wako TPP" OR "WSFR-TPP")	497
ProQuest Dissertations & Theses Search Date: 5/3/2019	ALL("Antioxidant TTP" OR "BRN 1888236" OR "Celluflex TPP" OR "DHPF 005" OR "Disflamoll TP" OR "NSC 57868" OR "O,O,O-Triphenyl phosphate" OR "Phenyl phosphate" OR "Phoscon FR 903N" OR "Phosflex TPP" OR "Phosphoric acid, triphenyl ester" OR "Phosphoric acid, triphenyl ester radical ion(1+)" OR "Reofos TPP" OR "Sumilizer TPP" OR "Triphenol phosphate" OR "Triphenoxyphosphine oxide" OR "Triphenyl phosphate" OR "Triphenylphosphat" OR "Triphenylphosphate" OR "UN 3077" OR "UNII-YZE19Z66EA" OR "Wako TPP" OR "WSFR-TPP") AND LA(ENG)	6
ProQuest Agricultural & Scientific Database Search Date:	ALL("Antioxidant TTP" OR "BRN 1888236" OR "Celluflex TPP" OR "DHPF 005" OR "Disflamoll TP" OR "NSC 57868" OR "O,O,O-Triphenyl phosphate" OR "Phenyl phosphate" OR "Phoscon FR 903N" OR "Phosflex TPP" OR "Phosphoric acid, triphenyl ester" OR "Phosphoric acid, triphenyl ester radical ion(1+)" OR "Reofos TPP" OR "Sumilizer TPP" OR "Triphenol phosphate" OR "Triphenoxyphosphine oxide" OR "Triphenyl phosphate" OR "Triphenylphosphat" OR "Triphenylphosphate" OR	1,092

Source	Source-Specific Search Strategy	Results
5/2/2019	"UN 3077" OR "UNII-YZE19Z66EA" OR "Wako TPP" OR "WSFR-TPP") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	
PubMed Search Date: 5/5/2019	"Antioxidant TTP" OR "BRN 1888236" OR "Celluflex TPP" OR "DHPF 005" OR "Disflamoll TP" OR "NSC 57868" OR "O,O,O-Triphenyl phosphate" OR "Phenyl phosphate" OR "Phoscon FR 903N" OR "Phosflex TPP" OR "Phosphoric acid, triphenyl ester" OR "Phosphoric acid, triphenyl ester radical ion(1+)" OR "Reofos TPP" OR "Sumilizer TPP" OR "Triphenol phosphate" OR "Triphenoxyphosphine oxide" OR "Triphenyl phosphate" OR "Triphenylphosphat" OR "Triphenylphosphate" OR "UN 3077" OR "UNII-YZE19Z66EA" OR "Wako TPP" OR "WSFR-TPP"	690
Science Direct Search Date: 5/2/2019	1. "Antioxidant TTP" OR "BRN 1888236" OR "Celluflex TPP" OR "DHPF 005" OR "Disflamoll TP" OR "NSC 57868" OR "O,O,O-Triphenyl phosphate" OR "Phenyl phosphate" OR "Phoscon FR 903N" 2. "Phosflex TPP" OR "Phosphoric acid, triphenyl ester" OR "Phosphoric acid, triphenyl ester radical ion(1+)" OR "Reofos TPP" OR "Sumilizer TPP" OR "Triphenol phosphate" OR "Triphenoxyphosphine oxide" OR "Triphenyl phosphate" OR "Triphenylphosphat" 3. "Triphenylphosphate" OR "UN 3077" OR "UNII-YZE19Z66EA" OR "Wako TPP" OR "WSFR-TPP"	258
ToxNet Search Date: 5/2/2019	1. 115-86-6 OR 106971-30-6 OR 402955-02-6 2. (("triphenyl phosphate" OR "phosflex tpp" OR "disflamoll tp" OR "celluflex tpp" OR 115-86-6 [rn]) OR 106971-30-6 [rn] OR 402955-02-6 [rn]) AND (eng [la]) AND (BIOSIS [org] OR NTIS [org] OR PESTAB [org] OR PubMed [org] OR TSCATS [org])	624
WoS Search Date: 5/2/2019	TS=("Antioxidant TTP" OR "BRN 1888236" OR "Celluflex TPP" OR "DHPF 005" OR "Disflamoll TP" OR "NSC 57868" OR "O,O,O-Triphenyl phosphate" OR "Phenyl phosphate" OR "Phoscon FR 903N" OR "Phosflex TPP" OR "Phosphoric acid, triphenyl ester" OR "Phosphoric acid, triphenyl ester radical ion(1+)" OR "Reofos TPP" OR "Sumilizer TPP" OR "Triphenol phosphate" OR "Triphenoxyphosphine oxide" OR "Triphenyl phosphate" OR "Triphenylphosphat" OR "Triphenylphosphate" OR "UN 3077" OR "UNII-YZE19Z66EA" OR "Wako TPP" OR "WSFR-TPP")	1,172
Unify[a] Search Date: 5/3/2019	Antioxidant TTP|BRN 1888236|Celluflex TPP|DHPF 005|Disflamoll TP|NSC 57868|O,O,O-Triphenyl phosphate|Phenyl phosphate|Phoscon FR 903N|Phosflex TPP|Phosphoric acid, triphenyl ester|Phosphoric acid, triphenyl ester radical ion(1+)|Reofos TPP|Sumilizer TPP|Triphenol phosphate|Triphenoxyphosphine oxide|Triphenyl phosphate|Triphenylphosphat|Triphenylphosphate|UN 3077|UNII-YZE19Z66EA|Wako TPP|WSFR-TPP	162
Total	**Represents total across all databases after deduplication**	**1,861**

[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.

Additional Strategies

Additional keywords have been added to supplement the initial pool references. These are the search terms for Phosphoric acid, triphenyl ester (TPP) used in the supplemental search strategies for each of the databases listed below:

"TPHP" OR "115-86-6"

Table_Apx C-14. Supplemental Peer-Reviewed Literature Search Strategy for TPP

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 5/5/2021	TIAB("TPHP" OR "115-86-6")	153
Current Contents Search Date: 5/5/2021	TS=("TPHP" OR "115-86-6")	328
ProQuest Dissertations & Theses Search Date: 5/5/2021	TIAB("TPHP" OR "115-86-6")	1
ProQuest Agricultural & Scientific Database Search Date: 5/5/2021	TIAB("TPHP" OR "115-86-6")	224
PubMed Search Date: 5/5/2021	("TPHP"[tw] OR "115-86-6"[tw])	313
Scopus Search Date: 5/5/2021	TITLE-ABS({TPHP} OR {115-86-6})	342
ToxLine Search Date: 5/5/2021	1. tox[subset] AND ("TPHP"[tw] OR "115-86-6"[tw]) 2. TIAB("TPHP" OR "115-86-6")	280
WoS Search Date: 5/5/2021	TS=("TPHP" OR "115-86-6")	328
Total	**Represents total across all databases after deduplication**	**375**

C.1.14 Query Strings for the Peer-Reviewed Literature Database Searches on Formaldehyde

These are the search terms compiled from the Chemical Report for formaldehyde used in the initial search strategies for each of the databases listed below:

"Caswell No. 465" OR "Chlodithan" OR "Chlodithane" OR "Fannoform" OR "F-gen" OR "Floguard 1015" OR "FM 282" OR "Fordor" OR "Formacide-B" OR "Formalaz" OR "formaldehido" OR "Formaldehyd" OR "Formaldehyde" OR "Formalin" OR "Formalin 40" OR "Formalin LM" OR "Formalin Taisei" OR "Formalina" OR "Formaline" OR "Formalith" OR "Formic aldehyde" OR "Formol" OR "Ivalon" OR "Karsan" OR "Lysoform" OR "Methaldehyde" OR "Methan 21" OR "Methanal" OR "Methanediol" OR "Methyl aldehyde" OR "Methylene glycol" OR "Methylene oxide" OR "Morbicid" OR "NCI-C02799" OR "NSC 298885" OR "Oplossingen" OR "Optilyse" OR "Oxomethane" OR "Oxymethylene" OR "Paracide-F" OR "Superlysoform" OR "Tetraoxy methylene"

Table_Apx C-15. Peer-Reviewed Literature Search Strategy for Formaldehyde

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 5/16/2019	1. Caswell No. 465; Chlodithan; Chlodithane; Fannoform; F-gen; Floguard 1015; FM 282; Fordor; Formacide-B; Formalaz 2. Formaldehido; Formaldehyd; Formaldehyde; Formalin; Formalin 40; Formalin LM; Formalin Taisei; Formalina; Formaline; Formalith 3. Formic aldehyde; Formol; Ivalon; Karsan; Lysoform; Methaldehyde; Methan 21; Methanal; Methanediol; Methyl aldehyde 4. Methylene glycol; Methylene oxide; Morbicid; NCI-C02799; NSC 298885; Oplossingen; Optilyse; Oxomethane; Oxymethylene; Paracide-F 5. Superlysoform; Tetraoxy methylene	7,048
Current Contents Search Date: 4/29/2019	TS=("Caswell No. 465" OR "Chlodithan" OR "Chlodithane" OR "Fannoform" OR "F-gen" OR "Floguard 1015" OR "FM 282" OR "Fordor" OR "Formacide-B" OR "Formalaz" OR "formaldehido" OR "Formaldehyd" OR "Formaldehyde" OR "Formalin" OR "Formalin 40" OR "Formalin LM" OR "Formalin Taisei" OR "Formalina" OR "Formaline" OR "Formalith" OR "Formic aldehyde" OR "Formol" OR "Ivalon" OR "Karsan" OR "Lysoform" OR "Methaldehyde" OR "Methan 21" OR "Methanal" OR "Methanediol" OR "Methyl aldehyde" OR "Methylene glycol" OR "Methylene oxide" OR "Morbicid" OR "NCI-C02799" OR "NSC 298885" OR "Oplossingen" OR "Optilyse" OR "Oxomethane" OR "Oxymethylene" OR "Paracide-F" OR "Superlysoform" OR "Tetraoxy methylene")	25,408
ProQuest Dissertations & Theses Search Date: 4/26/2019	ALL("Caswell No. 465" OR "Chlodithan" OR "Chlodithane" OR "Fannoform" OR "F-gen" OR "Floguard 1015" OR "FM 282" OR "Fordor" OR "Formacide-B" OR "Formalaz" OR "formaldehido" OR "Formaldehyd" OR "Formaldehyde" OR "Formalin" OR "Formalin 40" OR "Formalin LM" OR "Formalin Taisei" OR "Formalina" OR "Formaline" OR "Formalith" OR "Formic aldehyde" OR "Formol" OR "Ivalon" OR "Karsan" OR "Lysoform" OR "Methaldehyde" OR "Methan 21" OR "Methanal" OR "Methanediol" OR "Methyl aldehyde" OR "Methylene glycol" OR "Methylene oxide" OR "Morbicid" OR "NCI-C02799" OR "NSC 298885" OR "Oplossingen" OR "Optilyse" OR "Oxomethane" OR "Oxymethylene" OR "Paracide-F" OR "Superlysoform" OR "Tetraoxy methylene") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	397
ProQuest Agricultural & Scientific Database Search Date: 5/1/2019	ALL("Caswell No. 465" OR "Chlodithan" OR "Chlodithane" OR "Fannoform" OR "F-gen" OR "Floguard 1015" OR "FM 282" OR "Fordor" OR "Formacide-B" OR "Formalaz" OR "formaldehido" OR "Formaldehyd" OR "Formaldehyde" OR "Formalin" OR "Formalin 40" OR "Formalin LM" OR "Formalin Taisei" OR "Formalina" OR "Formaline" OR "Formalith" OR "Formic aldehyde" OR "Formol" OR "Ivalon" OR "Karsan" OR "Lysoform" OR "Methaldehyde" OR "Methan 21" OR "Methanal" OR "Methanediol" OR "Methyl aldehyde" OR "Methylene glycol" OR "Methylene oxide" OR "Morbicid" OR "NCI-C02799" OR "NSC 298885" OR "Oplossingen" OR "Optilyse" OR "Oxomethane" OR "Oxymethylene" OR "Paracide-F" OR "Superlysoform" OR "Tetraoxy methylene") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	33,035
PubMed Search Date: 10/30/2019	"Caswell No. 465" OR "Chlodithan" OR "Chlodithane" OR "Fannoform" OR "F-gen" OR "Floguard 1015" OR "FM 282" OR "Fordor" OR "Formacide-B" OR "Formalaz" OR "formaldehido" OR "Formaldehyd" OR "Formaldehyde" OR "Formalin" OR "Formalin 40" OR "Formalin LM" OR "Formalin Taisei" OR "Formalina" OR "Formaline" OR "Formalith" OR "Formic aldehyde" OR "Formol" OR "Ivalon" OR "Karsan" OR "Lysoform" OR "Methaldehyde" OR "Methan 21" OR "Methanal" OR "Methanediol" OR "Methyl aldehyde" OR "Methylene glycol" OR "Methylene oxide" OR "Morbicid" OR "NCI-C02799" OR	58,805

Source	Source-Specific Search Strategy	Results
	"NSC 298885" OR "Oplossingen" OR "Optilyse" OR "Oxomethane" OR "Oxymethylene" OR "Paracide-F" OR "Superlysoform" OR "Tetraoxy methylene"	
Science Direct Search Date: 5/13/2019	1. "Caswell No. 465" OR "Chlodithan" OR "Chlodithane" OR "Fannoform" OR "F-gen" OR "Floguard 1015" OR "FM 282" OR "Fordor" OR "Formacide-B" 2. "Formalaz" OR "formaldehido" OR "Formaldehyd" OR "Formaldehyde" OR "Formalin" OR "Formalin 40" OR "Formalin LM" OR "Formalin Taisei" OR "Formalina" 3. "Formaline" OR "Formalith" OR "Formic aldehyde" OR "Formol" OR "Ivalon" OR "Karsan" OR "Lysoform" OR "Methaldehyde" OR "Methan 21" 4. "Methanal" OR "Methanediol" OR "Methyl aldehyde" OR "Methylene glycol" OR "Methylene oxide" OR "Morbicid" OR "NCI-C02799" OR "NSC 298885" OR "Oplossingen" 5. "Optilyse" OR "Oxomethane" OR "Oxymethylene" OR "Paracide-F" OR "Superlysoform" OR "Tetraoxy methylene"	87,731
ToxNet Search Date: 5/4/2019	1. 50-00-0 OR 1053659-79-2 OR 1156543-56-4 OR 1158237-02-5 OR 1227476-28-9 2. ((formaldehyde OR formalin OR methanal OR "formaldehyde usp " OR superlysoform OR oxymethylene OR oxomethane OR morbicid OR "methylene oxide" OR "methyl aldehyde" OR lysoform OR fyde OR formol OR "formic aldehyde" OR formalith OR fannoform OR 50-00-0 [rn]) OR 1053659 79 2 OR 1156543 56 4 OR 1158237 02 5 OR 1227476 28 9) AND 1900:1990 [yr] AND (eng [la]) AND (BIOSIS [org] OR NTIS [org] OR PESTAB [org] OR PubMed [org] OR TSCATS [org]) 3. ((formaldehyde OR formalin OR methanal OR "formaldehyde usp " OR superlysoform OR oxymethylene OR oxomethane OR morbicid OR "methylene oxide" OR "methyl aldehyde" OR lysoform OR fyde OR formol OR "formic aldehyde" OR formalith OR fannoform OR 50-00-0 [rn]) OR 1053659 79 2 OR 1156543 56 4 OR 1158237 02 5 OR 1227476 28 9) AND 1991:2000 [yr] AND (eng [la]) AND (BIOSIS [org] OR NTIS [org] OR PESTAB [org] OR PubMed [org] OR TSCATS [org]) 4. ((formaldehyde OR formalin OR methanal OR "formaldehyde usp " OR superlysoform OR oxymethylene OR oxomethane OR morbicid OR "methylene oxide" OR "methyl aldehyde" OR lysoform OR fyde OR formol OR "formic aldehyde" OR formalith OR fannoform OR 50-00-0 [rn]) OR 1053659 79 2 OR 1156543 56 4 OR 1158237 02 5 OR 1227476 28 9) AND 2001:2010 [yr] AND (eng [la]) AND (BIOSIS [org] OR NTIS [org] OR PESTAB [org] OR PubMed [org] OR TSCATS [org]) 5. ((formaldehyde OR formalin OR methanal OR "formaldehyde usp " OR superlysoform OR oxymethylene OR oxomethane OR morbicid OR "methylene oxide" OR "methyl aldehyde" OR lysoform OR fyde OR formol OR "formic aldehyde" OR formalith OR fannoform OR 50-00-0 [rn]) OR 1053659 79 2 OR 1156543 56 4 OR 1158237 02 5 OR 1227476 28 9) AND 2011:2019 [yr] AND (eng [la]) AND (BIOSIS [org] OR NTIS [org] OR PESTAB [org] OR PubMed [org] OR TSCATS [org]) 6. 8005-38-7 OR 2230356 OR 8013-13-6 OR 112068-71-0 OR 1417997-02-4	16,899
WoS Search Date: 10/30/2019	TS=("Caswell No. 465" OR "Chlodithan" OR "Chlodithane" OR "Fannoform" OR "F-gen" OR "Floguard 1015" OR "FM 282" OR "Fordor" OR "Formacide-B" OR "Formalaz" OR "formaldehido" OR "Formaldehyd" OR "Formaldehyde" OR "Formalin" OR "Formalin 40" OR "Formalin LM" OR "Formalin Taisei" OR "Formalina" OR "Formaline" OR "Formalith" OR "Formic aldehyde" OR "Formol" OR "Ivalon" OR "Karsan" OR "Lysoform" OR "Methaldehyde" OR "Methan 21" OR "Methanal" OR	83,897

Source	Source-Specific Search Strategy	Results
	"Methanediol" OR "Methyl aldehyde" OR "Methylene glycol" OR "Methylene oxide" OR "Morbicid" OR "NCI-C02799" OR "NSC 298885" OR "Oplossingen" OR "Optilyse" OR "Oxomethane" OR "Oxymethylene" OR "Paracide-F" OR "Superlysoform" OR "Tetraoxy methylene")	
Unify[a] Search Date: 10/29/2019	Caswell No. 465|Chlodithan|Chlodithane|Fannoform|F-gen|Floguard 1015|FM 282|Fordor|Formacide-B|Formalaz|formaldehido|Formaldehyd|Formaldehyde|Formalin| Formalin 40|Formalin LM|Formalin Taisei|Formalina|Formaline|Formalith|Formic aldehyde|Formol|Ivalon|Karsan|Lysoform|Methaldehyde|Methan 21|Methanal|Methanediol|Methyl aldehyde|Methylene glycol|Methylene oxide|Morbicid|NCI-C02799|NSC 298885|Oplossingen|Optilyse|Oxomethane| Oxymethylene|Paracide-F|Superlysoform|Tetraoxy methylene	591
Total	**Represents total across all databases after deduplication**	**167,132**
[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.		

Additional Strategies

Additional keywords have been added to supplement the initial pool references. These are the search terms for Formaldehyde used in the supplemental search strategies for each of the databases listed below:

"Aldacide" OR "Caswell No. 633" OR "Ethanol, 2-ethoxy-, polymer with formaldehyde" OR "Flo-Mor" OR "Formaldegen" OR "Granuform" OR "Oilstop, Halowax" OR "para formaldehyde" OR "Paraform" OR "Paraformaldehyde" OR "Paraformaldehyde (as impurity only; no longer cleared as inert)" OR "Paraformaldehydum" OR "Paraformic aldehyde" OR "PFA" OR "Polymerised formaldehyde" OR "Polyoxymethylene glycol" OR "TransFix" OR "UN 2213" OR "UNII-Y19UC83H8E"

Table_Apx C-16. Supplemental Peer-Reviewed Literature Search Strategy for Unspecified Paraformaldehyde

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 2/29/2020	Aldacide; Caswell No. 633; Ethanol, 2-ethoxy-, polymer with formaldehyde; Flo-Mor; Formaldegen; Granuform; Oilstop, Halowax; para formaldehyde; Paraform; Paraformaldehyde Paraformaldehyde (as impurity only; no longer cleared as inert); Paraformaldehydum; Paraformic aldehyde; PFA; Polymerised formaldehyde; Polyoxymethylene glycol; TransFix; UN 2213; UNII-Y19UC83H8E	780
Current Contents Search Date: 2/27/2020	TS=("Aldacide" OR "Caswell No. 633" OR "Ethanol, 2-ethoxy-, polymer with formaldehyde" OR "Flo-Mor" OR "Formaldegen" OR "Granuform" OR "Oilstop, Halowax" OR "para formaldehyde" OR "Paraform" OR "Paraformaldehyde" OR "Paraformaldehyde (as impurity only; no longer cleared as inert)" OR "Paraformaldehydum" OR "Paraformic aldehyde" OR "PFA" OR "Polymerised formaldehyde" OR "Polyoxymethylene glycol" OR "TransFix" OR "UN 2213" OR "UNII-Y19UC83H8E")	2,987

Source	Source-Specific Search Strategy	Results
ProQuest Dissertations & Theses Search Date: 2/28/2020	ALL("Aldacide" OR "Caswell No. 633" OR "Ethanol, 2-ethoxy-, polymer with formaldehyde" OR "Flo-Mor" OR "Formaldegen" OR "Granuform" OR "Oilstop, Halowax" OR "para formaldehyde" OR "Paraform" OR "Paraformaldehyde" OR "Paraformaldehyde (as impurity only; no longer cleared as inert)" OR "Paraformaldehydum" OR "Paraformic aldehyde" OR "PFA" OR "Polymerised formaldehyde" OR "Polyoxymethylene glycol" OR "TransFix" OR "UN 2213" OR "UNII-Y19UC83H8E") AND LA(ENG)	54
ProQuest Agricultural & Scientific Database Search Date: 2/26/2020	ALL("Aldacide" OR "Caswell No. 633" OR "Ethanol, 2-ethoxy-, polymer with formaldehyde" OR "Flo-Mor" OR "Formaldegen" OR "Granuform" OR "Oilstop, Halowax" OR "para formaldehyde" OR "Paraform" OR "Paraformaldehyde" OR "Paraformaldehyde (as impurity only; no longer cleared as inert)" OR "Paraformaldehydum" OR "Paraformic aldehyde" OR "PFA" OR "Polymerised formaldehyde" OR "Polyoxymethylene glycol" OR "TransFix" OR "UN 2213" OR "UNII-Y19UC83H8E") AND LA(ENG)	4,009
PubMed Search Date: 2/27/2020	"Aldacide" OR "Caswell No. 633" OR "Ethanol, 2-ethoxy-, polymer with formaldehyde" OR "Flo-Mor" OR "Formaldegen" OR "Granuform" OR "Oilstop, Halowax" OR "para formaldehyde" OR "Paraform" OR "Paraformaldehyde" OR "Paraformaldehyde (as impurity only; no longer cleared as inert)" OR "Paraformaldehydum" OR "Paraformic aldehyde" OR "PFA" OR "Polymerised formaldehyde" OR "Polyoxymethylene glycol" OR "TransFix" OR "UN 2213" OR "UNII-Y19UC83H8E"	7,005
Science Direct Search Date: 2/27/2020	1. "Aldacide" OR "Caswell No. 633" OR "Ethanol, 2-ethoxy-, polymer with formaldehyde" OR "Flo-Mor" OR "Formaldegen" OR "Granuform" OR "Oilstop, Halowax" OR "para formaldehyde" OR "Paraform" 2. "Paraformaldehyde" OR "Paraformaldehyde (as impurity only; no longer cleared as inert)" OR "Paraformaldehydum" OR "Paraformic aldehyde" OR "PFA" OR "Polymerised formaldehyde" OR "Polyoxymethylene glycol" OR "TransFix" OR "UN 2213"	3,965
ToxLine Search Date: 2/27/2020	1. 30525-89-4 OR 53026-80-5 OR 104512-58-5 OR 104512-63-2 OR 104814-22-4 2. 1417997-02-4	158
WoS Search Date: 2/27/2020	TS=("Aldacide" OR "Caswell No. 633" OR "Ethanol, 2-ethoxy-, polymer with formaldehyde" OR "Flo-Mor" OR "Formaldegen" OR "Granuform" OR "Oilstop, Halowax" OR "para formaldehyde" OR "Paraform" OR "Paraformaldehyde" OR "Paraformaldehyde (as impurity only; no longer cleared as inert)" OR "Paraformaldehydum" OR "Paraformic aldehyde" OR "PFA" OR "Polymerised formaldehyde" OR "Polyoxymethylene glycol" OR "TransFix" OR "UN 2213" OR "UNII-Y19UC83H8E")	9,040
Unify[a] Search Date: 2/28/2020	Aldacide|Caswell No. 465|Caswell No. 633|Chlodithan|Chlodithane|Fannoform|F-gen|Floguard 1015|Flo-Mor|FM 282|Fordor|Formacide-B|Formalaz|formaldehido|Formaldehyd|Formaldehyde|Formalin|Formalin 40|Formalin LM|Formalin Taisei|Formalina|Formaline|Formalith|Formic aldehyde|Formol|Granuform|Ivalon|Karsan|Lysoform|Methaldehyde|Methan 21|Methanal|Methanediol|Methyl aldehyde|Methylene glycol|Methylene oxide|Morbicid|NCI-C02799|NSC 298885|Oilstop, Halowax|Oplossingen|Optilyse|Oxomethane|Oxymethylene|para formaldehyde|Paracide-F|Paraform|Paraformaldehyde|Paraformic aldehyde|Polymerised formaldehyde|Polyoxymethylene glycol|Superlysoform|Tetraoxy methylene|TransFix	18

Source	Source-Specific Search Strategy	Results
Total	**Represents total across all databases after deduplication**	**14,211**
[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.		

C.1.15 Query Strings for the Peer-Reviewed Literature Database Searches on Phthalic Anhydride

These are the search terms compiled from the Chemical Report for phthalic anhydride used in the initial search strategies for each of the databases listed below:

"Phthalic anhydride," "85-44-9," "Anidride ftalica"; "Phthalsaureanhydrid"; "Anhydride phtalique"; "Phthalanhydride"; "anhidrido ftalico"; "1,2-benzenedicaboxylic acid anhydride"; "1,3-Isobenzofurandione"; "isobenzofuran-1,3-dione"; ("phthalic anhydride" AND ("PA" OR "M 2" OR "PAN" OR "PSA" OR "PAD")); "Phthalandione"

Table_Apx C-17. Peer-Reviewed Literature Search Strategy for Phthalic Anhydride

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 10/6/2020	TIAB("Phthalic anhydride" OR "85-44-9" OR "Anidride ftalica" OR "Phthalsaureanhydrid" OR "Anhydride phtalique" OR "Phthalanhydride" OR "anhidrido ftalico" OR "1,2-benzenedicaboxylic acid anhydride" OR "1,3-Isobenzofurandione" OR "isobenzofuran-1,3-dione" OR ("phthalic anhydride" AND ("PA" OR "M 2" OR "PAN" OR "PSA" OR "PAD")) OR "Phthalandione")	73
Current Contents Search Date: 10/6/2020	(TS="Phthalic anhydride" OR TS="85-44-9" OR TS="Anidride ftalica" OR TS="Phthalsaureanhydrid" OR TS="Anhydride phtalique" OR TS="Phthalanhydride" OR TS="anhidrido ftalico" OR TS="1,2-benzenedicaboxylic acid anhydride" OR TS="1,3-Isobenzofurandione" OR TS="isobenzofuran-1,3-dione" OR (TS="phthalic anhydride" AND (TS="PA" OR TS="M 2" OR TS="PAN" OR TS="PSA" OR TS="PAD")) OR TS="Phthalandione")	3
ProQuest Dissertations & Theses Search Date: 10/6/2020	TIAB("Phthalic anhydride" OR "85-44-9" OR "Anidride ftalica" OR "Phthalsaureanhydrid" OR "Anhydride phtalique" OR "Phthalanhydride" OR "anhidrido ftalico" OR "1,2-benzenedicaboxylic acid anhydride" OR "1,3-Isobenzofurandione" OR "isobenzofuran-1,3-dione" OR ("phthalic anhydride" AND ("PA" OR "M 2" OR "PAN" OR "PSA" OR "PAD")) OR "Phthalandione")	0
ProQuest Agricultural & Scientific Database Search Date: 10/6/2020	TIAB("Phthalic anhydride" OR "85-44-9" OR "Anidride ftalica" OR "Phthalsaureanhydrid" OR "Anhydride phtalique" OR "Phthalanhydride" OR "anhidrido ftalico" OR "1,2-benzenedicaboxylic acid anhydride" OR "1,3-Isobenzofurandione" OR "isobenzofuran-1,3-dione" OR ("phthalic anhydride" AND ("PA" OR "M 2" OR "PAN" OR "PSA" OR "PAD")) OR "Phthalandione")	227

Source	Source-Specific Search Strategy	Results
PubMed Search Date: 10/6/2020	("Phthalic anhydride"[tw] OR "85-44-9"[rn] OR "Anidride ftalica"[tw] OR "Phthalsaureanhydrid"[tw] OR "Anhydride phtalique"[tw] OR "Phthalanhydride"[tw] OR "anhidrido ftalico"[tw] OR "1,2-benzenedicaboxylic acid anhydride"[tw] OR "1,3-Isobenzofurandione"[tw] OR "isobenzofuran-1,3-dione"[tw] OR ("phthalic anhydride"[tw] AND ("PA"[tw] OR "M 2"[tw] OR "PAN"[tw] OR "PSA"[tw] OR "PAD"[tw])) OR "Phthalandione"[tw])	392
Science Direct Search Date: 10/6/2020	1. "Phthalic anhydride" OR "85-44-9" OR "Anidride ftalica" OR "Phthalsaureanhydrid" OR "Anhydride phtalique" 2. "Phthalanhydride" OR "anhidrido ftalico" OR "1,2-benzenedicaboxylic acid anhydride" OR "1,3-Isobenzofurandione" OR "isobenzofuran-1,3-dione" OR "Phthalandione" 3. ("phthalic anhydride" AND ("PA" OR "M 2" OR "PAN" OR "PSA" OR "PAD"))	733
ToxLine Search Date: 10/6/2020	1. tox[subset] AND ("Phthalic anhydride"[tw] OR "85-44-9"[rn] OR "Anidride ftalica"[tw] OR "Phthalsaureanhydrid"[tw] OR "Anhydride phtalique"[tw] OR "Phthalanhydride"[tw] OR "anhidrido ftalico"[tw] OR "1,2-benzenedicaboxylic acid anhydride"[tw] OR "1,3-Isobenzofurandione"[tw] OR "isobenzofuran-1,3-dione"[tw] OR ("phthalic anhydride"[tw] AND ("PA"[tw] OR "M 2"[tw] OR "PAN"[tw] OR "PSA"[tw] OR "PAD"[tw])) OR "Phthalandione"[tw]) 2. TIAB("Phthalic anhydride" OR "85-44-9" OR "Anidride ftalica" OR "Phthalsaureanhydrid" OR "Anhydride phtalique" OR "Phthalanhydride" OR "anhidrido ftalico" OR "1,2-benzenedicaboxylic acid anhydride" OR "1,3-Isobenzofurandione" OR "isobenzofuran-1,3-dione" OR ("phthalic anhydride" AND ("PA" OR "M 2" OR "PAN" OR "PSA" OR "PAD")) OR "Phthalandione")	204
WoS Search Date: 10/6/2020	(TS="Phthalic anhydride" OR TS="85-44-9" OR TS="Anidride ftalica" OR TS="Phthalsaureanhydrid" OR TS="Anhydride phtalique" OR TS="Phthalanhydride" OR TS="anhidrido ftalico" OR TS="1,2-benzenedicaboxylic acid anhydride" OR TS="1,3-Isobenzofurandione" OR TS="isobenzofuran-1,3-dione" OR (TS="phthalic anhydride" AND (TS="PA" OR TS="M 2" OR TS="PAN" OR TS="PSA" OR TS="PAD")) OR TS="Phthalandione")	2,626
Total	**Represents total across all databases after deduplication**	**2,978**

Additional Strategies

Additional keywords have been added to supplement the initial pool references. These are the search terms for phthalic acid used in the supplemental search strategies for each of the databases listed below:

"Phthalic acid"; "88-99-3"; "Hydrogen phthalate"; ("phthalic acid" AND ("PA" OR "M 2" OR "PAN" OR "PSA" OR "PAD")); "o-Phthalic acid"; "ortho-phthalic acid"; "Benzene-1,2-dicarboxylic acid"; "Orthophthalic acid"; "acido ftalico"; "Enantic acid"; "1,2-benzenedicaboxylic acid"; "Acide phtalique"

Table_Apx C-18. Supplemental Peer-Reviewed Literature Search Strategy for Phthalic Acid

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 10/6/2020	TIAB("Phthalic acid" OR "88-99-3" OR "Hydrogen phthalate" OR ("phthalic acid" AND ("PA" OR "M 2" OR "PAN" OR "PSA" OR "PAD")) OR "o-Phthalic acid" OR "ortho-phthalic acid" OR "Benzene-1,2-dicarboxylic acid" OR "Orthophthalic acid" OR "acido ftalico" OR "Enantic acid" OR "1,2-benzenedicaboxylic acid" OR "Acide phtalique")	307
Current Contents Search Date: 10/6/2020	(TS="Phthalic acid" OR TS="88-99-3" OR TS="Hydrogen phthalate" OR (TS="phthalic acid" AND (TS="PA" OR TS="M 2" OR TS="PAN" OR TS="PSA" OR TS="PAD")) OR TS="o-Phthalic acid" OR TS="ortho-phthalic acid" OR TS="Benzene-1,2-dicarboxylic acid" OR TS="Orthophthalic acid" OR TS="acido ftalico" OR TS="Enantic acid" OR TS="1,2-benzenedicaboxylic acid" OR TS="Acide phtalique")	8
ProQuest Dissertations & Theses Search Date: 10/6/2020	TIAB("Phthalic acid" OR "88-99-3" OR "Hydrogen phthalate" OR ("phthalic acid" AND ("PA" OR "M 2" OR "PAN" OR "PSA" OR "PAD")) OR "o-Phthalic acid" OR "ortho-phthalic acid" OR "Benzene-1,2-dicarboxylic acid" OR "Orthophthalic acid" OR "acido ftalico" OR "Enantic acid" OR "1,2-benzenedicaboxylic acid" OR "Acide phtalique")	0
ProQuest Agricultural & Scientific Database Search Date: 10/6/2020	TIAB("Phthalic acid" OR "88-99-3" OR "Hydrogen phthalate" OR ("phthalic acid" AND ("PA" OR "M 2" OR "PAN" OR "PSA" OR "PAD")) OR "o-Phthalic acid" OR "ortho-phthalic acid" OR "Benzene-1,2-dicarboxylic acid" OR "Orthophthalic acid" OR "acido ftalico" OR "Enantic acid" OR "1,2-benzenedicaboxylic acid" OR "Acide phtalique")	829
PubMed Search Date: 10/6/2020	("Phthalic acid"[tw] OR "88-99-3"[rn] OR "Hydrogen phthalate"[tw] OR ("phthalic acid"[tw] AND ("PA"[tw] OR "M 2"[tw] OR "PAN"[tw] OR "PSA"[tw] OR "PAD"[tw])) OR "o-Phthalic acid"[tw] OR "ortho-phthalic acid"[tw] OR "Benzene-1,2-dicarboxylic acid"[tw] OR "Orthophthalic acid"[tw] OR "acido ftalico"[tw] OR "Enantic acid"[tw] OR "1,2-benzenedicaboxylic acid"[tw] OR "Acide phtalique"[tw])	2,813
Science Direct Search Date: 10/6/2020	1. "Phthalic acid" OR "88-99-3" OR "Hydrogen phthalate" OR "o-Phthalic acid" OR "ortho-phthalic acid" 2. "Benzene-1,2-dicarboxylic acid" OR "Orthophthalic acid" OR "acido ftalico" OR "Enantic acid" OR "1,2-benzenedicaboxylic acid" OR "Acide phtalique" 3. ("phthalic acid" AND ("PA" OR "M 2" OR "PAN" OR "PSA" OR "PAD"))	1,353
ToxLine Search Date: 10/6/2020	1. tox[subset] AND ("Phthalic acid"[tw] OR "88-99-3"[rn] OR "Hydrogen phthalate"[tw] OR ("phthalic acid"[tw] AND ("PA"[tw] OR "M 2"[tw] OR "PAN"[tw] OR "PSA"[tw] OR "PAD"[tw])) OR "o-Phthalic acid"[tw] OR "ortho-phthalic acid"[tw] OR "Benzene-1,2-dicarboxylic acid"[tw] OR "Orthophthalic acid"[tw] OR "acido ftalico"[tw] OR "Enantic acid"[tw] OR "1,2-benzenedicaboxylic acid"[tw] OR "Acide phtalique"[tw]) 2. TIAB("Phthalic acid" OR "88-99-3" OR "Hydrogen phthalate" OR ("phthalic acid" AND ("PA" OR "M 2" OR "PAN" OR "PSA" OR "PAD")) OR "o-Phthalic acid" OR "ortho-phthalic acid" OR "Benzene-1,2-dicarboxylic acid" OR "Orthophthalic acid" OR "acido ftalico" OR "Enantic acid" OR "1,2-benzenedicaboxylic acid" OR "Acide phtalique")	1,952

Source	Source-Specific Search Strategy	Results
WoS Search Date: 10/6/2020	(TS="Phthalic acid" OR TS="88-99-3" OR TS="Hydrogen phthalate" OR (TS="phthalic acid" AND (TS="PA" OR TS="M 2" OR TS="PAN" OR TS="PSA" OR TS="PAD")) OR TS="o-Phthalic acid" OR TS="ortho-phthalic acid" OR TS="Benzene-1,2-dicarboxylic acid" OR TS="Orthophthalic acid" OR TS="acido ftalico" OR TS="Enantic acid" OR TS="1,2-benzenedicaboxylic acid" OR TS="Acide phtalique")	7,169
Total	**Represents total across all databases after deduplication**	**8,095**

C.1.16 Query Strings for the Peer-Reviewed Literature Database Searches on DBP

These are the search terms compiled from the Chemical Report for dibutyl phthalate (DBP) used in the initial search strategies for each of the databases listed below:

"1,2-Benzenedicarboxylic acid dibutyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-dibutyl ester" OR "1,2-Benzenedicarboxylic acid, Bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, dibutyl ester" OR "Benzenedicarboxylic acid dibutyl ester" OR "Benzene-o-dicarboxylic acid di-n-butyl ester" OR "Bis-n-butyl phthalate" OR "BRN 1914064" OR "Butyl phthalate" OR "Caswell No. 292" OR "Celluflex DPB" OR "Corflex 440" OR "Di(n-butyl) 1,2-benzenedicarboxylate" OR "Di(n-butyl)1,2-benzenedicarboxylate" OR "Di(n-butyl)phthalate" OR "Dibutyl 1,2-benzenedicarboxylate" OR "Dibutyl benzene-1,2-dicarboxylate" OR "Dibutyl ester 1,2-benzenedicarboxylic acid" OR "Dibutyl o-phthalate" OR "Dibutyl phthalate" OR "Dibutyl phthalate" OR "DI-BUTYL PHTHALATE" OR "Dibutyl-o-phthalate" OR "Dibutylphthalat" OR "Dibutylphthalate" OR "Dibutylphthalate" OR "Diisobutyl phthalate" OR "Di-n-butyl phthalate" OR "Di-n-butylorthophthalate" OR "Di-n-butylphtalate" OR "EINECS 201-557-4" OR "Ergoplast FDB" OR "Ersoplast FDA" OR "Genoplast B" OR "Hatco DBP" OR "Hatcol DBP" OR "Hexaplas M/B" OR "Kodaflex DBP" OR "Monocizer DBP" OR "n-Butyl phthalate" OR "n-Butylphthalate" OR "NSC 6370" OR "o-Benzenedicarboxylic acid dibutyl ester" OR "o-Benzenedicarboxylic acid, dibutyl ester" OR "Palatinol C" OR "PHTHALATE, BUTYL" OR "Phthalate, dibutyl-" OR "Phthalate, di-n-butyl" OR "Phthalic acid dibutyl ester" OR "Phthalic acid di-n-butyl ester" OR "Phthalic acid, dibutyl ester" OR "PHTHALIC ACID, DIBUTYL ESTER" OR "Plasthall DBP" OR "Polycizer DBP" OR "RC Plasticizer DBP" OR "RCRA waste number U069" OR "Staflex DBP" OR "Uniflex DBP" OR "UNII-2286E5R2KE" OR "Unimoll DB" OR "Vestinol C" OR "Witcizer 300"

Table_Apx C-19. Peer-Reviewed Literature Search Strategy for DBP

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 7/9/2019	1. 1,2-Benzenedicarboxylic acid dibutyl ester; 1,2-Benzenedicarboxylic acid, 1,2-dibutyl ester; 1,2-Benzenedicarboxylic acid, Bis(2-methylpropyl) ester; 1,2-Benzenedicarboxylic acid, dibutyl ester; Benzenedicarboxylic acid dibutyl ester; Benzene-o-dicarboxylic acid; di-n-butyl ester; Bis-n-butyl phthalate; BRN 1914064; Butyl phthalate; Caswell No. 292 2. Celluflex DPB; Corflex 440; Di(n-butyl) 1,2-benzenedicarboxylate; Di(n-butyl)1,2-benzenedicarboxylate; Di(n-butyl)phthalate; Dibutyl 1,2-benzenedicarboxylate; Dibutyl benzene-1,2-dicarboxylate; Dibutyl ester 1,2-benzenedicarboxylic acid; Dibutyl o-phthalate; Dibutyl phthalate	2,159

Source	Source-Specific Search Strategy	Results
	3. Dibutyl phthalate; DI-BUTYL PHTHALATE; Dibutyl-o-phthalate; Dibutylphthalat; Dibutylphthalate; Dibutylphthalate; Diisobutyl phthalate; Di-n-butyl phthalate; Di-n-butylorthophthalate; Di-n-butylphtalate 4. EINECS 201-557-4; Ergoplast FDB; Ersoplast FDA; Genoplast B; Hatco DBP; Hatcol DBP; Hexaplas M/B; Kodaflex DBP; Monocizer DBP; n-Butyl phthalate 5. n-Butylphthalate; NSC 6370; o-Benzenedicarboxylic acid dibutyl ester; o-Benzenedicarboxylic acid, dibutyl ester; Palatinol C; PHTHALATE, BUTYL; Phthalate, dibutyl-; Phthalate, di-n-butyl; Phthalic acid dibutyl ester; Phthalic acid di-n-butyl ester 6. Phthalic acid, dibutyl ester; PHTHALIC ACID, DIBUTYL ESTER; Plasthall DBP; Polycizer DBP; RC Plasticizer DBP; RCRA waste number U069; Staflex DBP; Uniflex DBP; UNII-2286E5R2KE; Unimoll DB 7. Vestinol C; Witcizer 300	
Current Contents Search Date: 7/8/2019	TS=("1,2-Benzenedicarboxylic acid dibutyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-dibutyl ester" OR "1,2-Benzenedicarboxylic acid, Bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, dibutyl ester" OR "Benzenedicarboxylic acid dibutyl ester" OR "Benzene-o-dicarboxylic acid di-n-butyl ester" OR "Bis-n-butyl phthalate" OR "BRN 1914064" OR "Butyl phthalate" OR "Caswell No. 292" OR "Celluflex DPB" OR "Corflex 440" OR "Di(n-butyl) 1,2-benzenedicarboxylate" OR "Di(n-butyl)1,2-benzenedicarboxylate" OR "Di(n-butyl)phthalate" OR "Dibutyl 1,2-benzenedicarboxylate" OR "Dibutyl benzene-1,2-dicarboxylate" OR "Dibutyl ester 1,2-benzenedicarboxylic acid" OR "Dibutyl o-phthalate" OR "Dibutyl phthalate" OR "Dibutyl phthalate" OR "DI-BUTYL PHTHALATE" OR "Dibutyl-o-phthalate" OR "Dibutylphthalat" OR "Dibutylphthalate" OR "Dibutylphthalate" OR "Diisobutyl phthalate" OR "Di-n-butyl phthalate" OR "Di-n-butylorthophthalate" OR "Di-n-butylphtalate" OR "EINECS 201-557-4" OR "Ergoplast FDB" OR "Ersoplast FDA" OR "Genoplast B" OR "Hatco DBP" OR "Hatcol DBP" OR "Hexaplas M/B" OR "Kodaflex DBP" OR "Monocizer DBP" OR "n-Butyl phthalate" OR "n-Butylphthalate" OR "NSC 6370" OR "o-Benzenedicarboxylic acid dibutyl ester" OR "o-Benzenedicarboxylic acid, dibutyl ester" OR "Palatinol C" OR "PHTHALATE, BUTYL" OR "Phthalate, dibutyl-" OR "Phthalate, di-n-butyl" OR "Phthalic acid dibutyl ester" OR "Phthalic acid di-n-butyl ester" OR "Phthalic acid, dibutyl ester" OR "PHTHALIC ACID, DIBUTYL ESTER" OR "Plasthall DBP" OR "Polycizer DBP" OR "RC Plasticizer DBP" OR "RCRA waste number U069" OR "Staflex DBP" OR "Uniflex DBP" OR "UNII-2286E5R2KE" OR "Unimoll DB" OR "Vestinol C" OR "Witcizer 300")	3,391
ProQuest Dissertations & Theses Search Date: 7/11/2019	ALL("1,2-Benzenedicarboxylic acid dibutyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-dibutyl ester" OR "1,2-Benzenedicarboxylic acid, Bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, dibutyl ester" OR "Benzenedicarboxylic acid dibutyl ester" OR "Benzene-o-dicarboxylic acid di-n-butyl ester" OR "Bis-n-butyl phthalate" OR "BRN 1914064" OR "Butyl phthalate" OR "Caswell No. 292" OR "Celluflex DPB" OR "Corflex 440" OR "Di(n-butyl) 1,2-benzenedicarboxylate" OR "Di(n-butyl)1,2-benzenedicarboxylate" OR "Di(n-butyl)phthalate" OR "Dibutyl 1,2-benzenedicarboxylate" OR "Dibutyl benzene-1,2-dicarboxylate" OR "Dibutyl ester 1,2-benzenedicarboxylic acid" OR "Dibutyl o-phthalate" OR "Dibutyl phthalate" OR "Dibutyl phthalate" OR "DI-BUTYL PHTHALATE" OR "Dibutyl-o-phthalate" OR "Dibutylphthalat" OR "Dibutylphthalate" OR "Dibutylphthalate" OR "Diisobutyl phthalate" OR "Di-n-butyl phthalate" OR "Di-n-butylorthophthalate" OR "Di-n-butylphtalate" OR "EINECS 201-557-4" OR "Ergoplast FDB" OR "Ersoplast FDA" OR "Genoplast B" OR "Hatco DBP" OR "Hatcol DBP" OR "Hexaplas M/B" OR "Kodaflex DBP" OR "Monocizer DBP" OR "n-Butyl phthalate" OR "n-Butylphthalate" OR "NSC 6370" OR "o-Benzenedicarboxylic acid dibutyl ester" OR "o-Benzenedicarboxylic acid, dibutyl ester" OR "Palatinol C" OR "PHTHALATE, BUTYL" OR "Phthalate, dibutyl-" OR "Phthalate, di-n-butyl" OR "Phthalic acid dibutyl ester" OR "Phthalic acid di-n-butyl ester" OR "Phthalic acid, dibutyl ester" OR "PHTHALIC ACID, DIBUTYL ESTER" OR "Plasthall DBP" OR "Polycizer DBP" OR "RC Plasticizer DBP" OR "RCRA waste number U069" OR "Staflex DBP" OR "Uniflex DBP" OR "UNII-2286E5R2KE" OR	21

Source	Source-Specific Search Strategy	Results
	"Unimoll DB" OR "Vestinol C" OR "Witcizer 300") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	
ProQuest Agricultural & Scientific Database Search Date: 7/8/2019	ALL("1,2-Benzenedicarboxylic acid dibutyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-dibutyl ester" OR "1,2-Benzenedicarboxylic acid, Bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, dibutyl ester" OR "Benzenedicarboxylic acid dibutyl ester" OR "Benzene-o-dicarboxylic acid di-n-butyl ester" OR "Bis-n-butyl phthalate" OR "BRN 1914064" OR "Butyl phthalate" OR "Caswell No. 292" OR "Celluflex DPB" OR "Corflex 440" OR "Di(n-butyl) 1,2-benzenedicarboxylate" OR "Di(n-butyl)1,2-benzenedicarboxylate" OR "Di(n-butyl)phthalate" OR "Dibutyl 1,2-benzenedicarboxylate" OR "Dibutyl benzene-1,2-dicarboxylate" OR "Dibutyl ester 1,2-benzenedicarboxylic acid" OR "Dibutyl o-phthalate" OR "Dibutyl phthalate" OR "Dibutyl phthalate" OR "DI-BUTYL PHTHALATE" OR "Dibutyl-o-phthalate" OR "Dibutylphthalat" OR "Dibutylphthalate" OR "Dibutylphthalate" OR "Diisobutyl phthalate" OR "Di-n-butyl phthalate" OR "Di-n-butylorthophthalate" OR "Di-n-butylphtalate" OR "EINECS 201-557-4" OR "Ergoplast FDB" OR "Ersoplast FDA" OR "Genoplast B" OR "Hatco DBP" OR "Hatcol DBP" OR "Hexaplas M/B" OR "Kodaflex DBP" OR "Monocizer DBP" OR "n-Butyl phthalate" OR "n-Butylphthalate" OR "NSC 6370" OR "o-Benzenedicarboxylic acid dibutyl ester" OR "o-Benzenedicarboxylic acid, dibutyl ester" OR "Palatinol C" OR "PHTHALATE, BUTYL" OR "Phthalate, dibutyl-" OR "Phthalate, di-n-butyl" OR "Phthalic acid dibutyl ester" OR "Phthalic acid di-n-butyl ester" OR "Phthalic acid, dibutyl ester" OR "PHTHALIC ACID, DIBUTYL ESTER" OR "Plasthall DBP" OR "Polycizer DBP" OR "RC Plasticizer DBP" OR "RCRA waste number U069" OR "Staflex DBP" OR "Uniflex DBP" OR "UNII-2286E5R2KE" OR "Unimoll DB" OR "Vestinol C" OR "Witcizer 300") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	4,538
PubMed Search Date: 7/9/2019	"1,2-Benzenedicarboxylic acid dibutyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-dibutyl ester" OR "1,2-Benzenedicarboxylic acid, Bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, dibutyl ester" OR "Benzenedicarboxylic acid dibutyl ester" OR "Benzene-o-dicarboxylic acid di-n-butyl ester" OR "Bis-n-butyl phthalate" OR "BRN 1914064" OR "Butyl phthalate" OR "Caswell No. 292" OR "Celluflex DPB" OR "Corflex 440" OR "Di(n-butyl) 1,2-benzenedicarboxylate" OR "Di(n-butyl)1,2-benzenedicarboxylate" OR "Di(n-butyl)phthalate" OR "Dibutyl 1,2-benzenedicarboxylate" OR "Dibutyl benzene-1,2-dicarboxylate" OR "Dibutyl ester 1,2-benzenedicarboxylic acid" OR "Dibutyl o-phthalate" OR "Dibutyl phthalate" OR "Dibutyl phthalate" OR "DI-BUTYL PHTHALATE" OR "Dibutyl-o-phthalate" OR "Dibutylphthalat" OR "Dibutylphthalate" OR "Dibutylphthalate" OR "Diisobutyl phthalate" OR "Di-n-butyl phthalate" OR "Di-n-butylorthophthalate" OR "Di-n-butylphtalate" OR "EINECS 201-557-4" OR "Ergoplast FDB" OR "Ersoplast FDA" OR "Genoplast B" OR "Hatco DBP" OR "Hatcol DBP" OR "Hexaplas M/B" OR "Kodaflex DBP" OR "Monocizer DBP" OR "n-Butyl phthalate" OR "n-Butylphthalate" OR "NSC 6370" OR "o-Benzenedicarboxylic acid dibutyl ester" OR "o-Benzenedicarboxylic acid, dibutyl ester" OR "Palatinol C" OR "PHTHALATE, BUTYL" OR "Phthalate, dibutyl-" OR "Phthalate, di-n-butyl" OR "Phthalic acid dibutyl ester" OR "Phthalic acid di-n-butyl ester" OR "Phthalic acid, dibutyl ester" OR "PHTHALIC ACID, DIBUTYL ESTER" OR "Plasthall DBP" OR "Polycizer DBP" OR "RC Plasticizer DBP" OR "RCRA waste number U069" OR "Staflex DBP" OR "Uniflex DBP" OR "UNII-2286E5R2KE" OR "Unimoll DB" OR "Vestinol C" OR "Witcizer 300"	2,434
Science Direct Search Date: 7/9/2019	1. "1,2-Benzenedicarboxylic acid dibutyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-dibutyl ester" OR "1,2-Benzenedicarboxylic acid, Bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, dibutyl ester" OR "Benzenedicarboxylic acid dibutyl ester" OR "Benzene-o-dicarboxylic acid di-n-butyl ester" OR "Bis-n-butyl phthalate" OR "BRN 1914064" OR "Butyl phthalate"	2,108

Source	Source-Specific Search Strategy	Results
	2. "Caswell No. 292" OR "Celluflex DPB" OR "Corflex 440" OR "Di(n-butyl) 1,2-benzenedicarboxylate" OR "Di(n-butyl)1,2-benzenedicarboxylate" OR "Di(n-butyl)phthalate" OR "Dibutyl 1,2-benzenedicarboxylate" OR "Dibutyl benzene-1,2-dicarboxylate" OR "Dibutyl ester 1,2-benzenedicarboxylic acid" 3. "Dibutyl o-phthalate" OR "Dibutyl phthalate" OR "Dibutyl phthalate" OR "DI-BUTYL PHTHALATE" OR "Dibutyl-o-phthalate" OR "Dibutylphthalat" OR "Dibutylphthalate" OR "Dibutylphthalate" OR "Diisobutyl phthalate" 4. "Di-n-butyl phthalate" OR "Di-n-butylorthophthalate" OR "Di-n-butylphtalate" OR "EINECS 201-557-4" OR "Ergoplast FDB" OR "Ersoplast FDA" OR "Genoplast B" OR "Hatco DBP" OR "Hatcol DBP" 5. "Hexaplas M/B" OR "Kodaflex DBP" OR "Monocizer DBP" OR "n-Butyl phthalate" OR "n-Butylphthalate" OR "NSC 6370" OR "o-Benzenedicarboxylic acid dibutyl ester" OR "o-Benzenedicarboxylic acid, dibutyl ester" OR "Palatinol C" 6. "PHTHALATE, BUTYL" OR "Phthalate, dibutyl-" OR "Phthalate, di-n-butyl" OR "Phthalic acid dibutyl ester" OR "Phthalic acid di-n-butyl ester" 7. "Phthalic acid, dibutyl ester" OR "PHTHALIC ACID, DIBUTYL ESTER" OR "Plasthall DBP" OR "Polycizer DBP" OR "RC Plasticizer DBP" OR "RCRA waste number U069" OR "Staflex DBP" OR "Uniflex DBP" OR "UNII-2286E5R2KE" 8. "Unimoll DB" OR "Vestinol C" OR "Witcizer 300"	
ToxNet Search Date: 7/9/2019	84-74-2	2,259
WoS Search Date: 7/8/2019	TS=("1,2-Benzenedicarboxylic acid dibutyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-dibutyl ester" OR "1,2-Benzenedicarboxylic acid, Bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, dibutyl ester" OR "Benzenedicarboxylic acid dibutyl ester" OR "Benzene-o-dicarboxylic acid di-n-butyl ester" OR "Bis-n-butyl phthalate" OR "BRN 1914064" OR "Butyl phthalate" OR "Caswell No. 292" OR "Celluflex DPB" OR "Corflex 440" OR "Di(n-butyl) 1,2-benzenedicarboxylate" OR "Di(n-butyl)1,2-benzenedicarboxylate" OR "Di(n-butyl)phthalate" OR "Dibutyl 1,2-benzenedicarboxylate" OR "Dibutyl benzene-1,2-dicarboxylate" OR "Dibutyl ester 1,2-benzenedicarboxylic acid" OR "Dibutyl o-phthalate" OR "Dibutyl phthalate" OR "Dibutyl phthalate" OR "DI-BUTYL PHTHALATE" OR "Dibutyl-o-phthalate" OR "Dibutylphthalat" OR "Dibutylphthalate" OR "Dibutylphthalate" OR "Diisobutyl phthalate" OR "Di-n-butyl phthalate" OR "Di-n-butylorthophthalate" OR "Di-n-butylphtalate" OR "EINECS 201-557-4" OR "Ergoplast FDB" OR "Ersoplast FDA" OR "Genoplast B" OR "Hatco DBP" OR "Hatcol DBP" OR "Hexaplas M/B" OR "Kodaflex DBP" OR "Monocizer DBP" OR "n-Butyl phthalate" OR "n-Butylphthalate" OR "NSC 6370" OR "o-Benzenedicarboxylic acid dibutyl ester" OR "o-Benzenedicarboxylic acid, dibutyl ester" OR "Palatinol C" OR "PHTHALATE, BUTYL" OR "Phthalate, dibutyl-" OR "Phthalate, di-n-butyl" OR "Phthalic acid dibutyl ester" OR "Phthalic acid di-n-butyl ester" OR "Phthalic acid, dibutyl ester" OR "PHTHALIC ACID, DIBUTYL ESTER" OR "Plasthall DBP" OR "Polycizer DBP" OR "RC Plasticizer DBP" OR "RCRA waste number U069" OR "Staflex DBP" OR "Uniflex DBP" OR "UNII-2286E5R2KE" OR "Unimoll DB" OR "Vestinol C" OR "Witcizer 300")	4,285
Unify[a] Search Date: 7/22/2019	1,2-Benzenedicarboxylic acid dibutyl ester|1,2-Benzenedicarboxylic acid, 1,2-dibutyl ester|1,2-Benzenedicarboxylic acid, Bis(2-methylpropyl) ester|1,2-Benzenedicarboxylic acid, dibutyl ester|Benzenedicarboxylic acid dibutyl ester|Benzene-o-dicarboxylic acid di-n-butyl ester|Bis-n-butyl phthalate|BRN 1914064|Butyl phthalate|Caswell No. 292|Celluflex DPB|Corflex 440|Di(n-butyl) 1,2-benzenedicarboxylate|Di(n-butyl)1,2-benzenedicarboxylate|Di(n-butyl)phthalate|Dibutyl 1,2-benzenedicarboxylate|Dibutyl benzene-1,2-dicarboxylate|Dibutyl ester 1,2-benzenedicarboxylic acid|Dibutyl o-phthalate|Dibutyl phthalate|Dibutyl phthalate|DI-	358

Source	Source-Specific Search Strategy	Results
	BUTYL PHTHALATE|Dibutyl-o-phthalate|Dibutylphthalat|Dibutylphthalate|Dibutylphthalate|Diisobutyl phthalate|Di-n-butyl phthalate|Di-n-butylorthophthalate|Di-n-butylphtalate|EINECS 201-557-4|Ergoplast FDB|Ersoplast FDA|Genoplast B|Hatco DBP|Hatcol DBP|Hexaplas M/B|Kodaflex DBP|Monocizer DBP|n-Butyl phthalate|n-Butylphthalate|NSC 6370|o-Benzenedicarboxylic acid dibutyl ester|o-Benzenedicarboxylic acid, dibutyl ester|Palatinol C|PHTHALATE, BUTYL|Phthalate, dibutyl-|Phthalate, di-n-butyl|Phthalic acid dibutyl ester|Phthalic acid di-n-butyl ester|Phthalic acid, dibutyl ester|PHTHALIC ACID, DIBUTYL ESTER|Plasthall DBP|Polycizer DBP|RC Plasticizer DBP|RCRA waste number U069|Staflex DBP|Uniflex DBP|UNII-2286E5R2KE|Unimoll DB|Vestinol C|Witcizer 300	
Total	**Represents total across all databases after deduplication**	**5,642**
[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.		

C.1.17 Query Strings for the Peer-Reviewed Literature Database Searches on BBP

These are the search terms compiled from the Chemical Report for butyl benzyl phthalate (BBP) used in the initial search strategies for each of the databases listed below:

"1,2-Benzenedicarboxylic acid butyl phenylmethyl ester" OR "1,2-Benzenedicarboxylic acid, 1-butyl 2-(phenylmethyl) ester" OR "1,2-BENZENEDICARBOXYLIC ACID, BUTYL PHENYL METHYL ESTER" OR "1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester" OR "Benzyl butyl benzene-1,2-dicarboxylate" OR "Benzyl butyl phthalate" OR "Benzyl butylphthalate" OR "Benzyl n-butyl phthalate" OR "Benzylbutyl phthalate" OR "BRN 2062204" OR "Butyl benzyl phthalate" OR "Butyl phenylmethyl 1,2-benzenedicarboxylate" OR "Butylbenzyl Phthalate" OR "Butylbenzylphthalate" OR "Caswell No. 125G" OR "Diacizer D 160" OR "EINECS 201-622-7" OR "n-Butyl benzyl phthalate" OR "n-Butyl benzyl phthalate diester" OR "NCI-C54375" OR "NSC 71001" OR "Palatinol BB" OR "PHTHALATE, BENZYLBUTYL-" OR "PHTHALATE, BUTYL BENZYL" OR "Phthalic acid, benzyl butyl ester" OR "Sant 160" OR "Santicizer 160" OR "Santicizer C 160" OR "Santicizer S 106" OR "Sicol 160" OR "Spatozoate" OR "UNII-YPC4PJX59M" OR "Unimoll BB"

Table_Apx C-20. Peer-Reviewed Literature Search Strategy for BBP

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 7/9/2019	1. 1,2-Benzenedicarboxylic acid butyl phenylmethyl ester; 1,2-Benzenedicarboxylic acid, 1-butyl 2-(phenylmethyl) ester; 1,2-BENZENEDICARBOXYLIC ACID, BUTYL PHENYL METHYL ESTER; 1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester; Benzyl butyl benzene-1,2-dicarboxylate; Benzyl butyl phthalate; Benzyl butylphthalate; Benzyl n-butyl phthalate; Benzylbutyl phthalate; BRN 2062204 2. Butyl benzyl phthalate; Butyl phenylmethyl 1,2-benzenedicarboxylate; Butylbenzyl Phthalate; Butylbenzylphthalate; Caswell No. 125G; Diacizer D 160; EINECS 201-622-7; n-Butyl benzyl phthalate; n-Butyl benzyl phthalate diester; NCI-C54375 3. NSC 71001; Palatinol BB; PHTHALATE, BENZYLBUTYL-; PHTHALATE, BUTYL BENZYL; Phthalic acid, benzyl butyl ester; Sant 160; Santicizer 160; Santicizer C 160; Santicizer S 106; Sicol 160	229

Source	Source-Specific Search Strategy	Results
	4. Spatozoate; UNII-YPC4PJX59M; Unimoll BB	
Current Contents Search Date: 7/3/2019	TS=("1,2-Benzenedicarboxylic acid butyl phenylmethyl ester" OR "1,2-Benzenedicarboxylic acid, 1-butyl 2-(phenylmethyl) ester" OR "1,2-BENZENEDICARBOXYLIC ACID, BUTYL PHENYL METHYL ESTER" OR "1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester" OR "Benzyl butyl benzene-1,2-dicarboxylate" OR "Benzyl butyl phthalate" OR "Benzyl butylphthalate" OR "Benzyl n-butyl phthalate" OR "Benzylbutyl phthalate" OR "BRN 2062204" OR "Butyl benzyl phthalate" OR "Butyl phenylmethyl 1,2-benzenedicarboxylate" OR "Butylbenzyl Phthalate" OR "Butylbenzylphthalate" OR "Caswell No. 125G" OR "Diacizer D 160" OR "EINECS 201-622-7" OR "n-Butyl benzyl phthalate" OR "n-Butyl benzyl phthalate diester" OR "NCI-C54375" OR "NSC 71001" OR "Palatinol BB" OR "PHTHALATE, BENZYLBUTYL-" OR "PHTHALATE, BUTYL BENZYL" OR "Phthalic acid, benzyl butyl ester" OR "Sant 160" OR "Santicizer 160" OR "Santicizer C 160" OR "Santicizer S 106" OR "Sicol 160" OR "Spatozoate" OR "UNII-YPC4PJX59M" OR "Unimoll BB")	704
ProQuest Dissertations & Theses Search Date: 7/11/2019	ALL("1,2-Benzenedicarboxylic acid butyl phenylmethyl ester" OR "1,2-Benzenedicarboxylic acid, 1-butyl 2-(phenylmethyl) ester" OR "1,2-BENZENEDICARBOXYLIC ACID, BUTYL PHENYL METHYL ESTER" OR "1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester" OR "Benzyl butyl benzene-1,2-dicarboxylate" OR "Benzyl butyl phthalate" OR "Benzyl butylphthalate" OR "Benzyl n-butyl phthalate" OR "Benzylbutyl phthalate" OR "BRN 2062204" OR "Butyl benzyl phthalate" OR "Butyl phenylmethyl 1,2-benzenedicarboxylate" OR "Butylbenzyl Phthalate" OR "Butylbenzylphthalate" OR "Caswell No. 125G" OR "Diacizer D 160" OR "EINECS 201-622-7" OR "n-Butyl benzyl phthalate" OR "n-Butyl benzyl phthalate diester" OR "NCI-C54375" OR "NSC 71001" OR "Palatinol BB" OR "PHTHALATE, BENZYLBUTYL-" OR "PHTHALATE, BUTYL BENZYL" OR "Phthalic acid, benzyl butyl ester" OR "Sant 160" OR "Santicizer 160" OR "Santicizer C 160" OR "Santicizer S 106" OR "Sicol 160" OR "Spatozoate" OR "UNII-YPC4PJX59M" OR "Unimoll BB") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	2
ProQuest Agricultural & Scientific Database Search Date: 7/3/2019	ALL("1,2-Benzenedicarboxylic acid butyl phenylmethyl ester" OR "1,2-Benzenedicarboxylic acid, 1-butyl 2-(phenylmethyl) ester" OR "1,2-BENZENEDICARBOXYLIC ACID, BUTYL PHENYL METHYL ESTER" OR "1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester" OR "Benzyl butyl benzene-1,2-dicarboxylate" OR "Benzyl butyl phthalate" OR "Benzyl butylphthalate" OR "Benzyl n-butyl phthalate" OR "Benzylbutyl phthalate" OR "BRN 2062204" OR "Butyl benzyl phthalate" OR "Butyl phenylmethyl 1,2-benzenedicarboxylate" OR "Butylbenzyl Phthalate" OR "Butylbenzylphthalate" OR "Caswell No. 125G" OR "Diacizer D 160" OR "EINECS 201-622-7" OR "n-Butyl benzyl phthalate" OR "n-Butyl benzyl phthalate diester" OR "NCI-C54375" OR "NSC 71001" OR "Palatinol BB" OR "PHTHALATE, BENZYLBUTYL-" OR "PHTHALATE, BUTYL BENZYL" OR "Phthalic acid, benzyl butyl ester" OR "Sant 160" OR "Santicizer 160" OR "Santicizer C 160" OR "Santicizer S 106" OR "Sicol 160" OR "Spatozoate" OR "UNII-YPC4PJX59M" OR "Unimoll BB") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	1,243
PubMed Search Date: 7/3/2019	"1,2-Benzenedicarboxylic acid butyl phenylmethyl ester" OR "1,2-Benzenedicarboxylic acid, 1-butyl 2-(phenylmethyl) ester" OR "1,2-BENZENEDICARBOXYLIC ACID, BUTYL PHENYL METHYL ESTER" OR "1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester" OR "Benzyl butyl benzene-1,2-dicarboxylate" OR "Benzyl butyl phthalate" OR "Benzyl butylphthalate" OR "Benzyl n-butyl phthalate" OR "Benzylbutyl phthalate" OR "BRN 2062204" OR "Butyl benzyl phthalate" OR "Butyl phenylmethyl 1,2-benzenedicarboxylate" OR "Butylbenzyl Phthalate" OR "Butylbenzylphthalate" OR "Caswell No. 125G" OR "Diacizer D 160" OR "EINECS 201-622-7" OR "n-Butyl benzyl phthalate" OR "n-Butyl benzyl phthalate diester" OR "NCI-C54375" OR "NSC 71001" OR "Palatinol BB" OR "PHTHALATE, BENZYLBUTYL-" OR "PHTHALATE, BUTYL BENZYL"	637

Source	Source-Specific Search Strategy	Results
	OR "Phthalic acid, benzyl butyl ester" OR "Sant 160" OR "Santicizer 160" OR "Santicizer C 160" OR "Santicizer S 106" OR "Sicol 160" OR "Spatozoate" OR "UNII-YPC4PJX59M" OR "Unimoll BB"	
Science Direct Search Date: 7/3/2019	1. "1,2-Benzenedicarboxylic acid butyl phenylmethyl ester" OR "1,2-Benzenedicarboxylic acid, 1-butyl 2-(phenylmethyl) ester" OR "1,2-BENZENEDICARBOXYLIC ACID, BUTYL PHENYL METHYL ESTER" OR "1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester" OR "Benzyl butyl benzene-1,2-dicarboxylate" OR "Benzyl butyl phthalate" OR "Benzyl butylphthalate" OR "Benzyl n-butyl phthalate" OR "Benzylbutyl phthalate" 2. "BRN 2062204" OR "Butyl benzyl phthalate" OR "Butyl phenylmethyl 1,2-benzenedicarboxylate" OR "Butylbenzyl Phthalate" OR "Butylbenzylphthalate" OR "Caswell No. 125G" OR "Diacizer D 160" OR "EINECS 201-622-7" OR "n-Butyl benzyl phthalate" 3. "n-Butyl benzyl phthalate diester" OR "NCI-C54375" OR "NSC 71001" OR "Palatinol BB" OR "PHTHALATE, BENZYLBUTYL-" OR "PHTHALATE, BUTYL BENZYL" OR "Phthalic acid, benzyl butyl ester" OR "Sant 160" OR "Santicizer 160" 4. "Santicizer C 160" OR "Santicizer S 106" OR "Sicol 160" OR "Spatozoate" OR "UNII-YPC4PJX59M" OR "Unimoll BB"	202
ToxNet Search Date: 7/3/2019	85-68-7 OR 58128-78-2	722
WoS Search Date: 9/11/2019	TS=("1,2-Benzenedicarboxylic acid butyl phenylmethyl ester" OR "1,2-Benzenedicarboxylic acid, 1-butyl 2-(phenylmethyl) ester" OR "1,2-BENZENEDICARBOXYLIC ACID, BUTYL PHENYL METHYL ESTER" OR "1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester" OR "Benzyl butyl benzene-1,2-dicarboxylate" OR "Benzyl butyl phthalate" OR "Benzyl butylphthalate" OR "Benzyl n-butyl phthalate" OR "Benzylbutyl phthalate" OR "BRN 2062204" OR "Butyl benzyl phthalate" OR "Butyl phenylmethyl 1,2-benzenedicarboxylate" OR "Butylbenzyl Phthalate" OR "Butylbenzylphthalate" OR "Caswell No. 125G" OR "Diacizer D 160" OR "EINECS 201-622-7" OR "n-Butyl benzyl phthalate" OR "n-Butyl benzyl phthalate diester" OR "NCI-C54375" OR "NSC 71001" OR "Palatinol BB" OR "PHTHALATE, BENZYLBUTYL-" OR "PHTHALATE, BUTYL BENZYL" OR "Phthalic acid, benzyl butyl ester" OR "Sant 160" OR "Santicizer 160" OR "Santicizer C 160" OR "Santicizer S 106" OR "Sicol 160" OR "Spatozoate" OR "UNII-YPC4PJX59M" OR "Unimoll BB")	837
Unify[a] Search Date: 7/11/2019	1,2-Benzenedicarboxylic acid butyl phenylmethyl ester|1,2-Benzenedicarboxylic acid, 1-butyl 2-(phenylmethyl) ester|1,2-BENZENEDICARBOXYLIC ACID, BUTYL PHENYL METHYL ESTER|1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester|Benzyl butyl benzene-1,2-dicarboxylate|Benzyl butyl phthalate|Benzyl butylphthalate|Benzyl n-butyl phthalate|Benzylbutyl phthalate|BRN 2062204|Butyl benzyl phthalate|Butyl phenylmethyl 1,2-benzenedicarboxylate|Butylbenzyl Phthalate|Butylbenzylphthalate|Caswell No. 125G|Diacizer D 160|EINECS 201-622-7|n-Butyl benzyl phthalate|n-Butyl benzyl phthalate diester|NCI-C54375|NSC 71001|Palatinol BB|PHTHALATE, BENZYLBUTYL-|PHTHALATE, BUTYL BENZYL|Phthalic acid, benzyl butyl ester|Sant 160|Santicizer 160|Santicizer C 160|Santicizer S 106|Sicol 160|Spatozoate|UNII-YPC4PJX59M|Unimoll BB	239
Total	**Represents total across all databases after deduplication**	**1,901**

Source	Source-Specific Search Strategy	Results
[s] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.		

C.1.18 Query Strings for the Peer-Reviewed Literature Database Searches on DEHP

These are the search terms compiled from the Chemical Report for di-ethylhexyl phthalate (DEHP) used in the initial search strategies for each of the databases listed below:

"1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester" OR "1,2-Benzedicarboxylic acid, bis(2-ethyl-hexyl) ester" OR "1,2-Benzenedicarboxylic acid bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester" OR "1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl)ester" OR "1,2-Benzenedicarboxylic acid, Butyl phenylmethyl ester" OR "1,2-Benzenedicarboxylic acid, diisooctyl ester" OR "1,2-Benzenedicarboxylic acid,bis(2-ethylhexylester)" OR "2-Ethylhexyl phthalate" OR "AI3-27697-X" OR "Bis(2-ethylhexyl) 1,2-benzenedicarboxylate" OR "Bis(2-ethylhexyl) benzene-1,2-dicarboxylate" OR "Bis(2-ethylhexyl) o-phthalate" OR "Bis(2-ethylhexyl) phthalate" OR "Bis(2-ethylhexyl)ester, Phthalic acid" OR "Bis(2-ethylhexyl)phthalat" OR "Bis(2-ethylhexyl)phthalate" OR "Bis-(2-ethylhexyl)-phthalate" OR "Bis(ethylhexyl) phthalate" OR "Bisoflex 81" OR "Bisoflex DOP" OR "BRN 1890696" OR "Butylbenzyl Phthalate" OR "Butylbenzylphthalate" OR "Caswell No. 392K" OR "Codan Set L 86P" OR "Compound 889" OR "Corflex 400" OR "Corflex 880" OR "DEHP" OR "Di(2-ethylhexyl) o-phthalate" OR "Di(2-ethylhexyl) orthophthalate" OR "Di(2-ethylhexyl) phthalate" OR "Di-(2-ethylhexyl) phthalate" OR "Di(2-ethylhexyl)orthophthalate" OR "Di(2-ethylhexyl)phthalate" OR "di(alpha-Ethylhexyl) phthalate" OR "Di(ethylhexyl) phthalate" OR "Di-(Ethylhexyl)phthalate" OR "Di(isooctyl) phthalate" OR "Di-2-ethylhexlphthalate" OR "Di-2-ethylhexyl phthalate" OR "DI-2-ETHYLHEXYL-PHTHALATE" OR "Diacizer DOP" OR "Diethylhexyl phthalate" OR "Di-ethylhexyl phthalate" OR "Diethylhexylphthalate" OR "Diisooctyl 1,2-benzenedicarboxylate" OR "Diisooctyl ester 1,2-Benzenedicarboxylic acid" OR "Diisooctyl o-phthalate" OR "Diisooctyl phthalate" OR "di-iso-Octyl phthalate" OR "Diisooctylphthalat" OR "Diisooctylphthalate" OR "Dioctyl phthalate" OR "Diplast O" OR "Di-sec-octyl phthalate" OR "Ergoplast FDO" OR "Ergoplast FDO-S" OR "ESBO-D 82" OR "Etalon" OR "Ethylhexyl phthalate" OR "Ethylhexyl phthlate" OR "Eviplast 80" OR "Eviplast 81" OR "Fleximel" OR "Flexol DOD" OR "Flexol DOP" OR "Flexol Plasticizer DIOP" OR "Flexol Plasticizer DOP" OR "Garbeflex DOP-D 40" OR "Good-rite GP 264" OR "Hatco DOP" OR "Hatcol DOP" OR "Hercoflex 260" OR "Hexaplas DIOP" OR "Hexaplas M/O" OR "Isooctyl phthalate" OR "Isooctylphthalate" OR "Jayflex DIOP" OR "Jayflex DOP" OR "JSSD-DOP" OR "Kodaflex DEHP" OR "Kodaflex DOP" OR "Mollan O" OR "Monocizer DOP" OR "NCI-C52733" OR "NSC 17069" OR "NSC 6381" OR "Nuoplaz DOP" OR "Octoil" OR "Octyl phthalate" OR "Palatinol AH" OR "Palatinol AH-L" OR "Palatinol DOP" OR "PHTHALATE, BIS(2-ETHYLHEXYL)" OR "Phthalic acid bis(2-ethylhexyl) ester" OR "Phthalic acid di(2-ethylhexyl) ester" OR "Phthalic acid dioctyl ester" OR "Phthalic acid, bis(2-ethylhexyl) ester" OR "PHTHALIC ACID, BIS(2-ETHYLHEXYL)ESTER" OR "Phthalic acid, bis(6-methylheptyl)ester" OR "Phthalic acid, diisooctyl ester" OR "Pittsburgh PX 138" OR "Pittsburgh PX-138" OR "Plasthall DOP" OR "Platinol AH" OR "Platinol DOP" OR "RC Plasticizer DOP" OR "RCRA waste number U028" OR "Reomol D 79P" OR "Reomol DOP" OR "Sansocizer DOP" OR "Sansocizer R 8000" OR "Scandinol SC 1000" OR "Sconamoll

DOP" OR "Sicol 150" OR "Staflex DOP" OR "Truflex DOP" OR "Unem 5005" OR "UNII-6A121LGB40" OR "UNII-C42K0PH13C" OR "Vestinol AH" OR "Vinicizer 80" OR "Vinycizer 80" OR "Vinycizer 80K" OR "Witcizer 312"

Table_Apx C-21. Peer-Reviewed Literature Search Strategy for DEHP

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 7/10/2019	1. 1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester; 1,2-Benzedicarboxylic acid, bis(2-ethyl-hexyl) ester; 1,2-Benzenedicarboxylic acid bis(2-ethylhexyl) ester; 1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester; 1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester; 1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester; 1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl)ester; 1,2-Benzenedicarboxylic acid, Butyl phenylmethyl ester; 1,2-Benzenedicarboxylic acid, diisooctyl ester; 1,2-Benzenedicarboxylic acid,bis(2-ethylhexylester) 2. 2-Ethylhexyl phthalate; AI3-27697-X; Bis(2-ethylhexyl) 1,2-benzenedicarboxylate; Bis(2-ethylhexyl) benzene-1,2-dicarboxylate; Bis(2-ethylhexyl) o-phthalate; Bis(2-ethylhexyl) phthalate; Bis(2-ethylhexyl)ester, Phthalic acid; Bis(2-ethylhexyl)phthalat; Bis(2-ethylhexyl)phthalate; Bis-(2-ethylhexyl)-phthalate 3. Bis(ethylhexyl) phthalate; Bisoflex 81; Bisoflex DOP; BRN 1890696; Butylbenzyl Phthalate; Butylbenzylphthalate; Caswell No. 392K; Codan Set L 86P; Compound 889; Corflex 400 4. Corflex 880; DEHP; Di(2-ethylhexyl) o-phthalate; Di(2-ethylhexyl) orthophthalate; Di(2-ethylhexyl) phthalate; Di-(2-ethylhexyl) phthalate; Di(2-ethylhexyl)orthophthalate; Di(2-ethylhexyl)phthalate; di(alpha-Ethylhexyl) phthalate; Di(ethylhexyl) phthalate 5. Di-(Ethylhexyl)phthalate; Di(isooctyl) phthalate; Di-2-ethylhexlphthalate; Di-2-ethylhexyl phthalate; DI-2-ETHYLHEXYL-PHTHALATE; Diacizer DOP; Diethylhexyl phthalate; Di-ethylhexyl phthalate; Diethylhexylphthalate; Diisooctyl 1,2-benzenedicarboxylate 6. Diisooctyl ester 1,2-Benzenedicarboxylic acid; Diisooctyl o-phthalate; Diisooctyl phthalate; di-iso-Octyl phthalate; Diisooctylphthalat; Diisooctylphthalate; Dioctyl phthalate; Diplast O; Di-sec-octyl phthalate; Ergoplast FDO 7. Ergoplast FDO-S; ESBO-D 82; Etalon; Ethylhexyl phthalate; Ethylhexyl phthlate; Eviplast 80; Eviplast 81; Fleximel; Flexol DOD; Flexol DOP 8. Flexol Plasticizer DIOP; Flexol Plasticizer DOP; Garbeflex DOP-D 40; Good-rite GP 264; Hatco DOP; Hatcol DOP; Hercoflex 260; Hexaplas DIOP; Hexaplas M/O; Isooctyl phthalate 9. Isooctylphthalate; Jayflex DIOP; Jayflex DOP; JSSD-DOP; Kodaflex DEHP; Kodaflex DOP; Mollan O; Monocizer DOP; NCI-C52733; NSC 17069 10. NSC 6381; Nuoplaz DOP; Octoil; Octyl phthalate; Palatinol AH; Palatinol AH-L; Palatinol DOP; PHTHALATE, BIS(2-ETHYLHEXYL); Phthalic acid bis(2-ethylhexyl) ester; Phthalic acid di(2-ethylhexyl) ester 11. Phthalic acid dioctyl ester; Phthalic acid, bis(2-ethylhexyl) ester; PHTHALIC ACID, BIS(2-ETHYLHEXYL)ESTER; Phthalic acid, bis(6-methylheptyl)ester; Phthalic acid, diisooctyl ester; Pittsburgh PX 138; Pittsburgh PX-138; Plasthall DOP; Platinol AH; Platinol DOP 12. RC Plasticizer DOP; RCRA waste number U028; Reomol D 79P; Reomol DOP; Sansocizer DOP; Sansocizer R 8000; Scandinol SC 1000; Sconamoll DOP; Sicol 150; Staflex DOP 13. Truflex DOP; Unem 5005; UNII-6A121LGB40; UNII-C42K0PH13C; Vestinol AH; Vinicizer 80; Vinycizer 80; Vinycizer 80K; Witcizer 312	3,391

Source	Source-Specific Search Strategy	Results
Current Contents Search Date: 7/5/2019	TS=("1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester" OR "1,2-Benzedicarboxylic acid, bis(2-ethyl-hexyl) ester" OR "1,2-Benzenedicarboxylic acid bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester" OR "1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl)ester" OR "1,2-Benzenedicarboxylic acid, Butyl phenylmethyl ester" OR "1,2-Benzenedicarboxylic acid, diisooctyl ester" OR "1,2-Benzenedicarboxylic acid,bis(2-ethylhexylester)" OR "2-Ethylhexyl phthalate" OR "AI3-27697-X" OR "Bis(2-ethylhexyl) 1,2-benzenedicarboxylate" OR "Bis(2-ethylhexyl) benzene-1,2-dicarboxylate" OR "Bis(2-ethylhexyl) o-phthalate" OR "Bis(2-ethylhexyl) phthalate" OR "Bis(2-ethylhexyl)ester, Phthalic acid" OR "Bis(2-ethylhexyl)phthalat" OR "Bis(2-ethylhexyl)phthalate" OR "Bis-(2-ethylhexyl)-phthalate" OR "Bis(ethylhexyl) phthalate" OR "Bisoflex 81" OR "Bisoflex DOP" OR "BRN 1890696" OR "Butylbenzyl Phthalate" OR "Butylbenzylphthalate" OR "Caswell No. 392K" OR "Codan Set L 86P" OR "Compound 889" OR "Corflex 400" OR "Corflex 880" OR "DEHP" OR "Di(2-ethylhexyl) o-phthalate" OR "Di(2-ethylhexyl) orthophthalate" OR "Di(2-ethylhexyl) phthalate" OR "Di-(2-ethylhexyl) phthalate" OR "Di(2-ethylhexyl)orthophthalate" OR "Di(2-ethylhexyl)phthalate" OR "di(alpha-Ethylhexyl) phthalate" OR "Di(ethylhexyl) phthalate" OR "Di-(Ethylhexyl)phthalate" OR "Di(isooctyl) phthalate" OR "Di-2-ethylhexlphthalate" OR "Di-2-ethylhexyl phthalate" OR "DI-2-ETHYLHEXYL-PHTHALATE" OR "Diacizer DOP" OR "Diethylhexyl phthalate" OR "Di-ethylhexyl phthalate" OR "Diethylhexylphthalate" OR "Diisooctyl 1,2-benzenedicarboxylate" OR "Diisooctyl ester 1,2-Benzenedicarboxylic acid" OR "Diisooctyl o-phthalate" OR "Diisooctyl phthalate" OR "di-iso-Octyl phthalate" OR "Diisooctylphthalat" OR "Diisooctylphthalate" OR "Dioctyl phthalate" OR "Diplast O" OR "Di-sec-octyl phthalate" OR "Ergoplast FDO" OR "Ergoplast FDO-S" OR "ESBO-D 82" OR "Etalon" OR "Ethylhexyl phthalate" OR "Ethylhexyl phthlate" OR "Eviplast 80" OR "Eviplast 81" OR "Fleximel" OR "Flexol DOD" OR "Flexol DOP" OR "Flexol Plasticizer DIOP" OR "Flexol Plasticizer DOP" OR "Garbeflex DOP-D 40" OR "Good-rite GP 264" OR "Hatco DOP" OR "Hatcol DOP" OR "Hercoflex 260" OR "Hexaplas DIOP" OR "Hexaplas M/O" OR "Isooctyl phthalate" OR "Isooctylphthalate" OR "Jayflex DIOP" OR "Jayflex DOP" OR "JSSD-DOP" OR "Kodaflex DEHP" OR "Kodaflex DOP" OR "Mollan O" OR "Monocizer DOP" OR "NCI-C52733" OR "NSC 17069" OR "NSC 6381" OR "Nuoplaz DOP" OR "Octoil" OR "Octyl phthalate" OR "Palatinol AH" OR "Palatinol AH-L" OR "Palatinol DOP" OR "PHTHALATE, BIS(2-ETHYLHEXYL)" OR "Phthalic acid bis(2-ethylhexyl) ester" OR "Phthalic acid di(2-ethylhexyl) ester" OR "Phthalic acid dioctyl ester" OR "Phthalic acid, bis(2-ethylhexyl) ester" OR "PHTHALIC ACID, BIS(2-ETHYLHEXYL)ESTER" OR "Phthalic acid, bis(6-methylheptyl)ester" OR "Phthalic acid, diisooctyl ester" OR "Pittsburgh PX 138" OR "Pittsburgh PX-138" OR "Plasthall DOP" OR "Platinol AH" OR "Platinol DOP" OR "RC Plasticizer DOP" OR "RCRA waste number U028" OR "Reomol D 79P" OR "Reomol DOP" OR "Sansocizer DOP" OR "Sansocizer R 8000" OR "Scandinol SC 1000" OR "Sconamoll DOP" OR "Sicol 150" OR "Staflex DOP" OR "Truflex DOP" OR "Unem 5005" OR "UNII-6A121LGB40" OR "UNII-C42K0PH13C" OR "Vestinol AH" OR "Vinicizer 80" OR "Vinycizer 80" OR "Vinycizer 80K" OR "Witcizer 312")	9,488
ProQuest Dissertations & Theses Search Date: 7/11/2019	ALL("1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester" OR "1,2-Benzedicarboxylic acid, bis(2-ethyl-hexyl) ester" OR "1,2-Benzenedicarboxylic acid bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester" OR "1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl)ester" OR "1,2-Benzenedicarboxylic acid, Butyl phenylmethyl ester" OR "1,2-Benzenedicarboxylic acid, diisooctyl ester" OR "1,2-Benzenedicarboxylic acid,bis(2-ethylhexylester)" OR "2-Ethylhexyl phthalate" OR "AI3-27697-X" OR "Bis(2-ethylhexyl) 1,2-benzenedicarboxylate" OR "Bis(2-ethylhexyl) benzene-1,2-dicarboxylate" OR "Bis(2-ethylhexyl) o-phthalate" OR "Bis(2-ethylhexyl) phthalate" OR "Bis(2-ethylhexyl)ester, Phthalic acid"	85

Source	Source-Specific Search Strategy	Results
	OR "Bis(2-ethylhexyl)phthalat" OR "Bis(2-ethylhexyl)phthalate" OR "Bis-(2-ethylhexyl)-phthalate" OR "Bis(ethylhexyl) phthalate" OR "Bisoflex 81" OR "Bisoflex DOP" OR "BRN 1890696" OR "Butylbenzyl Phthalate" OR "Butylbenzylphthalate" OR "Caswell No. 392K" OR "Codan Set L 86P" OR "Compound 889" OR "Corflex 400" OR "Corflex 880" OR "DEHP" OR "Di(2-ethylhexyl) o-phthalate" OR "Di(2-ethylhexyl) orthophthalate" OR "Di(2-ethylhexyl) phthalate" OR "Di-(2-ethylhexyl) phthalate" OR "Di(2-ethylhexyl)orthophthalate" OR "Di(2-ethylhexyl)phthalate" OR "di(alpha-Ethylhexyl) phthalate" OR "Di(ethylhexyl) phthalate" OR "Di-(Ethylhexyl)phthalate" OR "Di(isooctyl) phthalate" OR "Di-2-ethylhexlphthalate" OR "Di-2-ethylhexyl phthalate" OR "DI-2-ETHYLHEXYL-PHTHALATE" OR "Diacizer DOP" OR "Diethylhexyl phthalate" OR "Di-ethylhexyl phthalate" OR "Diethylhexylphthalate" OR "Diisooctyl 1,2-benzenedicarboxylate" OR "Diisooctyl ester 1,2-Benzenedicarboxylic acid" OR "Diisooctyl o-phthalate" OR "Diisooctyl phthalate" OR "di-iso-Octyl phthalate" OR "Diisooctylphthalat" OR "Diisooctylphthalate" OR "Dioctyl phthalate" OR "Diplast O" OR "Di-sec-octyl phthalate" OR "Ergoplast FDO" OR "Ergoplast FDO-S" OR "ESBO-D 82" OR "Etalon" OR "Ethylhexyl phthalate" OR "Ethylhexyl phthlate" OR "Eviplast 80" OR "Eviplast 81" OR "Fleximel" OR "Flexol DOD" OR "Flexol DOP" OR "Flexol Plasticizer DIOP" OR "Flexol Plasticizer DOP" OR "Garbeflex DOP-D 40" OR "Good-rite GP 264" OR "Hatco DOP" OR "Hatcol DOP" OR "Hercoflex 260" OR "Hexaplas DIOP" OR "Hexaplas M/O" OR "Isooctyl phthalate" OR "Isooctylphthalate" OR "Jayflex DIOP" OR "Jayflex DOP" OR "JSSD-DOP" OR "Kodaflex DEHP" OR "Kodaflex DOP" OR "Mollan O" OR "Monocizer DOP" OR "NCI-C52733" OR "NSC 17069" OR "NSC 6381" OR "Nuoplaz DOP" OR "Octoil" OR "Octyl phthalate" OR "Palatinol AH" OR "Palatinol AH-L" OR "Palatinol DOP" OR "PHTHALATE, BIS(2-ETHYLHEXYL)" OR "Phthalic acid bis(2-ethylhexyl) ester" OR "Phthalic acid di(2-ethylhexyl) ester" OR "Phthalic acid dioctyl ester" OR "Phthalic acid, bis(2-ethylhexyl) ester" OR "PHTHALIC ACID, BIS(2-ETHYLHEXYL)ESTER" OR "Phthalic acid, bis(6-methylheptyl)ester" OR "Phthalic acid, diisooctyl ester" OR "Pittsburgh PX 138" OR "Pittsburgh PX-138" OR "Plasthall DOP" OR "Platinol AH" OR "Platinol DOP" OR "RC Plasticizer DOP" OR "RCRA waste number U028" OR "Reomol D 79P" OR "Reomol DOP" OR "Sansocizer DOP" OR "Sansocizer R 8000" OR "Scandinol SC 1000" OR "Sconamoll DOP" OR "Sicol 150" OR "Staflex DOP" OR "Truflex DOP" OR "Unem 5005" OR "UNII-6A121LGB40" OR "UNII-C42K0PH13C" OR "Vestinol AH" OR "Vinicizer 80" OR "Vinycizer 80" OR "Vinycizer 80K" OR "Witcizer 312") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	
ProQuest Agricultural & Scientific Database Search Date: 7/5/2019	ALL("1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester" OR "1,2-Benzedicarboxylic acid, bis(2-ethyl-hexyl) ester" OR "1,2-Benzenedicarboxylic acid bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester" OR "1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl)ester" OR "1,2-Benzenedicarboxylic acid, Butyl phenylmethyl ester" OR "1,2-Benzenedicarboxylic acid, diisooctyl ester" OR "1,2-Benzenedicarboxylic acid,bis(2-ethylhexylester)" OR "2-Ethylhexyl phthalate" OR "AI3-27697-X" OR "Bis(2-ethylhexyl) 1,2-benzenedicarboxylate" OR "Bis(2-ethylhexyl) benzene-1,2-dicarboxylate" OR "Bis(2-ethylhexyl) o-phthalate" OR "Bis(2-ethylhexyl) phthalate" OR "Bis(2-ethylhexyl)ester, Phthalic acid" OR "Bis(2-ethylhexyl)phthalat" OR "Bis(2-ethylhexyl)phthalate" OR "Bis-(2-ethylhexyl)-phthalate" OR "Bis(ethylhexyl) phthalate" OR "Bisoflex 81" OR "Bisoflex DOP" OR "BRN 1890696" OR "Butylbenzyl Phthalate" OR "Butylbenzylphthalate" OR "Caswell No. 392K" OR "Codan Set L 86P" OR "Compound 889" OR "Corflex 400" OR "Corflex 880" OR "DEHP" OR "Di(2-ethylhexyl) o-phthalate" OR "Di(2-ethylhexyl) orthophthalate" OR "Di(2-ethylhexyl) phthalate" OR "Di-(2-ethylhexyl) phthalate" OR "Di(2-ethylhexyl)orthophthalate" OR "Di(2-ethylhexyl)phthalate" OR "di(alpha-Ethylhexyl) phthalate" OR "Di(ethylhexyl) phthalate" OR "Di-(Ethylhexyl)phthalate" OR "Di(isooctyl) phthalate" OR "Di-2-ethylhexlphthalate" OR "Di-2-	13,506

Source	Source-Specific Search Strategy	Results
	ethylhexyl phthalate" OR "DI-2-ETHYLHEXYL-PHTHALATE" OR "Diacizer DOP" OR "Diethylhexyl phthalate" OR "Di-ethylhexyl phthalate" OR "Diethylhexylphthalate" OR "Diisooctyl 1,2-benzenedicarboxylate" OR "Diisooctyl ester 1,2-Benzenedicarboxylic acid" OR "Diisooctyl o-phthalate" OR "Diisooctyl phthalate" OR "di-iso-Octyl phthalate" OR "Diisooctylphthalat" OR "Diisooctylphthalate" OR "Dioctyl phthalate" OR "Diplast O" OR "Di-sec-octyl phthalate" OR "Ergoplast FDO" OR "Ergoplast FDO-S" OR "ESBO-D 82" OR "Etalon" OR "Ethylhexyl phthalate" OR "Ethylhexyl phthlate" OR "Eviplast 80" OR "Eviplast 81" OR "Fleximel" OR "Flexol DOD" OR "Flexol DOP" OR "Flexol Plasticizer DIOP" OR "Flexol Plasticizer DOP" OR "Garbeflex DOP-D 40" OR "Good-rite GP 264" OR "Hatco DOP" OR "Hatcol DOP" OR "Hercoflex 260" OR "Hexaplas DIOP" OR "Hexaplas M/O" OR "Isooctyl phthalate" OR "Isooctylphthalate" OR "Jayflex DIOP" OR "Jayflex DOP" OR "JSSD-DOP" OR "Kodaflex DEHP" OR "Kodaflex DOP" OR "Mollan O" OR "Monocizer DOP" OR "NCI-C52733" OR "NSC 17069" OR "NSC 6381" OR "Nuoplaz DOP" OR "Octoil" OR "Octyl phthalate" OR "Palatinol AH" OR "Palatinol AH-L" OR "Palatinol DOP" OR "PHTHALATE, BIS(2-ETHYLHEXYL)" OR "Phthalic acid bis(2-ethylhexyl) ester" OR "Phthalic acid di(2-ethylhexyl) ester" OR "Phthalic acid dioctyl ester" OR "Phthalic acid, bis(2-ethylhexyl) ester" OR "PHTHALIC ACID, BIS(2-ETHYLHEXYL)ESTER" OR "Phthalic acid, bis(6-methylheptyl)ester" OR "Phthalic acid, diisooctyl ester" OR "Pittsburgh PX 138" OR "Pittsburgh PX-138" OR "Plasthall DOP" OR "Platinol AH" OR "Platinol DOP" OR "RC Plasticizer DOP" OR "RCRA waste number U028" OR "Reomol D 79P" OR "Reomol DOP" OR "Sansocizer DOP" OR "Sansocizer R 8000" OR "Scandinol SC 1000" OR "Sconamoll DOP" OR "Sicol 150" OR "Staflex DOP" OR "Truflex DOP" OR "Unem 5005" OR "UNII-6A121LGB40" OR "UNII-C42K0PH13C" OR "Vestinol AH" OR "Vinicizer 80" OR "Vinycizer 80" OR "Vinycizer 80K" OR "Witcizer 312") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	
PubMed Search Date: 7/8/2019	"1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester" OR "1,2-Benzedicarboxylic acid, bis(2-ethyl-hexyl) ester" OR "1,2-Benzenedicarboxylic acid bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester" OR "1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl)ester" OR "1,2-Benzenedicarboxylic acid, Butyl phenylmethyl ester" OR "1,2-Benzenedicarboxylic acid, diisooctyl ester" OR "1,2-Benzenedicarboxylic acid,bis(2-ethylhexylester)" OR "2-Ethylhexyl phthalate" OR "AI3-27697-X" OR "Bis(2-ethylhexyl) 1,2-benzenedicarboxylate" OR "Bis(2-ethylhexyl) benzene-1,2-dicarboxylate" OR "Bis(2-ethylhexyl) o-phthalate" OR "Bis(2-ethylhexyl) phthalate" OR "Bis(2-ethylhexyl)ester, Phthalic acid" OR "Bis(2-ethylhexyl)phthalat" OR "Bis(2-ethylhexyl)phthalate" OR "Bis-(2-ethylhexyl)-phthalate" OR "Bis(ethylhexyl) phthalate" OR "Bisoflex 81" OR "Bisoflex DOP" OR "BRN 1890696" OR "Butylbenzyl Phthalate" OR "Butylbenzylphthalate" OR "Caswell No. 392K" OR "Codan Set L 86P" OR "Compound 889" OR "Corflex 400" OR "Corflex 880" OR "DEHP" OR "Di(2-ethylhexyl) o-phthalate" OR "Di(2-ethylhexyl) orthophthalate" OR "Di(2-ethylhexyl) phthalate" OR "Di-(2-ethylhexyl) phthalate" OR "Di(2-ethylhexyl)orthophthalate" OR "Di(2-ethylhexyl)phthalate" OR "di(alpha-Ethylhexyl) phthalate" OR "Di(ethylhexyl) phthalate" OR "Di-(Ethylhexyl)phthalate" OR "Di(isooctyl) phthalate" OR "Di-2-ethylhexlphthalate" OR "Di-2-ethylhexyl phthalate" OR "DI-2-ETHYLHEXYL-PHTHALATE" OR "Diacizer DOP" OR "Diethylhexyl phthalate" OR "Di-ethylhexyl phthalate" OR "Diethylhexylphthalate" OR "Diisooctyl 1,2-benzenedicarboxylate" OR "Diisooctyl ester 1,2-Benzenedicarboxylic acid" OR "Diisooctyl o-phthalate" OR "Diisooctyl phthalate" OR "di-iso-Octyl phthalate" OR "Diisooctylphthalat" OR "Diisooctylphthalate" OR "Dioctyl phthalate" OR "Diplast O" OR "Di-sec-octyl phthalate" OR "Ergoplast FDO" OR "Ergoplast FDO-S" OR "ESBO-D 82" OR "Etalon" OR "Ethylhexyl phthalate" OR "Ethylhexyl phthlate" OR "Eviplast 80" OR "Eviplast 81" OR "Fleximel" OR "Flexol DOD" OR "Flexol DOP" OR "Flexol Plasticizer DIOP" OR	8,331

Source	Source-Specific Search Strategy	Results
	"Flexol Plasticizer DOP" OR "Garbeflex DOP-D 40" OR "Good-rite GP 264" OR "Hatco DOP" OR "Hatcol DOP" OR "Hercoflex 260" OR "Hexaplas DIOP" OR "Hexaplas M/O" OR "Isooctyl phthalate" OR "Isooctylphthalate" OR "Jayflex DIOP" OR "Jayflex DOP" OR "JSSD-DOP" OR "Kodaflex DEHP" OR "Kodaflex DOP" OR "Mollan O" OR "Monocizer DOP" OR "NCI-C52733" OR "NSC 17069" OR "NSC 6381" OR "Nuoplaz DOP" OR "Octoil" OR "Octyl phthalate" OR "Palatinol AH" OR "Palatinol AH-L" OR "Palatinol DOP" OR "PHTHALATE, BIS(2-ETHYLHEXYL)" OR "Phthalic acid bis(2-ethylhexyl) ester" OR "Phthalic acid di(2-ethylhexyl) ester" OR "Phthalic acid dioctyl ester" OR "Phthalic acid, bis(2-ethylhexyl) ester" OR "PHTHALIC ACID, BIS(2-ETHYLHEXYL)ESTER" OR "Phthalic acid, bis(6-methylheptyl)ester" OR "Phthalic acid, diisooctyl ester" OR "Pittsburgh PX 138" OR "Pittsburgh PX-138" OR "Plasthall DOP" OR "Platinol AH" OR "Platinol DOP" OR "RC Plasticizer DOP" OR "RCRA waste number U028" OR "Reomol D 79P" OR "Reomol DOP" OR "Sansocizer DOP" OR "Sansocizer R 8000" OR "Scandinol SC 1000" OR "Sconamoll DOP" OR "Sicol 150" OR "Staflex DOP" OR "Truflex DOP" OR "Unem 5005" OR "UNII-6A121LGB40" OR "UNII-C42K0PH13C" OR "Vestinol AH" OR "Vinicizer 80" OR "Vinycizer 80" OR "Vinycizer 80K" OR "Witcizer 312"	
Science Direct Search Date: 7/5/2019	1. "1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester" OR "1,2-Benzedicarboxylic acid, bis(2-ethyl-hexyl) ester" OR "1,2-Benzenedicarboxylic acid bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester" OR "1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl)ester" OR "1,2-Benzenedicarboxylic acid, Butyl phenylmethyl ester" OR "1,2-Benzenedicarboxylic acid, diisooctyl ester" 2. "1,2-Benzenedicarboxylic acid,bis(2-ethylhexylester)" OR "2-Ethylhexyl phthalate" OR "AI3-27697-X" OR "Bis(2-ethylhexyl) 1,2-benzenedicarboxylate" OR "Bis(2-ethylhexyl) benzene-1,2-dicarboxylate" OR "Bis(2-ethylhexyl) o-phthalate" OR "Bis(2-ethylhexyl) phthalate" OR "Bis(2-ethylhexyl)ester, Phthalic acid" OR "Bis(2-ethylhexyl)phthalat" 3. "Bis(2-ethylhexyl)phthalate" OR "Bis-(2-ethylhexyl)-phthalate" OR "Bis(ethylhexyl) phthalate" OR "Bisoflex 81" OR "Bisoflex DOP" OR "BRN 1890696" OR "Butylbenzyl Phthalate" OR "Butylbenzylphthalate" OR "Caswell No. 392K" 4. "Codan Set L 86P" OR "Compound 889" OR "Corflex 400" OR "Corflex 880" OR "DEHP" OR "Di(2-ethylhexyl) o-phthalate" OR "Di(2-ethylhexyl) orthophthalate" OR "Di(2-ethylhexyl) phthalate" OR "Di-(2-ethylhexyl) phthalate" 5. "Di(2-ethylhexyl)orthophthalate" OR "Di(2-ethylhexyl)phthalate" OR "di(alpha-Ethylhexyl) phthalate" OR "Di(ethylhexyl) phthalate" OR "Di-(Ethylhexyl)phthalate" OR "Di(isooctyl) phthalate" OR "Di-2-ethylhexlphthalate" OR "Di-2-ethylhexyl phthalate" OR "DI-2-ETHYLHEXYL-PHTHALATE" 6. "Diacizer DOP" OR "Diethylhexyl phthalate" OR "Di-ethylhexyl phthalate" OR "Diethylhexylphthalate" OR "Diisooctyl 1,2-benzenedicarboxylate" 7. "Diisooctyl ester 1,2-Benzenedicarboxylic acid" OR "Diisooctyl o-phthalate" OR "Diisooctyl phthalate" OR "di-iso-Octyl phthalate" OR "Diisooctylphthalat" OR "Diisooctylphthalate" OR "Dioctyl phthalate" OR "Diplast O" OR "Di-sec-octyl phthalate" 8. "Ergoplast FDO" OR "Ergoplast FDO-S" OR "ESBO-D 82" OR "Etalon" OR "Ethylhexyl phthalate" OR "Ethylhexyl phthlate" OR "Eviplast 80" OR "Eviplast 81" OR "Fleximel" 9. "Flexol DOD" OR "Flexol DOP" OR "Flexol Plasticizer DIOP" OR "Flexol Plasticizer DOP" OR "Garbeflex DOP-D 40" OR "Good-rite GP 264" OR "Hatco DOP" OR "Hatcol DOP" OR "Hercoflex 260" 10. "Hexaplas DIOP" OR "Hexaplas M/O" OR "Isooctyl phthalate" OR "Isooctylphthalate" OR "Jayflex DIOP" OR "Jayflex DOP" OR "JSSD-DOP" OR "Kodaflex DEHP" OR "Kodaflex DOP"	3,332

Source	Source-Specific Search Strategy	Results
	11. "Mollan O" OR "Monocizer DOP" OR "NCI-C52733" OR "NSC 17069" OR "NSC 6381" OR "Nuoplaz DOP" OR "Octoil" OR "Octyl phthalate" OR "Palatinol AH" 12. "Palatinol AH-L" OR "Palatinol DOP" OR "PHTHALATE, BIS(2-ETHYLHEXYL)" OR "Phthalic acid bis(2-ethylhexyl) ester" OR "Phthalic acid di(2-ethylhexyl) ester" 13. "Phthalic acid dioctyl ester" OR "Phthalic acid, bis(2-ethylhexyl) ester" OR "PHTHALIC ACID, BIS(2-ETHYLHEXYL)ESTER" OR "Phthalic acid, bis(6-methylheptyl)ester" OR "Phthalic acid, diisooctyl ester" OR "Pittsburgh PX 138" OR "Pittsburgh PX-138" OR "Plasthall DOP" OR "Platinol AH" 14. "Platinol DOP" OR "RC Plasticizer DOP" OR "RCRA waste number U028" OR "Reomol D 79P" OR "Reomol DOP" OR "Sansocizer DOP" OR "Sansocizer R 8000" OR "Scandinol SC 1000" OR "Sconamoll DOP" 15. "Sicol 150" OR "Staflex DOP" OR "Truflex DOP" OR "Unem 5005" OR "UNII-6A121LGB40" OR "UNII-C42K0PH13C" OR "Vestinol AH" OR "Vinicizer 80" OR "Vinycizer 80" 16. "Vinycizer 80K" OR "Witcizer 312"	
ToxNet Search Date: 7/8/2019	1. 117-81-7 OR 27554-26-3 OR 8033-53-2 OR 40120-69-2 OR 50885-87-5 2. 109630-52-6 OR 126639-29-0 OR 137718-37-7 OR 205180-59-2 OR 275818-89-8 3. 607374-50-5 OR 1330-91-2 OR 25103-50-8 OR 41375-90-0	3,376
WoS Search Date: 9/11/2019	TS=("1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester" OR "1,2-Benzedicarboxylic acid, bis(2-ethyl-hexyl) ester" OR "1,2-Benzenedicarboxylic acid bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester" OR "1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl)ester" OR "1,2-Benzenedicarboxylic acid, Butyl phenylmethyl ester" OR "1,2-Benzenedicarboxylic acid, diisooctyl ester" OR "1,2-Benzenedicarboxylic acid,bis(2-ethylhexylester)" OR "2-Ethylhexyl phthalate" OR "AI3-27697-X" OR "Bis(2-ethylhexyl) 1,2-benzenedicarboxylate" OR "Bis(2-ethylhexyl) benzene-1,2-dicarboxylate" OR "Bis(2-ethylhexyl) o-phthalate" OR "Bis(2-ethylhexyl) phthalate" OR "Bis(2-ethylhexyl)ester, Phthalic acid" OR "Bis(2-ethylhexyl)phthalat" OR "Bis(2-ethylhexyl)phthalate" OR "Bis-(2-ethylhexyl)-phthalate" OR "Bis(ethylhexyl) phthalate" OR "Bisoflex 81" OR "Bisoflex DOP" OR "BRN 1890696" OR "Butylbenzyl Phthalate" OR "Butylbenzylphthalate" OR "Caswell No. 392K" OR "Codan Set L 86P" OR "Compound 889" OR "Corflex 400" OR "Corflex 880" OR "DEHP" OR "Di(2-ethylhexyl) o-phthalate" OR "Di(2-ethylhexyl) orthophthalate" OR "Di(2-ethylhexyl) phthalate" OR "Di-(2-ethylhexyl) phthalate" OR "Di(2-ethylhexyl)orthophthalate" OR "Di(2-ethylhexyl)phthalate" OR "di(alpha-Ethylhexyl) phthalate" OR "Di(ethylhexyl) phthalate" OR "Di-(Ethylhexyl)phthalate" OR "Di(isooctyl) phthalate" OR "Di-2-ethylhexlphthalate" OR "Di-2-ethylhexyl phthalate" OR "DI-2-ETHYLHEXYL-PHTHALATE" OR "Diacizer DOP" OR "Diethylhexyl phthalate" OR "Di-ethylhexyl phthalate" OR "Diethylhexylphthalate" OR "Diisooctyl 1,2-benzenedicarboxylate" OR "Diisooctyl ester 1,2-Benzenedicarboxylic acid" OR "Diisooctyl o-phthalate" OR "Diisooctyl phthalate" OR "di-iso-Octyl phthalate" OR "Diisooctylphthalat" OR "Diisooctylphthalate" OR "Dioctyl phthalate" OR "Diplast O" OR "Di-sec-octyl phthalate" OR "Ergoplast FDO" OR "Ergoplast FDO-S" OR "ESBO-D 82" OR "Etalon" OR "Ethylhexyl phthalate" OR "Ethylhexyl phthlate" OR "Eviplast 80" OR "Eviplast 81" OR "Fleximel" OR "Flexol DOD" OR "Flexol DOP" OR "Flexol Plasticizer DIOP" OR "Flexol Plasticizer DOP" OR "Garbeflex DOP-D 40" OR "Good-rite GP 264" OR "Hatco DOP" OR "Hatcol DOP" OR "Hercoflex 260" OR "Hexaplas DIOP" OR "Hexaplas M/O" OR "Isooctyl phthalate" OR "Isooctylphthalate" OR "Jayflex DIOP" OR "Jayflex DOP" OR "JSSD-DOP" OR "Kodaflex DEHP" OR "Kodaflex DOP" OR "Mollan O" OR "Monocizer DOP" OR "NCI-C52733" OR "NSC 17069" OR "NSC 6381" OR "Nuoplaz DOP" OR "Octoil" OR "Octyl phthalate" OR	14,279

Source	Source-Specific Search Strategy	Results
	"Palatinol AH" OR "Palatinol AH-L" OR "Palatinol DOP" OR "PHTHALATE, BIS(2-ETHYLHEXYL)" OR "Phthalic acid bis(2-ethylhexyl) ester" OR "Phthalic acid di(2-ethylhexyl) ester" OR "Phthalic acid dioctyl ester" OR "Phthalic acid, bis(2-ethylhexyl) ester" OR "PHTHALIC ACID, BIS(2-ETHYLHEXYL)ESTER" OR "Phthalic acid, bis(6-methylheptyl)ester" OR "Phthalic acid, diisooctyl ester" OR "Pittsburgh PX 138" OR "Pittsburgh PX-138" OR "Plasthall DOP" OR "Platinol AH" OR "Platinol DOP" OR "RC Plasticizer DOP" OR "RCRA waste number U028" OR "Reomol D 79P" OR "Reomol DOP" OR "Sansocizer DOP" OR "Sansocizer R 8000" OR "Scandinol SC 1000" OR "Sconamoll DOP" OR "Sicol 150" OR "Staflex DOP" OR "Truflex DOP" OR "Unem 5005" OR "UNII-6A121LGB40" OR "UNII-C42K0PH13C" OR "Vestinol AH" OR "Vinicizer 80" OR "Vinycizer 80" OR "Vinycizer 80K" OR "Witcizer 312")	
Unify[a] Search Date: 7/23/2019	1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester|1,2-Benzedicarboxylic acid, bis(2-ethyl-hexyl) ester|1,2-Benzenedicarboxylic acid bis(2-ethylhexyl) ester|1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester|1,2-Benzenedicarboxylic acid, 1,2-diisooctyl ester|1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester|1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl)ester|1,2-Benzenedicarboxylic acid, Butyl phenylmethyl ester|1,2-Benzenedicarboxylic acid, diisooctyl ester|1,2-Benzenedicarboxylic acid,bis(2-ethylhexylester)|2-Ethylhexyl phthalate|AI3-27697-X|Bis(2-ethylhexyl) 1,2-benzenedicarboxylate|Bis(2-ethylhexyl) benzene-1,2-dicarboxylate|Bis(2-ethylhexyl) o-phthalate|Bis(2-ethylhexyl) phthalate|Bis(2-ethylhexyl)ester, Phthalic acid|Bis(2-ethylhexyl)phthalat|Bis(2-ethylhexyl)phthalate|Bis-(2-ethylhexyl)-phthalate|Bis(ethylhexyl) phthalate|Bisoflex 81|Bisoflex DOP|BRN 1890696|Butylbenzyl Phthalate|Butylbenzylphthalate|Caswell No. 392K|Codan Set L 86P|Compound 889|Corflex 400|Corflex 880|DEHP|Di(2-ethylhexyl) o-phthalate|Di(2-ethylhexyl) orthophthalate|Di(2-ethylhexyl) phthalate|Di-(2-ethylhexyl) phthalate|Di(2-ethylhexyl)orthophthalate|Di(2-ethylhexyl)phthalate|di(alpha-Ethylhexyl) phthalate|Di(ethylhexyl) phthalate|Di-(Ethylhexyl)phthalate|Di(isooctyl) phthalate|Di-2-ethylhexlphthalate|Di-2-ethylhexyl phthalate|DI-2-ETHYLHEXYL-PHTHALATE|Diacizer DOP|Diethylhexyl phthalate|Di-ethylhexyl phthalate|Diethylhexylphthalate|Diisooctyl 1,2-benzenedicarboxylate|Diisooctyl ester 1,2-Benzenedicarboxylic acid|Diisooctyl o-phthalate|Diisooctyl phthalate|di-iso-Octyl phthalate|Diisooctylphthalat|Diisooctylphthalate|Dioctyl phthalate|Diplast O|Di-sec-octyl phthalate|Ergoplast FDO|Ergoplast FDO-S|ESBO-D 82|Etalon|Ethylhexyl phthalate|Ethylhexyl phthlate|Eviplast 80|Eviplast 81|Fleximel|Flexol DOD|Flexol DOP|Flexol Plasticizer DIOP|Flexol Plasticizer DOP|Garbeflex DOP-D 40|Good-rite GP 264|Hatco DOP|Hatcol DOP|Hercoflex 260|Hexaplas DIOP|Hexaplas M/O|Isooctyl phthalate|Isooctylphthalate|Jayflex DIOP|Jayflex DOP|JSSD-DOP|Kodaflex DEHP|Kodaflex DOP|Mollan O|Monocizer DOP|NCI-C52733|NSC 17069|NSC 6381|Nuoplaz DOP|Octoil|Octyl phthalate|Palatinol AH|Palatinol AH-L|Palatinol DOP|PHTHALATE, BIS(2-ETHYLHEXYL)|Phthalic acid bis(2-ethylhexyl) ester|Phthalic acid di(2-ethylhexyl) ester|Phthalic acid dioctyl ester|Phthalic acid, bis(2-ethylhexyl) ester|PHTHALIC ACID, BIS(2-ETHYLHEXYL)ESTER|Phthalic acid, bis(6-methylheptyl)ester|Phthalic acid, diisooctyl ester|Pittsburgh PX 138|Pittsburgh PX-138|Plasthall DOP|Platinol AH|Platinol DOP|RC Plasticizer DOP|RCRA waste number U028|Reomol D 79P|Reomol DOP|Sansocizer DOP|Sansocizer R 8000|Scandinol SC 1000|Sconamoll DOP|Sicol 150|Staflex DOP|Truflex DOP|Unem 5005|UNII-6A121LGB40|UNII-C42K0PH13C|Vestinol AH|Vinicizer 80|Vinycizer 80|Vinycizer 80K|Witcizer 312	523
Total	**Represents total across all databases after deduplication**	**14,772**

[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.

C.1.19 Query Strings for the Peer-Reviewed Literature Database Searches on DIBP

These are the search terms compiled from the Chemical Report for di-isobutyl phthalate (DIBP) used in the initial search strategies for each of the databases listed below:

"1,2-benzenedicarboxylic acid bis(2-methylpropyl) ester" OR "1,2-benzenedicarboxylic acid di(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid diisobutyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-Dibutyl ester" OR "1,2-Benzenedicarboxylic acid, bis-(2-methoxypropyl)ester" OR "1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, di(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, dibutyl ester" OR "1,2-bis(2-methylpropyl) benzene-1,2-dicarboxylate" OR "Bis(2-methylpropyl) benzene-1,2-dicarboxylate" OR "Bis(2-methylpropyl) o-phthalate" OR "Bis(2-methylpropyl) phthalate" OR "BRN 2054802" OR "Di(2-methylpropyl) phthalate" OR "di(i-butyl)phthalate" OR "Di(isobutyl) 1,2-benzenedicarboxylate" OR "Di(isobutyl)-1,2-benzenedicarboxylate" OR "di-2-methylpropyl phthalate" OR "Dibutyl phthalate" OR "Dibutylphthalate" OR "Diisobutyl phthalate" OR "Di-isobutyl phthalate" OR "Di-iso-Butyl phthalate" OR "Diisobutylester kyseliny ftalove" OR "Diisobutylphthalat" OR "di-l-butyl phthalate" OR "EINECS 201-553-2" OR "Hatcol DIBP" OR "Hexaplas M/1B" OR "Isobutyl phthalate" OR "isobutyl-o-phthalate" OR "Kodaflex DIBP" OR "NSC 15316" OR "Palatinol IC" OR "PHTHALATE, DIISOBUTYL" OR "Phthalic acic, diisobutyl ester" OR "Phthalic acid, diisobutyl ester" OR "Reomol DiBP" OR "UNII-IZ67FTN290"

Table_Apx C-22. Peer-Reviewed Literature Search Strategy for DIBP

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 7/11/2019	1. 1,2-benzenedicarboxylic acid bis(2-methylpropyl) ester; 1,2-benzenedicarboxylic acid di(2-methylpropyl) ester; 1,2-Benzenedicarboxylic acid diisobutyl ester; 1,2-Benzenedicarboxylic acid, 1,2-bis(2-methylpropyl) ester; 1,2-Benzenedicarboxylic acid, 1,2-Dibutyl ester; 1,2-Benzenedicarboxylic acid, bis-(2-methoxypropyl)ester; 1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester; 1,2-Benzenedicarboxylic acid, di(2-methylpropyl) ester; 1,2-Benzenedicarboxylic acid, dibutyl ester; 1,2-bis(2-methylpropyl)l; benzene-1,2-dicarboxylate 2. Bis(2-methylpropyl) benzene-1,2-dicarboxylate; Bis(2-methylpropyl) o-phthalate; Bis(2-methylpropyl) phthalate; BRN 2054802; Di(2-methylpropyl) phthalate; di(i-butyl)phthalate; Di(isobutyl) 1,2-benzenedicarboxylate; Di(isobutyl)-1,2-benzenedicarboxylate; di-2-methylpropyl phthalate; Dibutyl phthalate 3. Dibutylphthalate; Diisobutyl phthalate; Di-isobutyl phthalate; Di-iso-Butyl phthalate; Diisobutylester kyseliny ftalove; Diisobutylphthalat; di-l-butyl phthalate; EINECS 201-553-2; Hatcol DIBP; Hexaplas M/1B 4. Isobutyl phthalate; isobutyl-o-phthalate; Kodaflex DIBP; NSC 15316; Palatinol IC; PHTHALATE, DIISOBUTYL; Phthalic acic, diisobutyl ester; Phthalic acid, diisobutyl ester; Reomol DiBP; UNII-IZ67FTN290	703
Current Contents Search Date: 7/9/2019	TS=("1,2-benzenedicarboxylic acid bis(2-methylpropyl) ester" OR "1,2-benzenedicarboxylic acid di(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid diisobutyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-Dibutyl ester" OR "1,2-Benzenedicarboxylic acid, bis-(2-methoxypropyl)ester" OR "1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, di(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, dibutyl ester" OR "1,2-bis(2-methylpropyl) benzene-1,2-dicarboxylate" OR "Bis(2-methylpropyl) benzene-1,2-dicarboxylate" OR "Bis(2-methylpropyl) o-phthalate" OR "Bis(2-methylpropyl) phthalate" OR "BRN 2054802" OR "Di(2-methylpropyl) phthalate" OR "di(i-butyl)phthalate" OR "Di(isobutyl) 1,2-benzenedicarboxylate" OR "Di(isobutyl)-1,2-	2,108

Source	Source-Specific Search Strategy	Results
	benzenedicarboxylate" OR "di-2-methylpropyl phthalate" OR "Dibutyl phthalate" OR "Dibutylphthalate" OR "Diisobutyl phthalate" OR "Di-isobutyl phthalate" OR "Di-iso-Butyl phthalate" OR "Diisobutylester kyseliny ftalove" OR "Diisobutylphthalat" OR "di-l-butyl phthalate" OR "EINECS 201-553-2" OR "Hatcol DIBP" OR "Hexaplas M/1B" OR "Isobutyl phthalate" OR "isobutyl-o-phthalate" OR "Kodaflex DIBP" OR "NSC 15316" OR "Palatinol IC" OR "PHTHALATE, DIISOBUTYL" OR "Phthalic acic, diisobutyl ester" OR "Phthalic acid, diisobutyl ester" OR "Reomol DiBP" OR "UNII-IZ67FTN290")	
ProQuest Dissertations & Theses Search Date: 7/11/2019	ALL("1,2-benzenedicarboxylic acid bis(2-methylpropyl) ester" OR "1,2-benzenedicarboxylic acid di(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid diisobutyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-Dibutyl ester" OR "1,2-Benzenedicarboxylic acid, bis-(2-methoxypropyl)ester" OR "1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, di(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, dibutyl ester" OR "1,2-bis(2-methylpropyl) benzene-1,2-dicarboxylate" OR "Bis(2-methylpropyl) benzene-1,2-dicarboxylate" OR "Bis(2-methylpropyl) o-phthalate" OR "Bis(2-methylpropyl) phthalate" OR "BRN 2054802" OR "Di(2-methylpropyl) phthalate" OR "di(i-butyl)phthalate" OR "Di(isobutyl) 1,2-benzenedicarboxylate" OR "Di(isobutyl)-1,2-benzenedicarboxylate" OR "di-2-methylpropyl phthalate" OR "Dibutyl phthalate" OR "Dibutylphthalate" OR "Diisobutyl phthalate" OR "Di-isobutyl phthalate" OR "Di-iso-Butyl phthalate" OR "Diisobutylester kyseliny ftalove" OR "Diisobutylphthalat" OR "di-l-butyl phthalate" OR "EINECS 201-553-2" OR "Hatcol DIBP" OR "Hexaplas M/1B" OR "Isobutyl phthalate" OR "isobutyl-o-phthalate" OR "Kodaflex DIBP" OR "NSC 15316" OR "Palatinol IC" OR "PHTHALATE, DIISOBUTYL" OR "Phthalic acic, diisobutyl ester" OR "Phthalic acid, diisobutyl ester" OR "Reomol DiBP" OR "UNII-IZ67FTN290") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	13
ProQuest Agricultural & Scientific Database Search Date: 7/9/2019	ALL("1,2-benzenedicarboxylic acid bis(2-methylpropyl) ester" OR "1,2-benzenedicarboxylic acid di(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid diisobutyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-Dibutyl ester" OR "1,2-Benzenedicarboxylic acid, bis-(2-methoxypropyl)ester" OR "1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, di(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, dibutyl ester" OR "1,2-bis(2-methylpropyl) benzene-1,2-dicarboxylate" OR "Bis(2-methylpropyl) benzene-1,2-dicarboxylate" OR "Bis(2-methylpropyl) o-phthalate" OR "Bis(2-methylpropyl) phthalate" OR "BRN 2054802" OR "Di(2-methylpropyl) phthalate" OR "di(i-butyl)phthalate" OR "Di(isobutyl) 1,2-benzenedicarboxylate" OR "Di(isobutyl)-1,2-benzenedicarboxylate" OR "di-2-methylpropyl phthalate" OR "Dibutyl phthalate" OR "Dibutylphthalate" OR "Diisobutyl phthalate" OR "Di-isobutyl phthalate" OR "Di-iso-Butyl phthalate" OR "Diisobutylester kyseliny ftalove" OR "Diisobutylphthalat" OR "di-l-butyl phthalate" OR "EINECS 201-553-2" OR "Hatcol DIBP" OR "Hexaplas M/1B" OR "Isobutyl phthalate" OR "isobutyl-o-phthalate" OR "Kodaflex DIBP" OR "NSC 15316" OR "Palatinol IC" OR "PHTHALATE, DIISOBUTYL" OR "Phthalic acic, diisobutyl ester" OR "Phthalic acid, diisobutyl ester" OR "Reomol DiBP" OR "UNII-IZ67FTN290") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	3,040
PubMed Search Date: 7/10/2019	"1,2-benzenedicarboxylic acid bis(2-methylpropyl) ester" OR "1,2-benzenedicarboxylic acid di(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid diisobutyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-Dibutyl ester" OR "1,2-Benzenedicarboxylic acid, bis-(2-methoxypropyl)ester" OR "1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, di(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, dibutyl ester" OR "1,2-bis(2-methylpropyl) benzene-1,2-dicarboxylate" OR "Bis(2-methylpropyl)	1,476

Source	Source-Specific Search Strategy	Results
	benzene-1,2-dicarboxylate" OR "Bis(2-methylpropyl) o-phthalate" OR "Bis(2-methylpropyl) phthalate" OR "BRN 2054802" OR "Di(2-methylpropyl) phthalate" OR "di(i-butyl)phthalate" OR "Di(isobutyl) 1,2-benzenedicarboxylate" OR "Di(isobutyl)-1,2-benzenedicarboxylate" OR "di-2-methylpropyl phthalate" OR "Dibutyl phthalate" OR "Dibutylphthalate" OR "Diisobutyl phthalate" OR "Di-isobutyl phthalate" OR "Di-iso-Butyl phthalate" OR "Diisobutylester kyseliny ftalove" OR "Diisobutylphthalat" OR "di-l-butyl phthalate" OR "EINECS 201-553-2" OR "Hatcol DIBP" OR "Hexaplas M/1B" OR "Isobutyl phthalate" OR "isobutyl-o-phthalate" OR "Kodaflex DIBP" OR "NSC 15316" OR "Palatinol IC" OR "PHTHALATE, DIISOBUTYL" OR "Phthalic acic, diisobutyl ester" OR "Phthalic acid, diisobutyl ester" OR "Reomol DiBP" OR "UNII-IZ67FTN290"	
Science Direct Search Date: 7/10/2019	1. "1,2-benzenedicarboxylic acid bis(2-methylpropyl) ester" OR "1,2-benzenedicarboxylic acid di(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid diisobutyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-Dibutyl ester" OR "1,2-Benzenedicarboxylic acid, bis-(2-methoxypropyl)ester" OR "1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, di(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, dibutyl ester" 2. "1,2-bis(2-methylpropyl) benzene-1,2-dicarboxylate" OR "Bis(2-methylpropyl) benzene-1,2-dicarboxylate" OR "Bis(2-methylpropyl) o-phthalate" OR "Bis(2-methylpropyl) phthalate" OR "BRN 2054802" OR "Di(2-methylpropyl) phthalate" OR "di(i-butyl)phthalate" OR "Di(isobutyl) 1,2-benzenedicarboxylate" OR "Di(isobutyl)-1,2-benzenedicarboxylate" 3. "di-2-methylpropyl phthalate" OR "Dibutyl phthalate" OR "Dibutylphthalate" OR "Diisobutyl phthalate" OR "Di-isobutyl phthalate" OR "Di-iso-Butyl phthalate" OR "Diisobutylester kyseliny ftalove" OR "Diisobutylphthalat" OR "di-l-butyl phthalate" 4. "EINECS 201-553-2" OR "Hatcol DIBP" OR "Hexaplas M/1B" OR "Isobutyl phthalate" OR "isobutyl-o-phthalate" OR "Kodaflex DIBP" OR "NSC 15316" OR "Palatinol IC" OR "PHTHALATE, DIISOBUTYL" 5. "Phthalic acic, diisobutyl ester" OR "Phthalic acid, diisobutyl ester" OR "Reomol DiBP" OR "UNII-IZ67FTN290"	1,096
ToxNet Search Date: 7/10/2019	84-69-5	211
WoS Search Date: 9/11/2019	TS=("1,2-benzenedicarboxylic acid bis(2-methylpropyl) ester" OR "1,2-benzenedicarboxylic acid di(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid diisobutyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, 1,2-Dibutyl ester" OR "1,2-Benzenedicarboxylic acid, bis-(2-methoxypropyl)ester" OR "1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, di(2-methylpropyl) ester" OR "1,2-Benzenedicarboxylic acid, dibutyl ester" OR "1,2-bis(2-methylpropyl) benzene-1,2-dicarboxylate" OR "Bis(2-methylpropyl) benzene-1,2-dicarboxylate" OR "Bis(2-methylpropyl) o-phthalate" OR "Bis(2-methylpropyl) phthalate" OR "BRN 2054802" OR "Di(2-methylpropyl) phthalate" OR "di(i-butyl)phthalate" OR "Di(isobutyl) 1,2-benzenedicarboxylate" OR "Di(isobutyl)-1,2-benzenedicarboxylate" OR "di-2-methylpropyl phthalate" OR "Dibutyl phthalate" OR "Dibutylphthalate" OR "Diisobutyl phthalate" OR "Di-isobutyl phthalate" OR "Di-iso-Butyl phthalate" OR "Diisobutylester kyseliny ftalove" OR "Diisobutylphthalat" OR "di-l-butyl phthalate" OR "EINECS 201-553-2" OR "Hatcol DIBP" OR "Hexaplas M/1B" OR "Isobutyl phthalate" OR "isobutyl-o-phthalate" OR "Kodaflex DIBP" OR "NSC 15316" OR "Palatinol IC" OR "PHTHALATE,	2,707

Source	Source-Specific Search Strategy	Results
	DIISOBUTYL" OR "Phthalic acic, diisobutyl ester" OR "Phthalic acid, diisobutyl ester" OR "Reomol DiBP" OR "UNII-IZ67FTN290")	
Unify[a] Search Date: 7/23/2019	1,2-benzenedicarboxylic acid bis(2-methylpropyl) ester|1,2-benzenedicarboxylic acid di(2-methylpropyl) ester|1,2-Benzenedicarboxylic acid diisobutyl ester|1,2-Benzenedicarboxylic acid, 1,2-bis(2-methylpropyl) ester|1,2-Benzenedicarboxylic acid, 1,2-Dibutyl ester|1,2-Benzenedicarboxylic acid, bis-(2-methoxypropyl)ester|1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester|1,2-Benzenedicarboxylic acid, di(2-methylpropyl) ester|1,2-Benzenedicarboxylic acid, dibutyl ester|1,2-bis(2-methylpropyl) benzene-1,2-dicarboxylate|Bis(2-methylpropyl) benzene-1,2-dicarboxylate|Bis(2-methylpropyl) o-phthalate|Bis(2-methylpropyl) phthalate|BRN 2054802|Di(2-methylpropyl) phthalate|di(i-butyl)phthalate|Di(isobutyl) 1,2-benzenedicarboxylate|Di(isobutyl)-1,2-benzenedicarboxylate|di-2-methylpropyl phthalate|Dibutyl phthalate|Dibutylphthalate|Diisobutyl phthalate|Di-isobutyl phthalate|Di-iso-Butyl phthalate|Diisobutylester kyseliny ftalove|Diisobutylphthalat|di-l-butyl phthalate|EINECS 201-553-2|Hatcol DIBP|Hexaplas M/1B|Isobutyl phthalate|isobutyl-o-phthalate|Kodaflex DIBP|NSC 15316|Palatinol IC|PHTHALATE, DIISOBUTYL|Phthalic acic, diisobutyl ester|Phthalic acid, diisobutyl ester|Reomol DiBP|UNII-IZ67FTN290	28
Total	**Represents total across all databases after deduplication**	**2,702**
[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.		

C.1.20 Query Strings for the Peer-Reviewed Literature Database Searches on Dicyclohexyl Phthalate

These are the search terms compiled from the Chemical Report for dicyclohexyl phthalate used in the initial search strategies for each of the databases listed below:

"1,2-Benzenedicarboxylic acid, 1,2-dicyclohexyl ester" OR "1,2-Benzenedicarboxylic acid, dicyclohexyl ester" OR "1,2-Benzenedicarboxylic acid, Dicyclohexylester" OR "AI3-00515" OR "BRN 1889288" OR "Diclohexyl 1,2-benzenedicarboxylate" OR "Dicyclohexyl benzene-1,2-dicarboxylate" OR "Dicyclohexyl phthalate" OR "Dicyclohexylphthalat" OR "Dicyclohexylphthalate" OR "Edenol DCHP" OR "EINECS 201-545-9" OR "Ergoplast FDC" OR "HF 191" OR "Howflex CP" OR "Morflex 150" OR "NSC 6101" OR "Phthalic acid, dicyclohexyl ester" OR "UNII-CGD15M7H2N" OR "Unimoll 66" OR "Uniplex 250"

Table_Apx C-23. Peer-Reviewed Literature Search Strategy for Dicyclohexyl Phthalate

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 7/10/2019	1. 1,2-Benzenedicarboxylic acid, 1,2-dicyclohexyl ester; 1,2-Benzenedicarboxylic acid, dicyclohexyl ester; 1,2-Benzenedicarboxylic acid, Dicyclohexylester; AI3-00515; BRN 1889288; Diclohexyl 1,2-benzenedicarboxylate; Dicyclohexyl benzene-1,2-dicarboxylate; Dicyclohexyl phthalate; Dicyclohexylphthalat; Dicyclohexylphthalate 2. Edenol DCHP; EINECS 201-545-9; Ergoplast FDC; HF 191; Howflex CP; Morflex 150; NSC 6101; Phthalic acid, dicyclohexyl ester; UNII-CGD15M7H2N; Unimoll 66	37

Source	Source-Specific Search Strategy	Results
	3. Uniplex 250	
Current Contents Search Date: 7/10/2019	TS=("1,2-Benzenedicarboxylic acid, 1,2-dicyclohexyl ester" OR "1,2-Benzenedicarboxylic acid, dicyclohexyl ester" OR "1,2-Benzenedicarboxylic acid, Dicyclohexylester" OR "AI3-00515" OR "BRN 1889288" OR "Diclohexyl 1,2-benzenedicarboxylate" OR "Dicyclohexyl benzene-1,2-dicarboxylate" OR "Dicyclohexyl phthalate" OR "Dicyclohexylphthalat" OR "Dicyclohexylphthalate" OR "Edenol DCHP" OR "EINECS 201-545-9" OR "Ergoplast FDC" OR "HF 191" OR "Howflex CP" OR "Morflex 150" OR "NSC 6101" OR "Phthalic acid, dicyclohexyl ester" OR "UNII-CGD15M7H2N" OR "Unimoll 66" OR "Uniplex 250")	113
ProQuest Dissertations & Theses Search Date: 7/11/2019	ALL("1,2-Benzenedicarboxylic acid, 1,2-dicyclohexyl ester" OR "1,2-Benzenedicarboxylic acid, dicyclohexyl ester" OR "1,2-Benzenedicarboxylic acid, Dicyclohexylester" OR "AI3-00515" OR "BRN 1889288" OR "Diclohexyl 1,2-benzenedicarboxylate" OR "Dicyclohexyl benzene-1,2-dicarboxylate" OR "Dicyclohexyl phthalate" OR "Dicyclohexylphthalat" OR "Dicyclohexylphthalate" OR "Edenol DCHP" OR "EINECS 201-545-9" OR "Ergoplast FDC" OR "HF 191" OR "Howflex CP" OR "Morflex 150" OR "NSC 6101" OR "Phthalic acid, dicyclohexyl ester" OR "UNII-CGD15M7H2N" OR "Unimoll 66" OR "Uniplex 250") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	0
ProQuest Agricultural & Scientific Database Search Date: 7/10/2019	ALL("1,2-Benzenedicarboxylic acid, 1,2-dicyclohexyl ester" OR "1,2-Benzenedicarboxylic acid, dicyclohexyl ester" OR "1,2-Benzenedicarboxylic acid, Dicyclohexylester" OR "AI3-00515" OR "BRN 1889288" OR "Diclohexyl 1,2-benzenedicarboxylate" OR "Dicyclohexyl benzene-1,2-dicarboxylate" OR "Dicyclohexyl phthalate" OR "Dicyclohexylphthalat" OR "Dicyclohexylphthalate" OR "Edenol DCHP" OR "EINECS 201-545-9" OR "Ergoplast FDC" OR "HF 191" OR "Howflex CP" OR "Morflex 150" OR "NSC 6101" OR "Phthalic acid, dicyclohexyl ester" OR "UNII-CGD15M7H2N" OR "Unimoll 66" OR "Uniplex 250") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	181
PubMed Search Date: 7/10/2019	"1,2-Benzenedicarboxylic acid, 1,2-dicyclohexyl ester" OR "1,2-Benzenedicarboxylic acid, dicyclohexyl ester" OR "1,2-Benzenedicarboxylic acid, Dicyclohexylester" OR "AI3-00515" OR "BRN 1889288" OR "Diclohexyl 1,2-benzenedicarboxylate" OR "Dicyclohexyl benzene-1,2-dicarboxylate" OR "Dicyclohexyl phthalate" OR "Dicyclohexylphthalat" OR "Dicyclohexylphthalate" OR "Edenol DCHP" OR "EINECS 201-545-9" OR "Ergoplast FDC" OR "HF 191" OR "Howflex CP" OR "Morflex 150" OR "NSC 6101" OR "Phthalic acid, dicyclohexyl ester" OR "UNII-CGD15M7H2N" OR "Unimoll 66" OR "Uniplex 250"	113
Science Direct Search Date: 7/10/2019	1. "1,2-Benzenedicarboxylic acid, 1,2-dicyclohexyl ester" OR "1,2-Benzenedicarboxylic acid, dicyclohexyl ester" OR "1,2-Benzenedicarboxylic acid, Dicyclohexylester" OR "AI3-00515" OR "BRN 1889288" OR "Diclohexyl 1,2-benzenedicarboxylate" OR "Dicyclohexyl benzene-1,2-dicarboxylate" OR "Dicyclohexyl phthalate" OR "Dicyclohexylphthalat" 2. "Dicyclohexylphthalate" OR "Edenol DCHP" OR "EINECS 201-545-9" OR "Ergoplast FDC" OR "HF 191" OR "Howflex CP" OR "Morflex 150" OR "NSC 6101" OR "Phthalic acid, dicyclohexyl ester" 3. "UNII-CGD15M7H2N" OR "Unimoll 66" OR "Uniplex 250"	7
ToxNet Search Date: 7/10/2019	84-61-7 OR 169741-16-6 OR 55819-02-8	92

Source	Source-Specific Search Strategy	Results
WoS Search Date: 9/11/2019	TS=("1,2-Benzenedicarboxylic acid, 1,2-dicyclohexyl ester" OR "1,2-Benzenedicarboxylic acid, dicyclohexyl ester" OR "1,2-Benzenedicarboxylic acid, Dicyclohexylester" OR "AI3-00515" OR "BRN 1889288" OR "Diclohexyl 1,2-benzenedicarboxylate" OR "Dicyclohexyl benzene-1,2-dicarboxylate" OR "Dicyclohexyl phthalate" OR "Dicyclohexylphthalat" OR "Dicyclohexylphthalate" OR "Edenol DCHP" OR "EINECS 201-545-9" OR "Ergoplast FDC" OR "HF 191" OR "Howflex CP" OR "Morflex 150" OR "NSC 6101" OR "Phthalic acid, dicyclohexyl ester" OR "UNII-CGD15M7H2N" OR "Unimoll 66" OR "Uniplex 250")	126
Unify[a] Search Date: 7/23/2019	1,2-Benzenedicarboxylic acid, 1,2-dicyclohexyl ester|1,2-Benzenedicarboxylic acid, dicyclohexyl ester|1,2-Benzenedicarboxylic acid, Dicyclohexylester|AI3-00515|BRN 1889288|Diclohexyl 1,2-benzenedicarboxylate|Dicyclohexyl benzene-1,2-dicarboxylate|Dicyclohexyl phthalate|Dicyclohexylphthalat|Dicyclohexylphthalate|Edenol DCHP|EINECS 201-545-9|Ergoplast FDC|HF 191|Howflex CP|Morflex 150|NSC 6101|Phthalic acid, dicyclohexyl ester|UNII-CGD15M7H2N|Unimoll 66|Uniplex 250	16
Total	**Represents total across all databases after deduplication**	**206**
[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.		

C.1.21 Query Strings for the Peer-Reviewed Literature Database Searches on DIDP

These are the search terms compiled from the Chemical Report for diisodecyl phthalate (DIDP) used in the initial search strategies for each of the databases listed below:

"1,2-Benzenedicarboxylic acid diisodecyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisodecyl ester" OR "1,2-Benzenedicarboxylic acid, diisodecyl ester" OR "1,2-Benzenedi-carboxylic acid, diisodecyl ester" OR "1,2-Benzenedicarboxylic acid,diisodecyl ester" OR "1,2-bis(8-methylnonyl) benzene-1,2-dicarboxylate" OR "bis(7,7-dimethyloctyl) phthalate" OR "bis(8-methylnonyl) phthalate" OR "Bis(isodecyl) phthalate" OR "BIS(ISODECYL)PHTHALATE" OR "Di(i-decyl) phthalate" OR "Didodecylphthalate" OR "DIDP" OR "Diisodecyl phthalate" OR "Di-isodecyl phthalate" OR "Diisodecyl phthalate (mixed isomers)" OR "Diisodecylphthalate" OR "Emkarate 1020" OR "Isodecyl alcohol, phthalate (2:1)" OR "Isodecyl phthalate" OR "Jayflex DIDP" OR "Palatinol DIDP" OR "Palatinol Z" OR "PHTHALATE, DIISODECYL" OR "Phthalic acid, bis(8-methylnonyl) ester" OR "Phthalic acid, diisodecyl ester" OR "Plasticized ddp" OR "PX 120" OR "Reomol DiDP" OR "Sansocizer DIDP" OR "Sicol 184" OR "Vestinol DZ"

Table_Apx C-24. Peer-Reviewed Literature Search Strategy for DIDP

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 8/29/2019	1. 1,2-Benzenedicarboxylic acid diisodecyl ester; 1,2-Benzenedicarboxylic acid, 1,2-diisodecyl ester; 1,2-Benzenedicarboxylic acid, diisodecyl ester; 1,2-Benzenedi-carboxylic acid, diisodecyl ester; 1,2-Benzenedicarboxylic acid,diisodecyl ester; 1,2-bis(8-methylnonyl) benzene-1,2-dicarboxylate; bis(7,7-dimethyloctyl) phthalate; bis(8-methylnonyl) phthalate; Bis(isodecyl) phthalate; BIS(ISODECYL)PHTHALATE	47

Source	Source-Specific Search Strategy	Results
	2. Di(i-decyl) phthalate; Didodecylphthalate; DIDP; Diisodecyl phthalate; Di-isodecyl phthalate; Diisodecyl phthalate (mixed isomers); Diisodecylphthalate; Emkarate 1020; Isodecyl alcohol, phthalate (2:1); Isodecyl phthalate 3. Jayflex DIDP; Palatinol DIDP; Palatinol Z; PHTHALATE, DIISODECYL; Phthalic acid, bis(8-methylnonyl) ester; Phthalic acid, diisodecyl ester; Plasticized ddp; PX 120; Reomol DiDP; Sansocizer DIDP 4. Sicol 184; Vestinol DZ	
Current Contents Search Date: 8/28/2019	TS=("1,2-Benzenedicarboxylic acid diisodecyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisodecyl ester" OR "1,2-Benzenedicarboxylic acid, diisodecyl ester" OR "1,2-Benzenedi-carboxylic acid, diisodecyl ester" OR "1,2-Benzenedicarboxylic acid,diisodecyl ester" OR "1,2-bis(8-methylnonyl) benzene-1,2-dicarboxylate" OR "bis(7,7-dimethyloctyl) phthalate" OR "bis(8-methylnonyl) phthalate" OR "Bis(isodecyl) phthalate" OR "BIS(ISODECYL)PHTHALATE" OR "Di(i-decyl) phthalate" OR "Didodecylphthalate" OR "DIDP" OR "Diisodecyl phthalate" OR "Di-isodecyl phthalate" OR "Diisodecyl phthalate (mixed isomers)" OR "Diisodecylphthalate" OR "Emkarate 1020" OR "Isodecyl alcohol, phthalate (2:1)" OR "Isodecyl phthalate" OR "Jayflex DIDP" OR "Palatinol DIDP" OR "Palatinol Z" OR "PHTHALATE, DIISODECYL" OR "Phthalic acid, bis(8-methylnonyl) ester" OR "Phthalic acid, diisodecyl ester" OR "Plasticized ddp" OR "PX 120" OR "Reomol DiDP" OR "Sansocizer DIDP" OR "Sicol 184" OR "Vestinol DZ")	204
ProQuest Dissertations & Theses Search Date: 8/29/2019	ALL("1,2-Benzenedicarboxylic acid diisodecyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisodecyl ester" OR "1,2-Benzenedicarboxylic acid, diisodecyl ester" OR "1,2-Benzenedi-carboxylic acid, diisodecyl ester" OR "1,2-Benzenedicarboxylic acid,diisodecyl ester" OR "1,2-bis(8-methylnonyl) benzene-1,2-dicarboxylate" OR "bis(7,7-dimethyloctyl) phthalate" OR "bis(8-methylnonyl) phthalate" OR "Bis(isodecyl) phthalate" OR "BIS(ISODECYL)PHTHALATE" OR "Di(i-decyl) phthalate" OR "Didodecylphthalate" OR "DIDP" OR "Diisodecyl phthalate" OR "Di-isodecyl phthalate" OR "Diisodecyl phthalate (mixed isomers)" OR "Diisodecylphthalate" OR "Emkarate 1020" OR "Isodecyl alcohol, phthalate (2:1)" OR "Isodecyl phthalate" OR "Jayflex DIDP" OR "Palatinol DIDP" OR "Palatinol Z" OR "PHTHALATE, DIISODECYL" OR "Phthalic acid, bis(8-methylnonyl) ester" OR "Phthalic acid, diisodecyl ester" OR "Plasticized ddp" OR "PX 120" OR "Reomol DiDP" OR "Sansocizer DIDP" OR "Sicol 184" OR "Vestinol DZ") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	2
ProQuest Agricultural & Scientific Database Search Date: 8/28/2019	ALL("1,2-Benzenedicarboxylic acid diisodecyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisodecyl ester" OR "1,2-Benzenedicarboxylic acid, diisodecyl ester" OR "1,2-Benzenedi-carboxylic acid, diisodecyl ester" OR "1,2-Benzenedicarboxylic acid,diisodecyl ester" OR "1,2-bis(8-methylnonyl) benzene-1,2-dicarboxylate" OR "bis(7,7-dimethyloctyl) phthalate" OR "bis(8-methylnonyl) phthalate" OR "Bis(isodecyl) phthalate" OR "BIS(ISODECYL)PHTHALATE" OR "Di(i-decyl) phthalate" OR "Didodecylphthalate" OR "DIDP" OR "Diisodecyl phthalate" OR "Di-isodecyl phthalate" OR "Diisodecyl phthalate (mixed isomers)" OR "Diisodecylphthalate" OR "Emkarate 1020" OR "Isodecyl alcohol, phthalate (2:1)" OR "Isodecyl phthalate" OR "Jayflex DIDP" OR "Palatinol DIDP" OR "Palatinol Z" OR "PHTHALATE, DIISODECYL" OR "Phthalic acid, bis(8-methylnonyl) ester" OR "Phthalic acid, diisodecyl ester" OR "Plasticized ddp" OR "PX 120" OR "Reomol DiDP" OR "Sansocizer DIDP" OR "Sicol 184" OR "Vestinol DZ") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	317
PubMed Search Date: 8/28/2019	"1,2-Benzenedicarboxylic acid diisodecyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisodecyl ester" OR "1,2-Benzenedicarboxylic acid, diisodecyl ester" OR "1,2-Benzenedi-carboxylic acid, diisodecyl ester" OR "1,2-Benzenedicarboxylic acid,diisodecyl ester" OR "1,2-bis(8-methylnonyl) benzene-1,2-dicarboxylate" OR "bis(7,7-dimethyloctyl) phthalate" OR "bis(8-	164

Source	Source-Specific Search Strategy	Results
	methylnonyl) phthalate" OR "Bis(isodecyl) phthalate" OR "BIS(ISODECYL)PHTHALATE" OR "Di(i-decyl) phthalate" OR "Didodecylphthalate" OR "DIDP" OR "Diisodecyl phthalate" OR "Di-isodecyl phthalate" OR "Diisodecyl phthalate (mixed isomers)" OR "Diisodecylphthalate" OR "Emkarate 1020" OR "Isodecyl alcohol, phthalate (2:1)" OR "Isodecyl phthalate" OR "Jayflex DIDP" OR "Palatinol DIDP" OR "Palatinol Z" OR "PHTHALATE, DIISODECYL" OR "Phthalic acid, bis(8-methylnonyl) ester" OR "Phthalic acid, diisodecyl ester" OR "Plasticized ddp" OR "PX 120" OR "Reomol DiDP" OR "Sansocizer DIDP" OR "Sicol 184" OR "Vestinol DZ"	
Science Direct Search Date: 8/28/2019	1. "1,2-Benzenedicarboxylic acid diisodecyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisodecyl ester" OR "1,2-Benzenedicarboxylic acid, diisodecyl ester" OR "1,2-Benzenedi-carboxylic acid, diisodecyl ester" OR "1,2-Benzenedicarboxylic acid,diisodecyl ester" OR "1,2-bis(8-methylnonyl) benzene-1,2-dicarboxylate" OR "bis(7,7-dimethyloctyl) phthalate" OR "bis(8-methylnonyl) phthalate" OR "Bis(isodecyl) phthalate" 2. "BIS(ISODECYL)PHTHALATE" OR "Di(i-decyl) phthalate" OR "Didodecylphthalate" OR "DIDP" OR "Diisodecyl phthalate" OR "Di-isodecyl phthalate" OR "Diisodecyl phthalate (mixed isomers)" OR "Diisodecylphthalate" OR "Emkarate 1020" 3. "Isodecyl alcohol, phthalate (2:1)" OR "Isodecyl phthalate" OR "Jayflex DIDP" OR "Palatinol DIDP" OR "Palatinol Z" OR "PHTHALATE, DIISODECYL" OR "Phthalic acid, bis(8-methylnonyl) ester" OR "Phthalic acid, diisodecyl ester" OR "Plasticized ddp" 4. "PX 120" OR "Reomol DiDP" OR "Sansocizer DIDP" OR "Sicol 184" OR "Vestinol DZ"	154
ToxNet Search Date: 8/28/2019	1. 26761-40-0 OR 68515-49-1 OR 1341-39-5 OR 105009-98-1 OR 148384-02-5 2. (("diisodecyl phthalate" OR "vestinol dz" OR "sicol 184" OR "palatinol z" OR "di isodecyl phthalate" OR 26761-40-0 [rn]) OR ("ec 271 091 4" OR "diisodecyl phthalate" OR 68515-49-1 [rn]) OR 1341-39-5 [rn] OR 105009-98-1 [rn] OR 148384-02-5 [rn]) AND (eng [la]) AND (BIOSIS [org] OR NTIS [org] OR PESTAB [org] OR PubMed [org] OR TSCATS [org])	178
WoS Search Date: 9/11/2019	TS=("1,2-Benzenedicarboxylic acid diisodecyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisodecyl ester" OR "1,2-Benzenedicarboxylic acid, diisodecyl ester" OR "1,2-Benzenedi-carboxylic acid, diisodecyl ester" OR "1,2-Benzenedicarboxylic acid,diisodecyl ester" OR "1,2-bis(8-methylnonyl) benzene-1,2-dicarboxylate" OR "bis(7,7-dimethyloctyl) phthalate" OR "bis(8-methylnonyl) phthalate" OR "Bis(isodecyl) phthalate" OR "BIS(ISODECYL)PHTHALATE" OR "Di(i-decyl) phthalate" OR "Didodecylphthalate" OR "DIDP" OR "Diisodecyl phthalate" OR "Di-isodecyl phthalate" OR "Diisodecyl phthalate (mixed isomers)" OR "Diisodecylphthalate" OR "Emkarate 1020" OR "Isodecyl alcohol, phthalate (2:1)" OR "Isodecyl phthalate" OR "Jayflex DIDP" OR "Palatinol DIDP" OR "Palatinol Z" OR "PHTHALATE, DIISODECYL" OR "Phthalic acid, bis(8-methylnonyl) ester" OR "Phthalic acid, diisodecyl ester" OR "Plasticized ddp" OR "PX 120" OR "Reomol DiDP" OR "Sansocizer DIDP" OR "Sicol 184" OR "Vestinol DZ")	242
Unify[a] Search Date: 8/29/2019	1,2-Benzenedicarboxylic acid diisodecyl ester|1,2-Benzenedicarboxylic acid, 1,2-diisodecyl ester|1,2-Benzenedicarboxylic acid, diisodecyl ester|1,2-Benzenedi-carboxylic acid, diisodecyl ester|1,2-Benzenedicarboxylic acid,diisodecyl ester|1,2-bis(8-methylnonyl) benzene-1,2-dicarboxylate|bis(7,7-dimethyloctyl) phthalate|bis(8-methylnonyl) phthalate|Bis(isodecyl) phthalate|BIS(ISODECYL)PHTHALATE|Di(i-decyl) phthalate|Didodecylphthalate|DIDP|Diisodecyl phthalate|Di-isodecyl phthalate|Diisodecyl phthalate (mixed isomers)|Diisodecylphthalate|Emkarate 1020|Isodecyl alcohol, phthalate (2:1)|Isodecyl	33

Source	Source-Specific Search Strategy	Results
	phthalate|Jayflex DIDP|Palatinol DIDP|Palatinol Z|PHTHALATE, DIISODECYL|Phthalic acid, bis(8-methylnonyl) ester|Phthalic acid, diisodecyl ester|Plasticized ddp|PX 120|Reomol DiDP|Sansocizer DIDP|Sicol 184|Vestinol DZ	
MRRE Search Date: 3/15/2019	DIDP is a Manufacturer-Requested Risk Evaluation (MRRE). In accordance with this designation, industry stakeholders supplied additional references.	336
Total	**Represents total across all databases after deduplication**	**501**
[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.		

C.1.22 Query Strings for the Peer-Reviewed Literature Database Searches on DINP

These are the search terms compiled from the Chemical Report for diisononyl phthalate (DINP) used in the initial search strategies for each of the databases listed below:

"1,2-Benzenedicarboxylic acid diisononyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisononyl ester" OR "1,2-Benzenedicarboxylic acid, diisononyl ester" OR "1,2-Benzenedicarboxylic acid, di-isononyl ester" OR "Baylectrol 4200" OR "BIS-ISONONYL PHTHALATE" OR "Di(C8-10, C9 rich) branched alkyl phthalates" OR "Di(isononyl) phthalate branched" OR "Diacizer DINP" OR "Diisononyl phthalate" OR "Di-isononyl phthalate" OR "Diisononyl phthalate (mixed isomers)" OR "Diisononylphthalate" OR "DINP" OR "DINP branched" OR "Isononyl alcohol, phthalate (2:1)" OR "JAY-DINP" OR "Jayflex DINP" OR "Monocizer DINP" OR "Palatinol DINP" OR "Palatinol DN" OR "Palatinol N" OR "PHTHALATE, DIISONONYL" OR "Phthalic acid diisononyl ester" OR "Phthalic acid, diisononyl ester" OR "Phthalisocizer DINP" OR "Sansocizer DINP" OR "Vestinol 9" OR "Vestinol NN" OR "Vinycizer 90" OR "Vinylcizer 90" OR "Witamol 150"

Table_Apx C-25. Peer-Reviewed Literature Search Strategy for DINP

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 8/29/2019	1. 1,2-Benzenedicarboxylic acid diisononyl ester; 1,2-Benzenedicarboxylic acid, 1,2-diisononyl ester; 1,2-Benzenedicarboxylic acid, diisononyl ester; 1,2-Benzenedicarboxylic acid, di-isononyl ester; Baylectrol 4200; BIS-ISONONYL PHTHALATE; Di(C8-10, C9 rich) branched alkyl phthalates; Di(isononyl) phthalate branched; Diacizer DINP; Diisononyl phthalate 2. Di-isononyl phthalate; Diisononyl phthalate (mixed isomers); Diisononylphthalate; DINP; DINP branched; Isononyl alcohol, phthalate (2:1); JAY-DINP; Jayflex DINP; Monocizer DINP; Palatinol DINP 3. Palatinol DN; Palatinol N; PHTHALATE, DIISONONYL; Phthalic acid diisononyl ester; Phthalic acid, diisononyl ester; Phthalisocizer DINP; Sansocizer DINP; Vestinol 9; Vestinol NN; Vinycizer 90 4. Vinylcizer 90; Witamol 150	149

Source	Source-Specific Search Strategy	Results
Current Contents Search Date: 8/28/2019	TS=("1,2-Benzenedicarboxylic acid diisononyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisononyl ester" OR "1,2-Benzenedicarboxylic acid, diisononyl ester" OR "1,2-Benzenedicarboxylic acid, di-isononyl ester" OR "Baylectrol 4200" OR "BIS-ISONONYL PHTHALATE" OR "Di(C8-10, C9 rich) branched alkyl phthalates" OR "Di(isononyl) phthalate branched" OR "Diacizer DINP" OR "Diisononyl phthalate" OR "Di-isononyl phthalate" OR "Diisononyl phthalate (mixed isomers)" OR "Diisononylphthalate" OR "DINP" OR "DINP branched" OR "Isononyl alcohol, phthalate (2:1)" OR "JAY-DINP" OR "Jayflex DINP" OR "Monocizer DINP" OR "Palatinol DINP" OR "Palatinol DN" OR "Palatinol N" OR "PHTHALATE, DIISONONYL" OR "Phthalic acid diisononyl ester" OR "Phthalic acid, diisononyl ester" OR "Phthalisocizer DINP" OR "Sansocizer DINP" OR "Vestinol 9" OR "Vestinol NN" OR "Vinycizer 90" OR "Vinylcizer 90" OR "Witamol 150")	416
ProQuest Dissertations & Theses Search Date: 8/29/2019	ALL("1,2-Benzenedicarboxylic acid diisononyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisononyl ester" OR "1,2-Benzenedicarboxylic acid, diisononyl ester" OR "1,2-Benzenedicarboxylic acid, di-isononyl ester" OR "Baylectrol 4200" OR "BIS-ISONONYL PHTHALATE" OR "Di(C8-10, C9 rich) branched alkyl phthalates" OR "Di(isononyl) phthalate branched" OR "Diacizer DINP" OR "Diisononyl phthalate" OR "Di-isononyl phthalate" OR "Diisononyl phthalate (mixed isomers)" OR "Diisononylphthalate" OR "DINP" OR "DINP branched" OR "Isononyl alcohol, phthalate (2:1)" OR "JAY-DINP" OR "Jayflex DINP" OR "Monocizer DINP" OR "Palatinol DINP" OR "Palatinol DN" OR "Palatinol N" OR "PHTHALATE, DIISONONYL" OR "Phthalic acid diisononyl ester" OR "Phthalic acid, diisononyl ester" OR "Phthalisocizer DINP" OR "Sansocizer DINP" OR "Vestinol 9" OR "Vestinol NN" OR "Vinycizer 90" OR "Vinylcizer 90" OR "Witamol 150") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	2
ProQuest Agricultural & Scientific Database Search Date: 8/28/2019	ALL("1,2-Benzenedicarboxylic acid diisononyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisononyl ester" OR "1,2-Benzenedicarboxylic acid, diisononyl ester" OR "1,2-Benzenedicarboxylic acid, di-isononyl ester" OR "Baylectrol 4200" OR "BIS-ISONONYL PHTHALATE" OR "Di(C8-10, C9 rich) branched alkyl phthalates" OR "Di(isononyl) phthalate branched" OR "Diacizer DINP" OR "Diisononyl phthalate" OR "Di-isononyl phthalate" OR "Diisononyl phthalate (mixed isomers)" OR "Diisononylphthalate" OR "DINP" OR "DINP branched" OR "Isononyl alcohol, phthalate (2:1)" OR "JAY-DINP" OR "Jayflex DINP" OR "Monocizer DINP" OR "Palatinol DINP" OR "Palatinol DN" OR "Palatinol N" OR "PHTHALATE, DIISONONYL" OR "Phthalic acid diisononyl ester" OR "Phthalic acid, diisononyl ester" OR "Phthalisocizer DINP" OR "Sansocizer DINP" OR "Vestinol 9" OR "Vestinol NN" OR "Vinycizer 90" OR "Vinylcizer 90" OR "Witamol 150") AND STYPE("Scholarly Journals" OR Reports OR Thesis OR "Government Documents") AND LA(ENG)	686
PubMed Search Date: 8/28/2019	"1,2-Benzenedicarboxylic acid diisononyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisononyl ester" OR "1,2-Benzenedicarboxylic acid, diisononyl ester" OR "1,2-Benzenedicarboxylic acid, di-isononyl ester" OR "Baylectrol 4200" OR "BIS-ISONONYL PHTHALATE" OR "Di(C8-10, C9 rich) branched alkyl phthalates" OR "Di(isononyl) phthalate branched" OR "Diacizer DINP" OR "Diisononyl phthalate" OR "Di-isononyl phthalate" OR "Diisononyl phthalate (mixed isomers)" OR "Diisononylphthalate" OR "DINP" OR "DINP branched" OR "Isononyl alcohol, phthalate (2:1)" OR "JAY-DINP" OR "Jayflex DINP" OR "Monocizer DINP" OR "Palatinol DINP" OR "Palatinol DN" OR "Palatinol N" OR "PHTHALATE, DIISONONYL" OR "Phthalic acid diisononyl ester" OR "Phthalic acid, diisononyl ester" OR "Phthalisocizer DINP" OR "Sansocizer DINP" OR "Vestinol 9" OR "Vestinol NN" OR "Vinycizer 90" OR "Vinylcizer 90" OR "Witamol 150"	363
Science Direct Search Date:	1. "1,2-Benzenedicarboxylic acid diisononyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisononyl ester" OR "1,2-Benzenedicarboxylic acid, diisononyl ester" OR "1,2-Benzenedicarboxylic acid, di-isononyl ester" OR "Baylectrol 4200" OR	334

Source	Source-Specific Search Strategy	Results
8/28/3019	"BIS-ISONONYL PHTHALATE" OR "Di(C8-10, C9 rich) branched alkyl phthalates" OR "Di(isononyl) phthalate branched" OR "Diacizer DINP" 2. "Diisononyl phthalate" OR "Di-isononyl phthalate" OR "Diisononyl phthalate (mixed isomers)" OR "Diisononylphthalate" OR "DINP" OR "DINP branched" OR "Isononyl alcohol, phthalate (2:1)" OR "JAY-DINP" OR "Jayflex DINP" 3. "Monocizer DINP" OR "Palatinol DINP" OR "Palatinol DN" OR "Palatinol N" OR "PHTHALATE, DIISONONYL" OR "Phthalic acid diisononyl ester" OR "Phthalic acid, diisononyl ester" OR "Phthalisocizer DINP" OR "Sansocizer DINP" 4. "Vestinol 9" OR "Vestinol NN" OR "Vinycizer 90" OR "Vinylcizer 90" OR "Witamol 150"	
ToxNet Search Date: 8/28/2019	1. 28553-12-0 OR 68515-48-0 OR 58033-90-2 OR 105009-97-0 OR 41375-91-1 2. (("diisononyl phthalate" OR "enj 2065" OR "di isononyl phthalate" OR "236itamol 150" OR "vestinol nn" OR "sansocizer dinp" OR "palatinol n" OR "palatinol dn" OR dinp OR 28553-12-0 [rn]) OR ("ec 271 090 9" OR 68515-48-0 [rn]) OR 58033-90-2 [rn] OR 105009-97-0 [rn] OR 41375-91-1 [rn]) AND (eng [la]) AND (BIOSIS [org] OR NTIS [org] OR PESTAB [org] OR PubMed [org] OR TSCATS [org])	401
WoS Search Date: 8/28/2019	TS=("1,2-Benzenedicarboxylic acid diisononyl ester" OR "1,2-Benzenedicarboxylic acid, 1,2-diisononyl ester" OR "1,2-Benzenedicarboxylic acid, diisononyl ester" OR "1,2-Benzenedicarboxylic acid, di-isononyl ester" OR "Baylectrol 4200" OR "BIS-ISONONYL PHTHALATE" OR "Di(C8-10, C9 rich) branched alkyl phthalates" OR "Di(isononyl) phthalate branched" OR "Diacizer DINP" OR "Diisononyl phthalate" OR "Di-isononyl phthalate" OR "Diisononyl phthalate (mixed isomers)" OR "Diisononylphthalate" OR "DINP" OR "DINP branched" OR "Isononyl alcohol, phthalate (2:1)" OR "JAY-DINP" OR "Jayflex DINP" OR "Monocizer DINP" OR "Palatinol DINP" OR "Palatinol DN" OR "Palatinol N" OR "PHTHALATE, DIISONONYL" OR "Phthalic acid diisononyl ester" OR "Phthalic acid, diisononyl ester" OR "Phthalisocizer DINP" OR "Sansocizer DINP" OR "Vestinol 9" OR "Vestinol NN" OR "Vinycizer 90" OR "Vinylcizer 90" OR "Witamol 150")	474
Unify[a] Search Date: 8/29/2019	1,2-Benzenedicarboxylic acid diisononyl ester|1,2-Benzenedicarboxylic acid, 1,2-diisononyl ester|1,2-Benzenedicarboxylic acid, diisononyl ester|1,2-Benzenedicarboxylic acid, di-isononyl ester|Baylectrol 4200|BIS-ISONONYL PHTHALATE|Di(C8-10, C9 rich) branched alkyl phthalates|Di(isononyl) phthalate branched|Diacizer DINP|Diisononyl phthalate|Di-isononyl phthalate|Diisononyl phthalate (mixed isomers)|Diisononylphthalate|DINP|DINP branched|Isononyl alcohol, phthalate (2:1)|JAY-DINP|Jayflex DINP|Monocizer DINP|Palatinol DINP|Palatinol DN|Palatinol N|PHTHALATE, DIISONONYL|Phthalic acid diisononyl ester|Phthalic acid, diisononyl ester|Phthalisocizer DINP|Sansocizer DINP|Vestinol 9|Vestinol NN|Vinycizer 90|Vinylcizer 90|Witamol 150	41
MRRE 3/15/2019	DINP is a Manufacturer-Requested Risk Evaluation (MRRE). In accordance with this designation, industry stakeholders supplied additional references.	700
Total	**Represents total across all databases after deduplication**	**919**

[a] Unify is the internal back-end Oracle database and data entry user interface into which the chemical, reference, and toxicity tests and results for ECOTOX Knowledgebase are entered and managed.

C.1.23 Query Strings for the Peer-Reviewed Literature Database Searches on D4

These are the search terms compiled for octamethylcyclotetrasiloxane (D4) used in the initial search strategies for each of the databases listed below:

"Octamethylcyclotetrasiloxane" OR ("D4" AND "siloxane") OR "556-67-2" OR "OMCTS" OR "cyclotetrasiloxane" OR "Silbione" OR "Octamethylcyclotetrasiloxan" OR "VS 7207" OR "Cyclotetrasiloxane, octamethyl-" OR "Cyclic dimethylsiloxane tetramer" OR "Dow Corning 344" OR "Volasil 244" OR "DC 244" OR "DC 344" OR "Octamethylcyclotetrasiloxanes"

Table_Apx C-26. Peer-Reviewed Literature Search Strategy for D4

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 9/4/2020	ALL("Octamethylcyclotetrasiloxane" OR ("D4" AND "siloxane") OR "556-67-2" OR "OMCTS" OR "cyclotetrasiloxane" OR "Silbione" OR "Octamethylcyclotetrasiloxan" OR "VS 7207" OR "Cyclotetrasiloxane, octamethyl-" OR "Cyclic dimethylsiloxane tetramer" OR "Dow Corning 344" OR "Volasil 244" OR "DC 244" OR "DC 344" OR "Octamethylcyclotetrasiloxanes")	167
Current Contents Search Date: 9/4/2020	(TS="Octamethylcyclotetrasiloxane" OR (TS="D4" AND TS="siloxane") OR TS="556-67-2" OR TS="OMCTS" OR TS="cyclotetrasiloxane" OR TS="Silbione" OR TS="Octamethylcyclotetrasiloxan" OR TS="VS 7207" OR TS="Cyclotetrasiloxane, octamethyl-" OR TS="Cyclic dimethylsiloxane tetramer" OR TS="Dow Corning 344" OR TS="Volasil 244" OR TS="DC 244" OR TS="DC 344" OR TS="Octamethylcyclotetrasiloxanes")	801
ProQuest Dissertations & Theses Search Date: 9/4/2020	ALL("Octamethylcyclotetrasiloxane" OR ("D4" AND "siloxane") OR "556-67-2" OR "OMCTS" OR "cyclotetrasiloxane" OR "Silbione" OR "Octamethylcyclotetrasiloxan" OR "VS 7207" OR "Cyclotetrasiloxane, octamethyl-" OR "Cyclic dimethylsiloxane tetramer" OR "Dow Corning 344" OR "Volasil 244" OR "DC 244" OR "DC 344" OR "Octamethylcyclotetrasiloxanes")	4
ProQuest Agricultural & Scientific Database Search Date: 9/4/2020	ALL("Octamethylcyclotetrasiloxane" OR ("D4" AND "siloxane") OR "556-67-2" OR "OMCTS" OR "cyclotetrasiloxane" OR "Silbione" OR "Octamethylcyclotetrasiloxan" OR "VS 7207" OR "Cyclotetrasiloxane, octamethyl-" OR "Cyclic dimethylsiloxane tetramer" OR "Dow Corning 344" OR "Volasil 244" OR "DC 244" OR "DC 344" OR "Octamethylcyclotetrasiloxanes")	306
PubMed Search Date: 9/4/2020	("Octamethylcyclotetrasiloxane"[tw] OR ("D4"[tw] AND "siloxanes"[MeSH]) OR "556-67-2"[rn] OR "OMCTS"[tw] OR "cyclotetrasiloxane"[tw] OR "Silbione"[tw] OR "Octamethylcyclotetrasiloxan"[tw] OR "VS 7207"[tw] OR "Cyclotetrasiloxane, octamethyl-"[tw] OR "Cyclic dimethylsiloxane tetramer"[tw] OR "Dow Corning 344"[tw] OR "Volasil 244"[tw] OR "DC 244"[tw] OR "DC 344"[tw] OR "Octamethylcyclotetrasiloxanes"[tw])	259
Science Direct Search Date:	1. ("Octamethylcyclotetrasiloxane" OR ("D4" AND "siloxane") OR "556-67-2" OR "OMCTS" OR "cyclotetrasiloxane" OR "Silbione" OR "Octamethylcyclotetrasiloxan")	405

Source	Source-Specific Search Strategy	Results
9/4/2020	2. ("VS 7207" OR "Cyclotetrasiloxane, octamethyl-" OR "Cyclic dimethylsiloxane tetramer" OR "Dow Corning 344" OR "Volasil 244" OR "DC 244" OR "DC 344" OR "Octamethylcyclotetrasiloxanes")	
ToxLine Search Date: 9/4/2020	1. ALL("Octamethylcyclotetrasiloxane" OR ("D4" AND "siloxane") OR "556-67-2" OR "OMCTS" OR "cyclotetrasiloxane" OR "Silbione" OR "Octamethylcyclotetrasiloxan" OR "VS 7207" OR "Cyclotetrasiloxane, octamethyl-" OR "Cyclic dimethylsiloxane tetramer" OR "Dow Corning 344" OR "Volasil 244" OR "DC 244" OR "DC 344" OR "Octamethylcyclotetrasiloxanes") 2. tox [subset] AND ("Octamethylcyclotetrasiloxane"[tw] OR ("D4"[tw] AND "siloxanes"[MeSH]) OR "556-67-2"[rn] OR "OMCTS"[tw] OR "cyclotetrasiloxane"[tw] OR "Silbione"[tw] OR "Octamethylcyclotetrasiloxan"[tw] OR "VS 7207"[tw] OR "Cyclotetrasiloxane, octamethyl-"[tw] OR "Cyclic dimethylsiloxane tetramer"[tw] OR "Dow Corning 344"[tw] OR "Volasil 244"[tw] OR "DC 244"[tw] OR "DC 344"[tw] OR "Octamethylcyclotetrasiloxanes"[tw])	197
WoS Search Date: 9/4/2020	(TS="Octamethylcyclotetrasiloxane" OR (TS="D4" AND TS="siloxane") OR TS="556-67-2" OR TS="OMCTS" OR TS="cyclotetrasiloxane" OR TS="Silbione" OR TS="Octamethylcyclotetrasiloxan" OR TS="VS 7207" OR TS="Cyclotetrasiloxane, octamethyl-" OR TS="Cyclic dimethylsiloxane tetramer" OR TS="Dow Corning 344" OR TS="Volasil 244" OR TS="DC 244" OR TS="DC 344" OR TS="Octamethylcyclotetrasiloxanes")	1,162
MRRE 7/17/2020	D4 is a Manufacturer-Requested Risk Evaluation (MRRE). In accordance with this designation, industry stakeholders supplied additional references.	392
Total	**Represents total across all databases after deduplication**	**1,533**

Additional Strategies

Additional keywords have been added to supplement the initial pool references with additional literature on four degradants. These are the search terms for D4 used in the supplemental search strategies for each of the databases listed below:

1. *Octamethyltetrasiloxanediol:* Octamethyltetrasiloxanediol; 3081-07-0; 1,7-Tetrasiloxanediol, 1,1,3,3,5,5,7,7-octamethyl-; Octamethyltetrasiloxane-1,7-diol; Tetrasiloxane-1,7-diol, 1,1,3,3,5,5,7,7-octamethyl-
2. *Hexamethyltrisiloxanediol:* Hexamethyltrisiloxanediol; 3663-50-1; 1,5-Trisiloxanediol, 1,1,3,3,5,5-hexamethyl-; Hexamethyltrisiloxane-1,5-diol
3. *Tetramethyldisiloxanediol:* Tetramethyldisiloxanediol; 1118-15-6; Tetramethyldisiloxane-1,3-diol; 1,3-Disiloxanediol, 1,1,3,3-tetramethyl-
4. *Dimethylsilanediol:* Dimethylsilanediol; 1066-42-8; Dimethyldihydroxysilane; Dihydroxydimethylsilane; Silanediol, dimethyl-

Table_Apx C-27. Supplemental Peer-Reviewed Literature Search Strategy for D4 Degradants

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 1/13/2021	TIAB("Octamethyltetrasiloxanediol" OR "3081-07-0" OR "1,7-Tetrasiloxanediol, 1,1,3,3,5,5,7,7-octamethyl-" OR "Octamethyltetrasiloxane-1,7-diol" OR "Tetrasiloxane-1,7-diol, 1,1,3,3,5,5,7,7-octamethyl-" OR "Hexamethyltrisiloxanediol" OR "3663-50-1" OR "1,5-Trisiloxanediol, 1,1,3,3,5,5-hexamethyl-" OR "Hexamethyltrisiloxane-1,5-diol" OR "Tetramethyldisiloxanediol" OR "1118-15-6" OR "Tetramethyldisiloxane-1,3-diol" OR "1,3-Disiloxanediol, 1,1,3,3-tetramethyl-" OR "Dimethylsilanediol" OR "1066-42-8" OR "Dimethyldihydroxysilane" OR "Dihydroxydimethylsilane" OR "Silanediol, dimethyl-")	0
Current Contents Search Date: 1/13/2021	TS=("Octamethyltetrasiloxanediol" OR "3081-07-0" OR "1,7-Tetrasiloxanediol, 1,1,3,3,5,5,7,7-octamethyl-" OR "Octamethyltetrasiloxane-1,7-diol" OR "Tetrasiloxane-1,7-diol, 1,1,3,3,5,5,7,7-octamethyl-" OR "Hexamethyltrisiloxanediol" OR "3663-50-1" OR "1,5-Trisiloxanediol, 1,1,3,3,5,5-hexamethyl-" OR "Hexamethyltrisiloxane-1,5-diol" OR "Tetramethyldisiloxanediol" OR "1118-15-6" OR "Tetramethyldisiloxane-1,3-diol" OR "1,3-Disiloxanediol, 1,1,3,3-tetramethyl-" OR "Dimethylsilanediol" OR "1066-42-8" OR "Dimethyldihydroxysilane" OR "Dihydroxydimethylsilane" OR "Silanediol, dimethyl-")	0
ProQuest Dissertations & Theses Search Date: 1/13/2021	TIAB("Octamethyltetrasiloxanediol" OR "3081-07-0" OR "1,7-Tetrasiloxanediol, 1,1,3,3,5,5,7,7-octamethyl-" OR "Octamethyltetrasiloxane-1,7-diol" OR "Tetrasiloxane-1,7-diol, 1,1,3,3,5,5,7,7-octamethyl-" OR "Hexamethyltrisiloxanediol" OR "3663-50-1" OR "1,5-Trisiloxanediol, 1,1,3,3,5,5-hexamethyl-" OR "Hexamethyltrisiloxane-1,5-diol" OR "Tetramethyldisiloxanediol" OR "1118-15-6" OR "Tetramethyldisiloxane-1,3-diol" OR "1,3-Disiloxanediol, 1,1,3,3-tetramethyl-" OR "Dimethylsilanediol" OR "1066-42-8" OR "Dimethyldihydroxysilane" OR "Dihydroxydimethylsilane" OR "Silanediol, dimethyl-")	0
ProQuest Agricultural & Scientific Database Search Date: 1/13/2021	TIAB("Octamethyltetrasiloxanediol" OR "3081-07-0" OR "1,7-Tetrasiloxanediol, 1,1,3,3,5,5,7,7-octamethyl-" OR "Octamethyltetrasiloxane-1,7-diol" OR "Tetrasiloxane-1,7-diol, 1,1,3,3,5,5,7,7-octamethyl-" OR "Hexamethyltrisiloxanediol" OR "3663-50-1" OR "1,5-Trisiloxanediol, 1,1,3,3,5,5-hexamethyl-" OR "Hexamethyltrisiloxane-1,5-diol" OR "Tetramethyldisiloxanediol" OR "1118-15-6" OR "Tetramethyldisiloxane-1,3-diol" OR "1,3-Disiloxanediol, 1,1,3,3-tetramethyl-" OR "Dimethylsilanediol" OR "1066-42-8" OR "Dimethyldihydroxysilane" OR "Dihydroxydimethylsilane" OR "Silanediol, dimethyl-")	48
PubMed Search Date: 1/13/2021	"Octamethyltetrasiloxanediol"[tw] OR "3081-07-0"[rn] OR "1,7-Tetrasiloxanediol, 1,1,3,3,5,5,7,7-octamethyl-"[tw] OR "Octamethyltetrasiloxane-1,7-diol"[tw] OR "Tetrasiloxane-1,7-diol, 1,1,3,3,5,5,7,7-octamethyl-"[tw] OR "Hexamethyltrisiloxanediol"[tw] OR "3663-50-1"[rn] OR "1,5-Trisiloxanediol, 1,1,3,3,5,5-hexamethyl-"[tw] OR "Hexamethyltrisiloxane-1,5-diol"[tw] OR "Tetramethyldisiloxanediol"[tw] OR "1118-15-6"[rn] OR "Tetramethyldisiloxane-1,3-diol"[tw] OR "1,3-Disiloxanediol, 1,1,3,3-tetramethyl-"[tw] OR "Dimethylsilanediol"[tw] OR "1066-42-8"[rn] OR "Dimethyldihydroxysilane"[tw] OR "Dihydroxydimethylsilane"[tw] OR "Silanediol, dimethyl-"[tw]	22
Science Direct Search Date: 1/13/2021	1. "Octamethyltetrasiloxanediol" OR "3081-07-0" OR "1,7-Tetrasiloxanediol, 1,1,3,3,5,5,7,7-octamethyl-" OR "Octamethyltetrasiloxane-1,7-diol" OR "Tetrasiloxane-1,7-diol, 1,1,3,3,5,5,7,7-octamethyl-" OR "Hexamethyltrisiloxanediol" OR "3663-50-1"	0

Source	Source-Specific Search Strategy	Results
	2. "1,5-Trisiloxanediol, 1,1,3,3,5,5-hexamethyl-" OR "Hexamethyltrisiloxane-1,5-diol" OR "Tetramethyldisiloxanediol" OR "1118-15-6" OR "Tetramethyldisiloxane-1,3-diol" OR "1,3-Disiloxanediol, 1,1,3,3-tetramethyl-" OR "Dimethylsilanediol" OR "1066-42-8" 3. "Dimethyldihydroxysilane" OR "Dihydroxydimethylsilane" OR "Silanediol, dimethyl-"	
ToxLine Search Date: 1/13/2021	1. TIAB("Octamethyltetrasiloxanediol" OR "3081-07-0" OR "1,7-Tetrasiloxanediol, 1,1,3,3,5,5,7,7-octamethyl-" OR "Octamethyltetrasiloxane-1,7-diol" OR "Tetrasiloxane-1,7-diol, 1,1,3,3,5,5,7,7-octamethyl-" OR "Hexamethyltrisiloxanediol" OR "3663-50-1" OR "1,5-Trisiloxanediol, 1,1,3,3,5,5-hexamethyl-" OR "Hexamethyltrisiloxane-1,5-diol" OR "Tetramethyldisiloxanediol" OR "1118-15-6" OR "Tetramethyldisiloxane-1,3-diol" OR "1,3-Disiloxanediol, 1,1,3,3-tetramethyl-" OR "Dimethylsilanediol" OR "1066-42-8" OR "Dimethyldihydroxysilane" OR "Dihydroxydimethylsilane" OR "Silanediol, dimethyl-") 2. tox[subset] AND ("Octamethyltetrasiloxanediol"[tw] OR "3081-07-0"[rn] OR "1,7-Tetrasiloxanediol, 1,1,3,3,5,5,7,7-octamethyl-"[tw] OR "Octamethyltetrasiloxane-1,7-diol"[tw] OR "Tetrasiloxane-1,7-diol, 1,1,3,3,5,5,7,7-octamethyl-"[tw] OR "Hexamethyltrisiloxanediol"[tw] OR "3663-50-1"[rn] OR "1,5-Trisiloxanediol, 1,1,3,3,5,5-hexamethyl-"[tw] OR "Hexamethyltrisiloxane-1,5-diol"[tw] OR "Tetramethyldisiloxanediol"[tw] OR "1118-15-6"[rn] OR "Tetramethyldisiloxane-1,3-diol"[tw] OR "1,3-Disiloxanediol, 1,1,3,3-tetramethyl-"[tw] OR "Dimethylsilanediol"[tw] OR "1066-42-8"[rn] OR "Dimethyldihydroxysilane"[tw] OR "Dihydroxydimethylsilane"[tw] OR "Silanediol, dimethyl-"[tw])	10
WoS Search Date: 1/13/2021	TS=("Octamethyltetrasiloxanediol" OR "3081-07-0" OR "1,7-Tetrasiloxanediol, 1,1,3,3,5,5,7,7-octamethyl-" OR "Octamethyltetrasiloxane-1,7-diol" OR "Tetrasiloxane-1,7-diol, 1,1,3,3,5,5,7,7-octamethyl-" OR "Hexamethyltrisiloxanediol" OR "3663-50-1" OR "1,5-Trisiloxanediol, 1,1,3,3,5,5-hexamethyl-" OR "Hexamethyltrisiloxane-1,5-diol" OR "Tetramethyldisiloxanediol" OR "1118-15-6" OR "Tetramethyldisiloxane-1,3-diol" OR "1,3-Disiloxanediol, 1,1,3,3-tetramethyl-" OR "Dimethylsilanediol" OR "1066-42-8" OR "Dimethyldihydroxysilane" OR "Dihydroxydimethylsilane" OR "Silanediol, dimethyl-")	79
Total	**Represents total across all databases after deduplication**	**96**

C.1.24 Query Strings for the Peer-Reviewed Literature Database Searches on Asbestos Part 2

The literature strategy for Asbestos Part 2 is composed of three pieces: (1) reevaluation of all references used in Part 1, (2) evaluation of new literature produced by performing a Part 1 search update, and (3) evaluation of new literature produced by inclusion of additional asbestos fiber types. These are the search terms compiled for Asbestos used in the search strategies for each of the databases listed below:

Asbestos Part I Search Terms

"Asbestos" OR "12001-28-4" OR "12001-29-5" OR "12172-67-7" OR "12172-73-5" OR "1332-21-4" OR ("Asbestos" AND "exposure") OR ("Asbestos" AND ("fiber*" OR "fibre*")) OR "chrysotile" OR "Asbestos, exposure" OR ("Asbestos" AND "dust") OR "crocidolite" OR "chrysotile asbestos" OR "tremolite" OR "actinolite" OR ("chrysotile" AND "serpentine") OR "amosite" OR "Crocidolite asbestos" OR "Asbestos crocidolite" OR "Asbestos, crocidolite" OR "anthophyllite" OR "asbestos, amphibole" OR "amphibole asbestos" OR "Amosite asbestos" OR "Asbestos dust" OR "Asbestos, amosite" OR "riebeckite" OR "14567-73-8" OR "grunerite" OR ("Silicates" AND ("tremolite"

OR "asbestiform")) OR "Amiante" OR "blue asbestos" OR "17068-78-9" OR "asbestos, chrysotile" OR "Man-made mineral fibres" OR "Chrysotile A" OR "Tremolite asbestos" OR "Asbestiform minerals" OR "Asbest" OR "Asbesto" OR "Asbestose" OR "magnesioriebeckite" OR "Asbestos substitutes" OR ("Asbestos" AND "synthetic fibers") OR "white asbestos" OR "Ascarite" OR "Asbestos, tremolite" OR "serpentine chrysotile" OR "grunerite asbestos" OR "Brown asbestos" OR "riebeckite asbestos" OR "Amianthus" OR ("asbestos" AND ("Mountain" AND ("cork" OR "leather" OR "wood"))) OR ("asbestos" AND "MTM") OR "Asbestos, grunerite" OR "Chrysotile A asbestos" OR "Amorphous crocidolite asbestos" OR "Calidria RG 144" OR "Cassiar AK" OR "Fibrous crocidolite asbestos" OR "Fibrous grunerite" OR "metaxite")

Additional Fiber Types
"winchite" OR "12425-92-2" OR "richterite" OR "17068-76-7" OR "Libby amphibole" OR "Libby asbestos" OR "1318-09-8" OR "Hornblendeasbest" OR "Amphibole" OR "Amphybole"

Table_Apx C-28. Peer-Reviewed Literature Search Strategy for Asbestos Part 2

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 4/19/2021	TIAB("Asbestos" OR "12001-28-4" OR "12001-29-5" OR "12172-67-7" OR "12172-73-5" OR "1332-21-4" OR ("Asbestos" AND "exposure") OR ("Asbestos" AND ("fiber*" OR "fibre*")) OR "chrysotile" OR "Asbestos, exposure" OR ("Asbestos" AND "dust") OR "crocidolite" OR "chrysotile asbestos" OR "tremolite" OR "actinolite" OR ("chrysotile" AND "serpentine") OR "amosite" OR "Crocidolite asbestos" OR "Asbestos crocidolite" OR "Asbestos, crocidolite" OR "anthophyllite" OR "asbestos, amphibole" OR "amphibole asbestos" OR "Amosite asbestos" OR "Asbestos dust" OR "Asbestos, amosite" OR "riebeckite" OR "14567-73-8" OR "grunerite" OR ("Silicates" AND ("tremolite" OR "asbestiform")) OR "Amiante" OR "blue asbestos" OR "17068-78-9" OR "asbestos, chrysotile" OR "Man-made mineral fibres" OR "Chrysotile A" OR "Tremolite asbestos" OR "Asbestiform minerals" OR "Asbest" OR "Asbesto" OR "Asbestose" OR "magnesioriebeckite" OR "Asbestos substitutes" OR ("Asbestos" AND "synthetic fibers") OR "white asbestos" OR "Ascarite" OR "Asbestos, tremolite" OR "serpentine chrysotile" OR "grunerite asbestos" OR "Brown asbestos" OR "riebeckite asbestos" OR "Amianthus" OR ("asbestos" AND ("Mountain" AND ("cork" OR "leather" OR "wood"))) OR ("asbestos" AND "MTM") OR "Asbestos, grunerite" OR "Chrysotile A asbestos" OR "Amorphous crocidolite asbestos" OR "Calidria RG 144" OR "Cassiar AK" OR "Fibrous crocidolite asbestos" OR "Fibrous grunerite" OR "metaxite") (Part I Update limited to September 30, 2020 to April 19, 2021) TIAB("winchite" OR "12425-92-2" OR "richterite" OR "17068-76-7" OR "Libby amphibole" OR "Libby asbestos" OR "1318-09-8" OR "Hornblendeasbest" OR "Amphibole" OR "Amphybole")	770
Current Contents Search Date: 4/19/2021	TS=("Asbestos" OR "12001-28-4" OR "12001-29-5" OR "12172-67-7" OR "12172-73-5" OR "1332-21-4" OR ("Asbestos" AND "exposure") OR ("Asbestos" AND ("fiber*" OR "fibre*")) OR "chrysotile" OR "Asbestos, exposure" OR ("Asbestos" AND "dust") OR "crocidolite" OR "chrysotile asbestos" OR "tremolite" OR "actinolite" OR ("chrysotile" AND "serpentine") OR "amosite" OR "Crocidolite asbestos" OR "Asbestos crocidolite" OR "Asbestos, crocidolite" OR "anthophyllite" OR "asbestos, amphibole" OR "amphibole asbestos" OR "Amosite asbestos" OR "Asbestos dust" OR "Asbestos, amosite" OR "riebeckite" OR "14567-73-8" OR "grunerite" OR ("Silicates" AND ("tremolite" OR "asbestiform")) OR "Amiante" OR "blue asbestos" OR "17068-78-9" OR "asbestos, chrysotile" OR "Man-made mineral fibres" OR "Chrysotile A" OR "Tremolite asbestos" OR	7,081

Source	Source-Specific Search Strategy	Results
	"Asbestiform minerals" OR "Asbest" OR "Asbesto" OR "Asbestose" OR "magnesioriebeckite" OR "Asbestos substitutes" OR ("Asbestos" AND "synthetic fibers") OR "white asbestos" OR "Ascarite" OR "Asbestos, tremolite" OR "serpentine chrysotile" OR "grunerite asbestos" OR "Brown asbestos" OR "riebeckite asbestos" OR "Amianthus" OR ("asbestos" AND ("Mountain" AND ("cork" OR "leather" OR "wood"))) OR ("asbestos" AND "MTM") OR "Asbestos, grunerite" OR "Chrysotile A asbestos" OR "Amorphous crocidolite asbestos" OR "Calidria RG 144" OR "Cassiar AK" OR "Fibrous crocidolite asbestos" OR "Fibrous grunerite" OR "metaxite") AND PY=2020-2021 TS=("winchite" OR "12425-92-2" OR "richterite" OR "17068-76-7" OR "Libby amphibole" OR "Libby asbestos" OR "1318-09-8" OR "Hornblendeasbest" OR "Amphibole" OR "Amphybole")	
ProQuest Dissertations & Theses Search Date: 4/19/2021	TIAB("Asbestos" OR "12001-28-4" OR "12001-29-5" OR "12172-67-7" OR "12172-73-5" OR "1332-21-4" OR ("Asbestos" AND "exposure") OR ("Asbestos" AND ("fiber*" OR "fibre*")) OR "chrysotile" OR "Asbestos, exposure" OR ("Asbestos" AND "dust") OR "crocidolite" OR "chrysotile asbestos" OR "tremolite" OR "actinolite" OR ("chrysotile" AND "serpentine") OR "amosite" OR "Crocidolite asbestos" OR "Asbestos crocidolite" OR "Asbestos, crocidolite" OR "anthophyllite" OR "asbestos, amphibole" OR "amphibole asbestos" OR "Amosite asbestos" OR "Asbestos dust" OR "Asbestos, amosite" OR "riebeckite" OR "14567-73-8" OR "grunerite" OR ("Silicates" AND ("tremolite" OR "asbestiform")) OR "Amiante" OR "blue asbestos" OR "17068-78-9" OR "asbestos, chrysotile" OR "Man-made mineral fibres" OR "Chrysotile A" OR "Tremolite asbestos" OR "Asbestiform minerals" OR "Asbest" OR "Asbesto" OR "Asbestose" OR "magnesioriebeckite" OR "Asbestos substitutes" OR ("Asbestos" AND "synthetic fibers") OR "white asbestos" OR "Ascarite" OR "Asbestos, tremolite" OR "serpentine chrysotile" OR "grunerite asbestos" OR "Brown asbestos" OR "riebeckite asbestos" OR "Amianthus" OR ("asbestos" AND ("Mountain" AND ("cork" OR "leather" OR "wood"))) OR ("asbestos" AND "MTM") OR "Asbestos, grunerite" OR "Chrysotile A asbestos" OR "Amorphous crocidolite asbestos" OR "Calidria RG 144" OR "Cassiar AK" OR "Fibrous crocidolite asbestos" OR "Fibrous grunerite" OR "metaxite") (Part I Update limited to September 30, 2020 to April 19, 2021) TIAB("winchite" OR "12425-92-2" OR "richterite" OR "17068-76-7" OR "Libby amphibole" OR "Libby asbestos" OR "1318-09-8" OR "Hornblendeasbest" OR "Amphibole" OR "Amphybole")	14
ProQuest Agricultural & Scientific Database Search Date: 4/19/2021	TIAB("Asbestos" OR "12001-28-4" OR "12001-29-5" OR "12172-67-7" OR "12172-73-5" OR "1332-21-4" OR ("Asbestos" AND "exposure") OR ("Asbestos" AND ("fiber*" OR "fibre*")) OR "chrysotile" OR "Asbestos, exposure" OR ("Asbestos" AND "dust") OR "crocidolite" OR "chrysotile asbestos" OR "tremolite" OR "actinolite" OR ("chrysotile" AND "serpentine") OR "amosite" OR "Crocidolite asbestos" OR "Asbestos crocidolite" OR "Asbestos, crocidolite" OR "anthophyllite" OR "asbestos, amphibole" OR "amphibole asbestos" OR "Amosite asbestos" OR "Asbestos dust" OR "Asbestos, amosite" OR "riebeckite" OR "14567-73-8" OR "grunerite" OR ("Silicates" AND ("tremolite" OR "asbestiform")) OR "Amiante" OR "blue asbestos" OR "17068-78-9" OR "asbestos, chrysotile" OR "Man-made mineral fibres" OR "Chrysotile A" OR "Tremolite asbestos" OR "Asbestiform minerals" OR "Asbest" OR "Asbesto" OR "Asbestose" OR "magnesioriebeckite" OR "Asbestos substitutes" OR ("Asbestos" AND "synthetic fibers") OR "white asbestos" OR "Ascarite" OR "Asbestos, tremolite" OR "serpentine chrysotile" OR "grunerite asbestos" OR "Brown asbestos" OR "riebeckite asbestos" OR "Amianthus" OR ("asbestos" AND ("Mountain" AND ("cork" OR "leather" OR "wood"))) OR ("asbestos" AND "MTM") OR "Asbestos, grunerite" OR "Chrysotile A asbestos"	14,460

Source	Source-Specific Search Strategy	Results
	OR “Amorphous crocidolite asbestos” OR “Calidria RG 144” OR “Cassiar AK” OR “Fibrous crocidolite asbestos” OR “Fibrous grunerite” OR “metaxite”) (Part I Update limited to September 30, 2020 to April 19, 2021) TIAB(“winchite” OR “12425-92-2” OR “richterite” OR “17068-76-7” OR “Libby amphibole” OR “Libby asbestos” OR “1318-09-8” OR “Hornblendeasbest” OR “Amphibole” OR “Amphybole”)	
PubMed Search Date: 4/19/2021	(“Asbestos”[tw] OR “12001-28-4”[rn] OR “12001-29-5”[rn] OR “12172-67-7”[rn] OR “12172-73-5”[rn] OR “1332-21-4”[rn] OR (“Asbestos”[tw] AND “exposure”[tw]) OR (“Asbestos”[tw] AND (“fiber*”[tw] OR “fibre*”[tw])) OR “chrysotile”[tw] OR “Asbestos, exposure”[tw] OR (“Asbestos”[tw] AND “dust”[tw]) OR “crocidolite”[tw] OR “chrysotile asbestos”[tw] OR “tremolite”[tw] OR “actinolite”[tw] OR (“chrysotile”[tw] AND “serpentine”[tw]) OR “amosite”[tw] OR “Crocidolite asbestos”[tw] OR “Asbestos crocidolite”[tw] OR “Asbestos, crocidolite”[tw] OR “anthophyllite”[tw] OR “asbestos, amphibole”[tw] OR “amphibole asbestos”[tw] OR “Amosite asbestos”[tw] OR “Asbestos dust”[tw] OR “Asbestos, amosite”[tw] OR “riebeckite”[tw] OR “14567-73-8”[rn] OR “grunerite”[tw] OR (“Silicates”[tw] AND (“tremolite”[tw] OR “asbestiform”[tw])) OR “Amiante”[tw] OR “blue asbestos”[tw] OR “17068-78-9”[rn] OR “asbestos, chrysotile”[tw] OR “Man-made mineral fibres”[tw] OR “Chrysotile A”[tw] OR “Tremolite asbestos”[tw] OR “Asbestiform minerals”[tw] OR “Asbest”[tw] OR “Asbesto”[tw] OR “Asbestose”[tw] OR “magnesioriebeckite”[tw] OR “Asbestos substitutes”[tw] OR (“Asbestos”[tw] AND “synthetic fibers”[tw]) OR “white asbestos”[tw] OR “Ascarite”[tw] OR “Asbestos, tremolite”[tw] OR “serpentine chrysotile”[tw] OR “grunerite asbestos”[tw] OR “Brown asbestos”[tw] OR “riebeckite asbestos”[tw] OR “Amianthus”[tw] OR (“asbestos”[tw] AND (“Mountain”[tw] AND (“cork”[tw] OR “leather”[tw] OR “wood”[tw]))) OR (“asbestos”[tw] AND “MTM”[tw]) OR “Asbestos, grunerite”[tw] OR “Chrysotile A asbestos”[tw] OR “Amorphous crocidolite asbestos”[tw] OR “Calidria RG 144”[tw] OR “Cassiar AK”[tw] OR “Fibrous crocidolite asbestos”[tw] OR “Fibrous grunerite”[tw] OR “metaxite”[tw]) AND (“2020/09/30”[Date – Publication] : “3000”[Date – Publication]) (“winchite”[tw] OR “12425-92-2”[rn] OR “richterite”[tw] OR “17068-76-7”[rn] OR “Libby amphibole”[tw] OR “Libby asbestos”[tw] OR “1318-09-8”[rn] OR “Hornblendeasbest”[tw] OR “Amphibole”[tw] OR “Amphybole”[tw])	14,161
Scopus Search Date: 4/19/2021	TITLE-ABS({Asbestos} OR {12001-28-4} OR {12001-29-5} OR {12172-67-7} OR {12172-73-5} OR {1332-21-4} OR ({Asbestos} AND {exposure}) OR ({Asbestos} AND ({fiber*} OR {fibre*})) OR {chrysotile} OR {Asbestos, exposure} OR ({Asbestos} AND {dust}) OR {crocidolite} OR {chrysotile asbestos} OR {tremolite} OR {actinolite} OR ({chrysotile} AND {serpentine}) OR {amosite} OR {Crocidolite asbestos} OR {Asbestos crocidolite} OR {Asbestos, crocidolite} OR {anthophyllite} OR {asbestos, amphibole} OR {amphibole asbestos} OR {Amosite asbestos} OR {Asbestos dust} OR {Asbestos, amosite} OR {riebeckite} OR {14567-73-8} OR {grunerite} OR ({Silicates} AND ({tremolite} OR {asbestiform})) OR {Amiante} OR {blue asbestos} OR {17068-78-9} OR {asbestos, chrysotile} OR {Man-made mineral fibres} OR {Chrysotile A} OR {Tremolite asbestos} OR {Asbestiform minerals} OR {Asbest} OR {Asbesto} OR {Asbestose} OR {magnesioriebeckite} OR {Asbestos substitutes} OR ({Asbestos} AND {synthetic fibers}) OR {white asbestos} OR {Ascarite} OR {Asbestos, tremolite} OR {serpentine chrysotile} OR {grunerite asbestos} OR {Brown asbestos} OR {riebeckite asbestos} OR {Amianthus} OR ({asbestos} AND ({Mountain} AND ({cork} OR {leather} OR {wood}))) OR ({asbestos} AND {MTM}) OR {Asbestos, grunerite} OR {Chrysotile A asbestos} OR {Amorphous crocidolite asbestos} OR {Calidria RG 144} OR {Cassiar AK} OR {Fibrous crocidolite asbestos} OR {Fibrous grunerite} OR {metaxite})	16,364

Source	Source-Specific Search Strategy	Results
	(Part I Update limited to 2020-2021) TITLE-ABS({winchite} OR {12425-92-2} OR {richterite} OR {17068-76-7} OR {Libby amphibole} OR {Libby asbestos} OR {1318-09-8} OR {Hornblendeasbest} OR {Amphibole} OR {Amphybole})	
ToxLine Search Date: 4/19/2021	tox [subset] AND (“Asbestos”[tw] OR “12001-28-4”[rn] OR “12001-29-5”[rn] OR “12172-67-7”[rn] OR “12172-73-5”[rn] OR “1332-21-4”[rn] OR (“Asbestos”[tw] AND “exposure”[tw]) OR (“Asbestos”[tw] AND (“fiber*”[tw] OR “fibre*”[tw])) OR “chrysotile”[tw] OR “Asbestos, exposure”[tw] OR (“Asbestos”[tw] AND “dust”[tw]) OR “crocidolite”[tw] OR “chrysotile asbestos”[tw] OR “tremolite”[tw] OR “actinolite”[tw] OR (“chrysotile”[tw] AND “serpentine”[tw]) OR “amosite”[tw] OR “Crocidolite asbestos”[tw] OR “Asbestos crocidolite”[tw] OR “Asbestos, crocidolite”[tw] OR “anthophyllite”[tw] OR “asbestos, amphibole”[tw] OR “amphibole asbestos”[tw] OR “Amosite asbestos”[tw] OR “Asbestos dust”[tw] OR “Asbestos, amosite”[tw] OR “riebeckite”[tw] OR “14567-73-8”[rn] OR “grunerite”[tw] OR (“Silicates”[tw] AND (“tremolite”[tw] OR “asbestiform”[tw])) OR “Amiante”[tw] OR “blue asbestos”[tw] OR “17068-78-9”[rn] OR “asbestos, chrysotile”[tw] OR “Man-made mineral fibres”[tw] OR “Chrysotile A”[tw] OR “Tremolite asbestos”[tw] OR “Asbestiform minerals”[tw] OR “Asbest”[tw] OR “Asbesto”[tw] OR “Asbestose”[tw] OR “magnesioriebeckite”[tw] OR “Asbestos substitutes”[tw] OR (“Asbestos”[tw] AND “synthetic fibers”[tw]) OR “white asbestos”[tw] OR “Ascarite”[tw] OR “Asbestos, tremolite”[tw] OR “serpentine chrysotile”[tw] OR “grunerite asbestos”[tw] OR “Brown asbestos”[tw] OR “riebeckite asbestos”[tw] OR “Amianthus”[tw] OR (“asbestos”[tw] AND (“Mountain”[tw] AND (“cork”[tw] OR “leather”[tw] OR “wood”[tw])))) OR (“asbestos”[tw] AND “MTM”[tw]) OR “Asbestos, grunerite”[tw] OR “Chrysotile A asbestos”[tw] OR “Amorphous crocidolite asbestos”[tw] OR “Calidria RG 144”[tw] OR “Cassiar AK”[tw] OR “Fibrous crocidolite asbestos”[tw] OR “Fibrous grunerite”[tw] OR “metaxite”[tw]) AND (“2020/09/30”[Date – Publication] : “3000”[Date – Publication]) tox [subset] AND (“winchite”[tw] OR “12425-92-2”[rn] OR “richterite”[tw] OR “17068-76-7”[rn] OR “Libby amphibole”[tw] OR “Libby asbestos”[tw] OR “1318-09-8”[rn] OR “Hornblendeasbest”[tw] OR “Amphibole”[tw] OR “Amphybole”[tw]) TIAB(“Asbestos” OR “12001-28-4” OR “12001-29-5” OR “12172-67-7” OR “12172-73-5” OR “1332-21-4” OR (“Asbestos” AND “exposure”) OR (“Asbestos” AND (“fiber*” OR “fibre*”)) OR “chrysotile” OR “Asbestos, exposure” OR (“Asbestos” AND “dust”) OR “crocidolite” OR “chrysotile asbestos” OR “tremolite” OR “actinolite” OR (“chrysotile” AND “serpentine”) OR “amosite” OR “Crocidolite asbestos” OR “Asbestos crocidolite” OR “Asbestos, crocidolite” OR “anthophyllite” OR “asbestos, amphibole” OR “amphibole asbestos” OR “Amosite asbestos” OR “Asbestos dust” OR “Asbestos, amosite” OR “riebeckite” OR “14567-73-8” OR “grunerite” OR (“Silicates” AND (“tremolite” OR “asbestiform”)) OR “Amiante” OR “blue asbestos” OR “17068-78-9” OR “asbestos, chrysotile” OR “Man-made mineral fibres” OR “Chrysotile A” OR “Tremolite asbestos” OR “Asbestiform minerals” OR “Asbest” OR “Asbesto” OR “Asbestose” OR “magnesioriebeckite” OR “Asbestos substitutes” OR (“Asbestos” AND “synthetic fibers”) OR “white asbestos” OR “Ascarite” OR “Asbestos, tremolite” OR “serpentine chrysotile” OR “grunerite asbestos” OR “Brown asbestos” OR “riebeckite asbestos” OR “Amianthus” OR (“asbestos” AND (“Mountain” AND (“cork” OR “leather” OR “wood”))) OR (“asbestos” AND “MTM”) OR “Asbestos, grunerite” OR “Chrysotile A asbestos” OR “Amorphous crocidolite asbestos” OR “Calidria RG 144” OR “Cassiar AK” OR “Fibrous crocidolite asbestos” OR “Fibrous grunerite” OR “metaxite”) (Part I Update limited to September 30, 2020 to April 19, 2021)	12,298

Source	Source-Specific Search Strategy	Results
	TIAB("winchite" OR "12425-92-2" OR "richterite" OR "17068-76-7" OR "Libby amphibole" OR "Libby asbestos" OR "1318-09-8" OR "Hornblendeasbest" OR "Amphibole" OR "Amphybole")	
WoS Search Date: 4/19/2021	TS=("Asbestos" OR "12001-28-4" OR "12001-29-5" OR "12172-67-7" OR "12172-73-5" OR "1332-21-4" OR ("Asbestos" AND "exposure") OR ("Asbestos" AND ("fiber*" OR "fibre*")) OR "chrysotile" OR "Asbestos, exposure" OR ("Asbestos" AND "dust") OR "crocidolite" OR "chrysotile asbestos" OR "tremolite" OR "actinolite" OR ("chrysotile" AND "serpentine") OR "amosite" OR "Crocidolite asbestos" OR "Asbestos crocidolite" OR "Asbestos, crocidolite" OR "anthophyllite" OR "asbestos, amphibole" OR "amphibole asbestos" OR "Amosite asbestos" OR "Asbestos dust" OR "Asbestos, amosite" OR "riebeckite" OR "14567-73-8" OR "grunerite" OR ("Silicates" AND ("tremolite" OR "asbestiform")) OR "Amiante" OR "blue asbestos" OR "17068-78-9" OR "asbestos, chrysotile" OR "Man-made mineral fibres" OR "Chrysotile A" OR "Tremolite asbestos" OR "Asbestiform minerals" OR "Asbest" OR "Asbesto" OR "Asbestose" OR "magnesioriebeckite" OR "Asbestos substitutes" OR ("Asbestos" AND "synthetic fibers") OR "white asbestos" OR "Ascarite" OR "Asbestos, tremolite" OR "serpentine chrysotile" OR "grunerite asbestos" OR "Brown asbestos" OR "riebeckite asbestos" OR "Amianthus" OR ("asbestos" AND ("Mountain" AND ("cork" OR "leather" OR "wood"))) OR ("asbestos" AND "MTM") OR "Asbestos, grunerite" OR "Chrysotile A asbestos" OR "Amorphous crocidolite asbestos" OR "Calidria RG 144" OR "Cassiar AK" OR "Fibrous crocidolite asbestos" OR "Fibrous grunerite" OR "metaxite") AND PY=2020-2021 TS=("winchite" OR "12425-92-2" OR "richterite" OR "17068-76-7" OR "Libby amphibole" OR "Libby asbestos" OR "1318-09-8" OR "Hornblendeasbest" OR "Amphibole" OR "Amphybole")	40,176
Total	**Represents total across all databases and strategies after deduplication**	**53,774**

C.1.25 Query Strings for the Peer-Reviewed Literature Database Searches on 1,4-Dioxane Supplement

The literature strategy for the supplemental search for 1,4-dioxane is composed of an updated broad literature search and targeted searching of subsequent results to identify information areas not previously considered in the 2016 initiated risk evaluation for 1,4-dioxane. Below are the compiled search terms for the for 1,4-dioxane supplemental search, followed by specifics for each queried database (Table_Apx C-29).

1,4-Dioxane Supplemental Search Terms

"1,4-dioxane" OR "123-91-1" OR "Dioxan" OR "p-Dioxane" OR "Diethylene oxide" OR "1,4-diethylene dioxide" OR "Para-dioxane" OR "1,4-dioxacyclohexane" OR "Di(ethylene oxide)" OR "p-Dioxan" OR "diethylene ether" OR "Dioxyethylene ether" OR "diethylene dioxide" OR "dioxane"

Table_Apx C-29. Summary of Data Sources, Search Dates, and Number of Peer-Reviewed Literature Search Results for 1,4-Dioxane Supplement

Source	Source-Specific Search Strategy	Results
Agricola Search Date: 10/27/2021	TIAB("1,4-dioxane" OR "123-91-1" OR "Dioxan" OR "p-Dioxane" OR "Diethylene oxide" OR "1,4-diethylene dioxide" OR "Para-dioxane" OR "1,4-dioxacyclohexane" OR "Di(ethylene oxide)" OR "p-Dioxan" OR "diethylene ether" OR "Dioxyethylene ether" OR "diethylene dioxide" OR "dioxane")	596
Current Contents Search Date: 10/27/2021	TS=("1,4-dioxane" OR "123-91-1" OR "Dioxan" OR "p-Dioxane" OR "Diethylene oxide" OR "1,4-diethylene dioxide" OR "Para-dioxane" OR "1,4-dioxacyclohexane" OR "Di(ethylene oxide)" OR "p-Dioxan" OR "diethylene ether" OR "Dioxyethylene ether" OR "diethylene dioxide" OR "dioxane")	10,045
ProQuest Dissertations & Theses Search Date: 10/27/2021	TIAB("1,4-dioxane" OR "123-91-1" OR "Dioxan" OR "p-Dioxane" OR "Diethylene oxide" OR "1,4-diethylene dioxide" OR "Para-dioxane" OR "1,4-dioxacyclohexane" OR "Di(ethylene oxide)" OR "p-Dioxan" OR "diethylene ether" OR "Dioxyethylene ether" OR "diethylene dioxide" OR "dioxane")	15
ProQuest Agricultural & Scientific Database Search Date: 10/27/2021	TIAB("1,4-dioxane" OR "123-91-1" OR "Dioxan" OR "p-Dioxane" OR "Diethylene oxide" OR "1,4-diethylene dioxide" OR "Para-dioxane" OR "1,4-dioxacyclohexane" OR "Di(ethylene oxide)" OR "p-Dioxan" OR "diethylene ether" OR "Dioxyethylene ether" OR "diethylene dioxide" OR "dioxane")	1,230
PubMed Search Date: 10/27/2021	("1,4-dioxane"[tw] OR "123-91-1"[rn] OR "Dioxan"[tw] OR "p-Dioxane"[tw] OR "Diethylene oxide"[tw] OR "1,4-diethylene dioxide"[tw] OR "Para-dioxane"[tw] OR "1,4-dioxacyclohexane"[tw] OR "Di(ethylene oxide)"[tw] OR "p-Dioxan"[tw] OR "diethylene ether"[tw] OR "Dioxyethylene ether"[tw] OR "diethylene dioxide"[tw] OR "dioxane"[tw])	4,408
Scopus Search Date: 10/27/2021	TITLE-ABS({1,4-dioxane} OR {123-91-1} OR {Dioxan} OR {p-Dioxane} OR {Diethylene oxide} OR {1,4-diethylene dioxide} OR {Para-dioxane} OR {1,4-dioxacyclohexane} OR {Di(ethylene oxide)} OR {p-Dioxan} OR {diethylene ether} OR {Dioxyethylene ether} OR {diethylene dioxide} OR {dioxane})	16,820
ToxLine Search Date: 10/27/2021	TIAB("1,4-dioxane" OR "123-91-1" OR "Dioxan" OR "p-Dioxane" OR "Diethylene oxide" OR "1,4-diethylene dioxide" OR "Para-dioxane" OR "1,4-dioxacyclohexane" OR "Di(ethylene oxide)" OR "p-Dioxan" OR "diethylene ether" OR "Dioxyethylene ether" OR "diethylene dioxide" OR "dioxane") Tox[subset] AND ("1,4-dioxane"[tw] OR "123-91-1"[rn] OR "Dioxan"[tw] OR "p-Dioxane"[tw] OR "Diethylene oxide"[tw] OR "1,4-diethylene dioxide"[tw] OR "Para-dioxane"[tw] OR "1,4-dioxacyclohexane"[tw] OR "Di(ethylene oxide)"[tw] OR "p-Dioxan"[tw] OR "diethylene ether"[tw] OR "Dioxyethylene ether"[tw] OR "diethylene dioxide"[tw] OR "dioxane"[tw])	1,223

Source	Source-Specific Search Strategy	Results
WoS Search Date: 10/27/2021	TS=("1,4-dioxane" OR "123-91-1" OR "Dioxan" OR "p-Dioxane" OR "Diethylene oxide" OR "1,4-diethylene dioxide" OR "Para-dioxane" OR "1,4-dioxacyclohexane" OR "Di(ethylene oxide)" OR "p-Dioxan" OR "diethylene ether" OR "Dioxyethylene ether" OR "diethylene dioxide" OR "dioxane")	14,852
Total	**Represents total across all databases after deduplication**	**20,770**

Additional Strategies

Additional targeted searches were performed in SWIFT-Review to identify key information areas within the primary pool of 1,4-dioxane references. Search strings were developed from PECO (exposure) and RESO (engineering) elements, and performed during November 2021. Targeted searching was applied to the results of the broad 1,4-dioxane literature search, producing subsets of references relevant to each PECO and RESO element. Each subset was then deduplicated against references that had already been through screening in previous evaluation efforts, such that only unique references moved forward for review. The number of references deemed unique for each element are shown in the "References Identified" column of the targeted search summary tables. Table_Apx C-30 and Table_Apx C-31 provide the search strings used in the targeted strategies for the exposure and engineering, respectively, along with the resulting number of references identified.

Table_Apx C-30. Summary of PECO-related Search Strategies and Number of Peer-Reviewed Literature Search Results for 1,4-Dioxane Targeted Searches

PECO Element	Targeted Search	References Identified
Population	TIAB:("general population" OR "bystanders" OR "near-facility" OR "industrial facilit*" OR "commercial facilit*" OR "employee" OR "employees" OR "worker*" OR "manufacturer" OR "near-disposal" OR "near surface disposal" OR "child*" OR "teenage*" OR "susceptible population" OR "immunocompromised" OR "preschool" OR "senior*" OR "older adults" OR "elderly" OR "pregnant women" OR "preexisting condition*" OR "lactating women" OR "childbearing" OR "consumer*" OR "prenatal" OR "infant*" OR "adult*" OR "adolescen*")	42
Exposure	TIAB:("stabilizer" OR "stabilizer for chlorinated solvents" OR "purifying agent" OR "solvent release site" OR "PET manufactur*" OR "chlorinated solvent plume*" OR "solvent stabilizer" OR "landfill" OR "incineration" OR "wastewater" OR "GAC" OR "granular activated carbon" OR "reverse osmosis" OR "paint" OR "paint stripper" OR "grease" OR "antifreeze" OR "deicing fluid" OR "polyethylene terephthalate" OR "PET plastic" OR "adhesive") TIAB:("monitor*" AND ("indoor air" OR "vapor" OR "mist" OR "surface water" OR "groundwater" OR "outdoor air" OR "ambient air" OR "drinking water" OR "wastewater" OR "land disposal" OR "soil" OR "sediment" OR "biomonitoring")) TIAB:("exposure" AND ("inhal*" OR "respiratory" OR "oral" OR "dermal" OR "skin" OR "production" OR "short-term" OR "long-term"))	119

PECO Element	Targeted Search	References Identified
Comparator	TIAB:("drinking" OR "ingest*" OR "swallow*" OR "showering" OR "bathing" OR "swimming" OR "wading" OR "inhal*" OR "building" OR "painting" OR "industrial manufactur*" OR "residential construction" OR "commercial construction" OR "cleaning" OR "dishwash*" OR "printing" OR "food supplement*" OR "packaging" OR "nursing infants" OR "breast milk" OR "human milk" OR "intake rates" OR "laundry" OR "surface cleaner" OR "automotive")	142
Outcomes	TIAB:("reference concentration" OR "RfC" OR "NOAEL" OR "LOAEL" OR "benchmark concentration" OR "reference dose" OR "RfD" OR "chronic oral" OR "chronic inhalation" OR "oral slope factor" OR "soil screening level" OR "PEL" OR "permissible exposure limit" OR "weighted average" OR "weight fraction" OR "emission rate*" OR "inhalation unit risk" OR "IUR" OR "dose-response" OR "reverse dosimetry" OR "biomonitoring" OR "media concentration*" OR ("estimate*" AND ("acute" OR "subchronic" OR "chronic")) OR "single-dose" OR "repeated-dose" OR "daily intake")	32
Total	**Represents total across all searches**	**294**

Table_Apx C-31. Summary of RESO-related Search Strategies and Number of Peer-Reviewed Literature Search Results for 1,4-Dioxane Targeted Searches

RESO Element	Targeted Search	References Identified
Occupational Workers	tiab: ("at work" OR "employee" OR "employees" OR "factory" OR "factories" OR "migrant" OR "migrants" OR "miner" OR "miners" OR "occupation" OR "occupational" OR "occupations" OR "profession" OR "professionals" OR "time weighted average*" OR "workplace*" OR "worker*" OR "janitor*" OR "mechanic" OR "manufacturer" OR "laborer" OR "custodia*" OR "painter*" OR ("worker*" AND ("laboratory" OR "pharmaceutical")) OR "residential construction" OR "industrial construction")	53
Occupational Exposure	tiab: (("exposure" AND ("occupational" OR "industrial" OR "inhalation" OR "inhale*" OR "respiratory" OR "breath*" OR "oral" OR "dermal" OR "air" OR "dust" OR "chemical" OR "soil" OR "membrane" OR "skin")) OR ("sampling" OR "sample" AND ("direct reading" OR "personal pump" OR "passive" OR "grab" OR "detector tube" OR "gas bag" OR "diffusive" OR "active" OR "surface contamination" OR "bulk" OR "dust")) OR "TWA" OR "time weighted average" OR "STEL" OR "short-term exposure limit" OR "PEL" OR "permissible exposure limit" OR "REL" OR "recommended exposure limit" OR "ILV" OR "indicative limit value" OR "TLV" OR "threshold limit value" OR "daily intake" OR "OEL" OR "occupational exposure limit" OR "particle size" OR "particle distribution" OR "percent efficiency" OR "reference standard")	164
Releases	tiab: (("emissions" AND ("direct" OR "indirect" OR "industrial" OR "processing" OR "manufacturing" OR "construction" OR "N2O" OR "cement" OR "ferrous" OR "chemical" OR "wastewater treatment" OR "incineration" OR "efficiency")) OR "CO2 values" OR "pollution prevention" OR "source reduction" OR "conservation" OR "reuse" OR "ethoxylat*")	76
Product Lifecycle	tiab: (("MFG" OR "import" OR "processing" OR "manufactur*" OR "releases" OR "waste disposal" OR "reaction product" OR "repackaging" OR "recycling" OR "solvent*" OR "esterification" OR "industrial" OR "commercial" AND ("Additive*" OR "adhesive*" OR "agricultur*" OR "antifreeze" OR "automotive" OR "Blanket*" OR "blowing agent" OR "Cement" OR "Clean*"	

	OR “coating” OR “colorant*” OR “Concrete” OR “Coolant” OR “degreas*” OR “Deoderiz*” OR “detergent*” OR “dishwash*” OR “dye*” OR “Emulsi*” OR “fabric” OR “Fiberglass” OR “Film” OR “floor*” OR “foam” OR “fumigant*” OR “Fungicide*” OR “insulation” OR “lacquer” OR “laundry” OR “leather” OR “lubricant*” OR “Magnetic-tape” OR “metal” OR “Oxygen barrier” OR “paint” OR “paper” OR “petrochemical*” OR “petroleum” OR “pharmaceutical” OR “Photoresist*” OR “plastic*” OR “Polyester” OR “Polyether” OR “Polyol*” OR “printing” OR “pulp*” OR “rubber” OR “Sanitize*” OR “sealant*” OR “stabilizer” OR “Surfactant*” OR “textile” OR “Topcoat” OR “Washing liquid*” OR “Wetting agent*” OR “Yarn*”)) OR “throughput” OR “operating days” OR “production speed”)	69
Treatment Efficiencies	tiab: ((“wastewater” AND (“treatment” OR “plant” OR “effluent” OR “screening” OR “pumping” OR “aerating” OR “sludge” OR “residuals”)) OR “incineration” OR “engineering control” OR “exposure reduction” OR “disposal” OR “pollution prevention” OR “pollution control” OR “recycle” OR “recycling” OR “dewatering” OR “GAC” OR “granular activated carbon” OR “reverse osmosis” OR “advanced oxidation” OR “hydrogen peroxide with ultraviolet” OR (“hydrogen peroxide” AND “UV”) OR “hydrogen peroxide with ozone” OR (“hydrogen peroxide” AND “ozone”) OR “AOP” OR “Fenton's reagent” OR “bioremediation”)	207
Total	**Represents total across all searches**	**506**

Appendix D DATA GAP FILLING APPROACHES IN THE EVALUATION OF TSCA EXISTING CHEMICALS

Data gap filling approaches are briefly described in this appendix. Information resources are also provided that may assist EPA when evaluating the adequacy and robustness of the data derived from these data gap filling approaches.

D.1 Read-across Using Analogue Approaches

When little or no information on the chemical of interest can be located, EPA often turns to analogue analysis as a first step to filling data gaps. Analogue analysis is the practice of using empirical data from one or more similar chemical(s) to predict the same endpoint for the chemical under study, which is considered to be "similar."

The nature of the endpoint should be considered when deciding whether to use a quantitative or qualitative read-across approach. In most cases, the needs of the risk assessment drive the selection of the read-across approach, which could be quantitative or qualitative. For example, a quantitative read-across approach would be used to quantify risks if a hazard value is needed for risk estimation. The *OECD Guidance on Grouping of Chemicals* provides guidance on how to use analogues, including points to consider when assessing their adequacy for risk assessment purposes (OECD, 2014).
Many tools are available in the public domain for helping assessors identify analogues and associated data. Examples include EPA's tools, models, and approaches discussed under the Sustainable Futures program; other EPA programs and research initiatives; and methods available within the OECD QSAR Toolbox.

D.2 Chemical Class and Category Approaches

Chemicals whose physical and chemical, fate, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered a group, or 'category' of chemicals. Chemicals within a category are assessed on the basis of the evaluation of the category as a whole, rather than based on measured data for any one particular chemical alone. For a category member that lacks data for one or more endpoints, the data gap can be filled in a number of ways, including by read-across from one or more other category members.

Within a chemical category, the members are often related by a trend in an effect for a given endpoint, and a trend analysis can be carried out through deriving a model based on the data for the members of the category. The *OECD Guidance on Grouping of Chemicals* provides guidance on how to group chemicals in a category and assess the robustness of the chemical category in view of their predictive value for filling a data gap (OECD, 2017).

D.3 Other Predictive Tools and Models

To support chemical safety, EPA has developed many predictive tools and models to evaluate chemicals where data are lacking. They are used to assess a particular aspect of a chemical's possible impact on humans or the environment. For instance, these tools and models may be used for making predictions concerning chemical identity, physical and chemical properties, environmental transport and partitioning, environmental fate, human health and environmental toxicity, releases to the environment, environmental concentrations and exposure estimates to humans and environmental receptors.

Historically, EPA has pioneered development and use of QSAR and analogue approaches as part of the risk assessment process of new chemicals under TSCA. The main reason driving the predictive tool development has to do with the paucity of data submitted with new chemicals submissions and the short

regulatory timeframe for decisions to be made (*e.g.,* 90 days under section 5 of TSCA).

There is the possibility that QSAR models end up being useful for draft risk evaluations. In such circumstance, it is recommended to evaluate whether the QSAR prediction is adequate before relying on the predictive model for the assessment. The following documents contain guidance information on how to use QSAR models for risk assessment purposes, including considerations on how to evaluate the robustness of QSARs to fill data gaps.

1. OECD Manual for the Assessment of Chemicals provides guidance on the use of SAR in the HPV Chemicals Programme (OECD, 2011)
2. OECD Report on the Regulatory Uses and Applications in OECD Member Countries of (Q)SAR Models in the Assessment of New and Existing Chemicals (OECD, 2006) summarizes the experience of OECD member countries with (Q)SAR applications
3. OECD report on the principles for the validation, for regulatory purposes, of (Q)SAR models (OECD, 2004b) and an accompanying OECD guidance document (OECD, 2007)
1. Report of the Workshop on Structural Alerts for the OECD (Q)SAR Application Toolbox (OECD, 2009)
2. NAFTA TWG (2012). Technical working group on pesticides (Q)SAR guidance document.

Besides QSAR predictions, EPA has developed many other predictive tools and models that are useful in the risk evaluation of existing chemicals. These tools and models may be used to support the hazard, fate and exposure components of the draft risk evaluation. The degree of confidence required for the model results depends on the purpose of the prediction (*e.g.,* for screening and priority-setting of chemicals for further evaluation, hazard identification for risk assessment, classification and labeling, filling information requirements in different regulatory schemes).

Before using the models in the draft risk evaluations, EPA will review the model documentation explaining the underlying model framework and its assumptions and limitations to inform how they will be applied in the risk evaluation process. Refer to Appendix O for a list of considerations to consider when evaluating models for use in draft risk evaluations.

Appendix E LIST OF GRAY LITERATURE SOURCES

Table_Apx E-1 contains the list of gray literature sources that will generally be searched manually for the next TSCA risk evaluations, although automatic searches are possible for some sources. EPA will primarily use the chemical name and CASRN to search the gray literature sources.

EPA assembled this list of sources based on our experience integrating information from various disciplines (*i.e.*, physical and chemical properties, fate, engineering, exposure, environmental and human health hazard) into a chemical risk assessment. Sources of gray literature for physical and chemical properties are discussed in more detail in Appendix E.1 and in Appendix E.5.

E.1 Sources Used for the Gray Literature Search for the Physical and Chemical Property Topic Areas

Table_Apx E-1. Sources Used for the Gray Literature Search for the Physical and Chemical Property Topic Areas

Source	Description of the Data/Information Contained within the Source	Summary of Curation and Quality Control Processes
ChemSpider	ChemSpider seeks data from original sources for greater certainty about the data's provenance and accuracy. Most experimental property data sources are secondary sources, Safety Data Sheets (SDS) or other sources with limited details on the test method or study measuring the physical and chemical properties. It contains 277 cited and hyperlinked data sources for the next 20 chemicals undergoing risk evaluation (as of 11/2019). ChemSpider no longer accepts data from other secondary data sources.	New entries to the database are run through a series of automated filters to pick out unsuitable structures (incorrect valences, unbalanced charges, or missing stereochemistry). Basic name and synonym filtering are applied and regularly reviewed to continuously improve filters. Data/information are curated on an ongoing basis by ChemSpider staff and users to ensure data integrity and data quality. Any user can post comments regarding erroneous data on the website.
Chemistry Dashboard	EPA's Chemistry Dashboard is a compilation of data, including physical and chemical properties, sourced from many sources of chemical information. Most experimental physical and chemical property data sources are secondary sources, SDS or other sources with limited details on the test method or study measuring the physical and chemical properties. It links EPA's data sources and public domain online resources.	The database aggregates data over the past 15 years by both manual and auto-curation techniques. Expansion, curation and validation of the content is ongoing. The data in the dashboard are of varying quality and include: Expert curated: highest confidence in accuracy and consistency of unique chemical identifiers that are confirmed using multiple public sources. Programmatically curated from high quality EPA source(s) and unique chemical identifiers have no conflicts in ChemIDPlus and PubChem Programmatically curated from ACToR or PubChem. Unique chemical identifiers have low confidence and have a single public source.

Source	Description of the Data/Information Contained within the Source	Summary of Curation and Quality Control Processes
	Hyperlinks to ~70 external links for the next 20 chemicals undergoing risk evaluation (as of 11/2019).	
CRC Handbook of Chemistry and Physics	This handbook is a comprehensive resource of property data on chemical compounds and their physical and chemical properties that have been reported in literature. EPA uses both the online and hard copy. The data are derived from many sources including primary literature and curated collections of data. Original references are listed but not distinctly assigned to specific values or chemicals.	Manual data curation reported for several physical and chemical property data or endpoints. Normal melting and boiling point values for many compounds have been critically evaluated using expert-system software from NIST, ThermoData Engine (www.nist.gov/srd/nist103b.cfm). This software generates recommended values based on analysis of available data and uncertainties. Hard and electronic copies are available, highly interactive comprehensive scientific resource, containing over 700 tables in over 450 documents, regularly updated. Carefully reviewed by subject matter experts.
Hazardous Substances Data Bank (HSDB)	HSDB is a toxicology database providing information on human exposure, hazards, industrial hygiene, emergency handling procedures, environmental fate, regulatory requirements, nanomaterials, and related areas of chemical substances. It typically contains experimental physical and chemical property data sources from recognized, publicly available chemistry handbooks and indexes.	Assessed by the HSDB Scientific Review Panel. Data has been incorporated in PubChem.
OECD QSAR Toolbox	The OECD QSAR Toolbox is a software application that incorporates data and tools from various sources to identify and fill toxicological data gaps for the hazard assessment of chemical substances, including physical and chemical property information. It contains both experimental and predicted physical and chemical property data on the target chemical substance or analogues, as well as bibliographic citations.	There are 57 databases containing 2.5 million measured data points in the toolbox. There are 11 database inventories for substances without experimental data: Canada DSL, CosIng, EPA DSSTOX, ECHA PR, EINECS, HPVC OECD, METI Japan, NICNAS, REACH ECB, TSCA, U.S. HPV Challenge Program. The donated databases are incorporated into the Toolbox as they have been received with no quality assurance or peer review of data within the Toolbox.
Merck Index	The Merck Index is a comprehensive resource of chemistry information about chemical substances, drugs and biological molecules. EPA uses both the online and hard copy.	The Merck Index reports data as found in literature. Evaluates multiple sources of data/information and presents representative selections.

Source	Description of the Data/Information Contained within the Source	Summary of Curation and Quality Control Processes
	Primary sources are only provided for isolation, preparation or synthesis, patent information and structural studies; primary sources are not cited for physical and chemical property data.	Published by the Royal Society of Chemistry, curated by subject matter experts.
Reaxys	Reaxys provides experimentally derived chemistry data and information for chemical substances. It cites primary sources including journal articles, books, patents, reviews, conference proceedings, letters, reports, and handbooks.	Expert life scientists are involved in the evaluation of the information before posting it to the database. Chemistry journals, textbooks and patents are carefully selected for database inclusion. Manual indexing and data extraction are performed on the journals, textbooks and patents. Automated processes are used secondarily for content enrichment to chemistry-related periodicals.
STN/CAS	The STN/CAS database compiles scientific information on chemical substances related to their chemistry and related sciences, including both experimental and predicted property data and spectra. EPA has a subscription to the database. Bibliographic information could be obtained for a per chemical substance and time fee basis.	Indexes and summarizes articles from thousands of scientific journals, patents, conferences and other reputable sources of chemical information. Scientists collect and analyze published literature, extracting and verifying data that is included in the database.

E.2 Sources Used for the Gray Literature Search for the Fate, Engineering, Exposure, Environmental and Human Health Hazard Topic Areas

Table_Apx E-2. Sources Used for the Gray Literature Search for the Fate, Engineering, Exposure, Environmental, and Human Health Hazard Topic Areas

Source Organization	Source Tier	Source Coverage	Source Category	Source Type	Document Type
AICIS	II	AICIS, NICNAS	Assessment or Related Document	International Resources	Risk assessments

Source Organization	Source Tier	Source Coverage	Source Category	Source Type	Document Type
ATSDR	I	Publications	Technical Report	Other Resources	Occupational Exposure Values, Toxicological Profiles
CalEPA/OEHHA	I	OEHHA, CARB, Proposition 65, Publications	Database; Technical Report; Assessment or Related Document	Other U.S. agency Resources	Assessments, Datasets
ECHA	II	EU, REACH, Annexes XV, XVII, XIV, Dossiers	Assessment or Related Document	International Resources	EU risk assessments, Restriction reports, Chemical dossiers
eChemPortal	I	Encompasses these preferred resources: AICIS, OECD,[a] EPA, ECHA, HSDB,[a] ECOTOX, Environment Japan (J-CHECK), INCHEM (CCOHS & IPCS)	Database	International Resources	Risk assessments, Technical reports, Chemical dossiers, Datasets, QSAR Toolbox
ECOTOX	II	Third party publications	Database	Other U.S. agency Resources	Assessments, Technical Reports
Environment Canada	I	Federal Science Libraries Network; NRC Publications; NRC Digital Repository	Database; Assessment or Related Document	International Resources; Technical Reports	Risk assessments, CICADS, Toxic Substances List, Substances Search, State of the Science Reports
US EPA	I	IRIS, Generic Scenarios, AP-42, ECHO (DMR & TRI), BLS, USGS, Census Bureau, AQS, DfE[b], AEGL, NATA[b], NEI[b], Ambient Water Quality Criteria Documents, HPVIS, PPRTV[b], STORET and Water Quality Exchange (WQX), CDR (non-CBI & CBI), AMTIC Air Toxics Data, UCMRs, GLENDA, TNSSS[b], HAPs[b], CPDAT, Drinking Water Contaminant Human Health Effects[b] & CCL[b], Fish Tissue Studies, and SCDM	Database; Technical Report; Assessment or Related Document	US EPA Resources	Assessments, Guidance Documents, Databases, Statistical datasets

Source Organization	Source Tier	Source Coverage	Source Category	Source Type	Document Type
European Commission	II	IPCHeM, Publications	Assessment or Related Document	International Resources	Assessments; datasets
FDA	I	Guidance Documents (final drafts only); CEDI Database	Assessment or Related Document	Other U.S. agency Resources	Total Diet Study, RELs, Proposition 65, Technical Reports
Haz-Map	I	Database	Database	Other U.S. agency Resources	Chemical data
HSDB	II	NIH	Database	Other U.S. agency Resources	Chemical data
IARC	I	Book and Report Series & Non-Series Publications	Assessment or Related Document	International Resources	Monographs
J-CHECK	II	Environment Japan, NITE	Database; Assessment or Related Document	International Resources	Assessments, NITE database
Kirk-Othmer	I	Publications	Database	Other Resources	Encyclopedic data
CDC	I	NIEHS, CDC, NIOSH	Assessment or Related Document	Other U.S. agency Resources	NIEHS Tox Review, Publications, Survey Reports, HHEs, Guideline Documents, NHANES
NTP	I	NTP, OHAT, RoC	Assessment or Related Document	Other U.S. agency Resources	Monographs
OSHA	I	Occupational Chemical Database (PELs); Publications	Technical Report; Assessment or Related Document	Other U.S. agency Resources	PELs, Assessments
RIVM	I	Publications	Assessment or Related Document	International Resources	Risk assessments, Dietary intake, Criteria documents, Technical support documents

Source Organization	Source Tier	Source Coverage	Source Category	Source Type	Document Type
TERA	I	Publications	Assessment or Related Document	Other Resources	TERA Assessments
UNEP	I	Publications	Assessment or Related Document	International Resources	Risk profile, Stockholm Convention
ACGIH	I	Occupational exposure values, TLV/BEI	Technical Report	Other Resources	Occupational Exposure Values
CPSC	I	Publications	Assessment or Related Document	Other U.S. agency Resources	CHAP, Toxicity Reviews, Exposure/Risk Assessments
Environment Agency United Kingdom (UK)	I	Risk evaluations & PHE evaluations	Assessment or Related Document	International Resources	Environmental risk evaluation report, Risk assessments
ChemView	I	Publications	Database	U.S. EPA Resources	Hazard characterizations, Risk-based and hazard-based prioritization documents (for High Production Volume chemicals)

[a] Also searched for physical and chemical properties see Appendix E.1.
[b] Indicates resource is only checked for new submissions.

E.3 Sources Used for TSCA Submission Searches for All Discipline Areas

The sources in Table_Apx E-3 contain information submitted to EPA under various TSCA authorities, including TSCA sections 4, 5, 6, 8(d) and 8 (e), as well as FYI submissions.

Table_Apx E-3. Sources of Information Submitted to EPA under TSCA

Source Organization	Source Coverage	Source Category	Source Type	Document Type
TSCATS	Data submitted under multiple TSCA authorities maintained by contractor; data from any or all disciplines used in risk evaluations	Database	U.S. EPA Resources	Original guideline study reports and other data
ChemView	Substantial risk reports and test order data; data from any or all disciplines	Database	U.S. EPA Resources	Original guideline study reports and other data
EPA Chemical Information System	Data submitted under multiple TSCA authorities; data from any or all disciplines (confidential business information)	Database	U.S. EPA Resources	Original guideline study reports and other data
EPA 8e database	Data submitted under multiple TSCA authorities; data from any or all disciplines (confidential business information)	Database	U.S. EPA Resources	Original guideline study reports and other data

E.4 Search Terms Used for the Gray Literature Search for the Engineering Topic Area

Table_Apx E-4. Search Terms Used for the Gray Literature Search for the Engineering Topic Area

Chemical Full Name	Chemical CAS	Engineering-Specific Search Terms
p-Dichlorobenzene, 1,4-dichlorobenzene	106-46-7	"*p*-Dichlorobenzene", "manufactur*", "1,4 Dichlorobenzene", "formulat*", "CAS number 106-46-7", "process*", "production"
1,2-Dichloroethane, ethylene dichloride (EDC)	107-06-2	"1,2-Dichloroethane", "manufactur*", "12DCA", "formulat*", "CAS number 107-06-2", "process*", "Dichloroethane", "production"
trans-1,2-Dichloroethylene	156-60-5	"*trans*-1,2-dichloroethylene", "manufactur*", "*trans*-1,2-DCE", "formulat*", "1,2-dichloroethene", "process*", "1,2-dichloroethylene", "production", "CAS number 156-60-5"
o-Dichlorobenzene, 1,2-dichlorobenzene, orthodichlorobenzene (ODCB)	95-50-1	"o-Dichlorobenzene", "manufactur*", "1,2 Dichlorobenzene", "formulat*", "CAS number 95-50-1", "process*", "production"

Chemical Full Name	Chemical CAS	Engineering-Specific Search Terms
1,1,2-Trichloroethane (TCA)	79-00-5	"1,1,2-Trichloroethane", "1,1,2-TCA", "vinyl trichloride", "beta-trichloroethane", "CAS number 79-00-5", "manufactur*", "formulat*", "process*", "production"
1,2-Dichloropropane	78-87-5	"Dichloropropane", "DCP", "Propylene dichloride", "CAS number 78-87-5", "manufactur*", "formulat*", "process*", "production"
1,1-Dichloroethane	75-34-3	"1,1-Dichloroethane", "11DCA", "CAS number 75-34-3", "Dichloroethane", "manufactur*", "formulat*", "process*", "production"
Dibutyl phthalate (DBP) (1,2-Benzene- dicarboxylic acid, 1,2- dibutyl ester)	84-74-2	"Dibutyl Phthalate", "DBP", "Di-n-butyl phthalate", "Dibutylphthalate", "CASRN 84-74-2", "manufactur*", "formulat*", "process*", "production"
Butyl benzyl phthalate (BBP) – 1,2-Benzene-dicarboxylic acid, 1- butyl 2(phenylmethyl) ester	85-68-7	"BBP", "CAS number 85-68-7", "Butyl benzyl phthalate", "1,2-benzenedicarboxylic acid", "manufactur*", "formulat*", "process*", "production"
Di-ethylhexyl phthalate (DEHP) – (1,2-Benzene-dicarboxylic acid, 1,2-bis(2-ethylhexyl) ester)	117-81-7	"DEHP", "manufactur*", "CAS number 117-81-7", "formulat*", "1,2-Benzene- dicarboxylic acid*", "process*", "1,2- bis(2-ethylhexyl) ester", "production"
Di-isobutyl phthalate (DIBP) – (1,2-Benzene-dicarboxylic acid, 1,2- bis-(2methylpropyl) ester)	84-69-5	"Diisobutyl phthalate", "manufactur*", "DIBP", "formulat*", "Di(isobutyl) 1,2-benzenedicarboxylate", "process*", "Bis(2-methylpropyl) benzene-1,2-dicarboxylate", "production", "CAS number 84-69-5"
Dicyclohexyl phthalate	84-61-7	"DCHP", "CAS number 84-61-7", "Dicyclohexyl Phthalate*", "manufactur*", "formulat*", "process*", "production"
4,4'-(1-Methylethylidene)bis[2, 6-dibromophenol] (TBBPA), Tetrabromobisphenol A	79-94-7	"Tetrabromobisphenol A", "manufactur*", "TBBPA", "formulat*", "TBBP-A", "process*", "TBBA", "production", "CAS number 79-94-7"
Tris(2-chloroethyl) phosphate (TCEP)	115-96-8	"tris(2-chloroethyl) phosphate", "manufactur*", "TCEP", "formulat*", "2-chloroethanol phosphate", "process*", "tris(2-chloroethyl)orthophosphate", "production", "phosphate ester", "CAS number 115-96-8"
Phosphoric acid, triphenyl ester (TPP), Triphenyl phosphate (TPhP)	115-86-6	"Triphenyl Ester Phosphoric Acid", "manufactur*", "TPP", "formulat*", "Triphenyl phosphate", "process*", "phosphate ester", "production", "CAS number 115-86-6"
Ethylene dibromide (EDB), 1,2-dibromoethane	106-93-4	"Ethylene Dibromide", "CAS number 106-93-4", "1,2-Dibromoethane", "manufactur*", "Dibromoethanee", "formulat*", "Ethylenedibromide", "process*", "EDB", "production"
1,3-Butadiene	106-99-0	"1,3-Butadiene", "manufactur*", "Buta-1,3-diene", "formulat*", "Divinyl, process*", "Vinylethylene", "production", "CAS number 106-99-0"
1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (HHCB),	1222-05-5	"HHCB", "CAS number 1222-05-5", "1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta*", "Galaxolide", "manufactur*", "formulat*", "process*", "production"

Chemical Full Name	Chemical CAS	Engineering-Specific Search Terms
Galaxolide, pearlide, astrolide, Musk 50, Polarlide		
Formaldehyde, methanal	50-00-0	"Formaldehyde", "CAS number 50-00-0", "production", "manufactur*", "formulat*", "process*"
Phthalic anhydride	85-44-9	"phthalic anhydride", "manufactur*", "2-Benzofuran-1,3-dione", "formulat*", "Isobenzofuran-1,3-dione", "process*", "PAN", "production", "Benzene-1,2-Dicarbonic Acid Anhydride", "CAS number 85-44-9"

E.5 Search Terms Used for the Gray Literature Search for the Physical and Chemical Property, Fate, Exposure, Environmental, and Human Health Hazard Topic Areas

Table_Apx E-5. Search Terms Used for the Gray Literature Search

Chemical Full Name	Chemical CAS	All Disciplines Search Terms
p-Dichlorobenzene, 1,4-dichlorobenzene	106-46-7	"106-46-7", "*p*-Dichlorobenzene", "1,4-Dichlorobenzene"
1,2-Dichloroethane, ethylene dichloride (EDC)	107-06-2	"107-06-2", "1,2-Dichloroethane", "1,2-ethylene dichloride", "ethylene chloride", "glycol dichloride"
trans-1,2-Dichloroethylene	156-60-5	"156-60-5", "*trans*-1,2- Dichloroethylene", "€-1,2-Dichloroethylene", "€-1,2-Dichloroethene"
o-Dichlorobenzene, 1,2-dichlorobenzene, orthodichlorobenzene (ODCB)	95-50-1	"95-50-1", "*o*-Dichlorobenzene", "1,2-Dichlorobenzene"
1,1,2-Trichloroethane (TCA)	79-00-5	"79-00-5", "1,1,2-Trichloroethane"
1,2-Dichloropropane	78-87-5	"78-87-5", "1,2-Dichloropropane", "propylene dichloride"
1,1-Dichloroethane	75-34-3	"75-34-3", "1,1-Dichloroethane"
Dibutyl phthalate (DBP) (1,2-Benzene- dicarboxylic acid, 1,2- dibutyl ester)	84-74-2	"84-74-2", "Dibutyl phthalate", "1,2-Benzene- dicarboxylic acid, 1,2-dibutyl ester", "Dibutyl benzene-1,2-dicarboxylate", "1,2-Benzenedicarboxylic acid, dibutyl ester", "Di-n-butylorthophthalate"
Butyl benzyl phthalate (BBP) – 1,2-Benzene-dicarboxylic acid, 1- butyl 2(phenylmethyl) ester	85-68-7	"85-68-7", "Butyl benzyl phthalate", "1,2-Benzene- dicarboxylic acid, 1-butyl 2(phenylmethyl) ester", "Benzyl butyl phthalate", "Benzyl butyl benzene-1,2-dicarboxylate", "1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester", "1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester"
Di-ethylhexyl phthalate (DEHP) – (1,2-Benzene-dicarboxylic acid, 1,2-bis(2-ethylhexyl) ester)	117-81-7	"117-81-7", "Di-ethylhexyl phthalate", "1,2-Benzene- dicarboxylic acid, 1,2- bis(2-ethylhexyl) este", "Di(2-ethylhexyl) phthalate", "Bis(2-ethylhexyl) benzene-1,2-dicarboxylate", "di(alpha-Ethylhexyl) phthalate", "2-Ethylhexyl phthalate", "Di-(2-ethylhexyl) phthalate"

Chemical Full Name	Chemical CAS	All Disciplines Search Terms
Di-isobutyl phthalate (DIBP) – (1,2-Benzene-dicarboxylic acid, 1,2- bis-(2methylpropyl) ester)	84-69-5	“84-69-5”, “Di-isobutyl phthalate”, “1,2-Benzene- dicarboxylic acid, 1,2-bis-(2methylpropyl) este”, “Bis(2-methylpropyl) benzene-1,2-dicarboxylate”, “di-l-butyl phthalate”
Dicyclohexyl phthalate	84-61-7	“84-61-7”, “Dicyclohexyl phthalate”, “1,2-Benzenedicarboxylic acid, dicyclohexyl ester”, “Dicyclohexyl benzene-1,2-dicarboxylate”, “1,2-Benzenedicarboxylic acid, dicyclohexyl ester”
4,4’-(1-Methylethylidene)bis[2, 6-dibromophenol] (TBBPA), Tetrabromobisphenol A	79-94-7	“79-94-7”, “4,4’-(1-Methylethylidene)bis[2, 6-dibromophenol]”, “3,3’,5,5’-Tetrabromobisphenol A”, “4,4’-(Propane-2,2-diyl)bis(2,6-dibromophenol)”
Tris(2-chloroethyl) phosphate (TCEP)	115-96-8	“115-96-8”, “Tris(2-chloroethyl) phosphate”, “Ethanol, 2-chloro-, phosphate (3:1)”
Phosphoric acid, triphenyl ester (TPP), Triphenyl phosphate (TPhP)	115-86-6	“115-86-6”, “Phosphoric acid, triphenyl ester”, “Triphenyl phosphate”
Ethylene dibromide (EDB), 1,2-dibromoethane	106-93-4	“106-93-4”, “Ethylene dibromide”, “1,2-Dibromoethane”
1,3-Butadiene	106-99-0	“106-99-0”, “1,3-Butadiene”
1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (HHCB), Galaxolide, pearlide, astrolide, Musk 50, Polarlide	1222-05-5	“1222-05-5”, “1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran”, “4,6,6,7,8,8-Hexamethyl-1,3,4,6,7,8-hexahydroindeno[5,6-c]pyran”, “Indeno[5,6-c]pyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-“
Formaldehyde, methanal	50-00-0	“50-00-0”, “Formaldehyde”
Phthalic anhydride	85-44-9	“85-44-9”, “Phthalic anhydride”, “2-Benzofuran-1,3-dione”, “1,3-Isobenzofurandione”

Appendix F CHOICE OF SOFTWARE FOR HAZARD TITLE AND ABSTRACT SCREENING

For the 2019 high priority substances, MRREs, and asbestos, EPA performed title and abstract screening on the filtered references using either DistillerSR or SWIFT Active-Screener (see Table_Apx F-1) according to the screening criteria and environmental and human health data needs. Projects with larger numbers of citations were screened in SWIFT Active-Screener to take advantage of automatic screening resulting from iterative machine learning.

Table_Apx F-1. Platforms Used to Screen Title and Abstracts for Chemicals and Chemical Groups

Project	Title and Abstract Screening Platform
Dichlorobenzenes[a]	SWIFT Active-Screener
Triphenyl phosphate	DistillerSR
Phthalic anhydride/phthalic acid	SWIFT Active-Screener
Chlorinated solvents[b]	SWIFT Active-Screener
Tris(2-chloroethyl) phosphate	DistillerSR
4,4'-(1-Methylethylidene)bis[2,6-dibromophenol]	DistillerSR
1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran	DistillerSR
Ethylene dibromide	DistillerSR
Phthalates[c]	SWIFT Active-Screener
1,3-Butadiene	SWIFT Active-Screener
Formaldehyde	SWIFT Active-Screener
DIDP	DistillerSR
DINP	DistillerSR
D4	DistillerSR
Asbestos Part 2	SWIFT Active-Screener

[a] The dichlorobenzenes include *o*-dichlorobenzene and *p*-dichlorobenzene.

[b] The chlorinated solvents includes five chemicals (1,1-dichloroethane; 1,2-dichloroethane; 1,2-dichloropropane; *trans*-1,2-dichloroethylene; and 1,1,2-trichloroethane).

[c] The phthalates includes seven chemicals (butyl benzyl phthalate; diethylhexyl phthalate; di-isobutyl phthalate; dicyclohexyl phthalate; diisodecyl phthalate; dibutyl phthalate; and diisononyl phthalate)

Appendix G SPECIFIC FILTERING INFORMATION FOR SELECTED DISCIPLINES

This appendix presents additional details on the categorization and reference prioritization processes already available in SWIFT-Review or developed for use in SWIFT-Review for multiple disciplines.

G.1 Search Strings Used to Identify Physical and Chemical Property Literature in SWIFT-Review

The search string used for physical and chemical properties in SWIFT-Review was developed by EPA's ORD in collaboration with Sciome and is presented in Table_Apx G-1.

Table_Apx G-1. SWIFT-Review Search String for Identifying Peer-Reviewed Physical and Chemical Property References

tiab: ((“physical form” OR “physical state” OR “physical chemistry” OR “physical properties” AND (“solid” OR “liquid” OR “gaseous state” OR “crystal structure” OR “crystalline structure” OR “morphology” OR “particle size” OR “color” OR “scent” OR “odor” OR “odour” OR “smell”)) OR “melting point” OR “boiling point” OR “density” OR “vapor pressure” OR “vapour pressure” OR “vapor density” OR “vapour density” OR “water solubility” OR “aqueous solubility” OR “aqueous saturation point” OR “water saturation point” OR “octanol:water partition coefficient” OR “octanol-water partition coefficient” OR “octanol/water partition coefficient” OR “octanol water partition coefficient” OR “Kow” OR “Henry's Law constant” OR “heat of Henry” OR “Kaw” OR “air water partition” OR “pKa” OR “acid dissociation constant” OR “dissociation constant” OR “flash point” OR “autoflammability” OR “viscosity” OR “enthalpy of phase change” OR “enthalpy of vaporization” OR “heat of vaporization” OR “photoabsorption” OR “absorption spectra” OR “absorption spectrum” OR “transition state” OR “visible absorption” OR “UV-Vis” OR “zeta potential” OR “particle size” OR “particle surface area” OR “individual fiber diameter” OR “average fiber outer diameter” OR “particle dimension” OR “decomposition temperature” OR “KOA” OR “K(OA)” OR “log KOA” OR “octanol-air partition coefficient” OR “1-octanol-air partition coefficient” OR “octanol/air partition coefficient” OR “n-octanol/air partition coefficient” OR “Kd” OR “association constant” OR “λmax” OR “absorption wavelength” OR “extinction coefficient” OR “molar absorptivity” OR “absorption maxima” OR “ε” OR “uv + vis” OR “UV/Vis”)

G.2 Search Strings Used to Identify Environmental Fate Literature in SWIFT-Review

The search string used for environmental fate properties in SWIFT-Review was developed by EPA's ORD in collaboration with Sciome and is presented in Table_Apx G-2.

Table_Apx G-2. SWIFT-Review Search String for Identifying Peer-Reviewed Fate References

tiab: (“bioaccumulation” OR “bioconcentration” OR “biodegradability” OR “biodegradation” OR “bioisomerization” OR “biomagnification” OR “biotransformation” OR “dechlorination” OR “degradation” OR “dehalogenation” OR “fate” OR “food web” OR “groundwater” OR “hydrolysis” OR “landfill” OR “persistence” OR “photodegradation” OR “photolysis” OR “phototransformation” OR “sediment” OR “sludge” OR “soil” OR “trophic magnification” OR “volatilization” OR “waste” OR “wastewater” OR ((“concentration” OR “concentrations” OR “evaporation rates” OR “reaction” OR “sorption”) AND (“aquifer” OR “atmospheric” OR “tropospheric” OR “water”)) OR ((“destroy” OR “destroyed” OR “destroys” OR “destruction” OR “removal” OR “remove” OR “removed” OR “removes”) AND (“combust” OR “combusted” OR “combustion” OR “incinerate” OR “incinerated” OR “incineration” OR “incinerator” OR “incinerators”)))

G.3 Development of Search Strategies Used to Identify Engineering Literature in SWIFT-Review

EPA uses the SWIFT-Review’s automated document prioritization method to identify potentially relevant references for the engineering discipline from the overall search results of peer-reviewed literature. EPA developed the search strategies for this discipline using the steps below.

G.3.1 Step 1: Training the SWIFT-Review by Selecting Positive and Negative Seed References

EPA used the engineering literature pool for the first 10 TSCA risk evaluations to identify positive seed references. The positive seed references are a representative subset of peer-reviewed references that supported technical aspects of the engineering assessments for the TSCA risk evaluations of 1-bromopropane, asbestos, cyclic aliphatic bromide cluster (HBCD), methylene chloride, N-methylpyrrolidone (NMP), perchloroethylene, and trichloroethylene[20] (Table_Apx G-3). A total of 50 references were selected as positive seeds (see Appendix G.5.1 for a list of the studies used as seeds). Since these references were used in a risk evaluation, EPA assumed that the aggregated text in the titles and abstracts would make reasonable engineering-relevant positive seed references for the next TSCA risk evaluations. The bibliographic information of these references was already in EPA’s HERO database and thus, the engineering assessors provided the HERO IDs to facilitate loading of the positive seed references into SWIFT-Review.

Table_Apx G-3. Number of References from the First 10 Risk Evaluations that Were Selected as Positive Engineering Seeds

Chemical	Number of Positive Seeds
1-Bromopropane	7
Asbestos	8
Cyclic aliphatic bromide cluster	6
Methylene chloride	9
n-methylpyrrolidone	5
Trichloroethylene	2

[20] Note, not all of the first 10 TSCA risk evaluations utilized peer-reviewed references for the engineering assessment.

Chemical	Number of Positive Seeds
Perchloroethylene	6
Other (covers multiple chemicals)	7

These seeds were also manually classified into one of three engineering data types: general facility estimate, occupational exposure, and environmental release (or a combination of the three). Table_Apx G-4 shows the number of positive seed references given by the engineering data type. Note most seed references contain information related to occupational exposure. Based on EPA's experience, general facility estimates, and environmental release information often come from gray literature and are not commonly available from peer-reviewed sources.

Table_Apx G-4. Number of Positive Seeds by Engineering Data Element

Engineering Data Type	Number of Positive Seeds
General facility estimate	1
Occupational exposure	40
Environmental release	4
Multiple	5

SWIFT-Review requires at least 10 negative seeds in order to begin classification of a literature pool. In addition, the number of negative seeds should be similar to that of positive seeds. For engineering, the number of negative seeds was determined to be 50 (same as the number of positive seeds) to provide an unbiased training set for SWIFT-Review.

The literature pool for each chemical from the overall search of peer-reviewed literature was loaded into SWIFT-Review to facilitate review of titles, abstract, and journal titles, as well as ease of selecting and exporting the negative seed references. For each chemical, a reviewer manually examined the title and abstract in SWIFT-Review and selected 50 references that are irrelevant to engineering as negative seeds.

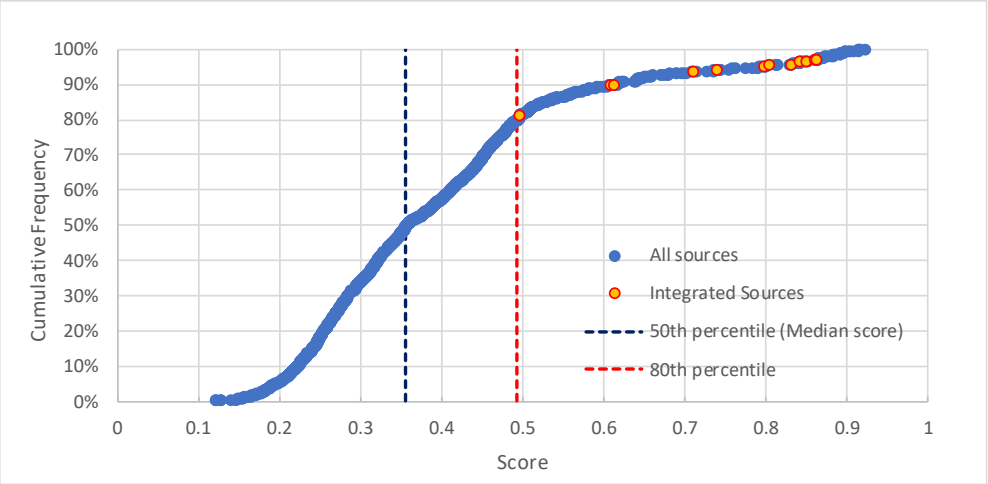
G.3.2 Step 2: Assessing the Performance of the Reference Prioritization Method

To ensure the selected positive seeds could accurately capture and prioritize engineering-relevant information, several test validation runs were performed to score a known set of literature references using these positive seeds within SWIFT-Review. Specifically, these seeds were used to score all references tagged for 1,4-dioxane, HBCD, 1-BP, NMP, and methylene chloride in HERO. Then, the reference scores were evaluated to ensure that the "integrated sources," or references that supported technical aspects of the engineering assessment within the TSCA risk evaluations received a higher score in SWIFT-Review relative to the rest of the references that were not integrated into the risk evaluation.

A total of five test validation runs were performed. below provide results from the 1-BP validation run as an example. The figure shows the cumulative frequency of the scores among all references in each dataset, including scores for the seed references used. The 50th percentile (median) and 80th percentile scores of the dataset are shown as reference value. The 50th percentile represents the group of references

(*i.e.*, the upper 50 percent of total references) that are ranked by the SWIFT-Review to be above a certain score obtained using the SWIFT-Review prioritization method (see Figure_Apx G-1). Next, the 80th percentile represents the group of references that are ranked above the threshold score value of the 80th percentile (*i.e.*, top 20 percent references), which are considered for the assessment. From all validation runs, it was observed that

1. With the exceptions noted below (see bullet on dioxane), all "integrated" peer-reviewed references score above the 80th percentile value of the respective dataset;
2. The positive seeds captured occupational exposure information well. This is expected as most positive seeds contain information relevant to occupational exposure. For engineering, peer-reviewed literature typically offer little information related to general facility estimate and environmental release; and
3. The 1,4-dioxane dataset was found to be a poor test example because the only integrated, peer-reviewed sources were two journal articles that contain process description specific to dioxane conditions of use. These two articles did not receive high scores in SWIFT-Review and would not serve as good seeds, as seeds should cover data elements that are chemical-agnostic.



Figure_Apx G-1. SWIFT-Review Scoring and Seed Validation Using 1-BP Dataset

Note the test datasets used for validation contain all references tagged in HERO. Therefore, some high-scoring references shown in Figure_Apx G-1 above may come from gray literature, because the datasets do not exclusively reflect peer-reviewed references.

Once the initial search of peer-reviewed sources has been completed (Section 4.1) for engineering, EPA conducts the following process in SWIFT-Review:

1. Upload the search per chemical from the HERO Database
2. Upload the 50 engineering positive seeds and mark has *Training item* and *Included*
3. Select the 50 negatives seeds by conducting a title and abstract screening directly in SWIFT-Review based on the inclusion/exclusion criteria of the RESO statement and marking them as *Training item*
4. Select the *Prioritize* option
5. Select the top 20 percent sources (*e.g.*, 1,3-butadiene initial peer-reviewed search was 15,324 sources, the 20 percent of 15,324 is 3,065)
6. Right-click and select *Send to Active Screener*
7. Add new project and create a name for the project (*e.g.*, 1,3-Butadiene_Eng)

To set up SWIFT Active-Screener, EPA conducted the following process:

1. Select the new project created
2. Add the following additional questions to the form:
    - Inclusion/Exclusion Tags:
        - Yes
        - No
        - Unsure
        - Supplemental
    - If included, what type of data in the reference?
        - General Facility Estimate
        - Occupational Exposure
        - Environmental Releases
3. Comments
4. Change the SWIFT Active-Screener project to have two screeners per source
5. Add screeners to the project
6. Upload the 50 positive seeds
7. Notify screener project is ready for title and abstract (TIAB) screening

Once TIAB screening starts, conflicts, if any, are resolved on a weekly basis by a third independent screener. TIAB screening is completed when 95 percent, in some cases 100 percent (see Table_Apx G-5), of the included references were screened, and there is no conflict. After TIAB is completed, an export of the user answer spreadsheet is generated and categorized based on the TIAB tags. Lastly, a request for PDF for all sources that were tag include/include and include/unsure is made, and once PDFs are available the source is uploaded in DistillerSR to conduct full-text screening.

Table_Apx G-5 provides a breakdown of the number of seeds per chemical used in SWIFT-Review, number of screeners during SWIFT Active-Screener, and percent of screened references during SWIFT Active-Screener for engineering. The first two projects done in SWIFT-Review and SWIFT Active-Screener have a lower number of seeds and just one screener. The other projects used 50 seeds (Table_Apx F-1). Projects with small numbers of references were 100 percent screened in SWIFT Active-Screener.

Table_Apx G-5. Number of Seeds, Screeners, and Percent Screened for Engineering

Project	Number of Seeds Used in SWIFT-Review	Number of Screeners for Tittle/Abstract Screening in SWIFT Active-Screener	% of Title/Abstract Screening Performed
o-Dichlorobenzene	30	1	95
TPP/TPHP	30	1	95
p-Dichlorobenzene	50	2	95
TBBPA	50	2	95
TCEP	50	2	100
Ethylene dibromide	50	2	95
HHCB	50	2	95

Project	Number of Seeds Used in SWIFT-Review	Number of Screeners for Tittle/Abstract Screening in SWIFT Active-Screener	% of Title/Abstract Screening Performed
Formaldehyde	50	2	95
1,3-Butadiene	50	2	95
1,1-dichloroethane	50	2	95
1,2-dichloroethane	50	2	95
trans-1,2-dicholoroethane	50	2	95
1,1,2-trichloroethane	50	2	95
1,2-dichlopropane	50	2	100
Phthalic anhydride/phthalic acid	50	2	95
DBP	50	2	95
BBP	50	2	95
DEHP	50	2	95
DIBP	50	2	95
DCHP	50	2	100
DIDP	50	2	100
DINP	50	2	100
D4	50	2	100
Asbestos Part 2	50	2	95

EPA performed various SWIFT-Review re-runs (see Table_Apx G-6) in some projects due to sources being available at a different time. Each additional SWIFT-Review run was done using the previous project for that chemical, adding the new sources, and following the SWIFT-Review process described in Section 4.2.4 of this document. Once SWIFT-Review prioritized the sources, a comparison was made to determine which sources had not gone through title and abstract screening, and an additional SWIFT Active-Screener project was made (see Table_Apx G-6).

Table_Apx G-6. SWIFT-Review Reruns and Additional SWIFT Active-Screener Projects

Project	Amount of SWIFT-Review Reruns	Amount of Swift Active-Screener Projects
TPP/TPHP	3	3
Phthalic anhydride/phthalic acid	2	2
DIDP	4	4
DINP	4	4
D4	5	5

G.4 Development of Search Strategies Used to Identify Exposure Literature in SWIFT-Review

EPA uses the SWIFT-Review's automated document prioritization method to identify potentially relevant references for the exposure discipline from the overall search results of peer-reviewed literature. EPA developed the search strategies for this discipline using the steps below.

G.4.1 Step 1: Training the Machine by Selecting Positive and Negative Seed References

For chemical substance exposure assessments, EPA uses SWIFT-Review to prioritize literature for further review. SWIFT-Review has keywords available that can be used to automatically categorize studies. However, these tags are very broad and do not suit the specific needs of the TSCA assessment. Instead, positive and negative seed studies are selected and used to build a classification model in SWIFT-Review. This model is then applied to the unclassified literature to generate a classification score for each reference; scores above a threshold value are then prioritized for further review.

To facilitate generation of the classification model, EPA determines positive seed studies (exposure-relevant) and negative seed studies (non-exposure-relevant). The positive seeds are identified using the exposure literature pool for EPA's first 10 TSCA risk evaluations, while the negative seeds are identified from a subset of literature from following 20 TSCA risk evaluations. These steps are described further below.

The positive seed references are identified in Appendix G.5.2 and were loaded into SWIFT-Review. These were references that supported technical aspects of the exposure assessments for the TSCA risk evaluations of 1-bromopropane, asbestos, cyclic aliphatic bromide cluster (HBCD), methylene chloride, N-methylpyrrolidone (NMP), perchloroethylene and trichloroethylene (Table_Apx G-7). Since these references were used in a risk evaluation, EPA assumed that the aggregated text in the titles and abstracts would make reasonable exposure-relevant positive seed references for the next TSCA risk evaluations. The large number of studies from the cyclic aliphatic bromide cluster (HBCD) reflects the nature of that database, which include a relatively large number of exposure-relevant references.

Table_Apx G-7. Number of Positive Seed References from the Exposure Literature Integrated from the First TSCA Risk Evaluations

Chemical Substance	Number of Positive Seeds
1-Bromopropane (1-BP)	11
Asbestos	7
Cyclic aliphatic bromide cluster (HBCD)	378
Methylene chloride	21
N-methylpyrrolidone (NMP)	1
Perchloroethylene	72
Trichloroethylene	12
Total unique references	481

Some references included more than one chemical; there were 481 unique references. These seeds were also manually classified into one of four exposure data types: consumer, human biomonitoring, environmental release, and dietary. Table_Apx G-8 shows the number of positive seed references given by the exposure data type.

Table_Apx G-8. Number of Positive Seed References Categorized by Exposure Data Type

Exposure Data Type	Number of Positive Seeds
Consumer	108
Dietary	36
Environmental release	288
Human biomonitoring	49

SWIFT-Review requires at least 10 negative seeds in order to begin classification of a literature pool. However, considering that the number of positive seeds was 481, it is unlikely that a basic machine learning model, like that implemented by SWIFT-Review, would be able to properly discern positive references (exposure-relevant) from negative reference (non-exposure-relevant) with such a biased training set. For this reason, EPA identified additional negative seed references from the search results of the peer-reviewed literature supporting the new TSCA risk evaluations for di-isobutyl-phthalate, di-isodecyl-phthalate, 1,2-dichloroethane, *o*-dichlorobenzene, 1,1,2 trichloroethane, and tris-2-chloroethyl-phosphate. These chemicals were selected because their literature pools were small enough to quickly export from HERO into SWIFT-Review but large enough to cover several decades of literature.

The literature pool for each chemical was loaded into SWIFT-Review to facilitate review of titles, abstract, and journal titles, as well as ease of selecting and exporting the correct negative seed references. Once the references were loaded, the exposure keywords in SWIFT-Review were used to automatically tag each reference to the built-in SWIFT-Review exposure tags; as discussed above, these

tags identify references that were unlikely to be on-topic to exposure. Only references that had no tag applied were further reviewed as candidate negative seeds.

For each literature pool, a reviewer examined the title, abstract, and journal titles of references in SWIFT-Review and selected at least 30, but not more than 100, references as negative seeds. References were selected by sorting the chemical pool first by descending year and then by alphabetical title. For the most recent years (2009 to 2019), the first five off-topic references within each year were selected; for years prior to 2009, the first reference was selected. If not enough off-topic references could be found within a given year, the balance was made up in subsequent years. Selecting references scattered throughout various years ensures inclusion of old terminology that may occur in literature pool classification. These seeds were determined to be off-topic to exposure as they contained information on purely analytical/organic synthesis/electrochemistry methodology development, structure analysis (either experimental or theoretical) of metallic-organic frameworks or disorder carbon networks, or bioremediation studies. Table_Apx G-9 provides the number of negative seeds selected from the six literature pools.

Table_Apx G-9. Number of Negative Seed References for the Exposure Topic Area

Chemical	Number of Negative Seeds
Di-isobutyl-phthalate	100
Di-isodecyl-phthalate	40
1,2-dichloroethane	100
o-dichlorobenzene	100
Trichloroethane	100
Tris-2-chloroethyl-phosphate	34

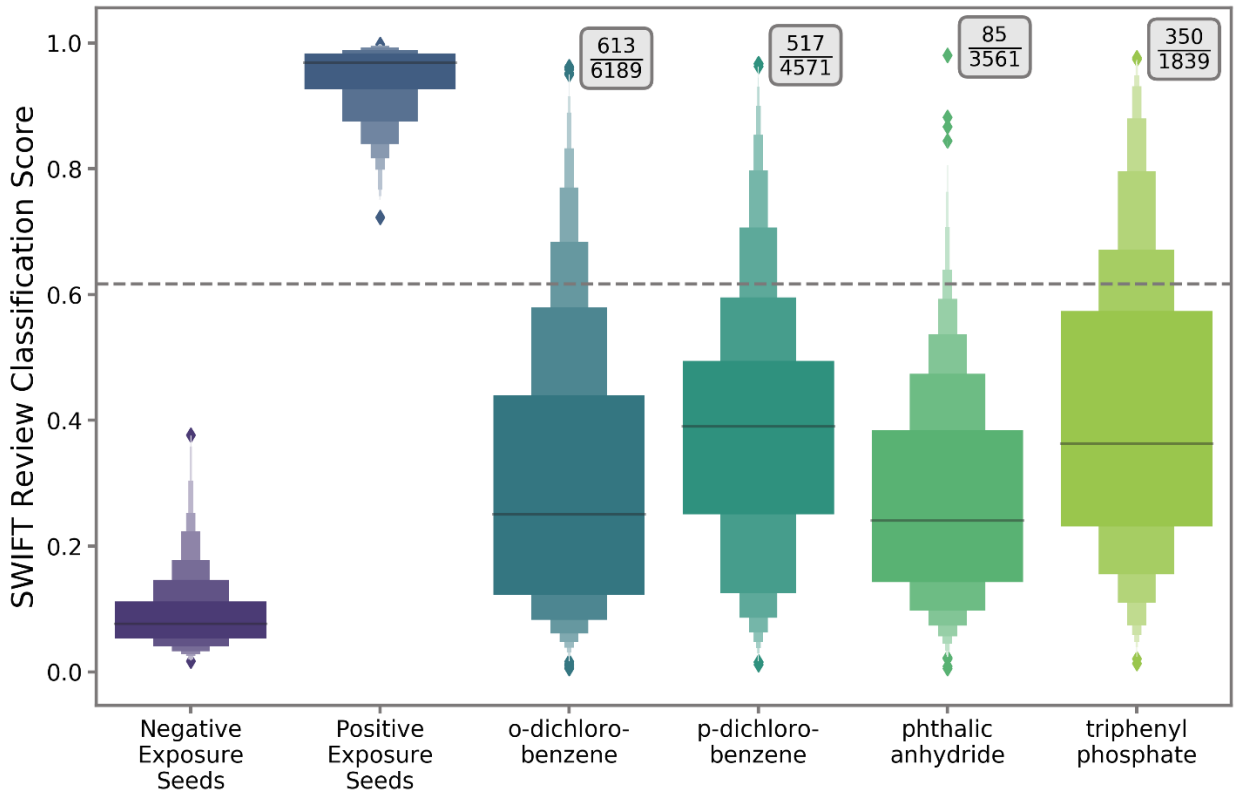
The positive and negative seeds were used to generate the statistical classification model in SWIFT-Review. Each reference was assigned a classification score based on the model. Any reference with a score above a given threshold value was prioritized for further review for the exposure discipline. One proposed method of determining the cut-off threshold is to look at the ranking of the positive reference seeds and to set a threshold value that captures the majority of the positive seeds, thus minimizing "false negatives." For the exposure screening, the threshold was set using the formula:

$$\text{Threshold} = (\min[\text{positive seed score}]) - 2 \times \text{std}(\text{positive seed score}).$$

The threshold is based on both the minimum positive seed score and the overall spread in the scores. Incorporating the spread (the subtraction of two standard deviations from the minimum score) will ensure that any potentially low-scoring references that may have been misclassified by SWIFT-Review will still proceed through to the next step in the workflow.

To determine the threshold, the methods were applied to four pilot chemicals (*o*-dichlorobenzene, *p*-dichlorobenzene, phthalic anhydride, and triphenyl phosphate). The results of the Seeded Ranking Classification step for these chemicals are shown in Figure_Apx G-2 , and the scores of the negative and positive exposure seeds are included for reference. The gray dotted line indicates the selected threshold value of 0.62, and the annotations to each chemical's distribution show the number of references that would be carried through to the active machine learning step over the total number of references in the

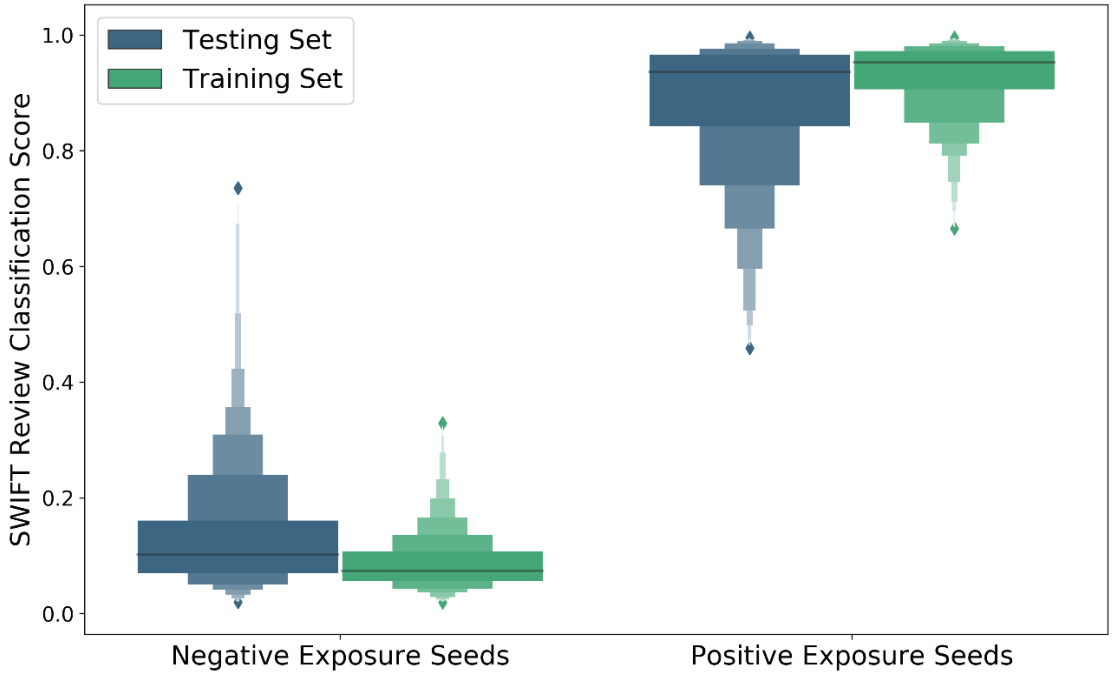
pool. This threshold ranges from 2.4 percent of the literature pool (phthalic anhydride) to 19.0 percent (triphenyl-phosphate).



Figure_Apx G-2. SWIFT-Review Classification Scores for the Six Chemicals Whose Literature Pools Were Used to Identify Negative Exposure Seeds

G.4.2 Step 2: Assessing the Performance of the Reference Prioritization Method

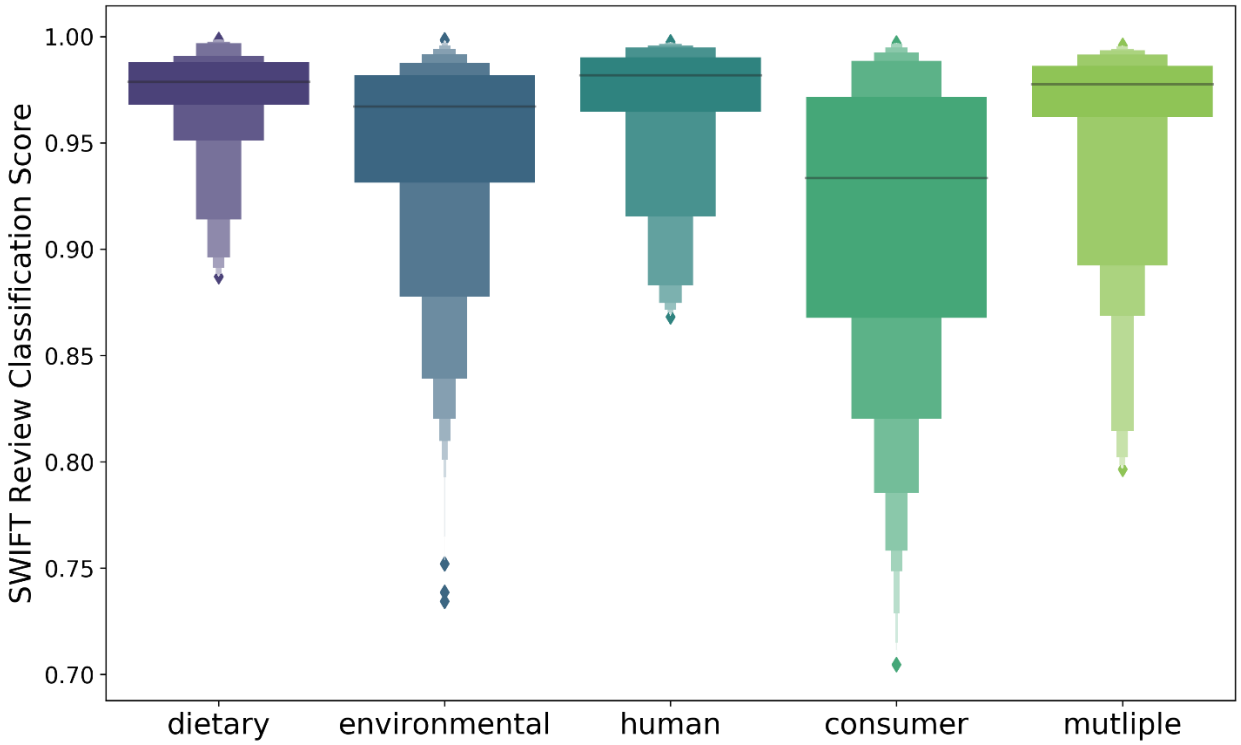
In order to determine how well SWIFT-Review performed the classification of on-topic and off-topic references for the exposure discipline, EPA performed a 5-fold cross validation test of the positive and negatives seed references. The test requires splitting the positive and negative seed references into five groups, or folds, with a relatively equally number of positive and negative references in each fold. SWIFT-Review classification begins by selecting one-fold to use as a test set and then using the remaining four folds as the training set. This process is carried out in a total of five iterations, with each fold serving as the test set in one of the iterations.



Figure_Apx G-3. Distribution of SWIFT-Review Classification Scores for the 5-fold Cross Validation Procedure

Similar to a box-and-whisker plot, Figure_Apx G-3 plots the distribution of classification scores for the positive or negative seeds serving as the testing or training sets during the cross validation test. The width and color of the box is proportional to the number of references within the box (*i.e.*, the darker and wider a box is, the more references it has). References were shown as points in the plot when their scores fell above the highest bin or below the lowest bin. To evaluate the results of the 5-fold cross validation test, the spread of scores for the positive seeds relative to the negative seeds in both the training and test sets were compared. As expected, the positive seeds cluster toward higher classification scores while the negative seeds cluster toward lower classification scores. In the training set, the scores for the positive and negative seeds do not overlap, indicating the statistical model was able to sufficiently discern the keywords that separate the positive and negative seed studies. When this model is applied to the test set, some negative seeds were assigned a relatively high classification score while some positive seeds were assigned a relatively low classification score. This overlap in scores denotes the level of misclassification in the test set. However, Figure_Apx G-3 indicates that while there is some overlap, the majority of the test set references are in the non-overlapping portions and misclassification is relatively minor. As with all machine learning methods, the model is only as good as the training data supplied to the model and some misclassification is inevitable.

As an additional evaluation of the classification methods, the classification scores for the positive seeds across the different exposure data types were compared. Distributions of classification scores of the positive exposure seeds were plotted by their data type in Figure_Apx G-4. Those references that contained relevant information on multiple exposure types were grouped together into a “multiple” category in the figure. In an unbiased model, the spread of scores across all the different data types should be similar.



Figure_Apx G-4. SWIFT-Review Classification Score for the Positive Exposure Seeds Categorized by Exposure Data Type

Figure_Apx G-4 shows that the majority of positive seed references had overlapping SWIFT-Review classification scores across the various exposure data types; in addition, the positive seeds are all above the threshold value of 0.62 used for further classification. The consumer data type has the lowest minimum scores and the lowest median value; however, the scores for the majority of the seeds overlap with the seeds in the other data types, suggesting limited bias for the consumer exposure data type relative to the other types. It also suggests that inclusion of the numerous HBCD positive seed studies, which cover the consumer data type well, did not introduce significant bias but instead help ensure coverage of this more nuanced data type.

G.5 Seed Studies Used for Literature Prioritization in SWIFT-Review

The tables in the sections below identify the positive seeds used to train the machine for the engineering and exposure disciplines, respectively.

G.5.1 Positive Seeds Used for Engineering Discipline

Table_Apx G-10. Bibliography Citation for Positive Seeds Used for Engineering SWIFT-Review Prioritization

HERO ID	Author	Year	Title	Data Type
3539720	Bader, M.; Rosenberger, W.; Rebe, T.; Keener, S. A.; Brock, T. H.; Hemmerling, H. J.; Wrbitzky, R.	2006	Ambient monitoring and biomonitoring of workers exposed to N-methyl-2-pyrrolidone in an industrial facility	Occupational Exposure

HERO ID	Author	Year	Title	Data Type
699224	Bakke, B; Stewart, P; Waters, M	2007	Uses of and exposure to trichloroethylene in U.S. industry: A systematic literature review	Occupational Exposure
3080338	Blake, CL; Van Orden, DR; Banasik, M; Harbison, RD	2003	Airborne asbestos concentration from brake changing does not exceed permissible exposure limit (PEL)	Occupational Exposure
1619253	Blando, JD; Schill, DP; De La Cruz, MP; Zhang, L; Zhang, J	2010	Preliminary study of propyl bromide exposure among New Jersey dry cleaners as a result of a pending ban on perchloroethylene	Occupational Exposure
5080435	Cherrie JW, Semple S, Brouwer D	2004	Gloves and dermal exposure to chemicals: Proposals for Evaluating Workplace Effectiveness. Annals of Occupational Hygiene 48: 607-615.	Occupational Exposure
730507	Dell, L. D.; Mundt, K. A.; Mcdonald, M.; Tritschler, J. P.; Mundt, D. J.	1999	Critical review of the epidemiology literature on the potential cancer risks of methylene chloride	Occupational Exposure
1737891	Eisenberg, J; Ramsey, J	2010	Evaluation of 1-Bromopropane Use in Four New Jersey Commercial Dry Cleaning Facilities	Occupational Exposure
3588270	Enander, R. T.; Cohen, H. J.; Gute, D. M.; Brown, L. C.; Desmaris, A. M.; Missaghian, R.	2004	Lead and methylene chloride exposures among automotive repair technicians	Occupational Exposure
730528	Estill, C. F.; Spencer, A. B.	1996	Case study: Control of methylene chloride exposures during furniture stripping	Occupational Exposure
2277546	Fairfax, R.; Porter, E.	2006	OSHA compliance issues – Evaluation of worker exposure to TDI, MOCA, and methylene chloride	Occupational Exposure
1247930	Frasch, H. F.; Dotson, G. S.; Barbero, A. M.	2011	*In vitro* human epidermal penetration of 1-bromopropane	Occupational Exposure
3230538	Frasch, HF; Bunge, A	2015	The transient dermal exposure II: post-exposure absorption and evaporation of volatile compounds	Occupational Exposure
5080256	Garrod ANI, Phillips AM, Pemberton JA	2001	Potential Exposure of Hands Inside Protective Gloves - a Summary of Data from Non-Agricultural Pesticide Surveys. Ann. Occup Hyg., Vol. 45, No. 1, pp. 55-60. (5080256)	Occupational Exposure
732615	Gilbert, D.; Goyer, M.; Lyman, W.; Magil, G.; Walker, P.; Wallace, D.; Wechsler, A.; Yee, J.	1982	An exposure and risk assessment for tetrachloroethylene	General Facility, Occupational Exposure, Environmental Release
631587	Gold, LS; De Roos, AJ; Waters, M; Stewart, P	2008	Systematic literature review of uses and levels of occupational exposure to tetrachloroethylene	Environmental Releases,

HERO ID	Author	Year	Title	Data Type
				Occupational Exposure
1597971	Gromiec, JP; Wesolowski, W; Brzeznicki, S; Wroblewska-Jakubowska, K; Kucharska, M	2002	Occupational exposure to rubber vulcanization products during repair of rubber conveyor belts in a brown coal mine	Environmental Releases, Occupational Exposure
1689090	Hanley, K. W.; Petersen, M. R.; Cheever, K. L.; Luo, L.	2010	Bromide and N-acetyl-S-(n-propyl)-L-cysteine in urine from workers exposed to 1-bromopropane solvents from vapor degreasing or adhesive manufacturing	Occupational Exposure
5018573	Kasting, BG; Miller, MA	2006	Kinetics of finite dose absorption through skin 2: Volatile compound	Occupational Exposure
2591959	Madl, AK; Gaffney, SH; Balzer, JL; Paustenbach, DJ	2009	Airborne Asbestos Concentrations Associated with Heavy Equipment Brake Removal	Occupational Exposure
730564	Mahmud, M.; Kales, S. N.	1999	Methylene chloride poisoning in a cabinet worker	Occupational Exposure
5079146	Managaki S; Miyake, Y.; Yokoyama, Y.; Hondo, H.; Masunaga, S.; Nakai, S.; Kobayashi, T.; Kameya, T.; Kimura, A.; Nakarai, T.; Oka, Y.; Otani, H.; Miyake, A.	2009	Emission load of hexabromocyclododecane in Japan based on the substance flow analysis	Environmental Release
3531143	Mangold, C; Clark, K; Madl, A; Paustenbach, D	2006	An Exposure Study of Bystanders and Workers During the Installation and Removal of Asbestos Gaskets and Packing	Occupational Exposure
5080455	Marquart H, Franken R, Goede H, Fransman W, Schinkel	2017	Validation of the dermal exposure model in ECETOC TRA. Annals of Work Exposures and Health. 61: 854-871.	Occupational Exposure
58325	Materna, BL	1985	Occupational exposure to perchloroethylene in the dry cleaning industry	Environmental Release, Occupational Exposure, General Facility
13526	McCammon, C. S., Jr; Glaser, R. A.; Wells, V. E.; Phipps, F. C.; Halperin, W. E.	1991	Exposure of workers engaged in furniture stripping to methylene chloride as determined by environmental and biological monitoring	Occupational Exposure
3539921	Meier, S.; Schindler, B. K.; Koslitz, S.; Koch, H. M.; Weiss, T.; Käfferlein, H. U.; Brüning, T.	2013	Biomonitoring of exposure to N-methyl-2-pyrrolidone in workers of the automobile industry	Occupational Exposure

HERO ID	Author	Year	Title	Data Type
3576615	Moon et al	2015	Exposure Monitoring and Health Risk Assessment of 1-Bromopropane as a Cleaning Solvent in the Workplace.	Occupational Exposure
1927966	Morf, L.; Buser, A. M.; Taverna, R.; Bader, H. P.; Scheidegger, R.	2008	Dynamic substance flow analysis as a valuable risk evaluation tool - A case study for brominated flame retardants as an example of potential endocrine disrupters	General Facility
3577026	Muenter, J.; Blach, R.	2010	Ecological technology: NMP-free leather finishing	Occupational Exposure
2991087	NIOSH	2007	Workers' exposures to n-propyl bromide at an adhesives and coating manufacturer.	Occupational Exposure
3080278	Paustenbach, DJ; Finley, BL; Lu, ET; Brorby, GP; Sheehan, PJ	2004	Environmental And Occupational Health Hazards Associated With The Presence Of Asbestos In Brake Linings and Pads (1900 To Present): A "Stateof-the-Art" Review	Occupational Exposure
1737898	Reh, C. M.; Mortimer, V. D.; Nemhauser, J. B.; Trout, D.	2002	NIOSH Health Hazard Evaluation Report: HETA No. 98-0153-2883, Custom Products, Inc. Mooresville, NC	Occupational Exposure
2548725	Richter, RO; Finley, BL; Paustenbach, DJ; Williams, PRD; Sheehan, PJ	2009	An evaluation of short-term exposures of brake mechanics to asbestos during automotive and truck brake cleaning and machining activities	Occupational Exposure
176	Rohl, AN; Langer, AM; Wolff, MS; Weisman, I	1976	Asbestos Exposure during Brake Lining Maintenance and Repair	Occupational Exposure
1300	Seiji, K; Inoue, O; Jin, C; Liu, YT; Cai, SX; Ohashi, M; Watanabe, T; Nakatsuka, H; Kawai, T; Ikeda, M	1989	Dose-excretion relationship in tetrachloroethylene-exposed workers and the effect of tetrachloroethylene co-exposure on trichloroethylene metabolism	Occupational Exposure
3043623	Solomon, G. M.; Morse, E. P.; Garbo, M. J.; Milton, D. K.	1996	Stillbirth after occupational exposure to N-methyl-2-pyrrolidone: A case report and review of the literature	Occupational Exposure
1953674	Stefaniak, AB; Breysse, PN; Murray, MPM; Rooney, BC; Schaefer, J	2000	An evaluation of employee exposure to volatile organic compounds in three photocopy centers	Environmental Releases, Occupational Exposure
524541	Steinsvag, K; Bratveit, M; Moen, BE	2007	Exposure to carcinogens for defined job categories in Norway's offshore petroleum industry, 1970 to 2005	Occupational Exposure
2343703	Takigami, H.; Watanabe, M.; Kajiwara, N.	2014	Destruction behavior of hexabromocyclododecanes during incineration of	Environmental Release

HERO ID	Author	Year	Title	Data Type
			solid waste containing expanded and extruded polystyrene insulation foams	
787728	Thomsen, C.; Molander, P.; Daae, H. L.; Janák, K.; Froshaug, M.; Liane, V. H.; Thorud, S.; Becher, G.; Dybing, E.	2007	Occupational exposure to hexabromocyclododecane at an industrial plant	Occupational Exposure
667565	Ukai, H.; Okamoto, S.; Takada, S.; Inui, S.; Kawai, T.; Higashikawa, K.; Ikeda, M.	1998	Monitoring of occupational exposure to dichloromethane by diffusive vapor sampling and urinalysis	Occupational Exposure
76565	Vincent, R.; Poirot, P.; Subra, I.; Rieger, B.; Cicolella, A.	1994	Occupational exposure to organic solvents during paint stripping and painting operations in the aeronautical industry	Occupational Exposure
3045042	Von Grote	2003	Reduction of Occupational Exposure to Perchloroethylene and Trichloroethylene in Metal Degreasing over the Last 30 years: Influence of Technology Innovation and Legislation.	Occupational Exposure
632592	von Grote, J; Hürlimann, C; Scheringer, M; Hungerbühler, K	2006	Assessing occupational exposure to perchloroethylene in dry cleaning	Occupational Exposure
3051984	Wadden *et al.*	1989	Emission Factors for Trichloroethylene Vapor Degreasers	Environmental Release
3531556	Weir, FW; Tolar, G; Meraz, LB	2001	Characterization of Vehicular Brake Service Personnel Exposure to Airborne Asbestos and Particulate	Occupational Exposure
3562767	Xiaofei, E.; Wada, Y.; Nozaki, J.; Miyauchi, H.; Tanaka, S.; Seki, Y.; Koizumi, A.	2000	A linear pharmacokinetic model predicts usefulness of N-methyl-2-pyrrolidone (NMP) in plasma or urine as a biomarker for biological monitoring for NMP exposure	Occupational Exposure
2797854	Yamada, K.; Kumagai, S.; Nagoya, T.; Endo, G.	2014	Chemical exposure levels in printing workers with cholangiocarcinoma	Occupational Exposure
3350493	Yi, S.; Liu, J. G.; Jin, J.; Zhu, J.	2016	Assessment of the occupational and environmental risks of hexabromocyclododecane (HBCD) in China	Occupational Exposure
1927576	Zhang, H.; Kuo, Y. Y.; Gerecke, A. C.; Wang, J.	2012	Co-release of hexabromocyclododecane (HBCD) and nano- and microparticles from thermal cutting of polystyrene foams	Environmental Release

G.5.2 Positive Seeds Used for Exposure Discipline

Table_Apx G-11. Bibliography Citation for Positive Seeds Used for Exposure SWIFT-Review Prioritization

HERO ID	Author	Year	Title	Seed Chemical						
				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
787629	Abb, M, Stahl, B, Lorenz, W	2011	Analysis of brominated flame retardants in house dust			X				
787630	Abdallah, MA, Harrad, S	2009	Personal exposure to HBCDs and its degradation products via ingestion of indoor dust			X				
787631	Abdallah, MA, Harrad, S	2011	Tetrabromobisphenol-A, hexabromocyclododecane and its degradation products in UK human milk: Relationship to external exposure			X				
5357275	Abdallah, MA, Harrad, S	2018	Dermal contact with furniture fabrics is a significant pathway of human exposure to brominated flame retardants			X				
1079114	Abdallah, MA, Harrad, S, Covaci, A	2008	Hexabromocyclododecanes and tetrabromobisphenol-A in indoor air and dust in Birmingham, U.K: Implications for human exposure			X				
1927749	Abdallah, MA, Ibarra, C, Neels, H, *et al.*	2008	Comparative evaluation of liquid chromatography-mass spectrometry (MS) vs. gas chromatography (GC)-mass spectrometry for the determination of hexabromocyclododecanes and their degradation products in indoor dust			X				
4659497	Abdallah, MA, Sharkey, M, Berresheim, H, *et al.*	2018	Hexabromocyclododecane in polystyrene packaging: A downside of recycling?			X				

HERO ID	Author	Year	Title	Seed Chemical						
				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
1927993	Abdallah, MAE, Harrad, S	2010	Modification and calibration of a passive air sampler for monitoring vapor and particulate phase brominated flame retardants in indoor air: Application to car interiors			X				
1079430	Abdallah, MAE, Harrad, S, Ibarra, C, *et al.*	2008	Hexabromocyclododecanes in indoor dust from Canada, the United Kingdom, and the United States			X				
658636	Abrahamsson, K, Dyrssen, D, Jogebrant, G, *et al.*	1989	Halocarbon concentrations in Askerofjorden related to the water exchange and inputs from the petrochemical site at Stenungsund						X	
632310	Adgate, JL, Church, TR, Ryan, AD, *et al.*	2004	Outdoor, indoor, and personal exposure to VOCs in children						X	
4149721	Aggazzotti, G, Predieri, G	1986	SURVEY OF VOLATILE HALOGENATED ORGANICS (VHO) IN ITALY - LEVELS OF VHO IN DRINKING WATERS, SURFACE WATERS AND SWIMMING POOLS						X	
1007825	Al Bitar, F	2004	Hazardous chemicals in Belgian house dust: Report on chemical content in house dust samples collected in Belgian homes and offices			X				
1927602	Ali, N, Dirtu, AC, van den Eede, N, *et al.*	2012	Occurrence of alternative flame retardants in indoor dust from New Zealand: Indoor sources and human exposure assessment			X				
3809206	Allchin, CR, Morris, S	2003	Hexabromocyclododecane (HBCD) diastereoisomers and brominated diphenyl ether congener (BDE) residues in edible fish from the rivers Skerne and Tees, U.K			X				

HERO ID	Author	Year	Title	Seed Chemical						
				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
1597662	Allen, JG, Stapleton, HM, Vallarino, J, *et al.*	2013	Exposure to flame retardant chemicals on commercial airplanes			X				
3455810	Allgood, JM, Jimah, T, Mcclaskey, CM, *et al.*	2016	Potential human exposure to halogenated flame-retardants in elevated surface dust and floor dust in an academic environment			X				
3350546	Al-Odaini, NA, Shim, WJ, Han, GM, *et al.*	2015	Enrichment of hexabromocyclododecanes in coastal sediments near aquaculture areas and a wastewater treatment plant in a semi-enclosed bay in South Korea			X				
2915586	Andersen, MS, Fuglei, E, König, M, *et al.*	2015	Levels and temporal trends of persistent organic pollutants (POPs) in arctic foxes (Vulpes lagopus) from Svalbard in relation to dietary habits and food availability			X				
3828881	Anim, AK, Drage, DS, Goonetilleke, A, *et al.*	2017	Distribution of PBDEs, HBCDs and PCBs in the Brisbane River estuary sediment			X				
787643	Antignac, JP, Cariou, R, Maume, D, *et al.*	2008	Exposure assessment of fetus and newborn to brominated flame retardants in France: Preliminary data			X				
3449916	Antignac, JP, Main, KM, Virtanen, HE, *et al.*	2016	Country-specific chemical signatures of persistent organic pollutants (POPs) in breast milk of French, Danish and Finnish women			X				
2343716	Arinaitwe, K, Muir, DC, Kiremire, BT, *et al.*	2014	Polybrominated diphenyl ethers and alternative flame retardants in air and precipitation samples from the northern Lake Victoria region, East Africa			X				

HERO ID	Author	Year	Title	Seed Chemical						
				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
1927640	Asante, KA, Adu-Kumi, S, Nakahiro, K, *et al.*	2011	Human exposure to PCBs, PBDEs and HBCDs in Ghana: Temporal variation, sources of exposure and estimation of daily intakes by infants			X				
1927546	Asante, KA, Takahashi, S, Itai, T, *et al.*	2013	Occurrence of halogenated contaminants in inland and coastal fish from Ghana: levels, dietary exposure assessment and human health implications			X				
3454553	Aznar-Alemany, Ò, Trabalón, L, Jacobs, S, *et al.*	2016	Occurrence of halogenated flame retardants in commercial seafood species available in European markets			X				
2815621	Bachman, MJ, Keller, JM, West, KL, *et al.*	2014	Persistent organic pollutant concentrations in blubber of 16 species of cetaceans stranded in the Pacific Islands from 1997 through 2011			X				
3350483	Barghi, M, Shin, ES, Son, MH, *et al.*	2016	Hexabromocyclododecane (HBCD) in the Korean food basket and estimation of dietary exposure			X				
3336454	Baron, E, Bosch, C, Manez, M, *et al.*	2015	Temporal trends in classical and alternative flame retardants in bird eggs from Donana Natural Space and surrounding areas (south-western Spain) between 1999 and 2013			X				
1065558	Batterman, S, Jia, C, Hatzivasilis, G	2007	Migration of volatile organic compounds from attached garages to residences: A major exposure source	X					X	
5352401	Bertilsson, J, Petersson, U, Fredriksson, PJ, *et al.*	2017	Use of pepper spray in policing: retrospective study of situational characteristics and implications for violent situations							X

HERO ID	Author	Year	Title	Seed Chemical						
				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
3489827	Bianchi, E, Lessing, G, Brina, KR, *et al.*	2017	Monitoring the Genotoxic and Cytotoxic Potential and the Presence of Pesticides and Hydrocarbons in Water of the Sinos River Basin, Southern Brazil				X			
3545919	Bjermo, H, Aune, M, Cantillana, T, *et al.*	2017	Serum levels of brominated flame retardants (BFRs: PBDE, HBCD) and influence of dietary factors in a population-based study on Swedish adults			X				
1927616	Björklund, JA, Sellström, U, de Wit, CA, *et al.*	2012	Comparisons of polybrominated diphenyl ether and hexabromocyclododecane concentrations in dust collected with two sampling methods and matched breast milk samples			X				
3501965	Blanco, S, Bécares, E	2010	Are biotic indices sensitive to river toxicants? A comparison of metrics based on diatoms and macro-invertebrates						X	
1927727	Bogdal, C, Schmid, P, Kohler, M, *et al.*	2008	Sediment record and atmospheric deposition of brominated flame retardants and organochlorine compounds in Lake Thun, Switzerland: lessons from the past and evaluation of the present			X				
3545920	Boyles, E, Tan, H, Wu, Y, *et al.*	2017	Halogenated flame retardants in bobcats from the midwestern United States			X				
198168	Brandli, RC, Kupper, T, Bucheli, TD, *et al.*	2007	Organic pollutants in compost and digestate. Part 2. Polychlorinated dibenzo-p-dioxins, and -furans, dioxin-like polychlorinated biphenyls, brominated flame retardants, perfluorinated alkyl substances, pesticides, and other compounds			X				
#N/A	Brandsma, SH, Leonards, P, Leslie, HA, *et al.*	2015	Tracing organophosphorus and brominated flame retardants and plasticizers in an estuarine food web	###	###	#N/A	###	###	###	###

HERO ID	Author	Year	Title	Seed Chemical						
				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
2528319	Brandsma, SH, Leonards, PE, Leslie, HA, *et al.*	2014	Tracing organophosphorus and brominated flame retardants and plasticizers in an estuarine food web	###	###	#N/A	###	###	###	###
3350522	Braune, BM, Letcher, RJ, Gaston, AJ, *et al.*	2015	Trends of polybrominated diphenyl ethers and hexabromocyclododecane in eggs of Canadian Arctic seabirds reflect changing use patterns			X				
1412405	Braune, BM, Mallory, ML, Grant Gilchrist, H, *et al.*	2007	Levels and trends of organochlorines and brominated flame retardants in ivory gull eggs from the Canadian Arctic, 1976 to 2004			X				
2277377	Bravo-Linares, CM, Mudge, SM, Loyola-Sepulveda, RH	2007	Occurrence of volatile organic compounds (VOCs) in Liverpool Bay, Irish Sea						X	
1927591	Bustnes, JO, Borgå, K, Dempster, T, *et al.*	2012	Latitudinal distribution of persistent organic pollutants in pelagic and demersal marine fish on the Norwegian coast			X				
1927758	Bustnes, JO, Yoccoz, NG, Bangjord, G, *et al.*	2007	Temporal trends (1986-2004) of organochlorines and brominated flame retardants in tawny owl eggs from northern Europe			X				
3350486	Butt, CM, Miranda, ML, Stapleton, HM	2016	Development of an analytical method to quantify PBDEs, OH-BDEs, HBCDs, 2,4,6-TBP, EH-TBB, and BEH-TEBP in human serum			X				
3016880	Cao, Z, Xu, F, Li, W, *et al.*	2015	Seasonal and particle size-dependent variations of hexabromocyclododecanes in settled dust: Implications for sampling			X				

HERO ID	Author	Year	Title	Seed Chemical						
				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
3978373	2017	Profiles & estimates: Tetrachloroethylene							X	
1927577	Carignan, CC, Abdallah, MA, Wu, N, *et al.*	2012	Predictors of tetrabromobisphenol-A (TBBP-A) and hexabromocyclododecanes (HBCD) in milk from Boston mothers			X				
27974	Chan, CC, Vainer, L, Martin, JW, *et al.*	1990	Determination of organic contaminants in residential indoor air using an adsorption-thermal desorption technique						X	
2535652	Chan, WR, Cohn, S, Sidheswaran, M, *et al.*	2014	Contaminant levels, source strengths, and ventilation rates in California retail stores						X	
5098225	Chang, JC, Guo, Z, Sparks, LE	1998	Exposure and emission evaluations of methyl ethyl ketoxime (MEKO) in alkyd paints						X	
1927722	Cheaib, Z, Grandjean, D, Kupper, T, *et al.*	2009	Brominated flame retardants in fish of Lake Geneva (Switzerland)			X				
1927627	Chen, D, La Guardia, MJ, Luellen, DR, *et al.*	2011	Do temporal and geographical patterns of HBCD and PBDE flame retardants in U.S. fish reflect evolving industrial usage?			X				
1851195	Chen, D, Letcher, RJ, Burgess, NM, *et al.*	2012	Flame retardants in eggs of four gull species (Laridae) from breeding sites spanning Atlantic to Pacific Canada			X				
3083368	Cheng, VK, O'Kelly, FJ	1986	Asbestos exposure in the motor vehicle repair and servicing industry in Hong Kong		X					

HERO ID	Author	Year	Title	Seed Chemical						
				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
2443355	Chin, JY, Godwin, C, Parker, E, *et al.*	2014	Levels and sources of volatile organic compounds in homes of children with asthma						X	
3350535	Chokwe, TB, Okonkwo, JO, Sibali, LL, *et al.*	2015	Alkylphenol ethoxylates and brominated flame retardants in water, fish (carp) and sediment samples from the Vaal River, South Africa			X				
3545930	Chokwe, TB, Okonkwo, OJ, Sibali, LL, *et al.*	2016	Occurrence and distribution pattern of alkylphenol ethoxylates and brominated flame retardants in sediment samples from Vaal River, South Africa			X				
3242836	Christof, O, Seifert, R, Michaelis, W	2002	Volatile halogenated organic compounds in European estuaries				X		X	
14003	Clayton, CA, Pellizzari, ED, Whitmore, RW, *et al.*	1999	National Human Exposure Assessment Survey (NHEXAS): Distributions and associations of lead, arsenic, and volatile organic compounds in EPA Region 5						X	
3809228	Climate and Pollution Agency	2010	New organic pollutants in air, 2007. Brominated flame retardants and polyfluorinated substances			X				
3350460	Coelho, SD, Sousa, AC, Isobe, T, *et al.*	2016	Brominated, chlorinated and phosphate organic contaminants in house dust from Portugal			X				
3350459	Coelho, SD, Sousa, AC, Isobe, T, *et al.*	2016	Brominated flame retardants and organochlorine compounds in duplicate diet samples from a Portuguese academic community			X				
1061439	Colles, A, Koppen, G, Hanot, V, *et al.*	2008	Fourth WHO-coordinated survey of human milk for persistent organic pollutants (POPs): Belgian results			X				

HERO ID	Author	Year	Title	Seed Chemical						
				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
3099264	Cooper, TC, Sheehy, JW, O'Brien, DM, *et al.*	1988	In-depth survey report: Evaluation of brake drum service controls at Cincinnati Gas and Electric Garages, Cincinnati, Evanston, and Monroe, Ohio and Covington, Kentucky		X					
787649	Covaci, A, Roosens, L, Dirtu, AC, *et al.*	2009	Brominated flame retardants in Belgian home-produced eggs: Levels and contamination sources			X				
2936564	Darnerud, P, Lignell, S, Aune, M, *et al.*	2015	Time trends of polybrominated diphenylether (PBDE) congeners in serum of Swedish mothers and comparisons to breast milk data			X				
787654	Darnerud, PO, Aune, M, Larsson, L, *et al.*	2011	Levels of brominated flame retardants and other pesistent organic pollutants in breast milk samples from Limpopo Province, South Africa			X				
2803418	Dawes, VJ, Waldock, MJ	1994	Measurement of volatile organic compounds at UK national monitoring plan stations						X	
1788276	de Blas, M, Navazo, M, Alonso, L, *et al.*	2012	Simultaneous indoor and outdoor on-line hourly monitoring of atmospheric volatile organic compounds in an urban building. The role of inside and outside sources						X	
3986474	de Boer, J, Leslie, HA, Leonards, PE, *et al.*	2004	Screening and time trend study of decabromodiphenylether and hexabromocyclododecane in birds			X				
1927617	de Wit, CA, Björklund, JA, Thuresson, K	2012	Tri-decabrominated diphenyl ethers and hexabromocyclododecane in indoor air and dust from Stockholm microenvironments 2: indoor sources and human exposure			X				

HERO ID	Author	Year	Title	Seed Chemical						
				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
3969306	de Wit, CA, ., Nylund, K, Eriksson, U, *et al.*	2007	Brominated flame retardants in slude from 50 Swedish sewage treatment plants: Evidence of anaerobic degradation of HBCD and TBBPA			X				
1937209	DELETE-EC/HC	2011	Screening assessment report on hexabromocyclododecane. Chemical Abstracts Service Registry Number (CASRN) 3194-55-6	###	###	#N/A	###	###	###	###
1927618	Devanathan, G, Subramanian, A, Sudaryanto, A, *et al.*	2012	Brominated flame retardants and polychlorinated biphenyls in human breast milk from several locations in India: Potential contaminant sources in a municipal dumping site			X				
644857	Dewulf, JP, Van Langenhove, HR, Van der Auwera, LF	1998	Air/water exchange dynamics of 13 volatile chlorinated C1- and C2-hydrocarbons and monocyclic aromatic hydrocarbons in the southern North Sea and the Scheldt estuary						X	
1578505	D'Hollander, W, Roosens, L, Covaci, A, *et al.*	2010	Brominated flame retardants and perfluorinated compounds in indoor dust from homes and offices in Flanders, Belgium			X				
5425310	Di Toro, D, .M.	1984	Probability Model of Stream Quality Due to Runoff. ASCE				X			
1927581	Dirtu, AC, Ali, N, van den Eede, N, *et al.*	2012	Country specific comparison for profile of chlorinated, brominated and phosphate organic contaminants in indoor dust. Case study for Eastern Romania, 2010			X				
1061566	Dirtu, AC, Covaci, A	2010	Estimation of daily intake of organohalogenated contaminants from food consumption and indoor dust ingestion in Romania			X				

HERO ID	Author	Year	Title	Seed Chemical						
				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
1065844	Dodson, RE, Levy, JI, Spengler, JD, *et al.*	2008	Influence of basements, garages, and common hallways on indoor residential volatile organic compound concentrations						X	
2557649	Dodson, RE, Perovich, LJ, Covaci, A, *et al.*	2012	After the PBDE phase-out: A broad suite of flame retardants in repeat house dust samples from California			X				
3350544	Drage, D, Mueller, JF, Birch, G, *et al.*	2015	Historical trends of PBDEs and HBCDs in sediment cores from Sydney estuary, Australia			X				
3545935	Drage, DS, Mueller, JF, Hobson, P, *et al.*	2017	Demographic and temporal trends of hexabromocyclododecanes (HBCDD) in an Australian population			X				
3350342	Drage, DS, Newton, S, de Wit, CA, *et al.*	2016	Concentrations of legacy and emerging flame retardants in air and soil on a transect in the UK West Midlands			X				
1252276	Driffield, M, Harmer, N, Bradley, E, *et al.*	2008	Determination of brominated flame retardants in food by LC-MS/MS: Diastereoisomer-specific hexabromocyclododecane and tetrabromobisphenol A			X				
2331366	D'Souza, JC, Jia, C, Mukherjee, B, *et al.*	2009	Ethnicity, housing and personal factors as determinants of VOC exposures						X	
3575294	Duan, H, Yu, D, Zuo, J, *et al.*	2016	Characterization of brominated flame retardants in construction and demolition waste components: HBCD and PBDEs			X				
3587944	Duclos, Y, Blanchard, M, Chesterikoff, A, *et al.*	2000	Impact of paris waste upon the chlorinated solvent concentrations of the river Seine (France)				X		X	

HERO ID	Author	Year	Title	Seed Chemical						
				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
#N/A	EC/HC	2011	Screening assessment report on hexabromocyclododecane	###	###	#N/A	###	###	###	###
3970747	ECHA	2008	Risk assessment: hexabromocyclododecane	###	###	#N/A	###	###	###	###
3970753	ECHA	2017	Chemical safety report: Hexabromocyclododecane and all major diastereoisomers identified, Part 2			X				
787656	Eggesbø, M, Thomsen, C, Jørgensen, JV, *et al.*	2011	Associations between brominated flame retardants in human milk and thyroid-stimulating hormone (TSH) in neonates			X				
1927572	Eguchi, A, Isobe, T, Ramu, K, *et al.*	2013	Soil contamination by brominated flame retardants in open waste dumping sites in Asian developing countries			X				
1927819	Eljarrat, E, de la Cal, A, Raldua, D, *et al.*	2005	Brominated flame retardants in Alburnus alburnus from Cinca River Basin (Spain)			X				
999290	Eljarrat, E, de la Cal, A, Raldua, D, *et al.*	2004	Occurrence and bioavailability of polybrominated diphenyl ethers and hexabromocyclododecane in sediment and fish from the Cinca River, a tributary of the Ebro River (Spain)			X				
2343701	Eljarrat, E, Gorga, M, Gasser, M, *et al.*	2014	Dietary exposure assessment of Spanish citizens to hexabromocyclododecane through the diet			X				
1927715	Eljarrat, E, Guerra, P, Martínez, E, *et al.*	2009	Hexabromocyclododecane in human breast milk: Levels and enantiomeric patterns			X				

HERO ID	Author	Year	Title	Seed Chemical						
				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
1060837	Emmerich, SJ, Gorfain, JE, Howard-Reed, C	2003	Air and pollutant transport from attached garages to residential living spaces - literature review and field tests	X						
5205098	U.S. EPA	2019	Consumer Exposure Model (CEM) 2.1 User Guide	X						
5205300	U.S. EPA	2019	Consumer Exposure Model (CEM) 2.1 User Guide - Appendices	X						
5205462	U.S. EPA	2019	IECCU 1.1 User's Guide. In Simulation Program for Estimating Chemical Emissions from Sources and Related Changes to Indoor Environmental Concentrations in Buildings with Conditioned and Unconditioned Zones (IECCU)	X						
5203414	U.S. EPA	2019	Multi-Chamber Concentration and Exposure Model (MCCEM) User Guide	X						
1927650	Esslinger, S, Becker, R, Jung, C, *et al.*	2011	Temporal trend (1988-2008) of hexabromocyclododecane enantiomers in herring gull eggs from the German coastal region			X				
2343720	Eulaers, I, Jaspers, VL, Pinxten, R, *et al.*	2014	Legacy and current-use brominated flame retardants in the Barn Owl			X				
469357	Evenset, A, Christensen, GN, Carroll, J, *et al.*	2007	Historical trends in persistent organic pollutants and metals recorded in sediment from Lake Ellasjoen, Bjornoya, Norwegian Arctic			X				
787664	Fängström, B, Athanassiadis, I, Odsjö, T, *et al.*	2008	Temporal trends of polybrominated diphenyl ethers and hexabromocyclododecane in milk from Stockholm mothers, 1980-2004			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
1927606	Feng, AH, Chen, SJ, Chen, MY, *et al.*	2012	Hexabromocyclododecane (HBCD) and tetrabromobisphenol A (TBBPA) in riverine and estuarine sediments of the Pearl River Delta in southern China, with emphasis on spatial variability in diastereoisomer- and enantiomer-specific distribution of HBCD			X				
1927760	Fernandes, A, Dicks, P, Mortimer, D, *et al.*	2008	Brominated and chlorinated dioxins, PCBs and brominated flame retardants in Scottish shellfish: Methodology, occurrence and human dietary exposure			X				
3350498	Fernandes, AR, Mortimer, D, Rose, M, *et al.*	2016	Bromine content and brominated flame retardants in food and animal feed from the UK			X				
200024	Fishbein, L	1992	Exposure from occupational vs. other sources						X	
3230538	Frasch, HF, Bunge, AL	2015	The transient dermal exposure II: post-exposure absorption and evaporation of volatile compounds				X			
3575380	Frederiksen, M, Vorkamp, K, Bossi, R, *et al.*	2007	Method development for simultaneous analysis of HBCD, TBBPA, and dimethyl-TBBPA in marine biota from Greenland and the Faroe Islands			X				
3127742	Fromme, H, Hilger, B, Albrecht, M, *et al.*	2016	Occurrence of chlorinated and brominated dioxins/furans, PCBs, and brominated flame retardants in blood of German adults			X				
2343719	Fromme, H, Hilger, B, Kopp, E, *et al.*	2014	Polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD) and “novel” brominated flame retardants in house dust in Germany			X				
4159524	2006	Brominated chemicals: UK dietary estimates				X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
4149731	Fytianos, K, Vasilikiotis, G, Weil, L	1985	Identification and determination of some trace organic compounds in coastal seawater of Northern Greece						X	
3350475	Gallen, C, Drage, D, Kaserzon, S, *et al.*	2016	Occurrence and distribution of brominated flame retardants and perfluoroalkyl substances in Australian landfill leachate and biosolids			X				
1927645	Gao, S, Wang, J, Yu, Z, *et al.*	2011	Hexabromocyclododecanes in surface soils from E-waste recycling areas and industrial areas in South China: Concentrations, diastereoisomer- and enantiomer-specific profiles, and inventory			X				
1927696	García-Valcárcel, AI, Tadeo, JL	2009	Determination of hexabromocyclododecane isomers in sewage sludge by LC-MS/MS			X				
1597132	Gauthier, LT, Hebert, CE, Weseloh, DV, *et al.*	2007	Current-use flame retardants in the eggs of herring gulls (Larus argentatus) from the Laurentian Great Lakes			X				
1927750	Gebbink, WA, Sonne, C, Dietz, R, *et al.*	2008	Target tissue selectivity and burdens of diverse classes of brominated and chlorinated contaminants in polar bears (Ursus maritimus) from East Greenland			X				
3283561	Gentes, ML, Letcher, RJ, Caron-Beaudoin, E, *et al.*	2012	Novel flame retardants in urban-feeding ring-billed gulls from the St. Lawrence River, Canada			X				
1927965	Gerecke, AC, Schmid, P, Bogdal, C, *et al.*	2008	Brominated flame retardants - Endocrine-disrupting chemicals in the Swiss environment			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
2149396	Gilchrist, TT, Letcher, RJ, Thomas, P, *et al.*	2014	Polybrominated diphenyl ethers and multiple stressors influence the reproduction of free-ranging tree swallows (Tachycineta bicolor) nesting at wastewater treatment plants			X				
1061450	Glynn, A, Lignell, S, Darnerud, PO, *et al.*	2011	Regional differences in levels of chlorinated and brominated pollutants in mother's milk from primiparous women in Sweden			X				
1676764	Gorga, M, Martínez, E, Ginebreda, A, *et al.*	2013	Determination of PBDEs, HBB, PBEB, DBDPE, HBCD, TBBPA and related compounds in sewage sludge from Catalonia (Spain)			X				
787666	Goscinny, S, Vandevijvere, S, Maleki, M, *et al.*	2011	Dietary intake of hexabromocyclododecane diastereoisomers (α-, β-, and γ-HBCD) in the Belgian adult population			X				
3986479	Granby, K; Cederberg,, TL,	2007	LC-MS/MS analysis of hexabromocyclododecane (HBCD) isomers and tetrabromobisphenol a (TBBPA) and levels in Danish fish for food consumption			X				
1927628	Guerra, P, Alaee, M, Jiménez, B, *et al.*	2012	Emerging and historical brominated flame retardants in peregrine falcon (Falco peregrinus) eggs from Canada and Spain			X				
3575325	Guerra, P, de la Cal, A, Marsh, G, *et al.*	2009	Transfer of hexabromocyclododecane from industrial effluents to sediments and biota: Case study in Cinca river (Spain)			X				
1040997	Guerra, P, Eljarrat, E, Barceló, D	2010	Simultaneous determination of hexabromocyclododecane, tetrabromobisphenol A, and related compounds in sewage sludge and sediment samples from Ebro River basin (Spain)			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
713690	Gulyas, H, Hemmerling, L	1990	Tetrachloroethene air pollution originating from coin-operated dry cleaning establishments						X	
1927955	Hajslova, J, Pulkrabova, J, Poustka, J, an, *et al.*	2007	Brominated flame retardants and related chlorinated persistent organic pollutants in fish from river Elbe and its main tributary Vltava			X				
1082335	Harrad, S, Abdallah, MA	2011	Brominated flame retardants in dust from UK cars-within-vehicle spatial variability, evidence for degradation and exposure implications			X				
3350532	Harrad, S, Abdallah, MA	2015	Concentrations of polybrominated diphenyl ethers, hexabromocyclododecanes and tetrabromobisphenol-A in breast milk from United Kingdom women do not decrease over twelve months of lactation			X				
1927694	Harrad, S, Abdallah, MA, Rose, NL, *et al.*	2009	Current-use brominated flame retardants in water, sediment, and fish from English lakes			X				
5239987	Harrad, S, Drage, D, Abdallah, M, *et al.*	2019	Evaluation of hand-held XRF for screening waste articles for exceedances of limit values for brominated flame retardants			X				
1076646	Harrad, S, Goosey, E, Desborough, J, *et al.*	2010	Dust from U.K. primary school classrooms and daycare centers: The significance of dust as a pathway of exposure of young U.K. children to brominated flame retardants and polychlorinated biphenyls			X				
3809208	Hashikawa, R, Isobe, T, Yano, S, i, *et al.*	2011	Contamination by brominated flame retardants (BFRs) in common cormorants from Lake Biwa			X				

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2528318	Hassan, Y, Shoeib, T	2014	Levels of polybrominated diphenyl ethers and novel flame retardants in microenvironment dust from Egypt: An assessment of human exposure			X				
1927703	Haukås, M, Hylland, K, Berge, JA, *et al.*	2009	Spatial diastereomer patterns of hexabromocyclododecane (HBCD) in a Norwegian fjord			X				
1927667	Haukås, M, Hylland, K, Nygård, T, *et al.*	2010	Diastereomer-specific bioaccumulation of hexabromocyclododecane (HBCD) in a coastal food web, Western Norway			X				
1927670	Haukås, M, Ruus, A, Hylland, K, *et al.*	2010	Bioavailability of hexabromocyclododecane to the polychaete Hediste diversicolor: Exposure through sediment and food from a contaminated fjord			X				
1927673	He, MJ, Luo, XJ, Yu, LH, *et al.*	2010	Tetrabromobisphenol-A and hexabromocyclododecane in birds from an e-waste region in South China: Influence of diet on diastereoisomer- and enantiomer-specific distribution and trophodynamics			X				
1927551	He, MJ, Luo, XJ, Yu, LH, *et al.*	2013	Diasteroisomer and enantiomer-specific profiles of hexabromocyclododecane and tetrabromobisphenol A in an aquatic environment in a highly industrialized area, South China: Vertical profile, phase partition, and bioaccumulation			X				
2532227	He, Z, Yang, G, Lu, X, *et al.*	2013	Halocarbons in the marine atmosphere and surface seawater of the south Yellow Sea during spring						X	
2128010	He, Z, Yang, G, Lu, X, *et al.*	2013	Distributions and sea-to-air fluxes of chloroform, trichloroethylene, tetrachloroethylene, chlorodibromomethane and bromoform in the Yellow Sea and the East China Sea during spring						X	

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22045	Heavner, DL, Morgan, WT, Ogden, MW	1995	Determination of volatile organic compounds and ETS apportionment in 49 homes						X	
1927723	Helgason, LB, Polder, A, Føreid, S, *et al.*	2009	Levels and temporal trends (1983-2003) of polybrominated diphenyl ethers and hexabromocyclododecanes in seabird eggs from north Norway			X				
1927712	Henny, CJ, Kaiser, JL, Grove, RA, *et al.*	2009	Polybrominated diphenyl ether flame retardants in eggs may reduce reproductive success of ospreys in Oregon and Washington, USA			X				
1927776	Hiebl, J, Vetter, W	2007	Detection of hexabromocyclododecane and its metabolite pentabromocyclododecene in chicken egg and fish from the official food control			X				
1927549	Hloušková, V, Lanková, D, Kalachová, K, *et al.*	2013	Occurrence of brominated flame retardants and perfluoroalkyl substances in fish from the Czech aquatic ecosystem			X				
2343734	Hloušková, V, Lanková, D, Kalachová, K, *et al.*	2014	Brominated flame retardants and perfluoroalkyl substances in sediments from the Czech aquatic ecosystem			X				
999242	Hoh, E, Hites, RA	2005	Brominated flame retardants in the atmosphere of the East-Central United States			X				
3227425	Hong, J, Gao, S, Chen, L, *et al.*	2016	Hexabromocyclododecanes in the indoor environment of two cities in South China: Their occurrence and implications of human inhalation exposure			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
2149601	Hong, SH, Shim, WJ, Han, GM, *et al.*	2014	Levels and profiles of persistent organic pollutants in resident and migratory birds from an urbanized coastal region of South Korea			X				
3545977	Houde, M, Wang, X, Ferguson, SH, *et al.*	2017	Spatial and temporal trends of alternative flame retardants and polybrominated diphenyl ethers in ringed seals (*Phoca hispida*) across the Canadian Arctic			X				
3970268	Household Products Database	2017	Household products database: Chemical information: Tetrachloroethylene				X		X	
58127	Howie, SJ	1981	Ambient perchloroethylene levels inside coin-operated laundries with drycleaning machines on the premises						X	
1927635	Hrádková, P, Pulkrabová, J, Kalachová, K, *et al.*	2012	Occurrence of halogenated contaminants in fish from selected river localities and ponds in the Czech Republic			X				
1224355	Hu, X, Hu, D, Song, Q, *et al.*	2011	Determinations of hexabromocyclododecane (HBCD) isomers in channel catfish, crayfish, hen eggs and fish feeds from China by isotopic dilution LC-MS/MS			X				
660096	Huybrechts, T, Dewulf, J, Van Langenhove, H	2005	Priority volatile organic compounds in surface waters of the southern North Sea						X	
1927598	Hwang, IK, Kang, HH, Lee, IS, *et al.*	2012	Assessment of characteristic distribution of PCDD/Fs and BFRs in sludge generated at municipal and industrial wastewater treatment plants			X				
2343678	Ichihara, M, Yamamoto, A, Takakura, K, *et al.*	2014	Distribution and pollutant load of hexabromocyclododecane (HBCD) in sewage treatment plants and water from Japanese Rivers			X				

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1927642	Ilyas, M, Sudaryanto, A, Setiawan, IE, *et al.*	2011	Characterization of polychlorinated biphenyls and brominated flame retardants in surface soils from Surabaya, Indonesia			X				
1927663	Ilyas, M, Sudaryanto, A, Setiawan, IE, *et al.*	2011	Characterization of polychlorinated biphenyls and brominated flame retardants in sediments from riverine and coastal waters of Surabaya, Indonesia			X				
2149566	Ilyas, M, Sudaryanto, A, Setiawan, IE, *et al.*	2013	Characterization of polychlorinated biphenyls and brominated flame retardants in sludge, sediment and fish from municipal dumpsite at Surabaya, Indonesia			X				
1927681	Ilyina, T, Hunziker, RW	2010	Scenarios of temporal and spatial evolution of hexabromocyclododecane in the North Sea			X				
2800175	Insogna, S, Frison, S, Marconi, E, *et al.*	2014	Trends of volatile chlorinated hydrocarbons and trihalomethanes in Antarctica						X	
3350587	Isaacs, K	2014	The consolidated human activity database - master version (CHAD-Master) technical memorandum				X		X	
1443833	Ismail, N, Gewurtz, SB, Pleskach, K, *et al.*	2009	Brominated and chlorinated flame retardants in Lake Ontario, Canada, lake trout (Salvelinus namaycush) between 1979 and 2004 and possible influences of food-web changes			X				
1927724	Isobe, T, Ochi, Y, Ramu, K, *et al.*	2009	Organohalogen contaminants in striped dolphins (Stenella coeruleoalba) from Japan: present contamination status, body distribution and temporal trends (1978-2003)			X				

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1927986	Isobe, T, Oda, H, Takayanagi, N, *et al.*	2009	Hexabromocyclododecanes in human adipose tissue from Japan			X				
1927584	Isobe, T, Ogawa, SP, Ramu, K, *et al.*	2012	Geographical distribution of non-PBDE-brominated flame retardants in mussels from Asian coastal waters			X				
1927646	Isobe, T, Oshihoi, T, Hamada, H, *et al.*	2011	Contamination status of POPs and BFRs and relationship with parasitic infection in finless porpoises (Neophocaena phocaenoides) from Seto Inland Sea and Omura Bay, Japan			X				
1927772	Isobe, T, Ramu, K, Kajiwara, N, *et al.*	2007	Isomer specific determination of hexabromocyclododecanes (HBCDs) in small cetaceans from the South China Sea-Levels and temporal variation			X				
1927813	Janák, K, Covaci, A, Voorspoels, S, *et al.*	2005	Hexabromocyclododecane in marine species from the Western Scheldt Estuary: diastereoisomer- and enantiomer-specific accumulation			X				
3350471	Jang, M, Shim, WJ, Han, GM, *et al.*	2016	Styrofoam Debris as a Source of Hazardous Additives for Marine Organisms			X				
4296220	Japanese Ministry of Environment	2003	Table 2-2: Detection results of the FY2003 initial environmental survey			X				
4152012	Jaspers, V, Covaci, A, Maervoet, J, *et al.*	2004	Brominated flame retardants in Belgian little owl (Athene noctua) eggs			X				
1927816	Jaspers, V, Covaci, A, Maervoet, J, *et al.*	2005	Brominated flame retardants and organochlorine pollutants in eggs of little owls (Athene noctua) from Belgium			X				

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3350513	Jeannerat, D, Pupier, M, Schweizer, S, *et al.*	2016	Discrimination of hexabromocyclododecane from new polymeric brominated flame retardant in polystyrene foam by nuclear magnetic resonance			X				
1927762	Jenssen, BM, Sørmo, EG, Baek, K, *et al.*	2007	Brominated flame retardants in North-East Atlantic marine ecosystems			X				
2343722	Jeong, GH, Hwang, NR, Hwang, EH, *et al.*	2014	Hexabromocyclododecanes in crucian carp and sediment from the major rivers in Korea			X				
1488206	Jia, C, Batterman, S, Godwin, C	2008	VOCs in industrial, urban and suburban neighborhoods, Part 1: Indoor and outdoor concentrations, variation, and risk drivers						X	
484177	Jia, CR, D'Souza, J, Batterman, S	2008	Distributions of personal VOC exposures: A population-based analysis						X	
1927644	Johansson, AK, Sellström, U, Lindberg, P, *et al.*	2011	Temporal trends of polybrominated diphenyl ethers and hexabromocyclododecane in Swedish Peregrine Falcon (Falco peregrinus peregrinus) eggs			X				
1927734	Johansson, AK, Sellström, U, Lindberg, P, *et al.*	2009	Polybrominated diphenyl ether congener patterns, hexabromocyclododecane, and brominated biphenyl 153 in eggs of peregrine falcons (Falco peregrinus) breeding in Sweden			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
4196989	Johnson, A, Friese, M		PBTs Analyzed in Bottom Fish from Four Washington Rivers and Lakes: Hexabromocyclododecane, Tetrabromobisphenol A, Chlorinated Paraffins, Polybrominated Diphenylethers, Polychlorinated Naphthalenes, Perfluorinated Organic Compounds, Lead, and Cadmium			X				
1676758	Johnson, PI, Stapleton, HM, Mukherjee, B, *et al.*	2013	Associations between brominated flame retardants in house dust and hormone levels in men			X				
1927767	Johnson-Restrepo, B, Adams, DH, Kannan, K	2008	Tetrabromobisphenol A (TBBPA) and hexabromocyclododecanes (HBCDs) in tissues of humans, dolphins, and sharks from the United States			X				
2149610	Jörundsdóttir, H, Löfstrand, K, Svavarsson, J, *et al.*	2013	Polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCD) in seven different marine bird species from Iceland			X				
2343706	Kajiwara, N, Hirata, O, Takigami, H, *et al.*	2014	Leaching of brominated flame retardants from mixed wastes in lysimeters under conditions simulating landfills in developing countries			X				
787682	Kakimoto, K, Akutsu, K, Konishi, Y, *et al.*	2008	Time trend of hexabromocyclododecane in the breast milk of Japanese women			X				
1927593	Kakimoto, K, Nagayoshi, H, Yoshida, J, *et al.*	2012	Detection of Dechlorane Plus and brominated flame retardants in marketed fish in Japan			X				

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1082293	Kakooei, H, Hormozy, M, Marioryad, H	2011	Evaluation of asbestos exposure during brake repair and replacement		X					
1927573	Kalachova, K, Hradkova, P, Lankova, D, *et al.*	2012	Occurrence of brominated flame retardants in household and car dust from the Czech Republic			X				
1927656	Kalantzi, OI, Geens, T, Covaci, A, *et al.*	2011	Distribution of polybrominated diphenyl ethers (PBDEs) and other persistent organic pollutants in human serum from Greece			X				
3100008	Kauppinen, T, Korhonen, K	1987	Exposure to Asbestos During Brake Maintenance of Automotive Vehicles by Different Methods		X					
#N/A	KemI	2008	Risk assessment: Hexabromocyclododecane	###	###	#N/A	###	###	###	###
#N/A	Kicinski, M, Viaene, MK, Den Hond, E, *et al.*	2012	Neurobehavioral function and low-level exposure to brominated flame retardants in adolescents: a cross-sectional study	###	###	#N/A	###	###	###	###
1927571	Kiciński, M, Viaene, MK, Den Hond, E, *et al.*	2012	Neurobehavioral function and low-level exposure to brominated flame retardants in adolescents: A cross-sectional study	###	###	#N/A	###	###	###	###
3545985	Kim, UJ, Lee, IS, Oh, JE	2016	Occurrence, removal and release characteristics of dissolved brominated flame retardants and their potential metabolites in various kinds of wastewater			X				
3371701	Kiurski, JS, Oros, IB, Kecic, VS, *et al.*	2016	The temporal variation of indoor pollutants in photocopying shop						X	

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683627	Klamer, HJ, Leonards, PE, Lamoree, MH, *et al.*	2005	A chemical and toxicological profile of Dutch North Sea surface sediments			X				
1443796	Klosterhaus, SL, Stapleton, HM, La Guardia, MJ, *et al.*	2012	Brominated and chlorinated flame retardants in San Francisco Bay sediments and wildlife			X				
1927755	Knutsen, HK, Kvalem, HE, Thomsen, C, *et al.*	2008	Dietary exposure to brominated flame retardants correlates with male blood levels in a selected group of Norwegians with a wide range of seafood consumption			X				
1927729	Kohler, M, Zennegg, M, Bogdal, C, *et al.*	2008	Temporal trends, congener patterns, and sources of octa-, nona-, and decabromodiphenyl ethers (PBDE) and hexabromocyclododecanes (HBCD) in Swiss lake sediments			X				
1928011	Kopp, EK, Fromme, H, Voelkel, W	2012	Analysis of common and emerging brominated flame retardants in house dust using ultrasonic assisted solvent extraction and on-line sample preparation via column switching with liquid chromatography-mass spectrometry			X				
1927674	Köppen, R, Becker, R, Esslinger, S, *et al.*	2010	Enantiomer-specific analysis of hexabromocyclododecane in fish from Etnefjorden (Norway)			X				
1024859	Kostopoulou, MN, Golfinopoulos, SK, Nikolaou, AD, *et al.*	2000	Volatile organic compounds in the surface waters of northern Greece						X	
2655630	Kowalska, J, Gierczak, T	2013	Qualitative and quantitative analyses of the halogenated volatile organic compounds emitted from the office equipment items						X	

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2343691	Kowalski, B, Mazur, M	2014	The simultaneous determination of six flame retardants in water samples using SPE pre-concentration and UHPLC-UV method			X				
3230512	Kuang, J, Ma, Y, Harrad, S	2016	Concentrations of "legacy" and novel brominated flame retardants in matched samples of UK kitchen and living room/bedroom dust			X				
5098223	Küçük, M, Korkmaz, Y	2012	The effect of physical parameters on sound absorption properties of natural fiber mixed nonwoven composites						X	
1927751	Kunisue, T, Takayanagi, N, Isobe, T, *et al.*	2008	Regional trend and tissue distribution of brominated flame retardants and persistent organochlorines in raccoon dogs (Nyctereutes procyonoides) from Japan			X				
947580	Kupper, T, de Alencastro, LF, Gatsigazi, R, *et al.*	2008	Concentrations and specific loads of brominated flame retardants in sewage sludge			X				
1443867	La Guardia, MJ, Hale, RC, Harvey, E, *et al.*	2010	Flame-retardants and other organohalogens detected in sewage sludge by electron capture negative ion mass spectrometry			X				
1927601	La Guardia, MJ, Hale, RC, Harvey, E, *et al.*	2012	*In situ* accumulation of HBCD, PBDEs, and several alternative flame-retardants in the bivalve (Corbicula fluminea) and gastropod (Elimia proxima)			X				
1927534	La Guardia, MJ, Hale, RC, Newman, B	2013	Brominated flame-retardants in sub-Saharan Africa: Burdens in inland and coastal sediments of the eThekwini metropolitan municipality, South Africa			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
1927700	Lam, JC, Lau, RK, Murphy, MB, *et al.*	2009	Temporal trends of hexabromocyclododecanes (HBCDs) and polybrominated diphenyl ethers (PBDEs) and detection of two novel flame retardants in marine mammals from Hong Kong, South China			X				
999306	Law, K, Halldorson, T, Danell, R, *et al.*	2006	Bioaccumulation and trophic transfer of some brominated flame retardants in a Lake Winnipeg (Canada) food web			X				
3969307	Law, RJ, ., Allchin, CR, ., de Boer, J, *et al.*	2006	Levels and trends of brominated flame retardants in the European environment			X				
#N/A	Law, RJ, Allchin, CR, De Boer, J, *et al.*	2006	Levels and trends of brominated flame retardants in the European environment	###	###	#N/A	###	###	###	###
#N/A	Law, RJ, Allchin, CR, de Boer, J, *et al.*	2006	Levels and trends of brominated flame retardants in the European environment	###	###	#N/A	###	###	###	###
1927795	Law, RJ, Bersuder, P, Allchin, CR, *et al.*	2006	Levels of the flame retardants hexabromocyclododecane and tetrabromobisphenol A in the blubber of harbor porpoises (Phocoena phocoena) stranded or bycaught in the U.K., with evidence for an increase in HBCD concentrations in recent years			X				
1927721	Law, RJ, Bersuder, P, Barry, J, *et al.*	2008	A significant downturn in levels of hexabromocyclododecane in the blubber of harbor porpoises (Phocoena phocoena) stranded or bycaught in the UK: an update to 2006			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
3350542	Lee, IS, Kang, HH, Kim, UJ, *et al.*	2015	Brominated flame retardants in Korean river sediments, including changes in polybrominated diphenyl ether concentrations between 2006 and 2009			X				
3350487	Lee, SC, Sverko, E, Harner, T, *et al.*	2016	Retrospective analysis of "new" flame retardants in the global atmosphere under the GAPS Network			X				
34460	Lehmann, I, Thoelke, A, Rehwagen, M, *et al.*	2002	The influence of maternal exposure to volatile organic compounds on the cytokine secretion profile of neonatal T cells						X	
3809246	Leonards, PEG, Santillo, D, Brigden, K, *et al.*	2001	Brominated flame retardants in office dust samples. Proceedings of the Second International Workshop on Brominated Flame Retardants, 14–16 May 2001			X				
1927659	Leslie, HA, Leonards, PE, Shore, RF, *et al.*	2011	Decabromodiphenylether and hexabromocyclododecane in wild birds from the United Kingdom, Sweden and The Netherlands: Screening and time trends			X				
1443826	Letcher, RJ, Gebbink, WA, Sonne, C, *et al.*	2009	Bioaccumulation and biotransformation of brominated and chlorinated contaminants and their metabolites in ringed seals (Pusa hispida) and polar bears (Ursus maritimus) from East Greenland			X				
3350541	Letcher, RJ, Lu, Z, Chu, S, *et al.*	2015	Hexabromocyclododecane flame retardant isomers in sediments from Detroit River and Lake Erie of the Laurentian Great Lakes of North America			X				
3546008	Li, F, Jin, J, Tan, D, *et al.*	2016	Hexabromocyclododecane and tetrabromobisphenol A in sediments and paddy soils from Liaohe River Basin, China: Levels, distribution and mass inventory			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
1927607	Li, H, Mo, L, Yu, Z, *et al.*	2012	Levels, isomer profiles and chiral signatures of particle-bound hexabromocyclododecanes in ambient air around Shanghai, China			X				
1927554	Li, H, Shang, H, Wang, P, *et al.*	2013	Occurrence and distribution of hexabromocyclododecane in sediments from seven major river drainage basins in China			X				
1927582	Li, H, Zhang, Q, Wang, P, *et al.*	2012	Levels and distribution of hexabromocyclododecane (HBCD) in environmental samples near manufacturing facilities in Laizhou Bay area, East China			X				
3351632	Li, W, Liu, L, Zhang, Z, iF, *et al.*	2016	Brominated flame retardants in the surrounding soil of two manufacturing plants in China: Occurrence, composition profiles and spatial distribution			X				
3355687	Li, WL, Huo, CY, Liu, LY, *et al.*	2016	Multi-year air monitoring of legacy and current-use brominated flame retardants in an urban center in northeastern China			X				
3809248	Lignell, S, Darnerud, PO, Aune, M, *et al.*	2003	Report to the Swedish Environmental Protection Agency: Persistent organic pollutants (POP) in breastmilk from primiparae women in Uppsala County, Sweden, 2002–2003			X				
1927824	Lindberg, P, Sellström, U, Häggberg, L, *et al.*	2004	Higher brominated diphenyl ethers and hexabromocyclododecane found in eggs of peregrine falcons (Falco peregrinus) breeding in Sweden			X				
78782	Lindstrom, AB, Proffitt, D, Fortune, CR	1995	Effects of modified residential construction on indoor air quality						X	

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3986475	López, D, Athanasiadou, M, Athanassiadis, I, *et al.*	2004	A preliminary study on PBDEs and HBCDD in blood and milk from Mexican women			X				
2919854	Luigi, V, Giuseppe, M, Claudio, R	2015	Emerging and priority contaminants with endocrine active potentials in sediments and fish from the River Po (Italy)			X				
1927794	Lundstedt-Enkel, K, Asplund, L, Nylund, K, *et al.*	2006	Multivariate data analysis of organochlorines and brominated flame retardants in Baltic Sea guillemot (Uria aalge) egg and muscle			X				
1927804	Lundstedt-Enkel, K, Johansson, AK, Tysklind, M, *et al.*	2005	Multivariate data analyses of chlorinated and brominated contaminants and biological characteristics in adult guillemot (Uria aalge) from the Baltic Sea			X				
3350521	Lyons, BP, Barber, JL, Rumney, HS, *et al.*	2015	Baseline survey of marine sediments collected from the State of Kuwait: PAHs, PCBs, brominated flame retardants and metal contamination			X				
3488897	Ma, H, Zhang, H, Wang, L, *et al.*	2014	Comprehensive screening and priority ranking of volatile organic compounds in Daliao River, China				X		X	
1927568	Malarvannan, G, Isobe, T, Covaci, A, *et al.*	2013	Accumulation of brominated flame retardants and polychlorinated biphenyls in human breast milk and scalp hair from the Philippines: Levels, distribution and profiles			X				
116881	Malarvannan, G, Kunisue, T, Isobe, T, *et al.*	2009	Organohalogen compounds in human breast milk from mothers living in Payatas and Malate, the Philippines: Levels, accumulation kinetics and infant health risk			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
5098227	Marolleau, A, Salaun, F, Dupont, D, *et al.*	2017	Influence of textile properties on thermal comfort						X	
498591	Marsh, G, Athanasiadou, M, Athanassiadis, I, *et al.*	2005	Identification, quantification, and synthesis of a novel dimethoxylated polybrominated biphenyl in marine mammals caught off the coast of Japan			X				
659075	Martinez, E, Llobet, I, Lacorte, S, *et al.*	2002	Patterns and levels of halogenated volatile compounds in Portuguese surface waters						X	
1927800	Marvin, CH, Tomy, GT, Alaee, M, *et al.*	2006	Distribution of hexabromocyclododecane in Detroit River suspended sediments			X				
1927686	Mchugh, B, Poole, R, Corcoran, J, *et al.*	2010	The occurrence of persistent chlorinated and brominated organic contaminants in the European eel (Anguilla anguilla) in Irish waters			X				
1927784	Mckinney, MA, Cesh, LS, Elliott, JE, *et al.*	2006	Brominated flame retardants and halogenated phenolic compounds in North American west coast bald eaglet (Haliaeetus leucocephalus) plasma			X				
1927652	Mckinney, MA, Letcher, RJ, Aars, J, *et al.*	2011	Flame retardants and legacy contaminants in polar bears from Alaska, Canada, East Greenland and Svalbard, 2005-2008			X				
1002260	Mckinney, MA, Stirling, I, Lunn, NJ, *et al.*	2010	The role of diet on long-term concentration and pattern trends of brominated and chlorinated contaminants in western Hudson Bay polar bears, 1991-2007			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
787696	Meijer, L, Weiss, J, van Velzen, M, *et al.*	2008	Serum concentrations of neutral and phenolic organohalogens in pregnant women and some of their infants in The Netherlands			X				
1058212	Meng, XZ, Duan, YP, Yang, C, *et al.*	2011	Occurrence, sources, and inventory of hexabromocyclododecanes (HBCDs) in soils from Chongming Island, the Yangtze River Delta (YRD)			X				
1927604	Meng, XZ, Xiang, N, Duan, YP, *et al.*	2012	Hexabromocyclododecane in consumer fish from South China: Implications for human exposure via dietary intake			X				
1441147	Miège, C, Peretti, A, Labadie, P, *et al.*	2012	Occurrence of priority and emerging organic compounds in fishes from the Rhone River (France)			X				
1274420	Miljeteig, C, Strøm, H, Gavrilo, MV, *et al.*	2009	High levels of contaminants in ivory gull Pagophila eburnea eggs from the Russian and Norwegian Arctic			X				
2528324	Miller, A, Elliott, JE, Elliott, KH, *et al.*	2014	Brominated flame retardant trends in aquatic birds from the Salish Sea region of the west coast of North America, including a mini-review of recent trends in marine and estuarine birds			X				
2528327	Miller, A, Elliott, JE, Elliott, KH, *et al.*	2014	Spatial and temporal trends in brominated flame retardants in seabirds from the Pacific coast of Canada			X				
1927778	Minh, NH, Isobe, T, Ueno, D, *et al.*	2007	Spatial distribution and vertical profile of polybrominated diphenyl ethers and hexabromocyclododecanes in sediment core from Tokyo Bay, Japan			X				

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3015040	Mizouchi, S, Ichiba, M, Takigami, H, *et al.*	2015	Exposure assessment of organophosphorus and organobromine flame retardants via indoor dust from elementary schools and domestic houses			X				
1927682	Montie, EW, Letcher, RJ, Reddy, CM, *et al.*	2010	Brominated flame retardants and organochlorine contaminants in winter flounder, harp and hooded seals, and North Atlantic right whales from the Northwest Atlantic Ocean			X				
3982731	Morales-Caselles, C, Desforges, JW, Dangerfield, N, *et al.*	2017	A risk-based characterization of sediment contamination by legacy and emergent contaminants of concern in coastal British Columbia, Canada			X				
1927817	Morris, S, Allchin, CR, Zegers, BN, *et al.*	2004	Distribution and fate of HBCD and TBBPA brominated flame retardants in North Sea estuaries and aquatic food webs			X				
5098332	Morrison, RD, Murphy, BL	2013	Chlorinated solvents: A forensic evaluation						X	
3350490	Müller, MH, Polder, A, Brynildsrud, OB, *et al.*	2016	Brominated flame retardants (BFRs) in breast milk and associated health risks to nursing infants in Northern Tanzania			X				
1927562	Munschy, C, Marchand, P, Venisseau, A, *et al.*	2013	Levels and trends of the emerging contaminants HBCDs (hexabromocyclododecanes) and PFCs (perfluorinated compounds) in marine shellfish along French coasts			X				
1927797	Murvoll, KM, Skaare, JU, Anderssen, E, *et al.*	2006	Exposure and effects of persistent organic pollutants in European shag (Phalacrocorax aristotelis) hatchlings from the coast of Norway			X				

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1927774	Murvoll, KM, Skaare, JU, Jensen, H, *et al.*	2007	Associations between persistent organic pollutants and vitamin status in Brünnich's guillemot and common eider hatchlings			X				
1414571	Murvoll, KM, Skaare, JU, Moe, B, *et al.*	2006	Spatial trends and associated biological responses of organochlorines and brominated flame retardants in hatchlings of North Atlantic kittiwakes (Rissa tridactyla)			X				
1927668	Nakagawa, R, Murata, S, Ashizuka, Y, *et al.*	2010	Hexabromocyclododecane determination in seafood samples collected from Japanese coastal areas			X				
630816	Nakai, JS, Stathopulos, PB, Campbell, GL, *et al.*	1999	Penetration of chloroform, trichloroethylene, and tetrachloroethylene through human skin						X	
2911989	Newton, S, Sellstrom, U, De Wit, CA	2015	Emerging flame retardants, PBDEs, and HBCDDs in indoor and outdoor media in Stockholm, Sweden			X				
1927552	Ni, HG, Zeng, H	2013	HBCD and TBBPA in particulate phase of indoor air in Shenzhen, China			X				
1443965	NICNAS	2012	Hexabromocyclododecane: Priority existing chemical assessment report no. 34			X				
4795760	NIOSH	2017	NIOSH Skin Notation (SK) Profile: Trichloroethylene (TCE) (CAS No. 79-01-6)							X
1927660	Nordlöf, U, Helander, B, Bignert, A, *et al.*	2010	Levels of brominated flame retardants and methoxylated polybrominated diphenyl ethers in eggs of white-tailed sea eagles breeding in different regions of Sweden			X				

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3827244	NWQMC	2017	Water quality portal				X			X
2343704	Oh, JK, Kotani, K, Managaki, S, *et al.*	2014	Levels and distribution of hexabromocyclododecane and its lower brominated derivative in Japanese riverine environment			X				
2528316	Okonski, K, Degrendele, C, Melymuk, L, *et al.*	2014	Particle size distribution of halogenated flame retardants and implications for atmospheric deposition and transport			X				
3016112	Olukunle, OI, Okonkwo, OJ	2015	Concentration of novel brominated flame retardants and HBCD in leachates and sediments from selected municipal solid waste landfill sites in Gauteng Province, South Africa			X				
1927653	Ortiz, X, Guerra, P, Díaz-Ferrero, J, *et al.*	2011	Diastereoisomer- and enantiomer-specific determination of hexabromocyclododecane in fish oil for food and feed			X				
508379	Palmquist, H, Hanaeus, J	2005	Hazardous substances in separately collected gray- and blackwater from ordinary Swedish households			X				
85812	Park, JH, Spengler, JD, Yoon, DW, *et al.*	1998	Measurement of air exchange rate of stationary vehicles and estimation of in-vehicle exposure						X	
1927743	Peck, AM, Pugh, RS, Moors, A, *et al.*	2008	Hexabromocyclododecane in white-sided dolphins: temporal trend and stereoisomer distribution in tissues			X				
3809261	Peters, R	2003	Hazardous chemicals in precipitation			X				
3809262	Peters, RJB	2004	Man-made chemicals in Human Blood			X				
510316	Peters, RJB, Beeltje, H, van Delft, RJ	2008	Xeno-estrogenic compounds in precipitation			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
707433	Poet, TS, Corley, RA, Thrall, KD, *et al.*	2000	Assessment of the percutaneous absorption of trichloroethylene in rats and humans using MS/MS real-time breath analysis and physiologically based pharmacokinetic modeling							X
1061432	Polder, A, Gabrielsen, GW, Odland, JØ, *et al.*	2008	Spatial and temporal changes of chlorinated pesticides, PCBs, dioxins (PCDDs/PCDFs) and brominated flame retardants in human breast milk from Northern Russia			X				
3347466	Polder, A, Muller, MB, Brynildsrud, OB, *et al.*	2016	Dioxins, PCBs, chlorinated pesticides and brominated flame retardants in free-range chicken eggs from peri-urban areas in Arusha, Tanzania: Levels and implications for human health			X				
2343683	Polder, A, Müller, MB, Lyche, JL, *et al.*	2014	Levels and patterns of persistent organic pollutants (POPs) in tilapia (Oreochromis sp.) from four different lakes in Tanzania: Geographical differences and implications for human health			X				
786310	Polder, A, Thomsen, C, Lindström, G, *et al.*	2008	Levels and temporal trends of chlorinated pesticides, polychlorinated biphenyls and brominated flame retardants in individual human breast milk samples from Northern and Southern Norway			X				
1927745	Polder, A, Venter, B, Skaare, JU, *et al.*	2008	Polybrominated diphenyl ethers and HBCD in bird eggs of South Africa			X				
2343685	Poma, G, Binelli, A, Volta, P, *et al.*	2014	Evaluation of spatial distribution and accumulation of novel brominated flame retardants, HBCD and PBDEs in an Italian subalpine lake using zebra mussel (Dreissena polymorpha)			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
2528332	Poma, G, Roscioli, C, Guzzella, L	2014	PBDE, HBCD, and novel brominated flame retardant contamination in sediments from Lake Maggiore (Northern Italy)			X				
2343698	Poma, G, Volta, P, Roscioli, C, *et al.*	2014	Concentrations and trophic interactions of novel brominated flame retardants, HBCD, and PBDEs in zooplankton and fish from Lake Maggiore (Northern Italy)			X				
1927763	Pulkrabová, J, Hajslová, J, Poustka, J, *et al.*	2007	Fish as biomonitors of polybrominated diphenyl ethers and hexabromocyclododecane in Czech aquatic ecosystems: Pollution of the Elbe River basin			X				
1927730	Pulkrabová, J, Hrádková, P, Hajslová, J, *et al.*	2009	Brominated flame retardants and other organochlorine pollutants in human adipose tissue samples from the Czech Republic			X				
2343693	Qi, H, Li, WL, Liu, LY, *et al.*	2014	Brominated flame retardants in the urban atmosphere of Northeast China: Concentrations, temperature dependence and gas-particle partitioning			X				
2528328	Qi, H, Li, WL, Liu, LY, *et al.*	2014	Levels, distribution and human exposure of new non-BDE brominated flame retardants in the indoor dust of China			X				
1927588	Qiu, Y, Strid, A, Bignert, A, *et al.*	2012	Chlorinated and brominated organic contaminants in fish from Shanghai markets: a case study of human exposure			X				
947611	Ramu, K, Isobe, T, Takahashi, S, *et al.*	2010	Spatial distribution of polybrominated diphenyl ethers and hexabromocyclododecanes in sediments from coastal waters of Korea			X				
1927780	Ramu, K, Kajiwara, N, Isobe, T, *et al.*	2007	Spatial distribution and accumulation of brominated flame retardants, polychlorinated biphenyls and organochlorine pesticides in blue mussels (Mytilus edulis) from coastal waters of Korea			X				

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2343697	Rani, M, Shim, WJ, Han, GM, *et al.*	2014	Hexabromocyclododecane in polystyrene based consumer products: An evidence of unregulated use			X				
2343738	Rawn, DF, Gaertner, DW, Weber, D, *et al.*	2014	Hexabromocyclododecane concentrations in Canadian human fetal liver and placental tissues			X				
2238553	Rawn, DF, Ryan, JJ, Sadler, AR, *et al.*	2014	Brominated flame retardant concentrations in sera from the Canadian Health Measures Survey (CHMS) from 2007 to 2009			X				
1927636	Rawn, DF, Sadler, A, Quade, SC, *et al.*	2011	Brominated flame retardants in Canadian chicken egg yolks			X				
2528326	Reindl, AR, Falkowska, L	2014	Flame retardants at the top of a simulated baltic marine food web- A case study concerning african penguins from the Gdansk zoo			X				
2919739	Reiner, JL, Becker, PR, Gribble, MO, *et al.*	2015	Organohalogen Contaminants and Vitamins in Northern Fur Seals (Callorhinus ursinus) Collected During Subsistence Hunts in Alaska			X				
1927826	Remberger, M, Sternbeck, J, Palm, A, *et al.*	2004	The environmental occurrence of hexabromocyclododecane in Sweden			X				
2343707	Rivière, G, Sirot, V, Tard, A, *et al.*	2014	Food risk assessment for perfluoroalkyl acids and brominated flame retardants in the French population: Results from the second French total diet study			X				
4152152	Roberts, DR	1980	Industrial hygiene survey report of the New York City sanitation, traffic, and police brake servicing facilities, Queens, New York		X					

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1391354	Robinson, KW, Flanagan, SM, Ayotte, JD, *et al.*	2004	Water Quality in the New England Coastal Basins, Maine, New Hampshire, Massachusetts, and Rhode Island, 1999-2001							X
2182416	Robson, M, Melymuk, L, Bradley, L, *et al.*	2013	Wet deposition of brominated flame retardants to the Great Lakes basin - Status and trends			X				
2128839	Roda, C, Kousignian, I, Ramond, A, *et al.*	2013	Indoor tetrachloroethylene levels and determinants in Paris dwellings						X	
2802879	Rogers, HR, Crathorne, B, Watts, CD	1992	Sources and fate of organic contaminants in the Mersey estuary: Volatile organohalogen compounds						X	
787720	Roosens, L, Abdallah, MA, Harrad, S, *et al.*	2009	Exposure to hexabromocyclododecanes (HBCDs) via dust ingestion, but not diet, correlates with concentrations in human serum: Preliminary results			X				
1927685	Roosens, L, Cornelis, C, D'Hollander, W, *et al.*	2010	Exposure of the Flemish population to brominated flame retardants: Model and risk assessment			X				
1927679	Roosens, L, D'Hollander, W, Bervoets, L, *et al.*	2010	Brominated flame retardants and perfluorinated chemicals, two groups of persistent contaminants in Belgian human blood and milk			X				
1927747	Roosens, L, Dirtu, AC, Goemans, G, *et al.*	2008	Brominated flame retardants and polychlorinated biphenyls in fish from the river Scheldt, Belgium			X				

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1927683	Roosens, L, Geeraerts, C, Belpaire, C, *et al.*	2010	Spatial variations in the levels and isomeric patterns of PBDEs and HBCDs in the European eel in Flanders			X				
1927623	Rüdel, H, Müller, J, Quack, M, *et al.*	2012	Monitoring of hexabromocyclododecane diastereomers in fish from European freshwaters and estuaries			X				
2343679	Ryan, JJ, Rawn, DF	2014	The brominated flame retardants, PBDEs and HBCD, in Canadian human milk samples collected from 1992 to 2005; concentrations and trends			X				
3445832	Ryan, JJ, Wainman, BC, Schecter, A, *et al.*	2006	Trends of the brominated flame retardants, PBDES and HBCD, in human milks from North America			X				
49414	Ryan, TJ, Hart, EM, Kappler, LL	2002	VOC exposures in a mixed-use university art building						X	
1927702	Sagerup, K, Helgason, LB, Polder, A, *et al.*	2009	Persistent organic pollutants and mercury in dead and dying glaucous gulls (Larus hyperboreus) at Bjørnøya (Svalbard)			X				
1927594	Sahlström, L, Sellström, U, de Wit, CA	2012	Clean-up method for determination of established and emerging brominated flame retardants in dust			X				
3012178	Sahlström, LM, Sellström, U, de Wit, CA, *et al.*	2015	Estimated intakes of brominated flame retardants via diet and dust compared to internal concentrations in a Swedish mother-toddler cohort			X				
2938748	Sahlström, LMO, Sellström, U, de Wit, CA, *et al.*	2015	Feasibility study of feces for noninvasive biomonitoring of brominated flame retardants in toddlers			X				

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1927779	Saito, I, Onuki, A, Seto, H	2007	Indoor organophosphate and polybrominated flame retardants in Tokyo			X				
1927566	Salamova, A, Hites, RA	2013	Brominated and chlorinated flame retardants in tree bark from around the globe			X				
1003986	Santillo, D, Johnston, P, Brigden, K	2001	The presence of brominated flame retardants and organotin compounds in dusts collected from Parliament buildings from eight countries			X				
1006146	Santillo, D, Labunska, I, Davidson, H, *et al.*	2003	Consuming chemicals: Hazardous chemicals in house dust as an indicator of chemical exposure in the home			X				
4152375	Sauer, TC	1981	Volatile organic compounds in open ocean and coastal surface waters							X
1066049	Sax, SN, Bennett, DH, Chillrud, SN, *et al.*	2004	Differences in source emission rates of volatile organic compounds in inner-city residences of New York City and Los Angeles						X	
787722	Schecter, A, Haffner, D, Colacino, J, *et al.*	2010	Polybrominated diphenyl ethers (PBDEs) and hexabromocyclodecane (HBCD) in composite U.S. food samples			X				
1401050	Schecter, A, Szabo, DT, Miller, J, *et al.*	2012	Hexabromocyclododecane (HBCD) stereoisomers in U.S. food from Dallas, Texas			X				
2528320	Schreder, ED, La Guardia, MJ	2014	Flame retardant transfers from U.S. households (dust and laundry wastewater) to the aquatic environment			X				

HERO ID	Author	Year	Title	Seed Chemical						
				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
3449771	Schwarz, S, Rackstraw, A, Behnisch, PA, *et al.*	2016	Peregrine falcon egg pollutants Mirror Stockholm POPs list including methylmercury			X				
4663208	Sebroski, J, Mason, M.	2017	Developing consensus standards for measuring chemical emissions from spray polyurethane foam (SPF) insulation	X						
999339	Sellström, U, Bignert, A, Kierkegaard, A, *et al.*	2003	Temporal trend studies on tetra- and pentabrominated diphenyl ethers and hexabromocyclododecane in guillemot egg from the Baltic Sea			X				
1715539	Sellstrom, U, Kierkkegaard, A, De Wit, C, *et al.*	1998	Polybrominated diphenyl ethers and hexabromocyclododecane in sediment and fish from a Swedish river			X				
730121	Sexton, K, Mongin, SJ, Adgate, JL, *et al.*	2007	Estimating volatile organic compound concentrations in selected microenvironments using time-activity and personal exposure data						X	
1443830	Shaw, SD, Berger, ML, Brenner, D, *et al.*	2009	Bioaccumulation of polybrominated diphenyl ethers and hexabromocyclododecane in the northwest Atlantic marine food web			X				
1927612	Shaw, SD, Berger, ML, Weijs, L, *et al.*	2012	Tissue-specific accumulation of polybrominated diphenyl ethers (PBDEs) including Deca-BDE and hexabromocyclododecanes (HBCDs) in harbor seals from the northwest Atlantic			X				
3655537	Sheehy, JW, Cooper, TC, O'Brien, DM, *et al.*	1989	Control of asbestos exposure during brake drum service		X					

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
1927559	Shi, Z, Jiao, Y, Hu, Y, *et al.*	2013	Levels of tetrabromobisphenol A, hexabromocyclododecanes and polybrominated diphenyl ethers in human milk from the general population in Beijing, China			X				
3975096	Shi, Z, Zhang, L, Zhao, Y, *et al.*	2017	Dietary exposure assessment of Chinese population to tetrabromobisphenol-A, hexabromocyclododecane and decabrominated diphenyl ether: Results of the 5th Chinese total diet study			X				
3828886	Shi, Z, Zhang, L, Zhao, Y, *et al.*	2017	A national survey of tetrabromobisphenol-A, hexabromocyclododecane and decabrominated diphenyl ether in human milk from China: Occurrence and exposure assessment			X				
1927708	Shi, ZX, Wu, YN, Li, JG, *et al.*	2009	Dietary exposure assessment of Chinese adults and nursing infants to tetrabromobisphenol-A and hexabromocyclododecanes: Occurrence measurements in foods and human milk			X				
3019586	Shoeib, M, Ahrens, L, Jantunen, L, *et al.*	2014	Concentrations in air of organobromine, organochlorine and organophosphate flame retardants in Toronto, Canada			X				
1927609	Shoeib, M, Harner, T, Webster, GM, *et al.*	2012	Legacy and current-use flame retardants in house dust from Vancouver, Canada			X				
29192	Singh, HB, Salas, LJ, Stiles, RE	1983	Selected man-made halogenated chemicals in the air and oceanic environment				X		X	X

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
3350528	Son, MH, Kim, J, Shin, ES, *et al.*	2015	Diastereoisomer- and species-specific distribution of hexabromocyclododecane (HBCD) in fish and marine invertebrates			X				
947918	Sørmo, EG, Jenssen, BM, Lie, E, *et al.*	2009	Brominated flame retardants in aquatic organisms from the North Sea in comparison with biota from the high Arctic marine environment			X				
1927631	Sørmo, EG, Lie, E, Ruus, A, *et al.*	2011	Trophic level determines levels of brominated flame-retardants in coastal herring gulls			X				
1927787	Sørmo, EG, Salmer, MP, Jenssen, BM, *et al.*	2006	Biomagnification of polybrominated diphenyl ether and hexabromocyclododecane flame retardants in the polar bear food chain in Svalbard, Norway			X				
697789	Stapleton, H, Allen, J, Kelly, S, *et al.*	2008	Alternate and new brominated flame retardants detected in U.S. house dust			X				
1676957	Stapleton, HM, Dodder, NG, Kucklick, JR, *et al.*	2006	Determination of HBCD, PBDEs and MeO-BDEs in California sea lions (Zalophus californianus) stranded between 1993 and 2003			X				
2343712	Stapleton, HM, Misenheimer, J, Hoffman, K, *et al.*	2014	Flame retardant associations between children's handwipes and house dust			X				
1953674	Stefaniak, AB, Breysse, PN, Murray, MPM, *et al.*	2000	An evaluation of employee exposure to volatile organic compounds in three photocopy centers						X	

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
3546060	Stiborova, H, Kolar, M, Vrkoslavova, J, *et al.*	2017	Linking toxicity profiles to pollutants in sludge and sediments			X				
3350527	Stiborova, H, Vrkoslavova, J, Pulkrabova, J, *et al.*	2015	Dynamics of brominated flame retardants removal in contaminated wastewater sewage sludge under anaerobic conditions			X				
2128575	Su, FC, Mukherjee, B, Batterman, S	2013	Determinants of personal, indoor and outdoor VOC concentrations: An analysis of the RIOPA data						X	
3345569	Su, G, Letcher, RJ, Moore, JN, *et al.*	2015	Spatial and temporal comparisons of legacy and emerging flame retardants in herring gull eggs from colonies spanning the Laurentian Great Lakes of Canada and United States			X				
2528335	Su, G, Saunders, D, Yu, Y, *et al.*	2014	Occurrence of additive brominated flame retardants in aquatic organisms from Tai Lake and Yangtze River in Eastern China, 2009-2012			X				
3350531	Su, J, Lu, Y, Liu, Z, *et al.*	2015	Distribution of polybrominated diphenyl ethers and HBCD in sediments of the Hunhe River in Northeast China			X				
1999	Su, WY, Jaskot, RH, Dreher, KL	2000	Particulate matter induction of pulmonary gelatinase A, gelatinase B, tissue inhibitor of metalloproteinase expression						X	
4158939	Sudaryanto, A, Isobe, T, Agusa, T, *et al.*	2007	Levels and distribution of organochlorine compounds and brominated flame retardants in fish from Laos			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
1927580	Sun, YX, Luo, XJ, Mo, L, *et al.*	2012	Hexabromocyclododecane in terrestrial passerine birds from e-waste, urban and rural locations in the Pearl River Delta, South China: Levels, biomagnification, diastereoisomer- and enantiomer-specific accumulation			X				
1927698	Takahashi, S, Oshihoi, T, Ramu, K, *et al.*	2010	Organohalogen compounds in deep-sea fishes from the western North Pacific, off-Tohoku, Japan: Contamination status and bioaccumulation profiles			X				
1927720	Takigami, H, Suzuki, G, Hirai, Y, *et al.*	2009	Flame retardants in indoor dust and air of a hotel in Japan			X				
4197589	Takigami, H, Suzuki, G, Hirai, Y, *et al.*	2007	Comparison of brominated flame retardants in indoor air and dust samples from two homes in Japan			X				
1927735	Takigami, H, Suzuki, G, Hirai, Y, *et al.*	2008	Transfer of brominated flame retardants from components into dust inside television cabinets			X				
198241	Takigami, H, Suzuki, G, Hirai, Y, *et al.*	2009	Brominated flame retardants and other polyhalogenated compounds in indoor air and dust from two houses in Japan			X				
4158941	Tanabe, S, Ramu, K, Isobe, T, *et al.*	2007	Levels and temporal trends of brominated flame retardants (PBDEs and HBCDs) in Asian waters using archived samples from ES-Bank, Ehime University, Japan			X				
2343699	Tang, J, Feng, J, Li, X, *et al.*	2014	Levels of flame retardants HBCD, TBBPA and TBC in surface soils from an industrialized region of East China			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
3350536	Tang, L, Shao, HY, Zhu, JY, *et al.*	2015	Hexabromocyclododecane diastereoisomers in surface sediments from river drainage basins of Shanghai, China: Occurrence, distribution, and mass inventory			X				
3862906	Tao, F, Abou-Elwafa Abdallah, M, Ashworth, DC, *et al.*	2017	Emerging and legacy flame retardants in UK human milk and food suggest slow response to restrictions on use of PBDEs and HBCDD			X				
3350488	Tao, F, Matsukami, H, Suzuki, G, *et al.*	2016	Emerging halogenated flame retardants and hexabromocyclododecanes in food samples from an e-waste processing area in Vietnam			X				
5349328	Tay, JH, Sellström, U, Papadopoulou, E, *et al.*	2018	Assessment of dermal exposure to halogenated flame retardants: Comparison using direct measurements from hand wipes with an indirect estimation from settled dust concentrations			X				
28307	Thomas, KW, Pellizzari, ED, Perritt, RL, *et al.*	1991	Effect of dry-cleaned clothes on tetrachloroethylene levels in indoor air, personal air, and breath for residents of several New Jersey homes						X	
1927761	Thomsen, C, Knutsen, HK, Liane, VH, *et al.*	2008	Consumption of fish from a contaminated lake strongly affects the concentrations of polybrominated diphenyl ethers and hexabromocyclododecane in serum			X				
1927620	Thuresson, K, Björklund, JA, de Wit, CA	2012	Tri-decabrominated diphenyl ethers and hexabromocyclododecane in indoor air and dust from Stockholm microenvironments 1: Levels and profiles			X				
27401	Tichenor, BA, Sparks, LE, Jackson, MD, *et al.*	1990	Emissions of perchloroethylene from dry cleaned fabrics						X	

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1927589	Toms, LM, Guerra, P, Eljarrat, E, *et al.*	2012	Brominated flame retardants in the Australian population: 1993-2009			X				
1927822	Tomy, GT, Budakowski, W, Halldorson, T, *et al.*	2004	Biomagnification of alpha- and gamma-hexabromocyclododecane isomers in a Lake Ontario food web			X				
1279130	Tomy, GT, Pleskach, K, Ferguson, SH, *et al.*	2009	Trophodynamics of some PFCs and BFRs in a western Canadian Arctic marine food web			X				
1443836	Tomy, GT, Pleskach, K, Oswald, T, *et al.*	2008	Enantioselective bioaccumulation of hexabromocyclododecane and congener-specific accumulation of brominated diphenyl ethers in an eastern Canadian Arctic marine food web			X				
1927648	Törnkvist, A, Glynn, A, Aune, M, *et al.*	2011	PCDD/F, PCB, PBDE, HBCD and chlorinated pesticides in a Swedish market basket from 2005- Levels and dietary intake estimations			X				
1927687	Tue, NM, Sudaryanto, A, Minh, TB, *et al.*	2010	Accumulation of polychlorinated biphenyls and brominated flame retardants in breast milk from women living in Vietnamese e-waste recycling sites			X				
1927567	Tue, NM, Takahashi, S, Suzuki, G, *et al.*	2013	Contamination of indoor dust and air by polychlorinated biphenyls and brominated flame retardants and relevance of non-dietary exposure in Vietnamese informal e-waste recycling sites			X				
29263	U.S. EPA	1977	Environmental monitoring near industrial sites methylchloroform							X
3808963	U.S. EPA	1994	Consumer exposure to paint stripper solvents					X		

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2991013	U.S. EPA	2007	Exposure and Fate Assessment Screening Tool (E-FAST), Version 2.0				X			
786546	U.S. EPA	2011	Exposure factors handbook: 2011 edition	X			X		X	X
3491015	U.S. EPA	2012	Toxicological review of tetrachloroethylene (perchloroethylene) (CAS No. 127-18-4) In support of summary information on the Integrated Risk Information System (IRIS)						X	
5176443	U.S. EPA	2016	EPA Discharge Monitoring Report Data				X			
3970104	U.S. EPA	2017	Chemical and product categories: tetrachloroethylene				X		X	
4154229	U.S. EPA	2017	Consumer Exposure Model (CEM) version 2.0: User guide				X		X	
3827328	U.S. EPA	2017	Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: 1-Bromopropane. Support document for Docket EPA-HQ-OPPT-2016-0741	X						
3986807	2017	Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: Tetrachloroethylene (Perchloroethylene)							X	
3834224	U.S. EPA	2017	Toxics Release Inventory (TRI), reporting year 2015	X						
5041148	U.S. EPA	2017	Toxics Release Inventory (TRI), reporting year 2016				X			
5176414	U.S. EPA	2017	Use and market profile for methylene chloride				X			
1927796	Ueno, D, Alaee, M, Marvin, C, *et al.*	2006	Distribution and transportability of hexabromocyclododecane (HBCD) in the Asia-Pacific region using skipjack tuna as a bioindicator			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
1927689	Ueno, D, Isobe, T, Ramu, K, *et al.*	2010	Spatial distribution of hexabromocyclododecanes (HBCDs), polybrominated diphenyl ethers (PBDEs) and organochlorines in bivalves from Japanese coastal waters			X				
3975046	USGS	2003	A national survey of methyl tert-butyl ether and other volatile organic compounds in drinking-water sources: Results of the random survey				X		X	X
3975042	USGS	2006	Water-quality conditions of Chester Creek, Anchorage, Alaska, 1998-2001						X	X
5425102	USGS	2013	Federal Standards and Procedures for the National Watershed Boundary Dataset (WBD): Techniques and Methods 11–A3				X			
5098226	Van Amber, RR, Niven, BE, Wilson, CA	2010	Effects of laundering and water temperature on the properties of silk and silk-blend knitted fabrics						X	
1927756	van Leeuwen, SP, de Boer, J	2008	Brominated flame retardants in fish and shellfish - Levels and contribution of fish consumption to dietary exposure of Dutch citizens to HBCD			X				
1274422	van Leeuwen, SP, van Velzen, MJ, Swart, CP, *et al.*	2009	Halogenated contaminants in farmed salmon, trout, tilapia, pangasius, and shrimp			X				
31210	Van Winkle, MR, Scheff, PA	2001	Volatile organic compounds, polycyclic aromatic hydrocarbons and elements in the air of 10 urban homes						X	
2695212	Venier, M, Dove, A, Romanak, K, *et al.*	2014	Flame retardants and legacy chemicals in Great Lakes' water			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
1927638	Venier, M, Hites, RA	2011	Flame retardants in the serum of pet dogs and in their food			X				
1927677	Venier, M, Wierda, M, Bowerman, WW, *et al.*	2010	Flame retardants and organochlorine pollutants in bald eagle plasma from the Great Lakes region			X				
3809193	Venkatesan, AK, Halden, RU	2014	Brominated flame retardants in U.S. biosolids from the EPA national sewage sludge survey and chemical persistence in outdoor soil mesocosms			X				
1927975	Verboven, N, Verreault, J, Letcher, RJ, *et al.*	2009	Differential investment in eggs by arctic-breeding glaucous gulls (Larus hyperboreus) exposed to persistent organic pollutants			X				
1927809	Verreault, J, Gabrielsen, GW, Chu, S, *et al.*	2005	Flame retardants and methoxylated and hydroxylated polybrominated diphenyl ethers in two Norwegian Arctic top predators: Glaucous gulls and polar bears			X				
4152199	Verreault, J, Gabrielsen, GW, Letcher, RJ, *et al.*	2004	New and established organohalogen contaminants and their metabolites in plasma and eggs of glaucous gulls from Bear Island. SPFO-report			X				
1927771	Verreault, J, Gebbink, WA, Gauthier, LT, *et al.*	2007	Brominated flame retardants in glaucous gulls from the Norwegian Arctic: More than just an issue of polybrominated diphenyl ethers			X				
531779	Verreault, J, Shahmiri, S, Gabrielsen, GW, *et al.*	2007	Organohalogen and metabolically-derived contaminants and associations with whole body constituents in Norwegian Arctic glaucous gulls			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
999346	Villanger, GD, Lydersen, C, Kovacs, KM, *et al.*	2011	Disruptive effects of persistent organohalogen contaminants on thyroid function in white whales (Delphinapterus leucas) from Svalbard			X				
3575217	Vojta, Š, Bečanová, J, Melymuk, L, *et al.*	2017	Screening for halogenated flame retardants in European consumer products, building materials and wastes			X				
1927578	Vorkamp, K, Bester, K, Rigét, FF	2012	Species-specific time trends and enantiomer fractions of hexabromocyclododecane (HBCD) in biota from East Greenland			X				
2343732	Vorkamp, K, Bossi, R, Bester, K, *et al.*	2014	New priority substances of the European Water Framework Directive: Biocides, pesticides and brominated flame retardants in the aquatic environment of Denmark			X				
3015562	Vorkamp, K, Bossi, R, Riget, FF, *et al.*	2015	Novel brominated flame retardants and dechlorane plus in Greenland air and biota			X				
1927649	Vorkamp, K, Rigét, FF, Bossi, R, *et al.*	2011	Temporal trends of hexabromocyclododecane, polybrominated diphenyl ethers and polychlorinated biphenyls in ringed seals from East greenland			X				
1927805	Vorkamp, K, Thomsen, M, Falk, K, *et al.*	2005	Temporal development of brominated flame retardants in peregrine Falcon (Falco peregrinus) eggs from South Greenland (1986-2003)			X				
1989	Waber, U, Im Hof, V, Geiser, M, *et al.*	1999	A new methodology for controlled particle inhalation by small rodents						X	

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
3350514	Wang, J, Jia, X, Gao, S, *et al.*	2016	Levels and distributions of polybrominated diphenyl ethers, hexabromocyclododecane, and tetrabromobisphenol A in sediments from Taihu Lake, China			X				
3546093	Wang, L, Zhang, M, Lou, Y, *et al.*	2017	Levels and distribution of tris-(2,3-dibromopropyl) isocyanurate and hexabromocyclododecanes in surface sediments from the Yellow River Delta wetland of China			X				
1927586	Wang, T, Han, S, Ruan, T, *et al.*	2013	Spatial distribution and inter-year variation of hexabromocyclododecane (HBCD) and tris-(2,3-dibromopropyl) isocyanurate (TBC) in farm soils at a peri-urban region			X				
1927688	Wang, X, Ren, N, Qi, H, *et al.*	2009	Levels and distribution of brominated flame retardants in the soil of Harbin in China			X				
3969313	Weiss, J, ana, Meijer, L, isethe, Sauer, P, ieter, *et al.*	2017	PBDE and HBCDD levels in blood from Dutch mothers and infants			X				
787751	Weiss, J, Wallin, E, Axmon, A, *et al.*	2006	Hydroxy-PCBs, PBDEs, and HBCDDs in serum from an elderly population of Swedish fishermen's wives and associations with bone density			X				
104106	Weissflog, L, Elansky, N, Putz, E, *et al.*	2004	Trichloroacetic acid in the vegetation of polluted and remote areas of both hemispheres - Part II: Salt lakes as novel sources of natural chlorohydrocarbons						X	
1005969	Westat	1987	Household solvent products: A national usage survey	X			X		X	X
3982306	WSDE	2016	Brominated flame retardants, alkylphenolic compounds, and hexabromocyclododecane in freshwater fish of Washington state rivers and lakes			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
1927678	Wu, JP, Guan, YT, Zhang, Y, *et al.*	2010	Trophodynamics of hexabromocyclododecanes and several other non-PBDE brominated flame retardants in a freshwater food web			X				
3223093	Wu, MH, Han, T, Xu, G, *et al.*	2016	Occurrence of Hexabromocyclododecane in soil and road dust from mixed-land-use areas of Shanghai, China, and its implications for human exposure			X				
3809127	2004	Chemical Check Up: An analysis of chemicals in the blood of members of the European parliament				X				
1927654	Xia, C, Lam, JC, Wu, X, *et al.*	2011	Hexabromocyclododecanes (HBCDs) in marine fishes along the Chinese coastline			X				
1927770	Xian, Q, Ramu, K, Isobe, T, *et al.*	2008	Levels and body distribution of polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecanes (HBCDs) in freshwater fishes from the Yangtze River, China			X				
1927542	Xu, J, Zhang, Y, Guo, C, *et al.*	2013	Levels and distribution of tetrabromobisphenol A and hexabromocyclododecane in Taihu Lake, China			X				
645789	Yamamoto, K, Fukushima, M, Kakutani, N, *et al.*	1997	Volatile organic compounds in urban rivers and their estuaries in Osaka, Japan				X		X	
2310570	Yamamoto, K, Fukushima, M, Kakutani, N, *et al.*	2001	Contamination of vinyl chloride in shallow urban rivers in Osaka, Japan						X	
3052892	Yang, B, Yang, GP, Lu, XL, *et al.*	2015	Distributions and sources of volatile chlorocarbons and bromocarbons in the Yellow Sea and East China Sea						X	

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
3350516	Yang, C, Rose, NL, Turner, SD, *et al.*	2016	Hexabromocyclododecanes, polybrominated diphenyl ethers, and polychlorinated biphenyls in radiometrically dated sediment cores from English lakes, ~1950-present			X				
2799613	Yang, G, uiP, Yang, B, in, Lu, XL, an, *et al.*	2014	Spatio-temporal variations of sea surface halocarbon concentrations and fluxes from southern Yellow Sea						X	
1927611	Yang, R, Wei, H, Guo, J, *et al.*	2012	Emerging brominated flame retardants in the sediment of the Great Lakes			X				
3080975	Yeung, P, Patience, K, Apthorpe, L, *et al.*	1999	An Australian study to evaluate worker exposure to chrysotile in the automotive service industry		X					
2528341	Yin, G, Asplund, L, Qiu, Y, *et al.*	2014	Chlorinated and brominated organic pollutants in shellfish from the Yellow Sea and East China Sea			X				
1927541	Yu, L, Luo, X, Zheng, X, *et al.*	2013	Occurrence and biomagnification of organohalogen pollutants in two terrestrial predatory food chains			X				
2343702	Yu, LH, Luo, XJ, Liu, HY, *et al.*	2014	Organohalogen contamination in passerine birds from three metropolises in China: Geographical variation and its implication for anthropogenic effects on urban environments			X				
1058394	Yu, Z, Chen, L, Mai, B, *et al.*	2008	Diastereoisomer- and enantiomer-specific profiles of hexabromocyclododecane in the atmosphere of an urban city in South China			X				
1049627	Yu, Z, Peng, P, Sheng, G, *et al.*	2008	Determination of hexabromocyclododecane diastereoisomers in air and soil by liquid chromatography-electrospray tandem mass spectrometry			X				

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				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
2343713	Zacs, D, Rjabova, J, Bartkevics, V	2014	New perspectives on diastereoselective determination of hexabromocyclododecane traces in fish by ultra high performance liquid chromatography-high resolution orbitrap mass spectrometry			X				
2528323	Zacs, D, Rjabova, J, Pugajeva, I, *et al.*	2014	Ultra high performance liquid chromatography-time-of-flight high resolution mass spectrometry in the analysis of hexabromocyclododecane diastereomers: Method development and comparative evaluation vs. ultra high performance liquid chromatography coupled to Orbitrap high resolution mass spectrometry and triple quadrupole tandem mass spectrometry			X				
787753	Zegers, BN, Mets, A, van Bommel, R, *et al.*	2005	Levels of hexabromocyclododecane in harbor porpoises and common dolphins from western European seas, with evidence for stereoisomer-specific biotransformation by cytochrome P450			X				
2528321	Zeng, L, Yang, R, Zhang, Q, *et al.*	2014	Current levels and composition profiles of emerging halogenated flame retardants and dehalogenated products in sewage sludge from municipal wastewater treatment plants in china			X				
2343681	Zeng, YH, Luo, XJ, Zheng, XB, *et al.*	2014	Species-specific bioaccumulation of halogenated organic pollutants and their metabolites in fish serum from an e-waste site, South China			X				
3350480	Zeng, YH, Tang, B, Luo, XJ, *et al.*	2016	Organohalogen pollutants in surface particulates from workshop floors of four major e-waste recycling sites in China and implications for emission lists			X				
3350497	Zhang, H, Bayen, S, Kelly, BC	2015	Co-extraction and simultaneous determination of multi-class hydrophobic organic contaminants in marine sediments and biota using GC-EI-MS/MS and LC-ESI-MS/MS			X				

HERO ID	Author	Year	Title	Seed Chemical						
				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
3350551	Zhang, L, Na, G, -S, He, C, -X, *et al.*	2016	A novel method through solid phase extraction combined with gradient elution for concentration and separation of 66 (ultra) trace persistent toxic pollutants in Antarctic waters			X				
1927707	Zhang, X, Yang, F, Luo, C, *et al.*	2009	Bioaccumulative characteristics of hexabromocyclododecanes in freshwater species from an electronic waste recycling area in China			X				
3350489	Zhang, Y, Li, Q, Lu, Y, *et al.*	2016	Hexabromocyclododecanes (HBCDDs) in surface soils from coastal cities in North China: Correlation between diastereoisomer profiles and industrial activities			X				
2343741	Zhang, Y, Sun, H, Liu, F, *et al.*	2013	Hexabromocyclododecanes in limnic and marine organisms and terrestrial plants from Tianjin, China: Diastereomer- and enantiomer-specific profiles, biomagnification, and human exposure			X				
1927597	Zheng, XB, Wu, JP, Luo, XJ, *et al.*	2012	Halogenated flame retardants in home-produced eggs from an electronic waste recycling region in South China: Levels, composition profiles, and human dietary exposure assessment			X				
3546047	Zhu, C, Wang, P, Li, Y, *et al.*	2017	Trophic transfer of hexabromocyclododecane in the terrestrial and aquatic food webs from an e-waste dismantling region in East China			X				
3546055	Zhu, H, Zhang, K, Sun, H, *et al.*	2017	Spatial and temporal distributions of hexabromocyclododecanes in the vicinity of an expanded polystyrene material manufacturing plant in Tianjin, China			X				
1927543	Zhu, N, Fu, J, Gao, Y, *et al.*	2013	Hexabromocyclododecane in alpine fish from the Tibetan Plateau, China			X				

HERO ID	Author	Year	Title	Seed Chemical						
				1-Bromopropane	Asbestos	Cyclic Aliphatic Bromide Cluster	Methylene Chloride	*n*-Methylpyrrolidone	Perchloroethylene	Trichloroethylene
1927595	Zhu, N, Li, A, Wang, T, *et al.*	2012	Tris(2,3-dibromopropyl) isocyanurate, hexabromocyclododecanes, and polybrominated diphenyl ethers in mollusks from Chinese Bohai Sea			X				
2343682	Zhu, N, Schramm, KW, Wang, T, *et al.*	2014	Environmental fate and behavior of persistent organic pollutants in Shergyla Mountain, southeast of the Tibetan Plateau of China			X				
2343705	Zhu, ZC, Chen, SJ, Zheng, J, *et al.*	2014	Occurrence of brominated flame retardants (BFRs), organochlorine pesticides (OCPs), and polychlorinated biphenyls (PCBs) in agricultural soils in a BFR-manufacturing region of North China			X				
2189687	Zoccolillo, L, Abete, C, Amendola, L, *et al.*	2004	Halocarbons in aqueous matrices from the Rennick Glacier and the Ross Sea (Antarctica)						X	

Appendix H SCREENING CRITERIA FOR EXPOSURE AND HAZARD EVIDENCE

The overall objective of the screening process is to select the most relevant evidence for inclusion in the assessment. Systematic reviews typically describe the study eligibility criteria in the form of PECO statements or a modified framework. PECO stands for **P**opulation, **E**xposure, **C**omparator and **O**utcome and the framework is used to formulate criteria about those characteristics that should be present in the data or information source in order to be eligible for inclusion in the review. EPA adopted PECO statements or a modified framework to guide the inclusion/exclusion decisions during the screening step. This appendix contains the eligibility criteria for the following data or evidence streams informing the TSCA risk evaluations: physical and chemical properties; environmental fate and transport; engineering and occupational exposure; exposure to the environment, the general population and consumers; and environmental and human health hazards.

H.1 Inclusion Criteria for Data Sources Reporting Physical and Chemical Properties

Assessors seek data and information on various chemical-specific physical and chemical properties or endpoints as listed in Table_Apx H-1.

Table_Apx H-1. Data or Information Needs for Physical and Chemical Properties

Property or Endpoint
Physical form or state (*e.g.*, solid, liquid, gas)
Physical properties (*e.g.*, color, scent)
Melting point
Boiling point
Density
Vapor pressure
Vapor density
Water solubility
Octanol:water partition coefficient (K_{OW})
Henry's law constant
Flash point
Autoflammability
Viscosity
Refractive index

EPA includes data or information sources that identify measured or estimated physical and chemical properties or endpoints under standard conditions for the chemical substance of interest, including mixtures of isomers as appropriate. Highly theoretical studies are excluded from further consideration.

H.2 Inclusion Criteria for Data Sources Reporting Environmental Fate Data

EPA developed a generic PESO statement to guide the screening of environmental fate data or information sources for the TSCA risk evaluations (Table_Apx H-2). PESO stands for **P**athways and **P**rocesses, **E**xposure, **S**etting or Scenario, and **O**utcomes. Data or information sources that comply with the inclusion criteria in the PESO statement are eligible for inclusion, considered for evaluation, and possibly included in the environmental fate assessment. On the other hand, data or information sources that fail to meet the criteria in the PESO statement are excluded from further consideration.

Assessors seek information on various chemical-specific fate endpoints and associated fate processes, environmental media and exposure pathways as part of the process of developing the environmental fate assessment for each risk evaluation. EPA uses the PESO statement (Table_Apx H-2) along with the information in Table_Apx H-3 when screening the fate data or information sources to ensure complete coverage of the processes, pathways and data or information relevant to the environmental fate and transport of the chemical substance undergoing risk evaluation. Quantitative data for the endpoints in Table_Apx H-3 should be included in the literature screening when data come from a primary source and are reported in the environmental media of interest.

Table_Apx H-2. Inclusion Criteria for Data or Information Sources Reporting Environmental Fate and Transport Data

PESO Element	Evidence
Pathways and **P**rocesses	Environmental fate, transport, partitioning and degradation behavior across environmental media to inform exposure pathways of the chemical substance of interest Exposure pathways included in the conceptual models: air, surface water, groundwater, wastewater, soil, sediment and biosolids. Processes associated with the target exposure pathways Bioconcentration and bioaccumulation Destruction and removal by incineration Please refer to the conceptual models for more information about the exposure pathways included in each TSCA risk evaluation.
Exposure	Environmental exposure of environmental receptors (*i.e.*, aquatic and terrestrial organisms) to the chemical substance of interest, mixtures including the chemical substance, and/or its degradation products and metabolites Environmental exposure of human receptors, including any PESS, to the chemical substance of interest, mixtures including the chemical substance, and/or its degradation products and metabolites Please refer to the conceptual models for more information about the environmental and human receptors included in each TSCA risk evaluation.
Setting or **S**cenario	Any setting or scenario resulting in releases of the chemical substance of interest into the natural or built environment (*e.g.*, buildings including homes or workplaces, or wastewater

PESO Element	Evidence
	treatment facilities) that would expose environmental (*i.e.*, aquatic and terrestrial organisms) or human receptors (*i.e.*, general population, and PESS)
Outcomes	Fate properties that allow assessments of exposure pathways: • Abiotic and biotic degradation rates, mechanisms, pathways, and products • Bioaccumulation magnitude and metabolism rates • Partitioning within and between environmental media (see Pathways and Processes)

Table_Apx H-3. Fate Endpoints and Associated Processes, Media, and Exposure Pathways Considered in the Development of the Environmental Fate Assessment

Fate Data Endpoint	Associated Process(es)	Associated Media/Exposure Pathways			
		Surface Water, Wastewater, Sediment	Soil, Biosolids	Groundwater	Air
Required environmental fate data					
Abiotic reduction rates or half-lives	Abiotic reduction, Abiotic dehalogenation	X			
Aerobic biodegradation rates or half-lives	Aerobic biodegradation	X	X		
Anaerobic biodegradation rates or half-lives	Anaerobic biodegradation	X	X	X	
Aqueous photolysis (direct and indirect) rates or half-lives	Aqueous photolysis (direct and indirect)	X			
Atmospheric photolysis (direct and indirect) rates or half-lives	Atmospheric photolysis (direct and indirect)				X
Bioconcentration factor (BCF), Bioaccumulation factor (BAF)	Bioconcentration, Bioaccumulation	X	X		X
Biomagnification and related information	Trophic magnification	X			
Desorption information	Sorption, Mobility	X	X	X	
Destruction and removal by incineration	Incineration				X
Hydrolysis rates or half-lives	Hydrolysis	X	X	X	

Fate Data Endpoint	Associated Process(es)	Associated Media/Exposure Pathways			
		Surface Water, Wastewater, Sediment	Soil, Biosolids	Groundwater	Air
K_{OC} and other sorption information	Sorption, Mobility	X	X	X	
Wastewater treatment removal information	Wastewater treatment	X	X		
Supplemental (or optional) environmental fate data					
Abiotic transformation products	Hydrolysis, Photolysis, Incineration	X			X
Aerobic biotransformation products	Aerobic biodegradation	X	X		
Anaerobic biotransformation products	Anaerobic biodegradation	X	X	X	
Atmospheric deposition information	Atmospheric deposition				X
Coagulation information	Coagulation, Mobility	X		X	
Incineration removal information	Incineration				X
Suspension/resuspension information	Suspension/resuspension, Mobility	X			

H.3 Inclusion Criteria for Data Sources Reporting Engineering, Environmental Release, and Occupational Exposure Data

EPA developed a generic RESO statement to guide the screening of engineering and occupational exposure data or information sources for the TSCA risk evaluations (Table_Apx H-4). RESO stands for **R**eceptors, **E**xposure, **S**etting or Scenario, and **O**utcomes. Data or information sources that comply with the inclusion criteria specified in the RESO statement are eligible for inclusion, considered for evaluation, and possibly included in the environmental release and occupational exposure assessments. On the other hand, data or information sources that fail to meet the criteria in the RESO statement are excluded from further consideration.

Assessors seek information on various chemical-specific engineering and occupational exposure data needs as part of the process of developing the exposure assessment for each risk evaluation. EPA uses the RESO statement (Table_Apx H-4) along with the information in when screening the engineering and occupational exposure data and information.

Table_Apx H-4. Inclusion Criteria for Data Sources Reporting Engineering and Occupational Exposure Data

RESO Element	Evidence
Receptors	• Humans: Workers, including occupational non-users • Environment: All environmental receptors (relevant release estimates input to Exposure) Please refer to the conceptual models for more information about the environmental and human receptors included in the TSCA risk evaluation.
Exposure	• Worker exposure to and relevant environmental releases of the chemical substance from occupational scenarios: o Dermal and inhalation exposure routes (as indicated in the conceptual model) o Oral route (as indicated in the conceptual model) Please refer to the conceptual models for more information about the routes and media/pathways included in the TSCA risk evaluation.
Setting or Scenario	• Any occupational setting or scenario resulting in worker exposure and relevant environmental releases (includes all manufacturing, processing, use, disposal.
Outcomes	• Quantitative estimates* of worker exposures and of relevant environmental releases from occupational settings • General information and data related and relevant to the occupational estimates[a]
[a] Metrics (*e.g.*, mg/kg/day or mg/m^3 for worker exposures, kg/site/day for releases) are determined by toxicologists for worker exposures and by exposure assessors for releases; also, the Engineering, Release and Occupational Exposure Data Needs (Table_Apx H-5) provides a list of related and relevant general information.	

Table_Apx H-5. Engineering, Environmental Release, and Occupational Exposure Data Necessary to Develop the Environmental Release and Occupational Exposure Assessments

Objective Determined during Scoping	Type of Data[a]
General Engineering Assessment (may apply to Occupational Exposures and/or Environmental Releases)	Description of the life cycle of the chemical(s) of interest, from manufacture to end-of-life (*e.g.*, each manufacturing, processing, or use step), and material flow between the industrial and commercial life cycle stages. The total annual U.S. volume (lb/yr or kg/yr) of the chemical(s) of interest manufactured, imported, processed, and used; and the share of total annual manufacturing and import volume that is processed or used in each life cycle step. Description of processes, equipment, and unit operations during each industrial/ commercial life cycle step. Material flows, use rates, and frequencies (lb/site-day or kg/site-day and days/yr; lb/site-batch and batches/yr) of the chemical(s) of interest during each industrial/ commercial life cycle step. Note: if available, include weight fractions of the chemicals (s) of interest and material flows of all associated primary chemicals (especially water). Number of sites that manufacture, process, or use the chemical(s) of interest for each industrial/ commercial life cycle step and site locations. Concentration of the chemical of interest
Occupational Exposure	Description of worker activities with exposure potential during the manufacture, processing, or use of the chemical(s) of interest in each industrial/commercial life cycle stage. Potential routes of exposure (*e.g.*, inhalation, dermal). Physical form of the chemical(s) of interest for each exposure route (*e.g.*, liquid, vapor, mist) and activity. Breathing zone (personal sample) measurements of occupational exposures to the chemical(s) of interest, measured as time-weighted averages (TWAs), short-term exposures, or peak exposures in each occupational life cycle stage (or in a workplace scenario similar to an occupational life cycle stage). Area or stationary measurements of airborne concentrations of the chemical(s) of interest in each occupational setting and life cycle stage (or in a workplace scenario similar to the life cycle stage of interest). For solids, bulk and dust particle size characterization data. Dermal exposure data. Exposure duration (hr/day). Exposure frequency (days/yr). Number of workers who potentially handle or have exposure to the chemical(s) of interest in each occupational life cycle stage. Personal protective equipment (PPE) types employed by the industries within scope. Engineering controls employed to reduce occupational exposures in each occupational life cycle stage (or in a workplace scenario similar to the life cycle stage of interest), and associated data or estimates of exposure reductions.
Environmental Release (to relevant	Description of sources of potential environmental releases, including cleaning of residues from process equipment and transport containers, involved during the manufacture, processing, or use of the chemical(s) of interest in each life cycle stage.

Objective Determined during Scoping	Type of Data[a]
environmental media)	Estimated mass (lb or kg) of the chemical(s) of interest released from industrial and commercial sites to each environmental medium (water) and treatment and disposal methods (POTW), including releases per site and aggregated over all sites (annual release rates, daily release rates) Release or emission factors. Number of release days per year. Waste treatment methods and pollution control devices employed by the industries within scope and associated data on release/emission reductions.
In addition to the data types listed above, EPA may identify additional data needs for mathematical modeling. These data needs will be determined on a case-by-case basis. [a] These tags are the tags included in the full-text screening form. The screener makes a selection from these specific tags, which describe more specific types of data or information.	

H.4 Inclusion Criteria for Data Sources Reporting Exposure Data on General Population, Consumers, and Environmental Receptors

Table_Apx H-6. Generic Inclusion Criteria for the Data Sources Reporting Exposure Data on General Population, Consumers, and Environmental Receptors

PECO Element	Evidence
Population	**Human:** General population; consumers; bystanders in the home; near-facility populations (includes industrial and commercial facilities manufacturing, processing, or using the chemical substance); children; susceptible populations (life stages, preexisting conditions, genetic factors), pregnant women; lactating women, women of childbearing age. Many human population groups may be exposed. No chemical-specific exclusions are suggested at this time.
	Environmental: Aquatic species, terrestrial species, terrestrial plants, aquatic plants (field studies only)
Exposure	**Expected Primary Exposure Sources, Pathways, Routes:** **Pathways:** Indoor air/vapor/mist; indoor dust; particles; outdoor/ambient air; surface water; biosolids; sediment; breastmilk; food items containing [chemical] including fish; consumer product uses in the home (including consumer product containing chemical); Routes of Exposure: Inhalation, Oral, Dermal
Comparator (Scenario)	**Human:** Consider media-specific background exposure scenarios and use/source specific exposure scenarios as well as which receptors are and are not reasonably exposed across the projected exposure scenarios.
	Environmental: Consider media-specific background exposure scenarios and use/source specific exposure scenarios as well as which receptors are and are not reasonably exposed across the projected exposure scenarios.

PECO Element	Evidence
Outcomes for Exposure Concentration or Dose	**Human:** Acute, subchronic, and/or indoor air and water concentration estimates (mg/m^3 or mg/L). Both external potential dose and internal dose based on biomonitoring and reverse dosimetry mg/kg/day will be considered. Characteristics of consumer products or articles (weight fraction, emission rates, etc) containing [chemical]
	Environmental: A wide range of ecological receptors will be considered (range depending on available ecotoxicity data) using surface water concentrations, sediment concentrations.

H.5 Inclusion Criteria for Data Sources Reporting Environmental and Human Health Hazards

EPA developed PECO statements to guide the screening of the environmental and human health hazard data or information sources for each of the TSCA risk evaluations. PECO stands for **P**opulation, **E**xposure, **C**omparator and **O**utcomes, and is used to focus the assessment question(s), search terms and inclusion/exclusion criteria in a systematic review. Statements are provided for title/abstract screening (in SWIFT Active for large data sets and DistillerSR for small data sets) and full-text screening in DistillerSR. As each screening project progressed the PECO and supplemental material criteria for each chemical evolved. Therefore, wording may vary among PECO statements.

Data or information sources that comply with the inclusion criteria specified in the PECO statement are eligible for inclusion, considered for evaluation, and possibly included in the hazard assessment. On the other hand, data or information sources that fail to meet the criteria in the PECO statement are excluded from further consideration. In addition to the PECO criteria, studies containing potentially relevant supplemental material were tracked and categorized during the literature screening process. Relevant supplemental material may be reviewed, evaluated for data quality, and incorporated into risk evaluations as needed for each chemical assessment.

H.5.1 PECO Statements for *p*-Dichlorobenzene and *o*-Dichlorobenzene

Table_Apx H-7. PECO Criteria for *p*-Dichlorobenzene (CASRN 106-46-7) and *o*-Dichlorobenzene (CASRN 95-50-1) – Title and Abstract Screening

PECO Element	Evidence
P	**Human:** Any population and lifestage (occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages). Include insects, spiders, amphibians, birds, crustaceans, fish, mollusks, reptiles, worms and invertebrates. Bacteria and viruses are not included. In most cases, transgenic animal models will get screened as "yes" or "unclear" at TIAB level. **Plants:** Aquatic and terrestrial species (live), all plants including algal, moss, lichen and fungi species

PECO Element	Evidence
E	**Relevant forms:** Dichlorobenzene *p*-dichlorobenzene (106-46-7) *o*-dichlorobenzene (95-50-1) **Human:** Any exposure to dichlorobenzene, *p*-dichlorobenzene (106-46-7), or *o*-dichlorobenzene (95-50-1) **Animal:** Any exposure to dichlorobenzene, *p*-dichlorobenzene (106-46-7), or *o*-dichlorobenzene (95-50-1) including via water, injection, diet, and dermal. **Plants:** Exposure to dichlorobenzene, *p*-dichlorobenzene (106-46-7), or *o*-dichlorobenzene (95-50-1) via water or soil, with reported concentration and duration. Studies involving exposures to mixtures will be included only if they include exposure to dichlorobenzene, *p*-dichlorobenzene (106-46-7), or *o*-dichlorobenzene (95-50-1) alone. **Chemical exposures for aquatic plants where only sediment concentrations are reported from field studies are excluded; laboratory-based sediment studies are retained.**
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of dichlorobenzene or exposure to dichlorobenzene for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement).
O	**Human:** All health outcomes (both cancer and non-cancer) **Animal and Plants:** All biological effects (including bioaccumulation from laboratory studies with concurrently measured water and tissue concentrations)

Table_Apx H-8. Major Categories of Potentially Relevant Supplemental Material for *p*-Dichlorobenzene (CASRN 106-46-7) and *o*-Dichlorobenzene (CASRN 95-50-1) – Title and Abstract Screening

Category	Evidence
Mechanistic studies	Studies reporting measurements related to a health outcome that inform the biological or chemical events associated with phenotypic effects, in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo* (by various non-inhalation routes of exposure), *ex vivo*, and *in silico* studies.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype.
Mixture studies	Mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest.

Category	Evidence
Case reports or case series/studies	Case reports (n ≤ 3 cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Exposure studies	Exposure studies with biomonitoring or biomarker information (*e.g.*, DCBs metabolites in blood or urine or DCB measured in whole body human/animals) are considered ADME. Environmental exposure studies (*e.g.*, DCB in dust) are EXCLUDED.

Table_Apx H-9. PECO Criteria for *p*-Dichlorobenzene (CASRN 106-46-7) and *o*-Dichlorobenzene (CASRN 95-50-1) – Full-Text Screening

PECO Element	Evidence
P	**Human:** Any population and life stage (occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) of any life stage (including preconception, in utero, lactation, peripubertal, and adult stages). Include insects, spiders, amphibians, birds crustaceans, fish, mollusks, reptiles, worms and invertebrates. Bacteria and viruses are not included. In most cases, transgenic animal models will get screened as "yes" or "unclear" at TIAB level. Although certain non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), for simplicity animal models will be further inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotox only). • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles), including wild mammals (*e.g.*, *Peromyscus* sp.). **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen, and fungi species.
E	**Relevant forms:** • *p*-Dichlorobenzene or 1,4-dichlorobenzene (CASRN 106-46-7) and *o*-dichlorobenzene or 1,2- dichlorobenzene (CASRN 95-50-1) • *p*-Dichlorobenzene (CASRN 106-46-7) has a number of synonyms that can be found on the EPA Chemistry Dashboard. *o*-Dichlorobenzene (CASRN 95-50-1) has a number of synonyms that can be found on the EPA Chemistry Dashboard. • Forms that should be excluded: m-Dichlorobenzene or 1,3-dichlorobenzene (CASRN 541-73-1) • No isomers were included for *p*-dichlorobenzene (CASRN 106-46-7) and *o*-dichlorobenzene (CASRN 95-50-1)

PECO Element	Evidence
	Human: Any exposure to *p*-dichlorobenzene (CASRN 106-46-7) or *o*-dichlorobenzene (CASRN 95-50-1). **Animal:** Any exposure to *p*-dichlorobenzene (CASRN 106-46-7) or *o*-dichlorobenzene (CASRN 95-50-1), including via water, soil or sediment, injection (oral or topical), diet, dermal, and inhalation. **Plants:** Exposure to *p*-dichlorobenzene (CASRN 106-46-7) and *o*-dichlorobenzene (CASRN 95-50-1) via water or soil, with reported concentration and duration. Studies involving exposures to mixtures will be included only if they also include exposure to *p*-dichlorobenzene (CASRN 106-46-7) and *o*-dichlorobenzene (CASRN 95-50-1) alone. Chemical exposures for aquatic plants where only sediment concentrations are reported from field studies are excluded; laboratory-based sediment studies are retained.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of *p*-Dichlorobenzene (CASRN 106-46-7) or *o*-Dichlorobenzene (CASRN 95-50-1), or exposure to *p*-Dichlorobenzene (CASRN 106-46-7) or *o*-Dichlorobenzene (CASRN 95-50-1) for shorter periods of time. Case reports and case series will be tracked as "potentially relevant supplemental information." **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement).
O	**Human:** All health outcomes (cancer and non-cancer). **Animal and Plants:** All biological effects (including bioaccumulation from laboratory studies with concurrently measured water and tissue concentrations).

Table_Apx H-10. Major Categories of Potentially Relevant Supplemental Material for *p*-Dichlorobenzene (CASRN 106-46-7) and *o*-Dichlorobenzene (CASRN 95-50-1) – Full-Text Screening

Category	Evidence
Mechanistic studies	Studies reporting measurements related to a health outcome that inform the biological or chemical events associated with phenotypic effects, in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo* (by various non-inhalation routes of exposure), *ex vivo*, and *in silico* studies.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype.
Mixture studies	Mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Only use for experimental studies, not epidemiological studies.

Category	Evidence
Case reports or case series/studies	Case reports (n ≤ 3 cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Exposure studies	Exposure studies with biomonitoring or biomarker information (*e.g.*, DCBs metabolites in blood or urine or DCB measured in whole body human/animals) are considered ADME. Environmental exposure studies (*e.g.*, DCB in dust) are EXCLUDED.

H.5.2 PECO Statements for Various Chlorinated Solvents: 1,2-Dichloroethane (CASRN 107-06-2), *Trans*-1,2- Dichloroethylene (CASRN 156-60-5), 1,2-Dichloropropane (CASRN 78-87-5), 1,1-Dichloroethane (CASRN 75-34-3), and 1,1,2-Trichloroethane (CASRN 79-00-5) – Title and Abstract and Full-Text screening

Table_Apx H-11. PECO Criteria for Various Chlorinated Solvents: 1,2-Dichloroethane (CASRN 107-06-2), *Trans*-1,2- Dichloroethylene (CASRN 156-60-5), 1,2-Dichloropropane (CASRN 78-87-5), 1,1-Dichloroethane (CASRN 75-34-3), and 1,1,2-Trichloroethane (CASRN 79-00-5) – Title and Abstract Screening

PECO Element	Evidence
P	**Human:** Any population and life stage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any life stage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Tests of the single toxicants in *in vitro* systems or on live, whole, taxonomically verifiable organisms (*e.g.*, gametes, embryos, or plant or fungal sections capable of forming whole, new organisms) that are not bacteria, humans, monkeys, viruses, or yeast. In most cases, transgenic animal models will get screened as "yes" or "unclear" at the Title and Abstract (TIAB) screening level. Although certain non-mammalian model systems are increasing used to identify potential human health hazards (*e.g.*, *Xenopus* and zebrafish), for simplicity animal models will be further inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotox only) • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species.

PECO Element	Evidence
	Screener note: • To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential ecological hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and eco hazard. • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species).
E	**Relevant forms and related isomers:** • **1,2-Dichloroethane (CASRN 107-06-2)** • ***trans*-1,2- Dichloroethylene (CASRN 156-60-5)** ○ 1,2-Dichloroethylene - 540-59-0 ○ cis-1,2-Dichloroethylene - 156-59-2 • **1,2-Dichloropropane (CASRN 78-87-5)** ○ 1,1-Dichloropropane - 78-99-9 ○ 1,3-Dichloropropane - 142-28-9 ○ 2,2-Dichloropropane - 594-20-7 • **1,1-Dichloroethane (CASRN 75-34-3)** ○ 1,2-Dichloroethane - 107-06-2 (Related) isomer ○ Dichloroethane - 1300-21-6 (Related) isomer • **1,1,2-Trichloroethane (CASRN 79-00-5)** ○ 1,1,1-Trichloroethane - 71-55-6 ○ Trichloroethane - 25323-89-1 For synonyms see of validated synonyms on the EPA Chemistry Dashboard. **Human:** Any exposure to 1,2-Dichloroethane, *trans*-1,2- Dichloroethylene, 1,2-Dichloropropane, 1,1-Dichloroethane, and/or 1,1,2-Trichloroethane **Animal:** Any exposure to 1,2-Dichloroethane, *trans*-1,2- Dichloroethylene, 1,2-Dichloropropane, 1,1-Dichloroethane, OR 1,1,2-Trichloroethane, including via water, soil or sediment, injection (*i.e.*, oral or topical), gavage, diet, dermal, and inhalation. **Plants:** Exposure to 1,2-Dichloroethane,1,2-Dichloroethane, *trans*-1,2- Dichloroethylene, 1,2-Dichloropropane, 1,1-Dichloroethane, OR 1,1,2-Trichloroethane via water and/or soil, with reported concentration and duration. Studies involving exposures to mixtures will be included only if they also include exposure to one of these solvents alone. **Screener note:** Field studies with media concentrations (surface water, interstitial water, soil) and/or body/tissue concentrations of animals or plants are to be identified as ***Supplemental*** if any biological effects are reported. • Tag all field studies as supplemental (regardless of there being an effect)

PECO Element	Evidence
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of 1,2-Dichloroethane, *trans*-1,2- Dichloroethylene, 1,2-Dichloropropane, 1,1-Dichloroethane, and/or 1,1,2-Trichloroethane, or exposure to one of these solvents for shorter periods of time. Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, nested case-control study designs are all **included**. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as **unclear** during Title/Abstract Screening. • All case reports and case studies/series describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as "potentially relevant supplemental information."
O	**Human**: All health outcomes (cancer and non-cancer). **Animal and Plants**: All biological effects (including bioaccumulation from laboratory studies with concurrently measured water and tissue concentrations). **Screener note: Measurable biological effects relevant for humans, animals and plants may include but are not limited to:** mortality, behavioral, population, cellular, physiological, growth, reproduction of an acceptable organism to a chemical toxicant.

Table_Apx H-12. Major Categories of Potentially Relevant Supplemental Material for Various Chlorinated Solvents: 1,2-Dichloroethane (CASRN 107-06-2), *Trans*-1,2- Dichloroethylene (CASRN 156-60-5), 1,2-Dichloropropane (CASRN 78-87-5), 1,1-Dichloroethane (CASRN 75-34-3), and 1,1,2-Trichloroethane (CASRN 79-00-5) – Title and Abstract Screening

Category	Evidence
Mechanistic studies	Studies reporting measurements related to a health outcome that inform the biological or chemical events associated with phenotypic effects, in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo* (by various non-inhalation routes of exposure), *ex vivo*, and in silico studies.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype.
Mixture studies	Mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest.

Category	Evidence
Case reports or case series	Case reports (n ≤ 3 cases) and case series/studies (<20 cases) will be tracked as potentially relevant supplemental information.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies where there are accompanying body/tissue concentrations of animals without any biological effects reported

Table_Apx H-13. PECO Criteria for Various Chlorinated Solvents: 1,2-Dichloroethane (CASRN 107-06-2), *Trans*-1,2- Dichloroethylene (CASRN 156-60-5), 1,2-Dichloropropane (CASRN 78-87-5), 1,1-Dichloroethane (CASRN 75-34-3), and 1,1,2-Trichloroethane (CASRN 79-00-5) – Full-Text Screening

PECO Element	Evidence
P	**Human:** Any population and life stage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any life stage (*e.g.*, preconception, *in utero*, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotoxicity only). • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note:** • To identify human health and environmental hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential environmental hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and environmental hazard. • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Test of the single toxicants in *in vitro* and *ex vivo* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as

PECO Element	Evidence
	potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.

E	**Relevant forms and isomers:**
	• 1,2-Dichloroethane (CASRN 107-06-2)
	• *trans*-1,2- Dichloroethylene (CASRN 156-60-5)
	  ○ Related isomers:
	  ○ 1,2-Dichloroethylene (CASRN 540-59-0)
	  ○ cis-1,2-Dichloroethylene (CASRN 156-59-2)
	• 1,2-Dichloropropane (CASRN 78-87-5)
	  ○ Related isomers:
	  ○ 1,1-Dichloropropane (CASRN 78-99-9)
	  ○ 1,3-Dichloropropane (CASRN 142-28-9)
	  ○ 2,2-Dichloropropane (CASRN 594-20-7)
	• 1,1-Dichloroethane (CASRN 75-34-3)
	  ○ Related isomers:
	  ○ 1,2-Dichloroethane (CASRN 107-06-2)
	  ○ Dichloroethane (CASRN 1300-21-6)
	• 1,1,2-Trichloroethane (CASRN 79-00-5)
	  ○ Related isomers:
	  ○ 1,1,1-Trichloroethane (CASRN 71-55-6)
	  ○ Trichloroethane (CASRN 25323-89-1)
	• For synonyms see the EPA Chemistry Dashboard.
	
	Human: Any exposure to 1,2-Dichloroethane, *trans*-1,2- Dichloroethylene, 1,2-Dichloropropane, 1,1-Dichloroethane, and/or 1,1,2-Trichloroethane singularly or in mixture, including exposure as measured by internal concentrations of these chemicals or metabolites of these chemicals in a biological matrix (*i.e.*, urine, blood, semen, etc).
	
	Animal: Any exposure to 1,2-Dichloroethane, *trans*-1,2- Dichloroethylene, 1,2-Dichloropropane, 1,1-Dichloroethane, and/or 1,1,2-Trichloroethane including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation.
	
	Plants: Any exposure to 1,2-Dichloroethane, *trans*-1,2- Dichloroethylene, 1,2-Dichloropropane, 1,1-Dichloroethane, and/or 1,1,2-Trichloroethane including via water, soil, sediment.
	
	Screener note:
	• Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as Supplemental if any biological effects are reported.
	• Animal and plant studies involving exposures to mixtures will be included only if they also include exposure to 1,2-Dichloroethane, *trans*-1,2- Dichloroethylene, 1,2-Dichloropropane, 1,1-Dichloroethane, and/or 1,1,2-Trichloroethane alone. Otherwise, animal and plant mixture studies will be tagged as Supplemental. Human mixture studies are included.
	• Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (not field studies) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no

PECO Element	Evidence
	prescribed exposure dose(s) will be excluded if there is no evaluated hazardous effect, and tagged as supplemental field, if there is an evaluated hazardous effect.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of 1,2-Dichloroethane, *trans*-1,2- Dichloroethylene, 1,2-Dichloropropane, 1,1-Dichloroethane, and/or 1,1,2-Trichloroethane, or exposure to 1,2-Dichloroethane, *trans*-1,2-Dichloroethylene, 1,2-Dichloropropane, 1,1-Dichloroethane, and/or 1,1,2-Trichloroethane for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening. • All case reports and case studies/series describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked tracked as ***Supplemental***. Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, nested case-control study designs are all Included.
O	**Human**: All health outcomes (cancer and non-cancer) at the organ level or higher. **Animal and Plants**: All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth. **Screener note:** • Measurable biological effects relevant for humans, animals and plants may include but are not limited to: mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects. • Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.

Table_Apx H-14. Major Categories of Potentially Relevant Supplemental Material for Various Chlorinated Solvents: 1,2-Dichloroethane (CASRN 107-06-2), *Trans*-1,2- Dichloroethylene (CASRN 156-60-5), 1,2-Dichloropropane (CASRN 78-87-5), 1,1-Dichloroethane (CASRN 75-34-3), and 1,1,2-Trichloroethane (CASRN 79-00-5) – Full-Text Screening

Category	Evidence
Mechanistic studies	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro, in vivo, ex vivo,* and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.

Category	Evidence
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, life stage, or genotype. This tag applies primarily during full-text screening. **Screener note:** if biological susceptibility issues are clearly present or *strongly* implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract.
Mixture studies	Mixture studies that are not considered PECO-relevant because they do not contain exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Case reports or case series	Case reports (n ≤ 3 cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials, or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field studies	Field studies where there are accompanying body/tissue concentrations of animals without any biological effects are reported.
Isomer	PECO-relevant studies with an exposure to one of the identified isomers, if any.

H.5.3 PECO Statements for Ethylene Dibromide

Table_Apx H-15. PECO Criteria for Ethylene Dibromide (CASRN 106-93-4) – Title and Abstract Screening

PECO Element	Evidence
P	**Human:** Any population and lifestage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any lifestage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotox only) • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species.

PECO Element	Evidence
	Screener note: • To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential ecological hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and eco hazard • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Tests of the single toxicants in *in vitro* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as **potentially supplemental** (mechanistic studies) but are otherwise **excluded**. Studies on viruses are **excluded.**
E	**Relevant forms and isomers:** Ethylene Dibromide (CASRN 106-93-4) No **isomers** were included for Ethylene Dibromide. **Synonyms** include ethylene dibromide, ethylene bromide, sym-dibromoethane, ethane 1,2 dibromo, alpha beta-dibromoethane, 1,2-dibromaethan, and 1,2-dibromethan. For more **synonyms,** see a list of validated synonyms on the EPA Chemistry Dashboard**.** **Human:** Any exposure to Ethylene Dibromide (CASRN 106-93-4) **Animal:** Any exposure to Ethylene Dibromide (CASRN 106-93-4) including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plants:** Any exposure to Ethylene Dibromide (CASRN 106-93-4) including via water, soil, or sediment. **Screener note:** Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as ***Supplemental*** if any biological effects are reported. Studies involving exposures to mixtures will be **included** only if they also include exposure to Ethylene Dibromide (CASRN 106-93-4) alone. Otherwise, mixture studies will be tagged as **Supplemental.** Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (**not field studies**) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be **excluded** if there is no evaluated hazardous effect, and tagged as **supplemental** field, if there is an evaluated hazardous effect.

PECO Element	Evidence
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of Ethylene Dibromide (CASRN 106-93-4), or exposure to Ethylene Dibromide (CASRN 106-93-4) for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening. • All case series and case studies describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as ***Supplemental.*** Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, nested case-control study designs are all ***Included*.**
O	**Human**: All health outcomes (both cancer and non-cancer) **Animal and Plants**: All biological effects (including bioaccumulation from laboratory studies with concurrently measured water and tissue concentrations). **Screener note: Measurable biological effects relevant for humans, animals and plants may include but are not limited to:** mortality, behavioral, population, cellular, physiological, growth, reproduction, systemic, point of contact effects.

Table_Apx H-16. Major Categories of Potentially Relevant Supplemental Material for Ethylene Dibromide (CASRN 106-93-4) – Title and Abstract Screening

Category	Evidence
Mechanistic studies	Studies reporting measurements related to a health outcome that inform the biological or chemical events associated with phenotypic effects, in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo* (by various non-inhalation routes of exposure), *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, life stage, or genotype. This tag applies primarily during full-text screening. **Screener note:** if biological susceptibility issues are clearly present or *strongly* implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If

Category	Evidence
	uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported.

Table_Apx H-17. PECO Criteria for Ethylene Dibromide (CASRN 106-93-4) – Full-Text Screening

PECO Element	Evidence
P	**Human:** Any population and life stage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any life stage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotoxicity only). • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note:** • To identify human health and environmental hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential environmental hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and environmental hazards. • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species).

PECO Element	Evidence
	• Tests of the single toxicants in *in vitro* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.
E	**Relevant forms and isomers:** • Ethylene Dibromide (CASRN 106-93-4) • **Synonyms** include ethylene dibromide, ethylene bromide, sym-dibromoethane, ethane 1,2 dibromo, alpha beta-dibromoethane, 1,2-dibromaethan, and 1,2-dibroomethaan. For more, see the EPA Chemistry Dashboard. • No **isomers** were included for Ethylene Dibromide. **Human:** Any exposure to Ethylene Dibromide (CASRN 106-93-4). **Animal:** Any exposure to Ethylene Dibromide (CASRN 106-93-4) including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plants:** Any exposure to Ethylene Dibromide (CASRN 106-93-4) including via water, soil, sediment. **Screener note:** • Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as ***Supplemental*** if any biological effects are reported. • Studies involving exposures to mixtures will be included only if they also include exposure to Ethylene Dibromide (CASRN 106-93-4) alone. Otherwise, mixture studies will be tagged as ***Supplemental***. • Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (**not field studies**) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be **excluded** if there is no evaluated hazardous effect, and tagged as **supplemental** field, if there is an evaluated hazardous effect.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of Ethylene Dibromide (106-93-4), or exposure to Ethylene Dibromide (106-93-4) for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening.

PECO Element	Evidence
	• All case series and case studies describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as ***Supplemental***. Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, nested case-control study designs are all ***Included***.
O	**Human**: All health outcomes (cancer and non-cancer). **Animal and Plants**: All biological effects (including bioaccumulation from laboratory studies with concurrently measured water and tissue concentrations). **Screener note:** • Measurable biological effects relevant for humans, animals and plants may include but are not limited to mortality, behavioral, population, cellular, physiological, growth, reproduction, systemic, point of contact effects

Table_Apx H-18. Major Categories of Potentially Relevant Supplemental Material for Ethylene Dibromide (CASRN 106-93-4) – Full-Text Screening

Category	Evidence
Mechanistic studies	Studies reporting measurements related to a health outcome that inform the biological or chemical events associated with phenotypic effects, in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo* (by various non-inhalation routes of exposure), *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, life stage, or genotype. This tag applies primarily during full-text screening. **Screener note:** if biological susceptibility issues are clearly present or *strongly* implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.

Category	Evidence
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported.
Isomer	PECO-relevant studies with an exposure to one of the identified isomers, if any.

H.5.4 PECO Statements for 1,3-Butadiene

Table_Apx H-19. PECO Criteria for 1,3-Butadiene (CASRN 106-99-0) – Title and Abstract Screening

PECO Element	Evidence
P	**Human:** Any population and lifestage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any lifestage (*e.g.*, preconception, *in utero*, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotox only) • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note:** • To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential ecological hazard. Neurotoxicity studies performed in hens (*e.g,.* OECD 418 and 419) are considered relevant to both human and eco hazard • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Tests of single toxicants in *in vitro* and *ex vivo* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially

PECO Element	Evidence
	supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.
E	**Relevant forms and related isomers:** • 1,3-Butadiene (CASRN 106-99-0) ○ *Related isomer*: 1,1-Dibromoethane - 557-91-5 For synonyms see of validated synonyms on the EPA Chemistry Dashboard. **Human:** Any exposure to 1,3-Butadiene (106-99-0), singularly or in mixture, including exposure as measured by internal concentrations of these chemicals or metabolites of these chemicals in a biological matrix (*i.e.*, urine, blood, semen, etc.). **Animal:** Any exposure to 1,3-Butadiene (106-99-0) including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plants:** Any exposure to 1,3-Butadiene (106-99-0) including via water, soil, sediment. **Screener note:** • Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as **Supplemental** if any biological effects are reported. • Animal and plant studies involving exposures to mixtures will be included only if they also include exposure to 1,3-Butadiene (106-99-0) alone. Otherwise, animal and plant mixture studies will be tagged as supplemental. Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (**not field studies**) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be **excluded** if there is no evaluated hazardous effect, and tagged as **supplemental** field, if there is an evaluated hazardous effect.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of 1,3-Butadiene (106-99-0), or exposure to 1,3-Butadiene (106-99-0) for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening. • All case series and case studies describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as ***Supplemental.*** Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, nested case-control study designs are all ***Included.***
O	**Human**: All health outcomes (cancer and non-cancer) at the organ level or higher.

PECO Element	Evidence
	Animal and Plants: All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth. **Screener note:** • **Measurable biological effects relevant for humans, animals and plants may include but are not limited to** mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects. • Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.

Table_Apx H-20. Major Categories of Potentially Relevant Supplemental Material for 1,3-Butadiene (CASRN 106-99-0) – Title and Abstract Screening

Category	Evidence
Mechanistic studies	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo*, *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, life stage, or genotype. This tag applies primarily during full-text screening. **Screener note:** if biological susceptibility issues are clearly present or *strongly* implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.

Category	Evidence
Field Studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported.

Table_Apx H-21. PECO Criteria for 1,3-Butadiene (CASRN 106-99-0) – Full-Text Screening

PECO Element	Evidence
P	**Human:** Any population and life stage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any life stage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotoxicity only). • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note:** • To identify human health and environmental hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential environmental hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human health and environmental hazards. • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Tests of the single toxicants in *in vitro* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.

E	**Relevant forms and isomers:**
	• 1,3-Butadiene (CASRN 106-99-0)
	  ○ Related isomer:
	  ○ 1,1-Dibromoethane (CASRN 557-91-5)
	• For **synonyms** see the EPA Chemistry Dashboard.
	
	Human: Any exposure to 1,3-Butadiene (CASRN 106-99-0), singularly or in mixture, including exposure as measured by internal concentrations of these chemicals or metabolites of these chemicals in a biological matrix (*i.e.*, urine, blood, semen, etc.).

PECO Element	Evidence
	Animal: Any exposure to 1,3-Butadiene (CASRN 106-99-0) including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plants:** Any exposure to 1,3-Butadiene (CASRN 106-99-0) including via water, soil, sediment. **Screener note:** • Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as **Supplemental** if any biological effects are reported. • Animal and plant studies involving exposures to mixtures will be included only if they also include exposure to 1,3-Butadiene (CASRN 106-99-0) alone. Otherwise, mixture studies will be tagged as **Supplemental**. • Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (**not field studies**) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be **excluded** if there is no evaluated hazardous effect, and tagged as **supplemental** field, if there is an evaluated hazardous effect.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of 1,3-Butadiene (CASRN 106-99-0), or exposure to 1,3-Butadiene (CASRN 106-99-0) for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening. • All case series and case studies describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as ***Supplemental***. Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, nested case-control study designs are all ***Included***.
O	**Human**: All health outcomes (cancer and non-cancer) at the organ level or higher. **Animal and Plants**: All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth. **Screener note:** **Measurable biological effects relevant for humans, animals and plants may include but are not limited to:** mortality, behavioral, population, cellular, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects. Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.

Table_Apx H-22. Major Categories of Potentially Relevant Supplemental Material for 1,3-Butadiene (CASRN 106-99-0) – Full-Text Screening

Category	Evidence
Mechanistic studies	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo*, *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, life stage, or genotype. This tag applies primarily during full-text screening. **Screener note:** if biological susceptibility issues are clearly present or *strongly* implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported.
Isomer	PECO-relevant studies with an exposure to one of the identified isomers, if any.

H.5.5 PECO Statements for HHCB

Table_Apx H-23. PECO Criteria for HHCB (CASRN 1222-05-5) – Title and Abstract Screening

PECO Element	Evidence
P	**Human:** Any population and lifestage *(e.g.*, occupational or general population, including children and other sensitive populations).

PECO Element	Evidence
	Animal: Aquatic and terrestrial species (live, whole organism) from any lifestage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotox only). • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note:** • To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, Xenopus, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential ecological hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and eco hazard. • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Tests of the single toxicants in *in vitro* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.
E	**Relevant forms and isomers:** • 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (HHCB) (CASRN 1222-05-5) • No isomers were included for HHCB. • For **synonyms** see the EPA Chemistry Dashboard. **Human:** Any exposure to HHCB (CASRN 1222-05-5). **Animal:** Any exposure to HHCB (CASRN 1222-05-5) including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plants:** Any exposure to HHCB (CASRN 1222-05-5) including water, soil or sediment. **Screener note:** • Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as Supplemental if any biological effects are reported. • Studies involving exposures to mixtures will be included only if they also include exposure to HHCB (CASRN 1222-05-5) alone. Otherwise, mixture studies will be tagged as ***Supplemental***. • Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (not

PECO Element	Evidence
	field studies) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be **excluded** if there is no evaluated hazardous effect, and tagged as **supplemental** field, if there is an evaluated hazardous effect.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of HHCB (CASRN 1222-05-5), or exposure to HHCB (CASRN 1222-05-5) for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening. • All case series and case studies describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as ***Supplemental***. Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, nested case-control study designs are all ***Included***.
O	**Human**: All health outcomes (both cancer and non-cancer). **Animal and Plants**: All biological effects (including bioaccumulation from laboratory studies with concurrently measured water and tissue concentrations). **Screener note:** • Measurable biological effects relevant for humans, animals and plants may include but are not limited to: mortality, behavioral, population, cellular, physiological, growth, reproduction, systemic, point of contact effects.

Table_Apx H-24. Major Categories of Potentially Relevant Supplemental Material for HHCB (CASRN 1222-05-5) – Title and Abstract Screening

Category	Evidence
Mechanistic studies	Studies reporting measurements related to a health outcome that inform the biological or chemical events associated with phenotypic effects, in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo* (by various non-inhalation routes of exposure), *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype. This tag applies during full-text screening.

Category	Evidence
	Screener note: if biological susceptibility issues are clearly present or *strongly* implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects are reported.

Table_Apx H-25. PECO Criteria for HHCB (CASRN 1222-05-5) – Full-Text Screening

PECO Element	Evidence
P	**Human:** Any population and lifestage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any lifestage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotoxicity only). • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note:** • To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, Xenopus, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential ecological hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and eco hazard • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is

PECO Element	Evidence
	lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Tests of the single toxicants in *in vitro* and *ex vivo* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as **potentially supplemental** (mechanistic studies) but are otherwise **excluded**. Studies on viruses are **excluded.**

E	**Relevant forms and isomers:**
	• 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (CASRN 1222-05-5)
	• **Isomers:**
	  • Cyclopenta[g]-2-benzopyran,1,3,4,6,7,8-hexahydro4,6,6,7,8,8-hexamethyl-, (4S,7S)- - 172339-62-7
	  • Cyclopenta[g]-2-benzopyran,1,3,4,6,7,8-hexahydro4,6,6,7,8,8-hexamethyl-, (4R,7S)- - 172339-63-8
	  • Cyclopenta[g]-2-benzopyran,1,3,4,6,7,8-hexahydro4,6,6,7,8,8-hexamethyl-, (4S,7R)- - 252332-95-9
	  • Cyclopenta[g]-2-benzopyran,1,3,4,6,7,8-hexahydro4,6,6,7,8,8-hexamethyl-, (4R,7R)- - 252332-96-0
	  • Cyclopenta[g]-2-benzopyran,1,3,4,6,7,8-hexahydro4,6,6,7,8,8-hexamethyl-, (4R,7R)-rel - 252933-48-5
	  • Cyclopenta[g]-2-benzopyran,1,3,4,6,7,8-hexahydro4,6,6,7,8,8-hexamethyl-, (4R,7S) rel - 252933-49-6
	  • Cyclopenta[g]-2-benzopyran, 1,3,4,6,7,8-hexahydro-4,4,6,6,8,8-hexamethyl - 1222-06-6
	  • Cyclopenta[g]-2-benzopyran, 1,3,4,6,7,8-hexahydro-3,6,6,7,8,8-hexamethyl - 857091-61-3
	  • Cyclopenta[g]-1-benzopyran, 2,3,4,6,7,8-hexahydro-4,4,6,6,8,8-hexamethyl - 102296-64-0
	  • Cyclopenta[g]-1-benzopyran,2,3,4,6,7,8hexahydro4,6,6,7,8,8-hexamethyl - 135546-43-9
	  • Cyclopenta[g]-2-benzopyran, 1,3,4,6,7,8-hexahydro-1,6,6,7,8,8-hexamethyl - 135546-42-8
	  • Cyclopenta[h]-2-benzopyran, 1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl - 114109-63-6
	  • Cyclopenta[f][2]benzopyran, 1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl - 114109-62-5
	  • Cyclopenta[g]-2-benzopyran, 6-ethyl1,3,4,6,7,8-hexahydro-4,6,8,8-tetramethyl - 78448-48-3
	  • Cyclopenta[g]-2-benzopyran, 8-ethyl1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethyl - 78448-49-4
	• For **synonyms** see the EPA Chemistry Dashboard.

PECO Element	Evidence
	Human: Any exposure to HHCB (CASRN 1222-05-5) singularly or in mixture, including exposure as measured by internal concentrations of these chemicals or metabolites of these chemicals in a biological matrix (*i.e.*, urine, blood, semen, etc.). **Animal:** Any exposure to HHCB (CASRN 1222-05-5) including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plants:** Any exposure to HHCB (CASRN 1222-05-5) including via water, soil or sediment. **Screener note:** • Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as ***Supplemental*** if any biological effects are reported. • Animal and plant studies involving exposures to mixtures will be **included** only if they also include exposure to HHCB (CASRN 1222-05-5) alone. Otherwise, animal and plant mixture studies will be tagged as ***Supplemental.*** Human mixture studies are ***included.*** • Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (**not field studies**) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be **excluded** if there is no evaluated hazardous effect, and tagged as **supplemental** field, if there is an evaluated hazardous effect.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of HHCB (CASRN 1222-05-5), or exposure to HHCB (CASRN 1222-05-5) for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening. • All case series and case studies describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as ***Supplemental.*** Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, nested case-control study designs are all ***Included.***
O	**Human**: All health outcomes (both cancer and non-cancer) at the organ level or higher. **Animal and Plants**: All apical biological effects (effects measured at the organ level or higher) including bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival and growth. **Screener note:**

PECO Element	Evidence
	• **Measurable biological effects relevant for humans, animals and plants may include but are not limited to:** mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects. • Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.

Table_Apx H-26. Major Categories of Potentially Relevant Supplemental Material for HHCB (CASRN 1222-05-5) – Full-Text Screening

Category	Evidence
Mechanistic studies	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro, in vivo, ex vivo,* and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype. This tag applies primarily during full-text screening. **Screener note:** if biological susceptibility issues are clearly present or *strongly* implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Experimental mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported.
Isomer	PECO-relevant studies with an exposure to one of the identified isomers, if any.

H.5.6 PECO Statements for TBBPA

Table_Apx H-27. PECO Criteria for TBBPA (CASRN 79-94-7) – Title and Abstract Screening

PECO Element	Evidence
P	**Human:** Any population and lifestage (*e.g.*, occupational or general population, including children and other sensitive populations. **Animal:** Aquatic and terrestrial species (live, whole organism) from any lifestage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotox only) • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** Aquatic and terrestrial species (live), all plants including algal, moss, lichen and fungi species. **Screener note:** • To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, Xenopus, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential ecological hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and eco hazard. • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). Tests of the single toxicants in *in vitro* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.
E	**Relevant forms and isomers:** • 3,3',5,5' – Tetrabromobisphenol A (CASRN 79-94-7) • For synonyms see the EPA Chemistry Dashboard. • No isomers were included for TBBPA. **Human:** Any exposure to 3,3',5,5' – Tetrabromobisphenol A (TBBPA 79-94-7). **Animal:** Any exposure to 3,3',5,5' – Tetrabromobisphenol A (TBBPA 79-94-7) including via water, injection, gavage, diet, dermal, and inhalation. **Plants:** Exposure to 3,3',5,5' – Tetrabromobisphenol A (TBBPA 79-94-7) via water or soil, with reported concentration and duration. Studies involving exposures to mixtures will be included only if they also include exposure to 3,3',5,5' – Tetrabromobisphenol A (CASRN 79-94-7) alone. Chemical exposures for aquatic plants where only sediment concentrations are reported from field studies are excluded; laboratory-based sediment studies are retained.

PECO Element	Evidence
	Screener note: • Field studies with media concentrations (surface water, interstitial water, soil) and/or body/tissue concentrations of animals or plants are to be identified as ***Supplemental*** if any biological effects are reported.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of 3,3',5,5' – Tetrabromobisphenol A (TBBPA 79-94-7), or exposure to 3,3',5,5' – Tetrabromobisphenol A (TBBPA 79-94-7). All case reports and case studies/series describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as "potentially relevant supplemental information." **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening. • All case series and case studies describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as ***Supplemental.*** Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, nested case-control study designs are all ***Included***.
O	**Human**: All health outcomes (both cancer and non-cancer). **Animal and Plants**: All biological effects. **Screener note:** • **Measurable biological effects relevant for humans, animals and plants may include but are not limited to:** mortality, behavioral, population, cellular, physiological, growth, reproduction, systemic, point of contact effects of an acceptable organism to a chemical toxicant.

Table_Apx H-28. Major Categories of Potentially Relevant Supplemental Material for TBBPA (CASRN 79-94-7) − Title and Abstract Screening

Category	Evidence
Mechanistic studies	Studies reporting measurements related to a health outcome that inform the biological or chemical events associated with phenotypic effects, in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo* (by various non-inhalation routes of exposure), *ex vivo*, and in silico studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.

Category	Evidence
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype. This tag applies during full-text screening.
Mixture studies	Mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies where there are accompanying body/tissue concentrations of animals or plants if biological effects are reported.

Table_Apx H-29. PECO Criteria for TBBPA (CASRN 79-94-7) – Full-Text Screening

PECO Element	Evidence
P	**Human:** Any population and life stage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any life stage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotoxicity only). • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note:** • To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential ecological hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and eco hazard • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species)

PECO Element	Evidence
	• Tests of single toxicants in *in vitro* and *ex vivo* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.
E	**Relevant forms and isomers:** • 3, 3', 5, 5' - Tetrabromobisphenol A (CASRN 79-94-7) • For synonyms see the EPA Chemistry Dashboard. • No isomers were included for TBBPA. **Human:** Any exposure to 3,3',5,5' – Tetrabromobisphenol A (TBBPA 79-94-7), singularly or in mixture, including exposure as measured by internal concentrations of these chemicals or metabolites of these chemicals in a biological matrix (*i.e.*, urine, blood, semen, etc.). **Animal:** Any exposure to 3,3',5,5' – Tetrabromobisphenol A (TBBPA 79-94-7), including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plants:** Any exposure to 3,3',5,5' – Tetrabromobisphenol A (TBBPA 79-94-7) including via water, soil, sediment. **Screener note:** • Field studies with media concentrations (surface water, interstitial water, soil) and/or body/tissue concentrations of animals or plants are to be identified as ***Supplemental*** if any biological effects are reported. • Animal and plant studies involving exposures to mixtures will be included only if they also include exposure to (chemical name(s) and CASRN)alone. Otherwise, animal and plant mixture studies will be tagged as **Supplemental.** Human mixture studies are ***included***. • Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (**not field studies**) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be **excluded** if there is no evaluated hazardous effect, and tagged as **supplemental** field, if there is an evaluated hazardous effect.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of 3,3',5,5' – Tetrabromobisphenol A (TBBPA 79-94-7), or exposure to 3,3',5,5' – Tetrabromobisphenol A (TBBPA 79-94-7). All case reports and case studies/series describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as "potentially relevant supplemental information." **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:**

PECO Element	Evidence
	• If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening. • All case series and case studies describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as ***Supplemental.*** Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, nested case-control study designs are all ***Included.***
O	**Human**: All health outcomes (cancer and non-cancer) at the organ level or higher. **Animal and Plants**: All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth. **Screener note:** • **Measurable biological effects relevant for humans, animals and plants may include, but are not limited to:** mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects. • Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.

Table_Apx H-30. Major Categories of Potentially Relevant Supplemental Material for TBBPA (CASRN 79-94-7) − Full-Text Screening

Category	Evidence
Mechanistic studies	Studies reporting measurements related to a health outcome that inform the biological or chemical events associated with phenotypic effects, in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo* (by various non-inhalation routes of exposure), *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, life stage, or genotype. This tag applies during full-text screening.
Mixture studies	Mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.

Category	Evidence
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials, or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies where there are accompanying body/tissue concentrations of animals or plants if biological effects reported.
Isomer	PECO-relevant studies with an exposure to one of the identified isomers, if any.

H.5.7 PECO Statements for TCEP

Table_Apx H-31. PECO Criteria for TCEP (CASRN 115-96-8) – Title and Abstract Screening

PECO Element	Evidence
P	**Human:** Any population and lifestage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any life stage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotox only). • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note:** • To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential ecological hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and eco hazard • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Tests of the single toxicants in *in vitro* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.
E	**Relevant forms and isomers:**

PECO Element	Evidence
	• Tris(2-chloroethyl) phosphate) (CASRN 115-96-8) • For synonyms see the EPA Chemistry Dashboard. • No **isomers** were included for TCEP **Human:** Any exposure to Tris(2-chloroethyl) phosphate) (TCEP 115-96-8). **Animal:** Any exposure to Tris(2-chloroethyl) phosphate) (TCEP 115-96-8) including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plants:** Exposure to Tris(2-chloroethyl) phosphate) (TCEP 115-96-8) via water or soil, with reported concentration and duration. Studies involving exposures to mixtures will be included only if they also include exposure to Tris(2-chloroethyl) phosphate) (CASRN 115-96-8) alone. **Screener note:** • Field studies with media concentrations (surface water, interstitial water, soil) and/or body/tissue concentrations of animals or plants are to be identified as ***Supplemental*** if any biological effects are reported.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of Tris(2-chloroethyl) phosphate) (TCEP 115-96-8), or exposure to Tris(2-chloroethyl) phosphate) (TCEP 115-96-8) for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening. • All case series and case studies describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as ***Supplemental.*** Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, nested case-control study designs are all ***Included***.
O	**Human**: All health outcomes (both cancer and non-cancer). **Animal and Plants**: All biological effects (including bioaccumulation from laboratory studies with concurrently measured water and tissue concentrations). **Screener note:** • **Measurable biological effects relevant for humans, animals and plants may include but are not limited to:** mortality, behavioral, population, cellular, physiological, growth, reproduction, systemic, point of contact effects.

Table_Apx H-32. Major Categories of Potentially Relevant Supplemental Material for TCEP (CASRN 115-96-8) – Title and Abstract Screening

Category	Evidence
Mechanistic studies	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo*, *ex vivo*, and *in silico*

Category	Evidence
	studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, life stage, or genotype. This tag applies primarily during full-text screening.
Mixture studies	Experimental mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials, or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies where there are accompanying body/tissue concentrations of animals or plants if biological effects reported.

Table_Apx H-33. Populations, Exposures, Comparators, and Outcomes (PECO) Criteria for TCEP (CASRN 115-96-8) – Full-Text Screening

PECO Element	Evidence
P	**Human:** Any population and life stage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any life stage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotoxicity only). • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note:**

PECO Element	Evidence
	• To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential ecological hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and eco hazard. • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Tests of the single toxicants in *in vitro* and *ex vivo* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.
E	**Relevant forms and isomers:** • Tris(2-chloroethyl) phosphate) (CASRN 115-96-8) • For synonyms see the EPA Chemistry Dashboard. • No isomers were included for TCEP. **Human:** Any exposure to Tris(2-chloroethyl) phosphate) (TCEP 115-96-8) singularly or in mixture, including exposure as measured by internal concentrations of these chemicals or metabolites of these chemicals in a biological matrix (*i.e.*, urine, blood, semen, etc.). **Animal:** Any exposure to Tris(2-chloroethyl) phosphate) (TCEP 115-96-8) including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plants:** Exposure to Tris(2-chloroethyl) phosphate) (TCEP 115-96-8) including via water, soil, or sediment. **Screener note:** Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as ***Supplemental*** if any biological effects are reported. Animal and plant studies involving exposures to mixtures will be included only if they also include exposure to Tris(2-chloroethyl) phosphate) (TCEP 115-96-8) alone. Otherwise, animal and plant mixture studies will be tagged as **Supplemental**. Human mixture studies are ***included.*** Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (**not field studies**) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be **excluded** if there is no evaluated hazardous effect, and tagged as **supplemental** field, if there is an evaluated hazardous effect.

PECO Element	Evidence
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of Tris(2-chloroethyl) phosphate) (TCEP 115-96-8), or exposure to Tris(2-chloroethyl) phosphate) (TCEP 115-96-8) for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening. • All case series and case studies describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as ***Supplemental.*** Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, nested case-control study designs are all ***Included.***
O	**Human**: All health outcomes (cancer and non-cancer) at the organ level or higher. **Animal and Plants**: All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth). **Screener note:** • **Measurable biological effects relevant for humans, animals and plants may include but are not limited to:** mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact effects. • Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.

Table_Apx H-34. Major Categories of Potentially Relevant Supplemental Material for TCEP (CASRN 115-96-8) – Full-Text Screening

Category	Evidence
Mechanistic studies	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro, in vivo, ex vivo,* and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.

Category	Evidence
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype. This tag applies primarily during full-text screening. **Screener note**: • If biological susceptibility issues are clearly present or ***strongly*** implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Experimental mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials, or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported.

H.5.8 PECO Statements for TPP

Table_Apx H-35. PECO Criteria for TPP (CASRN 115-86-6) – Title and Abstract Screening

PECO Element	Evidence
P	**Human:** Any population and lifestage (occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages). Include insects, spiders, amphibians, birds, crustaceans, fish, mollusks, reptiles, worms and invertebrates. Bacteria and viruses are not included. In most cases, transgenic animal models will get screened as "yes" or "unclear" at TIAB level. **Plants:** Aquatic and terrestrial species (live), all plants including algal, moss, lichen and fungi species. **Screener note:** • Mechanistic information including *in-vitro* assays will be tagged as supplemental material.
E	**Relevant forms and isomers:** • Triphenyl phosphate (CASRN 115-86-6) • For synonyms see the EPA Chemistry Dashboard.

PECO Element	Evidence
	• Other forms should be excluded: phosphoric acid. **Human:** Any exposure to triphenyl phosphate. **Animal:** Any exposure to triphenyl phosphate including via water, injection, diet, and dermal. **Plants:** Exposure to triphenyl phosphate via water or soil, with reported concentration and duration. Studies involving exposures to mixtures will be included only if they include exposure to triphenyl phosphate alone. Chemical exposures for aquatic plants where only sediment concentrations are reported from field studies are excluded; laboratory-based sediment studies are retained.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of triphenyl phosphate, or exposure to triphenyl phosphate for shorter periods of time. Case reports and case series will be tracked as "potentially relevant supplemental information." **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement).
O	**Human**: All health outcomes (both cancer and non-cancer). **Animal and Plants:** All biological effects (including bioaccumulation from laboratory studies with concurrently measured water and tissue concentrations).

Table_Apx H-36. Major Categories of Potentially Relevant Supplemental Material for TPP (CASRN 115-86-6) − Title and Abstract

Category	Evidence
Mechanistic studies	Studies reporting measurements related to a health outcome that inform the biological or chemical events associated with phenotypic effects, in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo* (by various non-inhalation routes of exposure), *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype. This tag applies primarily during full-text screening. **Screener note:** if biological susceptibility issues are clearly present or ***strongly*** implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.

Category	Evidence
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials, or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field studies	Field studies where there are accompanying body/tissue concentrations of animals or plants if biological effects are reported.
Isomer	PECO-relevant studies with an exposure to one of the identified isomers, if any.

Table_Apx H-37. PECO Criteria for TPP (CASRN 115-86-6) – Full-Text Screening

PECO Element	Evidence
P	**Human:** Any population and lifestage (occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages). Include insects, spiders, amphibians, birds, crustaceans, fish, mollusks, reptiles, worms and invertebrates. Bacteria and viruses are not included. In most cases, transgenic animal models will get screened as "yes" or "unclear" at TIAB level. **Plants:** Aquatic and terrestrial species (live), all plants including algal, moss, lichen and fungi species. **Screener note:** • Mechanistic information including *in-vitro* assays will be tagged as supplemental material.
E	**Relevant forms and isomers:** • Triphenyl phosphate (CASRN 115-86-6) • For synonyms see the EPA Chemistry Dashboard. • Other forms should be excluded: phosphoric acid. **Human:** Any exposure to triphenyl phosphate. **Animal:** Any exposure to triphenyl phosphate including via water, injection, diet, and dermal. Studies involving exposures to mixtures will be included only if they include exposure to triphenyl phosphate alone. **Plants:** Exposure to triphenyl phosphate via water or soil, with reported concentration and duration. Studies involving exposures to mixtures will be included only if they include exposure to triphenyl phosphate alone. Chemical exposures for aquatic plants where only sediment concentrations are reported from field studies are excluded; laboratory-based sediment studies are retained.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of triphenyl phosphate, or exposure to triphenyl phosphate for shorter

PECO Element	Evidence
	periods of time. Case reports and case series will be tracked as "potentially relevant supplemental information." **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement).
O	**Human**: All health outcomes (both cancer and non-cancer). **Animal and Plants**: All biological effects (including bioaccumulation from laboratory studies with concurrently measured water and tissue concentrations).

Table_Apx H-38. Major Categories of Potentially Relevant Supplemental Material for TPP (CASRN 115-86-6) − Full-Text Screening

Category	Evidence
Mechanistic studies	Studies reporting measurements related to a health outcome that inform the biological or chemical events associated with phenotypic effects, in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo* (by various non-inhalation routes of exposure), *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype. This tag applies primarily during full-text screening. **Screener note:** if biological susceptibility issues are clearly present or ***strongly*** implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials, or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.

Category	Evidence
Field studies	Field studies where there are accompanying body/tissue concentrations of animals or plants if biological effects are reported.
Isomer	PECO-relevant studies with an exposure to one of the identified isomers, if any.

H.5.9 PECO Statements for Formaldehyde

Table_Apx H-39. PECO Criteria for Formaldehyde (CASRN 50-00-0) – Title and Abstract Screening

PECO Element	Evidence
P	**Human:** Any population and lifestage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any lifestage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotox only) • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note**: • To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential ecological hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and eco hazard • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Tests of single toxicants in *in vitro* and *ex vivo* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.

E	**Relevant forms and isomers**:
	• Formaldehyde (CAS No. 50-00-0)
	  ○ Relevant isomer:
	  ▪ Paraformaldehyde (CAS No. 30525-89-4)

PECO Element	Evidence
	• Synonyms include formalin and other validated synonyms. See a list of validated synonyms on the EPA Chemistry Dashboard. **Human:** Any exposure to formaldehyde or paraformaldehyde singularly or in mixture, including exposure as measured by internal concentrations of these chemicals or metabolites of these chemicals in a biological matrix (*i.e.*, urine, blood, semen, etc.). Studies on occupations known to use or produce formaldehyde (*e.g.*, pathologists, funeral directors, embalmers) should be considered a relevant proxy for formaldehyde exposure. **Animal:** Any exposure to formaldehyde or paraformaldehyde including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plants:** Any exposure to formaldehyde or paraformaldehyde including via water, soil, sediment. **Screener note**: • Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as Supplemental if any biological effects are reported. • Animal and plant studies involving exposures to mixtures will be included only if they also include exposure to formaldehyde or paraformaldehyde alone. Otherwise, animal and plant mixture studies will be tagged as Human mixture studies are included. • Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (not field studies) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be Excluded if there is no evaluated hazardous effect, and tagged as Supplemental field, if there is an evaluated hazardous effect. • Human studies in an occupational population that present any exposure data on formaldehyde (including synonyms and isomers), without mention of a health effect will be tagged as Supplemental-case-study. Human studies with both formaldehyde exposure and health effect(s) at organ-level or higher will be Included. Human studies with formaldehyde exposure and health effects below organ-level will be considered Supplemental – mechanistic. • Epidemiologic studies that evaluate health effects in association with a proxy occupation (particularly pathologists, funeral directors, embalmers, wood workers, garment/textile workers, hospital nurses, cosmetologists, and other workers in industries involved in the production or use of formaldehyde resins, such as wood-products, paper, textiles, foundries) will be considered Included, even if the chemical terms are not explicitly stated in the title/abstract.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of formaldehyde or paraformaldehyde, or exposure to formaldehyde or paraformaldehyde for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as Unclear during Title/Abstract Screening.

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

Table_Apx H-40. Major Categories of Potentially Relevant Supplemental Material for Formaldehyde (CASRN 50-00-0) − Title and Abstract

Category	Evidence
Mechanistic studies or studies with below organ-level effects	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo*, *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype. This tag applies primarily during full-text screening. **Screener note:** if biological susceptibility issues are clearly present or *strongly* implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Experimental mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.

Category	Evidence
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported
Isomer	PECO-relevant studies with an exposure to one of the identified isomers, if any.
Use of formaldehyde as a reference compound to induce a sensitization response	Formaldehyde is a known sensitizer and can be used as a reference compound to induce sensitization responses in experimental studies (*e.g.*, formalin tests, dermatitis, airway sensitization, or other all ergenic response). Such studies were tagged s supplements. However, studies that fo cused on characterizing a sensitization response that included an apical outcome wer e considered PECO relevant.

Table_Apx H-41. PECO Criteria for Formaldehyde (CASRN 50-00-0) – Full-Text Screening

PECO Element	Evidence
P	**Human:** Any population and life stage (occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) of any life stage (including preconception, *in utero*, lactation, peripubertal, and adult stages). Animal models will be further inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotoxicity only). • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** Aquatic and terrestrial species (live), all plants including algal, moss, lichen and fungi species. **Screener note**: • To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential ecological hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and eco hazard. • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Tests of single toxicants in *in vitro* and *ex vivo* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially

PECO Element	Evidence
	supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.

E	**Relevant forms and isomers**:
	• Formaldehyde (CASRN 50-00-0)
	  ○ Relevant isomer:
	  ○ Paraformaldehyde (CASRN 30525-89-4)
	• Synonyms include formalin and other validated synonyms. See a list of validated synonyms on the EPA Chemistry Dashboard.
	
	Human: Any exposure to formaldehyde or paraformaldehyde singularly or in mixture, including exposure as measured by internal concentrations of these chemicals or metabolites of these chemicals in a biological matrix (*i.e.*, urine, blood, semen, etc.). Studies on occupations known to use or produce formaldehyde (*e.g.*, pathologists, funeral directors, embalmers) should be considered a relevant proxy for formaldehyde exposure.
	
	Animal: Any exposure to formaldehyde or paraformaldehyde including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation.
	
	Plants: Any exposure to formaldehyde or paraformaldehyde including via water, soil, sediment.

C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of formaldehyde or paraformaldehyde, or exposure to formaldehyde or paraformaldehyde for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement).
O	**Human**: All health outcomes (cancer and non-cancer) at the organ level or higher. **Animal and Plants**: All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth.

Table_Apx H-42. Major Categories of Potentially Relevant Supplemental Material for Formaldehyde (CASRN 50-00-0) – Full-Text Screening

Category	Evidence
Mechanistic studies or studies with below organ-level effects	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo*, *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.

Category	Evidence
Case reports or case series	Case reports (n ≤ 3 cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, life stage, or genotype. This tag applies primarily during full-text screening.
Mixture studies	Experimental mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported
Isomer	PECO-relevant studies with an exposure to one of the identified isomers, if any.
Use of formaldehyde as a reference compound to induce a sensitization response	Formaldehyde is a known sensitizer and can be used as a reference compound to induce sensitization responses in experimental studies (*e.g.*, formalin tests, dermatitis, airway sensitization, or other allergenic response). Such studies were tagged s supplements. However, studies that focused on characterizing a sensitization response that included an apical outcome were considered PECO relevant.

H.5.10 PECO Statements for Phthalic Anhydride and Phthalic Acid

Table_Apx H-43. PECO Criteria for Phthalic Anhydride (CASRN 85-44-9) and Phthalic Acid (CASRN 88-99-3) – Title and Abstract Screening

PECO Element	Evidence
P	**Human:** Any population and lifestage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any lifestage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotox only). • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note:** • To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential ecological hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and eco hazard • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Tests of single toxicants in in vitro and ex vivo systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.

PECO Element	Evidence
E	**Relevant forms and isomers:** No **isomers** were included for phthalic anhydride (CASRN 85-44-9) or phthalic acid (CASRN 88-99-3). **Human:** Any exposure to phthalic anhydride (CASRN 85-44-9) or phthalic acid (CASRN 88-99-3) singularly or in mixture, including exposure as measured by internal concentrations of these chemicals or metabolites of these chemicals in a biological matrix (*i.e.*, urine, blood, semen, etc.). **Animal:** Any exposure to phthalic anhydride (CASRN 85-44-9) or phthalic acid (CASRN 88-99-3) including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plants:** Any exposure to phthalic anhydride (CASRN 85-44-9) or phthalic acid (CASRN 88-99-3) including via water, soil, sediment. **Screener note:** • Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as Supplemental if any biological effects are reported. • Studies involving exposures to mixtures will be included only if they also include exposure to phthalic anhydride (CASRN 85-44-9) or phthalic acid (CASRN 88-99-3) alone. Otherwise, mixture studies will be tagged as **Supplemental**. • Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (**not field studies**) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be **excluded** if there is no evaluated hazardous effect, and tagged as **supplemental** field, if there is an evaluated hazardous effect.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of phthalic anhydride (CASRN 85-44-9) or phthalic acid (CASRN 88-99-3), or exposure to phthalic acid for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*,by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening. • All case series and case studies describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as ***Supplemental*** Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, nested case-control study designs are all ***Included***.

PECO Element	Evidence
O	**O (Outcome)** **Human:** All health outcomes (cancer and noncancer) at the organ level or higher. **Animal and Plants:** All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth. **Screener note:** • **Measurable biological effects relevant for humans, animals and plants may include but are not limited to** mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects. • Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.

Table_Apx H-44. Major Categories of Potentially Relevant Supplemental Material for Phthalic Anhydride (CASRN 85-44-9) and Phthalic Acid (CASRN 88-99-3) − Title and Abstract

Category	Evidence
Mechanistic studies	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo*, *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype. This tag applies primarily during full-text screening. **Screener note:** if biological susceptibility issues are clearly present or *strongly* implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Experimental mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.

Category	Evidence
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported
Use of phthalic anhydride as reference compound to induce sensitization response	Phthalic anhydride is a known sensitizer and can be used as a reference compound to induce sensitization responses in experimental studies (*e.g.*, dermatitis, airway sensitization, or other allergenic response). Studies were tagged as supplemental in cases where it was (1) used as reagent to induce sensitization for the purpose of testing another compound (co-exposure); or (2) the endpoints evaluated were only mechanistic or biochemical and not apical (*e.g.*, cytokine mRNA levels). However, studies that focused on characterizing a sensitization response that included an apical outcome (*e.g.*, local lymph node assay) were considered PECO relevant

Table_Apx H-45. PECO Criteria for Phthalic Anhydride (CASRN 85-44-9) and Phthalic Acid (CASRN 88-99-3) – Full-Text Screening

PECO Element	Evidence
P	**Human:** Any population and lifestage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any lifestage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotox only). • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note:** • To identify human health and environmental hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential environmental hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and environmental hazards. • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species).

PECO Element	Evidence
	• Tests of single toxicants in *in vitro* and *ex vivo* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.
E	**Relevant forms and isomers:** • No **isomers** were included for phthalic anhydride (CASRN 85-44-9) or phthalic acid (CASRN 88-99-3). **Human:** Any exposure to phthalic anhydride (CASRN 85-44-9) or phthalic acid (CASRN 88-99-3) singularly or in mixture, including exposure as measured by internal concentrations of these chemicals or metabolites of these chemicals in a biological matrix (*i.e.*, urine, blood, semen, etc.). **Animal:** Any exposure to phthalic anhydride (CASRN 85-44-9) or phthalic acid (CASRN 88-99-3) including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plants:** Any exposure to phthalic anhydride (CASRN 85-44-9) or phthalic acid (CASRN 88-99-3) including via water, soil, sediment. **Screener note:** • Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as ***Supplemental*** if any biological effects are reported. • Studies involving exposures to mixtures will be included only if they also include exposure to phthalic anhydride (CASRN 85-44-9) or phthalic acid (CASRN 88-99-3) alone. Otherwise, mixture studies will be tagged as ***Supplemental***. • Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (**not field studies**) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be **excluded** if there is no evaluated hazardous effect, and tagged as **supplemental** field, if there is an evaluated hazardous effect.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of phthalic anhydride (CASRN 85-44-9) or phthalic acid (CASRN 88-99-3), or exposure to phthalic acid for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening.

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

Table_Apx H-46. Major Categories of Potentially Relevant Supplemental Material for Phthalic Anhydride (CASRN 85-44-9) and Phthalic Acid (CASRN 88-99-3) – Full-Text Screening

Category	Evidence
Mechanistic studies	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo*, *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype. This tag applies primarily during full-text screening. Screener note: if biological susceptibility issues are clearly present or strongly implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Experimental mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Case reports or case series/studies	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.

Category	Evidence
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Abstract or summary	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field studies	Field studies with media concentrations (*e.g.,* surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported.
Use of phthalic anhydride as a reference compound to induce a sensitization response	Phthalic anhydride is a known sensitizer and can be used as a reference compound to induce sensitization responses in experimental studies (*e.g.,* dermatitis, airway sensitization, or other allergenic response). Studies were tagged as supplemental in cases where it was (1) used as a reagent to induce sensitization for the purpose of testing another compound (co-exposure); or (2) the endpoints evaluated were only mechanistic or biochemical and not apical (*e.g.,* cytokine mRNA levels). However, studies that focused on characterizing a sensitization response that included an apical outcome (*e.g.,* local lymph node assay) were considered PECO relevant.

H.5.11 PECO Statements for Various Phthalates: DBP, BBP, DEHP, DIBP, Dicyclohexyl Phthalate, DIDP, and DINP

Table_Apx H-47. PECO Criteria for Various Phthalates: DBP (CASRN 84-74-2), BBP (CASRN 85-68-7), DEHP (CASRN 117-81-7), DIBP (CASRN 84-69-5), Dicyclohexyl Phthalate (CASRN 84-61-7), DIDP (CASRN 26761-40-0), and DINP (CASRN 28553-12-0) – Title and Abstract Screening

PECO Element	Evidence
P	**Human:** Any population and lifestage (*e.g.,* occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any lifestage (*e.g.,* preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotox only). • Ecotoxicological models: invertebrates (*e.g.,* insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.,* mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note:** • To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g., Xenopus,* zebrafish), and traditional human health models (*e.g.,* rodents) can be used to identify potential ecological hazard. Neurotoxicity studies performed in hens (e.g, OECD 418 and 419) are considered relevant to both human and eco hazard • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.,* substance is

PECO Element	Evidence
	lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Tests of single toxicants in *in vitro* and *ex vivo* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.
E	**Relevant forms:** • Dibutyl phthalate (DBP) (CASRN 84-74-2) • Butyl benzyl phthalate (BBP) (CASRN 85-68-7) • Diethylhexyl phthalate (DEHP) (CASRN 117-81-7) ○ ***Isomer***: Isooctyl phthalate - 27554-26-3 • Di-isobutyl phthalate (DIBP) (CASRN 84-69-5) • Dicyclohexyl phthalate (CASRN 84-61-7) • Diisodecyl Phthalate (DIDP) (CASRN 26761-40-0) ○ ***Isomer***: Di-isodecyl phthalate (mixed isomers) - 68515-49-1 • Diisononyl Phthalate (DINP) (CASRN 28553-12-0) ○ ***Isomer***: Di-isononyl phthalate (mixed isomers) - 68515-48-0 • For synonyms see the EPA Chemistry Dashboard. **Human:** Any exposure to DBP, BBP, DEHP, DIBP, dicyclohexyl phthalate, DIDP and/or DINP singularly or in mixture, including exposure as measured by internal concentrations of these chemicals or metabolites of these chemicals in a biological matrix (*i.e.*, urine, blood, semen, etc.). See list of common metabolites for each phthalate below. **Animal:** Any exposure to DBP, BBP, DEHP, DIBP, dicyclohexyl phthalate, DIDP and/or DINP including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plants:** Any exposure to DBP, BBP, DEHP, DIBP, dicyclohexyl phthalate, DIDP and/or DINP including via water or soil, or sediment. **Screener note:** • Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as ***Supplemental*** if any biological effects are reported. • Studies involving exposures to mixtures will be included only if they also include exposure to DBP, BBP, DEHP, DIBP, dicyclohexyl phthalate, DIDP or DINP alone. Otherwise, mixture studies will be tagged as mixture studies will be tagged as supplemental. • Animal and plant studies involving exposures to mixtures will be **included** only if they also include exposure to DBP, BBP, DEHP, DIBP, dicyclohexyl phthalate, DIDP and/or DINP alone. Otherwise, animal and plant mixture studies will be tagged as **Supplemental**. Human mixture studies are ***included.***

PECO Element	Evidence
	• Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (**not field studies**) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be **excluded** if there is no evaluated hazardous effect, and tagged as **supplemental** field, if there is an evaluated hazardous effect.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of DBP, BBP, DEHP, DIBP, dicyclohexyl phthalate, DIDP and/or DINP, or exposure to DBP, BBP, DEHP, DIBP, dicyclohexyl phthalate, DIDP and/or DINP for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening. • All case series and case studies describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as ***Supplemental*** Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, nested case-control study designs are all ***Included*.**
O	**Human:** All health outcomes (cancer and non-cancer) at the organ level or higher. **Animal and Plants:** All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth. **Screener note:** • **Measurable biological effects relevant for humans, animals and plants may include but are not limited to:** mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects. • Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.

Table_Apx H-48. Major Categories of Potentially Relevant Supplemental Material for Various Phthalates: DBP (CASRN 84-74-2), BBP (CASRN 85-68-7), DEHP (CASRN 117-81-7), DIBP (CASRN 84-69-5), Dicyclohexyl Phthalate (CASRN 84-61-7), DIDP (CASRN 26761-40-0), and DINP (CASRN 28553-12-0) – Title and Abstract

Category	Evidence
Mechanistic studies	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo*, *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.

Category	Evidence
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype. This tag applies primarily during full-text screening. **Screener note:** if biological susceptibility issues are clearly present or *strongly* implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Experimental mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported
Isomer	PECO-relevant studies with an exposure to one of the identified isomers, if any.

Table_Apx H-49. PECO Criteria for Various Phthalates: DBP (CASRN 84-74-2), BBP (CASRN 85-68-7), DEHP (CASRN 117-81-7), DIBP (CASRN 84-69-5), Dicyclohexyl Phthalate (CASRN 84-61-7), DIDP (CASRN 26761-40-0), and DINP (CASRN 28553-12-0) – Full-Text Screening

PECO Element	Evidence
P	**Human:** Any population and life stage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any life stage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotoxicity only).

PECO Element	Evidence
	• Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note:** • To identify human health and environmental hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential environmental hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and eco hazard • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Tests of the single toxicants in *in vitro* and *ex vivo* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.

E	**Relevant forms:**
	• Dibutyl phthalate (DBP) (CASRN 84-74-2)
	• Butyl benzyl phthalate (BBP) (CASRN 85-68-7)
	• Diethylhexyl phthalate (DEHP) (CASRN 117-81-7)
	  • *Isomer:* Isooctyl phthalate - CASRN 27554-26-3
	• Di-isobutyl phthalate (DIBP) (CASRN 84-69-5)
	• Dicyclohexyl phthalate (CASRN 84-61-7)
	• Diisodecyl Phthalate (DIDP) (CASRN 26761-40-0)
	  • *Isomer:* Di-isodecyl phthalate (mixed isomers) - CASRN 68515-49-1
	• Diisononyl Phthalate (DINP) (CASRN 28553-12-0)
	  • *Isomer:* Di-isononyl phthalate (mixed isomers) - CASRN 68515-48-0
	
	• For synonyms see the EPA Chemistry Dashboard.
	• No isomers were included for DBP, BBP, DIBP, or dicyclohexyl phthalate.
	
	Human: Any exposure to DBP, BBP, DEHP, DIBP, dicyclohexyl phthalate, DIDP and/or DINP singularly or in mixture, including exposure as measured by internal concentrations of these chemicals or metabolites of these chemicals in a biological matrix (*i.e.*, urine, blood, semen, etc.). See list of common metabolites for each phthalate below.
	
	Animal: Any exposure to DBP, BBP, DEHP, DIBP, dicyclohexyl phthalate, DIDP and/or DINP including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation.

PECO Element	Evidence
	Plants: Any exposure to DBP, BBP, DEHP, DIBP, dicyclohexyl phthalate, DIDP and/or DINP including via water or soil, or sediment. **Screener note:** • Field studies with media concentrations (surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as ***Supplemental*** if any biological effects are reported. • Studies involving exposures to mixtures will be ***Included*** **only** if they also include exposure to DBP, BBP, DEHP, DIBP, dicyclohexyl phthalate, DIDP and/or DINP alone. Otherwise, mixture studies will be tagged as ***Supplemental***. • Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (not field studies) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be excluded if there is no evaluated hazardous effect, and tagged as ***Supplemental*** field, if there is an evaluated hazardous effect.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of DBP, BBP, DEHP, DIBP, dicyclohexyl phthalate, DIDP and/or DINP, or exposure to DBP, BBP, DEHP, DIBP, dicyclohexyl phthalate, DIDP and/or DINP for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening. • All case series and case studies describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as ***Supplemental.*** Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, nested case-control study designs are all ***Included***.
O	**Human:** All health outcomes (cancer and non-cancer) at the organ level or higher. **Animal and Plants:** All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations). Apical endpoints include but are not limited to reproduction, survival, and growth. **Screener note:** • Measurable biological effects relevant for humans, animals and plants may include but are not limited to: mortality, behavioral, population, cellular, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects. • Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.

Table_Apx H-50. Major Categories of Potentially Relevant Supplemental Material for Various Phthalates: DBP (CASRN 84-74-2), BBP (CASRN 85-68-7), DEHP (CASRN 117-81-7), DIBP (CASRN 84-69-5), Dicyclohexyl Phthalate (CASRN 84-61-7), DIDP (CASRN 26761-40-0), and DINP (CASRN 28553-12-0) – Full-Text Screening

Category	Evidence
Mechanistic studies	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo*, *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, life stage, or genotype. This tag applies primarily during full-text screening. **Screener note:** If biological susceptibility issues are clearly present or *strongly* implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Experimental mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and environmental animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported.
Isomer	PECO-relevant studies with an exposure to one of the identified isomers, if any.

H.5.12 PECO Statements for D4

Table_Apx H-51. PECO Criteria for D4 (CASRN: 556-67-2) – Title and Abstract Screening

PECO Element	Evidence
P	**Human:** Any population and lifestage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any lifestage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotox only) • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** Aquatic and terrestrial species (live), all plants including algal, moss, lichen and fungi species. **Screener note:** • To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential ecological hazard. Neurotoxicity studies performed in hens (e.g, OECD 418 and 419) are considered relevant to both human and eco hazard. • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Tests of the single toxicants in *in vitro* and *ex vivo* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.

E	**Relevant forms and isomers:**
	• Octamethylcyclotetra- siloxane (D4); CASRN: 556-67-2
	• No isomers were included for D4
	• D4 degradants listed below are also included
	  ○ octamethyltetrasiloxanediol (CASRN 3081-07-0),
	  ○ hexamethyltrisiloxanediol (CASRN 3663-50-1),
	  ○ tetramethyldisiloxanediol (CASRN 1118-15-6) and
	  ○ dimethylsilanediol (CASRN 1066-42-8)
	For **synonyms** see a list of validated synonyms on the EPA Chemistry Dashboard

PECO Element	Evidence
	Human: Any exposure to Octamethylcyclotetra- siloxane (D4; CASRN: 556-67-2) singularly or in a mixture, including exposure as measured by internal concentrations of these chemicals or metabolites of these chemicals in a biological matrix (*i.e.*, urine, blood, semen, etc.). The four D4 degradants listed above are also included. **Animal:** Any exposure to Octamethylcyclotetra- siloxane (D4; CASRN: 556-67-2) including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. The four D4 degradants listed above are also included. **Plants:** Any exposure to Octamethylcyclotetra- siloxane (D4; CASRN: 556-67-2) including via water, soil, sediment. The four D4 degradants listed above are also included**.** **Screener note:** • Field studies with media concentrations (surface water, interstitial water, soil) and/or body/tissue concentrations of animals or plants are to be identified as **Supplemental** if any biological effects are reported. • Studies involving exposures to mixtures will be included only if they also include exposure to Octamethylcyclotetra- siloxane (D4; CASRN: 556-67-2) or the four D4 degradants (listed above) alone. Otherwise, mixture studies will be tagged as **Supplemental.** • Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (**not field studies**) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be **excluded** if there is no evaluated hazardous effect, and tagged as **supplemental** field, if there is an evaluated hazardous effect. • D4 degradants (4) and other relevant siloxane structures (6) are also identified and should be tagged as supplemental if PECO-relevant.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of Octamethylcyclotetra- siloxane (D4; CASRN: 556-67-2) , and the four D4 degradants, or exposure to Octamethylcyclotetra- siloxane (D4; CASRN: 556-67-2) and the four D4 degradants for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • Field studies with media concentrations (surface water, interstitial water, soil) and/or body/tissue concentrations of animals or plants are to be identified as Supplemental if any biological effects are reported. • Studies involving exposures to mixtures will be included only if they also include exposure to Octamethylcyclotetra- siloxane (D4; CASRN: 556-67-2) or the four D4 degradants (listed above) alone. Otherwise, mixture studies will be tagged as Supplemental. • Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (not field studies) because there is a known and prescribed exposure dose(s) and an evaluation of

PECO Element	Evidence
	hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be excluded if there is no evaluated hazardous effect, and tagged as supplemental field, if there is an evaluated hazardous effect. • D4 degradants (4) and other relevant siloxane structures (6) are also identified and should be tagged as supplemental if PECO-relevant.
O	**Human**: All health outcomes (both cancer and non-cancer) at the organ level or higher. **Animal and Plants**: All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth. **Screener note:** • **Measurable biological effects relevant for humans, animals and plants may include but are not limited to:** mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects. • Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.

Table_Apx H-52. Major Categories of Potentially Relevant Supplemental Material for D4 (CASRN: 556-67-2) − Title and Abstract

Category	Evidence
Mechanistic studies	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo*, *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype. This tag applies primarily during full-text screening. **Screener note:** if biological susceptibility issues are clearly present or *strongly* implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Experimental mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.

Category	Evidence
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials, or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported
Other relevant chemical structures	PECO-relevant studies with other chemical structures such as metabolites or degradants that may be useful later. For example, identified degradants for D4 include octamethyltetrasiloxanediol (CASRN 3081-07-0), hexamethyltrisiloxanediol (CASRN 3663-50-1), tetramethyldisiloxanediol (CASRN 1118-15-6) and dimethylsilanediol (CASRN 1066-42-8). In addition, six other relevant siloxane structures, should also be tagged as supplemental: octamethyltrisiloxane (L3), decamethyltetrasiloxane (L4), dodecamethylpentasiloxane (L5), hexamethylcyclotrisiloxane (D3), decamethylcyclopentasiloxane (D5) and dodecamethylcyclohexasiloxane (D6).

Table_Apx H-53. PECO Criteria for D4 (CASRN: 556-67-2) – Full-Text Screening

PECO Element	Evidence
P	**Human:** Any population and lifestage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any lifestage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Human health models: rat, mouse, rabbit, dog, hamster, guinea pig, cat, non-human primate, pig, hen (neurotox only). • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note:** • To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential ecological hazard.

PECO Element	Evidence
	Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and eco hazard • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Tests of single toxicants in *in vitro* and *ex vivo* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.

E	**Relevant forms and isomers:**
	• Octamethylcyclotetra- siloxane (D4); CASRN: 556-67-2
	• No **isomers** were included for D4
	• Degradants listed below were also included:
	  ○ Octamethyltetrasiloxanediol (CASRN 3081-07-0)
	  ○ Hexamethyltrisiloxanediol (CASRN 3663-50-1)
	  ○ Tetramethyldisiloxanediol (CASRN 1118-15-6)
	  ○ Dimethylsilanediol (CASRN 1066-42-8)
	• For **synonyms** see a list of validated synonyms on the EPA Chemistry Dashboard
	
	Human: Any exposure to Octamethylcyclotetra- siloxane (D4); CASRN: 556-67-2 singularly or in mixture, including exposure as measured by internal concentrations of these chemicals or metabolites of these chemicals in a biological matrix (*i.e.*, urine, blood, semen, etc.). The four D4 degradants listed above are also included.
	
	Animal: Any exposure to Octamethylcyclotetra- siloxane (D4); CASRN: 556-67-2 including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. The four D4 degradants listed above are also included.
	
	Plants: Any exposure to Octamethylcyclotetra- siloxane (D4); CASRN: 556-67-2 including via water, soil, sediment. The four D4 degradants listed above are also included.
	
	Screener note:
	• Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as ***Supplemental*** if any biological effects are reported.
	• Studies involving exposures to mixtures will be included only if they also include exposure to Octamethylcyclotetra- siloxane (D4); CASRN: 556-67-2, or the four D4 degradants listed above alone. Otherwise, mixture studies will be tagged as ***Supplemental***.
	• Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (**not field studies**) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no

PECO Element	Evidence
	prescribed exposure dose(s) will be **excluded** if there is no evaluated hazardous effect, and tagged as ***Supplemental*** field, if there is an evaluated hazardous effect. • Other relevant siloxane structures (6) are also identified and should be tagged as supplemental if PECO-relevant.
C	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of Octamethylcyclotetra- siloxane (D4); CASRN: 556-67-2, and the four D4 degradants listed above, or exposure to Octamethylcyclotetra- siloxane (D4); CASRN: 556-67-2 and the four D4 degradants listed above for shorter periods of time. **Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening. • All case series and case reports describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as ***Supplemental*** • Case-control, case-crossover, case-referent, case-only, case-specular, case-cohort, case-parent, cross sectional, nested case-control study designs are all ***Included.****
O	**Human**: All health outcomes (cancer and non-cancer) at the organ level or higher. **Animal and Plants**: All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth. **Screener note:** • Measurable biological effects relevant for humans, animals and plants may include but are not limited to: mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects. • Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.

Table_Apx H-54. Major Categories of Potentially Relevant Supplemental Material for D4 (CASRN: 556-67-2) – Full-Text Screening

Category	Evidence
Mechanistic studies or studies with below organ-level effects	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo*, *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.

Category	Evidence
Case reports or case series	Case reports (n ≤ 3 cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype. This tag applies primarily during full-text screening. Screener note: if biological susceptibility issues are clearly present or strongly implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Experimental mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported.
Other relevant chemical structures	PECO-relevant studies with other chemical structures such as metabolites or degradants that may be useful later. For example, identified degradants for D4 include octamethyltetrasiloxanediol (CASRN 3081-07-0), hexamethyltrisiloxanediol (CASRN 3663-50-1), tetramethyldisiloxanediol (CASRN 1118-15-6) and dimethylsilanediol (CASRN 1066-42-8). In addition, six other relevant siloxane structures, should also be tagged as supplemental: octamethyltrisiloxane (L3), decamethyltetrasiloxane (L4), dodecamethylpentasiloxane (L5), hexamethylcyclotrisiloxane (D3), decamethylcyclopentasiloxane (D5), and dodecamethylcyclohexasiloxane (D6).

H.5.13 PECO Statements for Asbestos Part 2

Table_Apx H-55. PECO Criteria for Asbestos Part 2 (Supplemental Evaluation Including Legacy Uses and Associated Disposals) – Title and Abstract Screening

PECO Element	Evidence
P	**Human:** Any population and life stage (*e.g.*, occupational or general population, including children and other sensitive populations).

PECO Element	Evidence
	Animal: Aquatic and terrestrial species (live, whole organism) from any lifestage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note:** • To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential ecological hazard. Neurotoxicity studies performed in hens (e.g, OECD 418 and 419) are considered relevant to both human and eco hazard. • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Tests of single toxicants in *in vitro* and *ex vivo* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.
E	**Relevant forms:** Asbestos, as defined by the following fiber types (or mixtures of fiber types): • asbestos: 1332-21-4 • chrysotile (serpentine): 12001-29-5 • crocidolite (riebeckite): 12001-28-4 • amosite (grunerite): 12172-73-5 • anthophyllite: 17068-78-9 • tremolite: 14567-73-8 • actinolite: 12172-67-7 • winchite: 12425-92-2 • richterite: 17068-76-7 • Libby amphibole: 1318-09-8 • Exposure reported as PCM or TEM (including conversion factors for dust) For **synonyms** see a list of validated synonyms on the EPA Chemistry Dashboard.

PECO Element	Evidence
	Human: Any exposure to one or more of the 8 asbestos fiber types, singularly or mixed, that meets the following conditions: • Exposure based on measured or estimated concentrations of asbestos • May be combined with estimates of duration of exposure, such as exposure biomonitoring data (*e.g.*, lung tissue specimens), environmental or occupational-setting monitoring data (*e.g.*, ambient air levels), job title or residence. • Quantitative measures or estimates of exposure only • For categorical exposures, a minimum of 2 exposure groups (referent group + 1) **Eco Animal:** Any exposure to asbestos fiber types including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plants:** Any exposure to asbestos fiber types including via water, soil, sediment. **Screener note:** • Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as **Supplemental** if any biological effects are reported. • Studies involving exposures to mixtures (with other chemicals or fiber types other than the ones listed above) will be included only if they also include exposure to any of the 8 asbestos fiber types (alone or in combination). Otherwise, mixture studies will be tagged as • Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (**not field studies**) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be **excluded** if there is no evaluated hazardous effect, and tagged as **Supplemental** field, if there is an evaluated hazardous effect. • Papers reporting exposure to "asbestos" generally and not specific fiber type of asbestos will be included for further consideration.
C	**Human:** the source meets either of the following conditions: • Contains a comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of asbestos, and other relevant forms listed above. **Eco Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as **unclear** during Title/Abstract Screening.

PECO Element	Evidence
	• All case reports and case studies/series describing findings in a sample size of less than 20 people in any setting (*e.g.*, occupation, general population) will be tracked as "potentially relevant supplemental information."
O	**Human**: Health outcomes including lung cancer, mesothelioma, laryngeal cancer, and ovarian cancer and all non-cancer at the system level (*e.g.*, immune, cardiovascular, respiratory) or higher. **Eco Animal and Plants**: All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth. **Screener note:** • **Measurable biological effects relevant for humans, animals and plants may include but are not limited to:** mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects. • Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.

Table_Apx H-56. Major Categories of Potentially Relevant Supplemental Material for Asbestos Part 2 (Supplemental Evaluation Including Legacy Uses and Associated Disposals) – Title and Abstract

Category	Evidence
Mechanistic studies	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo*, *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype. This tag applies primarily during full-text screening. **Screener note:** if biological susceptibility issues are clearly present or *strongly* implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Experimental mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.

Category	Evidence
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported
Studies that investigate talc or magnesium silicate	Studies with measured hazard endpoints (apical or mechanistic) where the exposure is to talc or magnesium silicate as defined below should be tagged as supplemental: • *Talc:* 14807-96-6, 35592-05-3, talcum, agalite, antimyst, asbestine, trimagnesium, soapstone, steatite, french chalk • *Magnesium silicate:* 1343-88-0, Magnesium silicate, Magnesium oxosilanediolate, Silicic acid, magnesium salt, Florisil, magnesium silandiolate However, please exclude synthetic magnesium silicate (lab-synthesized and thus, not asbestos-relevant) or synthetic magnesium silicate-products.

Table_Apx H-57. PECO Criteria for Asbestos Part 2 (Supplemental Evaluation Including Legacy Uses and Associated Disposals) – Full-Text Screening

PECO Element	Evidence
P	**Human:** Any population and lifestage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any lifestage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). All hen studies (including neurotoxicity studies) will be included for ecotoxicological models. **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen and fungi species. **Screener note:** • To identify human health and ecological hazards, other organisms not listed above in their respective categories can also be used. Non-mammalian model systems are increasingly used to identify potential human health hazards (*e.g.*, *Xenopus*, zebrafish), and traditional human health models (*e.g.*, rodents) can be used to identify potential

PECO Element	Evidence
	ecological hazard. Neurotoxicity studies performed in hens (*e.g.*, OECD 418 and 419) are considered relevant to both human and eco hazard • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). • Tests of single toxicants in *in vitro* and *ex vivo* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses are excluded.
E	**Relevant forms:** Asbestos, as defined by the following fiber types (or mixtures of fiber types): • asbestos: 1332-21-4 • chrysotile (serpentine): 12001-29-5 • crocidolite (riebeckite): 12001-28-4 • amosite (grunerite): 12172-73-5 • anthophyllite: 17068-78-9 • tremolite: 14567-73-8 • actinolite: 12172-67-7 • winchite: 12425-92-2 • richterite: 17068-76-7 • Libby amphibole: 1318-09-8 • Exposure reported as PCM or TEM (including conversion factors for dust) For **synonyms** see a list of validated synonyms on the EPA Chemistry Dashboard. **Human:** Any exposure to one or more of the 8 asbestos fiber types, singularly or mixed, that meets the following conditions: • Exposure based on measured or estimated concentrations of asbestos • May be combined with estimates of duration of exposure, such as exposure biomonitoring data (*e.g.*, lung tissue specimens), environmental or occupational-setting monitoring data (*e.g.*, ambient air levels), job title or residence. • Quantitative measures or estimates of exposure *only* • For categorical exposures, a minimum of 2 exposure groups (referent group + 1) **Eco Animal:** Any exposure to asbestos fiber types including via water (including environmental aquatic exposures), soil or sediment, diet, gavage, injection, dermal, and inhalation. **Plants:** Any exposure to asbestos fiber types including via water, soil, sediment.

PECO Element	Evidence
	Screener note: • Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as **Supplemental** if any biological effects are reported. • Studies involving exposures to mixtures (with other chemicals or fiber types other than the ones listed above) will be included only if they also include exposure to any of the 8 asbestos fiber types (alone or in combination). Otherwise, mixture studies will be tagged as **Supplemental.** • Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (**not field studies**) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) will be **excluded** if there is no evaluated hazardous effect, and tagged as **Supplemental** field, if there is an evaluated hazardous effect. • Papers reporting exposure to "asbestos" generally and not specific fiber type of asbestos will be included for further consideration.
C	**Human:** the source meets either of the following conditions: • Contains a comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of asbestos, and other relevant forms listed above. **Eco Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **Screener note:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during Title/Abstract Screening.
O	**Human**: Health outcomes including lung cancer, mesothelioma, laryngeal cancer, and ovarian cancer and all non-cancer at the system level (*e.g.*, immune, cardiovascular, respiratory) or higher. **Eco Animal and Plants**: All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth. **Screener note:** • **Measurable biological effects relevant for humans, animals and plants may include but are not limited to:** mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects. • Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.

Table_Apx H-58. Major Categories of Potentially Relevant Supplemental Material for Asbestos Part 2 (Supplemental Evaluation Including Legacy Uses and Associated Disposals) – Title and Abstract and Full-Text Screening

Category	Evidence
Mechanistic studies	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo*, *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion (ADME), toxicokinetic studies, or physiologically based pharmacokinetic (PBPK) models.
Case reports or case series	Case reports ($n \leq 3$ cases) and case series (non-occupational) will be tracked as potentially relevant supplemental information.
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype. This tag applies primarily during full-text screening. **Screener note:** if biological susceptibility issues are clearly present or *strongly* implied in the title/abstract, this supplemental tag may be applied at the title abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Mixture studies	Experimental mixture studies that are not considered PECO-relevant because they do not contain an exposure or treatment group assessing only the chemical of interest. Human health animal model and eco animal model/plant will be tagged separately for mixture studies.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials, or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported
Studies that investigate talc or magnesium silicate	Studies with measured hazard endpoints (apical or mechanistic) where the exposure is to talc or magnesium silicate as defined below should be tagged as supplemental: • *Talc:* 14807-96-6, 35592-05-3, talcum, agalite, antimyst, asbestine, trimagnesium, soapstone, steatite, French chalk • *Magnesium silicate:* 1343-88-0, Magnesium silicate, Magnesium oxosilanediolate, Silicic acid, magnesium salt, Florisil, magnesium silandiolate However, please exclude synthetic magnesium silicate (lab-synthesized and thus, not asbestos-relevant) or synthetic magnesium silicate-products.

H.5.14 PECO Statements for 1,4-Dioxane Supplement

Table_Apx H-59. PECO Inclusion Criteria for the Data Sources Reporting Exposure Data on General Population, Consumers and Commercial Receptors – 1,4-Dioxane (Supplementary Evaluation)

PECO Element	Evidence
Population	**Human:** General population; consumers[a]; bystanders[a] in the home; near-facility populations (includes industrial and commercial facilities manufacturing, processing, or using the chemical substance); near-disposal-facility populations; children; susceptible populations (lifestages, preexisting conditions, genetic factors), pregnant women; lactating women, women of childbearing age. Many human population groups may be exposed. The consumer uses evaluated in the original evaluation and consumer by-stander population associated with those uses are NOT PECO-relevant in the supplementary evaluation because they have already been evaluated and OPPT is not re-evaluating them in the supplementary evaluation. However, the population will be included at the title-abstract screening phase to ensure that consumer data which could be used as a surrogate for commercial receptors are included.
Exposure	**Expected Primary Exposure Sources, Pathways, Routes:** • Sources: All current and newly introduced uses, including associated disposals, commercial and consumer uses, are included. • Pathways: any monitoring data available for indoor air/vapor/mist; surface water; groundwater; outdoor/ambient air; drinking water; wastewater; land disposal; soil; sediment; dietary. • Routes of Exposure: Inhalation, Oral, Dermal **Chemical of Interest[a]** • 1,4-Dioxane (parent only)
Comparator (Scenario)	**Human:** • Consider media-specific background exposure scenarios and use/source specific exposure scenarios as well as which receptors are and are not reasonably exposed across the projected exposure scenarios. • Concentrations in media resulting from spills and improper disposal are considered PECO Supplemental.
Outcomes for Exposure Concentration or Dose	**Human:** • Acute, subchronic, and/or chronic external dose estimates. • Acute, subchronic, and/or chronic media concentration estimates. • Both external potential dose and internal dose based on biomonitoring and reverse dosimetry mg/kg/day will be considered. • Characteristics of commercial and non-commercial products or articles (weight fraction, emission rates, etc) containing 1,4-dioxane
[a]Articles will not be screened for chemical relevancy at the Title Abstract screening level. Screening for chemical relevancy will start at the Full-Text screening level.	

Appendix I INTERACTIVE LITERATURE TREES AND EVIDENCE TABLE EVERGREEN LINKS

Table_Apx I-1. Interactive Literature Inventory Trees for 2019 HPS and MRREs

Chemical Name	Discipline	Data Date	URL
o-Dichlorobenzene	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500155/references/visualization/
	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500131/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500513/
	Hazard	6/10/20	https://hawcprd.epa.gov/summary/visual/100500385/
p-Dichlorobenzene	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500158/references/visualization/
	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500134/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500524/
	Hazard	6/10/20	https://hawcprd.epa.gov/summary/visual/100500384/
1,2-Dichloroethane	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500157/references/visualization/
	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500133/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500514/
	Hazard	6/2/20	https://hawcprd.epa.gov/summary/visual/100500388/
trans-1,2- Dichloroethylene	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500156/references/visualization/

Chemical Name	Discipline	Data Date	URL
	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500132/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500512/
	Hazard	6/10/20	https://hawcprd.epa.gov/summary/visual/100500387/
1,1,2-Trichloroethane	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500154/references/visualization/
	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500130/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500525/
	Hazard	6/2/20	https://hawcprd.epa.gov/summary/visual/100500390/
1,2-Dichloropropane	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500153/references/visualization/
	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500129/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500516/
	Hazard	6/2/20	https://hawcprd.epa.gov/summary/visual/100500386/
1,1-Dichloroethane	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500152/references/visualization/
	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500128/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500506/
	Hazard	6/2/20	https://hawcprd.epa.gov/summary/visual/100500389/
Ethylene dibromide	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500144/references/visualization/

Chemical Name	Discipline	Data Date	URL
	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500119/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500515/
	Hazard	6/10/20	https://hawcprd.epa.gov/summary/visual/100500381/
1,3-Butadiene	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500143/references/visualization/
	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500118/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500520/
	Hazard	6/16/20	https://hawcprd.epa.gov/summary/visual/100500471/
1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (HHCB)	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500140/references/visualization/
	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500115/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500510/
	Hazard	6/10/20	https://hawcprd.epa.gov/summary/visual/100500382/
4,4’-(1-Methylethylidene)bis[2, 6-dibromophenol] (TBBPA)	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500146/references/visualization/
	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500121/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500509/
	Hazard	6/9/20	https://hawcprd.epa.gov/summary/visual/100500373/
Tris(2-chloroethyl) phosphate (TCEP)	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500145/references/visualization/

Chemical Name	Discipline	Data Date	URL
	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500120/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500522/
	Hazard	5/18/20	https://hawcprd.epa.gov/summary/visual/100500374/
Phosphoric acid, triphenyl ester (TPP)	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500135/references/visualization/
	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500109/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500523/
	Hazard	6/10/20	https://hawcprd.epa.gov/summary/visual/100500383/
Formaldehyde	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500142/references/visualization/
	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500117/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500519/
	Hazard	8/3/20	https://hawcprd.epa.gov/summary/visual/100500465/
Phthalic anhydride	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500141/references/visualization/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500466/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500511/
	Hazard	6/10/20	https://hawcprd.epa.gov/summary/visual/100500464/
	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500151/references/visualization/

Chemical Name	Discipline	Data Date	URL
Dibutyl phthalate (DBP) (1,2-Benzene- dicarboxylic acid, 1,2-dibutyl ester)	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500127/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500517/
	Hazard	6/16/20	https://hawcprd.epa.gov/summary/visual/100500467/
Butyl benzyl phthalate (BBP) - 1,2-Benzene- dicarboxylic acid, 1- butyl 2(phenylmethyl) ester	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500150/references/visualization/
	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500126/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500518/
	Hazard	6/16/20	https://hawcprd.epa.gov/summary/visual/100500468/
Di-ethylhexyl phthalate (DEHP) - (1,2-Benzene- dicarboxylic acid, 1,2-bis(2-ethylhexyl) ester)	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500149/references/visualization/
	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500125/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500526/
	Hazard	6/16/20	https://hawcprd.epa.gov/summary/visual/100500469/
Di-isobutyl phthalate (DIBP) - (1,2-Benzene- dicarboxylic acid, 1,2- bis-(2methylpropyl) ester)	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500148/references/visualization/
	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500124/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500505/
	Hazard	6/16/20	https://hawcprd.epa.gov/summary/visual/100500454/
Dicyclohexyl phthalate	Fate	6/2/20	https://hawcprd.epa.gov/lit/assessment/100500147/references/visualization/

Chemical Name	Discipline	Data Date	URL
Dicyclohexyl phthalate (cont.)	Engineering	8/5/20	https://hawcprd.epa.gov/lit/assessment/100500122/references/visualization/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500507/
	Hazard	6/16/20	https://hawcprd.epa.gov/summary/visual/100500470/
Di-isodecyl phthalate (DIDP)	Fate	4/26/21	https://hawcprd.epa.gov/summary/visual/100500607/
	Physical and Chemical Properties	4/12/21	https://hawcprd.epa.gov/summary/visual/100500618/
	Engineering	4/21/21	https://hawcprd.epa.gov/summary/visual/100500608/
	Exposure	4/28/21	https://hawcprd.epa.gov/summary/visual/100500504/
	Hazard	5/03/21	https://hawcprd.epa.gov/summary/visual/100500455/
Di-isononyl phthalate (DINP)	Fate	4/26/21	https://hawcprd.epa.gov/summary/visual/100500602/
	Physical and Chemical Properties	4/12/21	https://hawcprd.epa.gov/summary/visual/100500617/
	Engineering	4/21/21	https://hawcprd.epa.gov/summary/visual/100500609/
	Exposure	4/28/21	https://hawcprd.epa.gov/summary/visual/100500521/
	Hazard	5/03/21	https://hawcprd.epa.gov/summary/visual/100500463/
Octamethylcyclotetra- siloxane (D4)	Fate	5/7/21	https://hawcprd.epa.gov/summary/visual/100500603/
	Physical and Chemical Properties	5/6/21	https://hawcprd.epa.gov/summary/visual/100500601/
	Engineering	5/6/21	https://hawcprd.epa.gov/summary/visual/100500605/
	Exposure	5/5/21	https://hawcprd.epa.gov/summary/visual/100500606/

Chemical Name	Discipline	Data Date	URL
	Hazard	5/6/21	https://hawcprd.epa.gov/summary/visual/100500604/
Asbestos	Fate	9/27/21	https://hawcprd.epa.gov/summary/visual/100500776/
	Physical and Chemical Properties	9/27/21	https://hawcprd.epa.gov/summary/visual/100500775/
	Engineering	9/27/21	https://hawcprd.epa.gov/summary/visual/100500773/
	Exposure	9/27/21	https://hawcprd.epa.gov/summary/visual/100500774/
	Hazard	9/27/21	https://hawcprd.epa.gov/summary/visual/100500772/

Table_Apx I-2. Links to Interactive Evidence Tables for 2019 HPS and MRREs

Chemical Name	Discipline	Data Date	URL
o-Dichlorobenzene	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500411/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500484/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500429/
	Hazard	7/1/20	https://hawcprd.epa.gov/summary/visual/100500398/
p-Dichlorobenzene	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500408/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500481/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500432/
	Hazard	7/1/20	https://hawcprd.epa.gov/summary/visual/100500399/
1,2-Dichloroethane	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500409/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500482/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500431/

Chemical Name	Discipline	Data Date	URL
	Hazard	6/8/20	https://hawcprd.epa.gov/summary/visual/100500404/
trans-1,2- Dichloroethylene	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500410/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500483/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500428/
	Hazard	6/8/20	https://hawcprd.epa.gov/summary/visual/100500406/
1,1,2-Trichloroethane	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500412/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500480/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500433/
	Hazard	6/8/20	https://hawcprd.epa.gov/summary/visual/100500401/
1,2-Dichloropropane	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500413/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500485/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500430/
	Hazard	6/8/20	https://hawcprd.epa.gov/summary/visual/100500405/
1,1-Dichloroethane	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500414/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500486/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500436/
	Hazard	6/8/20	https://hawcprd.epa.gov/summary/visual/100500400/
Ethylene dibromide	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500417/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500494/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500437/

Chemical Name	Discipline	Data Date	URL
	Hazard	6/29/20	https://hawcprd.epa.gov/summary/visual/100500394/
1,3-Butadiene	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500418/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500495/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500427/
	Hazard	6/16/20	https://hawcprd.epa.gov/summary/visual/100500393/
1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta [g]-2-benzopyran (HHCB)	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500420/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500498/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500422/
	Hazard	6/29/20	https://hawcprd.epa.gov/summary/visual/100500395/
4,4’-(1-Methylethylidene)bis[2, 6-dibromophenol] (TBBPA)	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500415/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500492/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500423/
	Hazard	5/18/20	https://hawcprd.epa.gov/summary/visual/100500397/
Tris(2-chloroethyl) phosphate (TCEP)	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500416/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500493/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500425/
	Hazard	5/20/20	https://hawcprd.epa.gov/summary/visual/100500407/
Phosphoric acid, triphenyl ester (TPP)	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500421/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500501/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500426/

Chemical Name	Discipline	Data Date	URL
	Hazard	5/18/20	https://hawcprd.epa.gov/summary/visual/100500396/
Formaldehyde	Fate	6/2/20	N/A
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500496/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500443/
	Hazard	8/3/20	https://hawcprd.epa.gov/summary/visual/100500453/
Phthalic anhydride	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500419/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500497/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500434/
	Hazard	6/29/20	https://hawcprd.epa.gov/summary/visual/100500392/
Dibutyl phthalate (DBP) (1,2-Benzene- dicarboxylic acid, 1,2-dibutyl ester)	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500446/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500487/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500441/
	Hazard	6/16/20	https://hawcprd.epa.gov/summary/visual/100500456/
Butyl benzyl phthalate (BBP) - 1,2-Benzene- dicarboxylic acid, 1- butyl 2(phenylmethyl) ester	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500451/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500488/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500442/
	Hazard	6/16/20	https://hawcprd.epa.gov/summary/visual/100500457/
Di-ethylhexyl phthalate (DEHP) - (1,2-Benzene- dicarboxylic acid, 1,2-bis(2-ethylhexyl) ester)	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500450/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500489/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500440/

Chemical Name	Discipline	Data Date	URL
	Hazard	6/16/20	https://hawcprd.epa.gov/summary/visual/100500458/
Di-isobutyl phthalate (DIBP) - (1,2-Benzene- dicarboxylic acid, 1,2- bis-(2methylpropyl) ester)	Fate	6/2/20	https://hawcprd.epa.gov/summary/visual/100500449/
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500490/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500439/
	Hazard	6/16/20	https://hawcprd.epa.gov/summary/visual/100500459/
Dicyclohexyl phthalate	Fate	N/A	N/A
	Engineering	8/5/20	https://hawcprd.epa.gov/summary/visual/100500491/
	Exposure	7/31/20	https://hawcprd.epa.gov/summary/visual/100500438/
	Hazard	6/16/20	https://hawcprd.epa.gov/summary/visual/100500460/
Di-isodecyl phthalate (DIDP)	Fate	4/26/21	https://hawcprd.epa.gov/summary/visual/100500447/
	Engineering	4/21/21	https://hawcprd.epa.gov/summary/visual/100500500/
	Exposure	4/28/21	https://hawcprd.epa.gov/summary/visual/100500445/
	Hazard	5/03/21	https://hawcprd.epa.gov/summary/visual/100500462/
Di-isononyl phthalate (DINP)	Fate	4/26/21	https://hawcprd.epa.gov/summary/visual/100500448/
	Engineering	4/21/21	https://hawcprd.epa.gov/summary/visual/100500499/
	Exposure	4/28/21	https://hawcprd.epa.gov/summary/visual/100500444/
	Hazard	5/03/21	https://hawcprd.epa.gov/summary/visual/100500461/
Octamethylcyclotetra- siloxane (D4)	Fate	5/7/21	https://hawcprd.epa.gov/summary/visual/100500610/
	Engineering	5/6/21	https://hawcprd.epa.gov/summary/visual/100500612/
	Exposure	5/5/21	https://hawcprd.epa.gov/summary/visual/100500611/

Chemical Name	Discipline	Data Date	URL
	Hazard	5/6/21	https://hawcprd.epa.gov/summary/visual/100500599/
Asbestos	Fate	9/27/21	https://hawcprd.epa.gov/summary/visual/100500890/
	Engineering	9/27/21	https://hawcprd.epa.gov/summary/visual/100500888/
	Exposure	9/27/21	https:/hawcprd.epa.gov/summary/visual/100500885/
	Hazard	9/27/21	https://hawcprd.epa.gov/summary/visual/100500891/
Talc/MS-Asbestos	Fate	9/27/21	https://hawcprd.epa.gov/summary/visual/assessment/100500280/TSCA-Fate-Literature-Inventory-Heat-Maps-Talc/
	Engineering	9/27/21	https://hawcprd.epa.gov/summary/visual/assessment/100500277/TSCA-Eng-Literature-Inventory-Heat-Maps-TalcASB/
	Exposure	9/27/21	https://hawcprd.epa.gov/summary/visual/assessment/100500276/TSCA-Exposure-Literature-Inventory-Heat-Maps-Talc/
	Hazard	9/27/21	https://hawcprd.epa.gov/summary/visual/assessment/100500278/Asbestos-Hazards-Evidence-Map-Talc/

Appendix J OPPT EVIDENCE SOURCE TAG STRUCTURE

J.1 Peer-Reviewed Literature

These tags represent literature procured from peer-reviewed databases. The parent tag, "*Peer-Reviewed Literature,*" encompasses all references within the subsequent child tags. "*LitSearch: Dates*" encompasses all references found during a peer-reviewed literature search event. The associated dates identify the date range used when searching for references. For instance, "LitSearch: July 2010-Feb 2021" would indicate that any references from this search should fall between July 2010 and February 2021.

Individual database tags, like "*Agricola*" and "*ProQuest,*" contain references found from those sources. The only exception is "*Toxline,*" which is based upon its predecessor, "*ToxNet.*" Since the ToxNet database went offline, references it once housed were dispersed to other databases. EPA is specifically interested in the Toxline subset of these references, which were divided and relocated to PubMed and ProQuest. As a result, the "*Toxline*" tag is composed of references identified from the PubMed and ProQuest subsets within their parent database.

2019 Starts: For 2019 Starts (risk evaluations with a 2019 start date), the "*Additional Sources*" tag houses peer-reviewed literature from initial literature searches that entered the systematic review process without source database information.

Risk evaluations that are part of the 2019 Starts or earlier retain "*Science Direct*" as an individual database tag. Risk evaluations moving forward will replace "*Science Direct*" with "*Scopus.*"

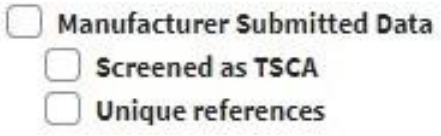
J.2 Gray Literature

Gray Literature for 2019 Starts is composed of gray literature searches performed by the ICF and ERG consulting groups, or HERO librarians. If the searches were performed by a consulting group, the results of each search are tagged to "*ERG Search*" and "*ICF Search,*" respectively. The results of HERO searches will be tagged to "*Gray Literature*" at the root level.

Because of the complex nature of gray literature, these references go through a specialized binning process, called the "*Decision Tree*" to aid screening efforts. References are assessed on various criteria, resulting in an "*Include,*" "*Exclude,*" or "*TSCA*" determination. "*Excluded*" references do not move forward, but "*Included*" references are distributed to relevant disciplines. As references identified as TSCA Submissions are evaluated through a separate process, they are tagged here to keep them separate from other gray literature. They will also be tagged to "*Identified in Gray*" under the "*TSCA Submissions*" category.

Although not shown here, when a gray supplemental search is performed, a child tag under "*Gray Literature*" will be created and named for it. Results of the supplemental search will be located there.

J.3 Manufacturer Submitted Data

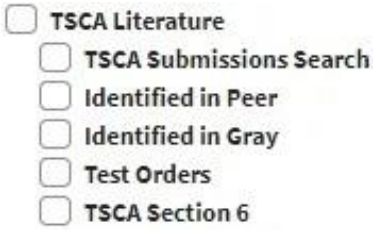


Manufacturer-submitted data for manufacturer-requested risk evaluations (MRRE data) consists of information and literature supplied by the requesting manufacturers. Unlike other source categories, these references must be kept together and accounted for in a single grouping, regardless of the type of overlap.

Specifically, TSCA records are removed from other source categories and screened separately. References that are both MRRE and TSCA are still screened separately using TSCA criteria. However, because they cannot be removed from the Manufacturer Submitted Data pool, they must be identified in another way. These references are tagged to "*Screened as TSCA,*" with the knowledge that they will only move forward in TSCA screening, not other screening efforts. Sometimes the MRRE will identify a HERO ID for a TSCA submission that differs from a duplicate HERO ID that EPA will use for the same record; EPA may give preference to the HERO ID EPA already identified because the study might be more complete or might be a final version of a study that was identified in the MRRE.

Items tagged to "*Unique references*" are those references found only within the MRRE source pool, and nowhere else. This is used primarily as a reference for Venn Diagram graphics.

J.4 TSCA Literature



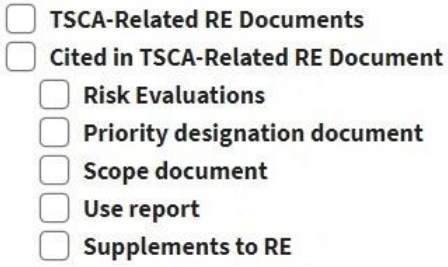
TSCA Submissions are any reports or data that have been submitted to EPA under provisions of TSCA as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act. These include sections 4, 5, 6, 8(d), 8(e) and any FYI submissions. Due to the specialized nature of TSCA submissions, they must undergo a screening process separate from other sources of literature. As such, TSCA submissions that are found in other literature sources must be identified and set aside.

The "*Identified in Peer*" tag is composed of TSCA references discovered in the peer-reviewed literature. Upon discovery of TSCA submissions in peer-reviewed literature, they are untagged from "*Peer Literature*" and retagged to "*Identified in Peer.*" Similarly, TSCA Submissions that are found within Gray Literature are untagged from "*Gray Literature*" and retagged to "*Identified in Gray.*" This allows us to reassign TSCA submissions while maintaining the original source information.

"*Test Orders*" houses references relevant to test orders for a given project. "*TSCA section 6*" houses references relevant to section 6 of TSCA.

Note: In accordance with the specialized screening performed on TSCA submissions, screening outcomes are captured in "*Title Screening,*" which is further broken down into "*Included*" articles and "*Excluded*" articles. Title Screening tags will be hidden for 2019 Starts.

J.5 TSCA-Related RE Documents



References in these categories are relevant to risk evaluations and contribute to the overall direction of the risk evaluation.

"*TSCA-Related RE Documents*" is a root level tag that houses official documents contributing to the overall direction of a risk evaluation. This tag will typically include the risk evaluation (drafts and final), priority designation, scope(s), supplements produced during the risk evaluation, and use reports, but might include other TSCA documents as dictated by the needs of the project.

"*Cited in TSCA-Related RE Documents*" is a root level tag, housing the references cited within the official documents housed in "*TSCA-Related RE Documents.*" "*Risk Evaluations*" houses references

cited in the final risk evaluation. "*Priority Designation*" houses references cited in the priority designation of the chemical being evaluated. "*Scope Document*" houses any references that were cited in the scope document relevant to the chemical being evaluated. "*Supplements to RE*" houses supplemental materials produced during the risk evaluation. "*Use Report*" houses references cited in the use report for the chemical being evaluated.

J.6 Additional Literature

"*Additional Literature*" houses any literature that is captured outside of the pre-defined source categories including the supplemental searches. It may include literature related to the predefined tags but could have additional tags determined by the needs of the project.

"*Industry Submissions*" houses additional submissions from industry outside of MRRE Submissions. "*Peer Reviewer Recommendations*" houses literature suggested by peer reviewers not otherwise captured during literature acquisition. References tagged as "*Identified in Other Review*" are those discovered during screening efforts for other chemical projects as being relevant to the chemical in question. For example, a reference identified as being relevant to DINP but found during screening for DEHP would be tagged here. "*ECA Document*" houses the ECA document, and the references cited within. "*IRIS-Identified References*" houses information originally generated by IRIS that is being re-used for OPPT risk evaluations. "*FIFRA Studies*" contains FIFRA information used during the risk evaluation. "*EDSP Studies*" contains EDSP information used during the risk evaluation. "*Support Articles*" contains methodology studies that are referenced by primary studies already in systematic review.

The "*Public Comments*" tag is reserved for docketed references submitted by members of the public, including organizations outside of EPA, during the public comment period for potential inclusion in a risk evaluation. Items tagged to "*Unique references*" are those references found only within the public comment source pool, and nowhere else. Comments from the SACC are housed under "*SACC Comments.*"

Risk evaluations sometimes require additional, targeted searching to acquire literature for a given endpoint or area of study. Some risk evaluations may require multiple supplemental searches, while others will require none. Whenever a supplemental search is needed, it will be named according to the primary focus of the search (*e.g.*, D4's Degradants or 1,4-Dioxane's Consumer Use) and nested under "*Supplemental Searches.*"

J.7 Systematic Review

OPPT Systematic Review is a process divided into disciplines: Engineering, Exposure, Fate, Physical and Chemical Properties, and Hazard. For each discipline, EPA performs two levels of screening, Title & Abstract and Full Text, which are further divided into levels of consideration. After screening is completed, articles that have been identified as necessary for the risk evaluation are submitted for data evaluation. References may be deemed relevant to multiple disciplines.

"*Title & Abstract Review*" contains all references provided to a discipline for screening based on title and abstract content and is the first level of review. References from every source category are filtered against preset, PECO-relevant topic models in SWIFT-Review to determine their relevance to a specific discipline, except for Engineering and Exposure. Engineering and Exposure receive all references for more specific seed filtering. References that are deemed relevant to a discipline at this stage are tagged to its discipline's "*Title & Abstract Review*" tag in the Systematic Review section.

Per discipline, at the end of Title & Abstract level screening, references are tagged according to their level of consideration. "*Excluded*" references are those that have not been deemed useful for the risk evaluation and thus are excluded from further consideration. "*Supplemental*" references are items that are not necessarily in consideration for full-text screening but may contain information that is supplemental to the risk evaluation. "*Included*" references are those that will move forward to full-text screening.

"*Full-Text Review*" contains all references that were deemed included for further review after Title & Abstract screening. This level of screening is based on the contents of the full text of the article. "*Excluded*" references are those that have not been deemed useful for the risk evaluation and thus are excluded from data evaluation. "*Supplemental*" references are items that are not necessarily in consideration for Data Evaluation but may contain information that is supplemental to the risk evaluation. "*Included*" references are those that will move forward to "*Data Evaluation.*"

"*Data Evaluation*" is the final screening level in which the full contents of articles included at the Full Text level are examined in depth. Note that the Hazard discipline divides references into Ecotoxicology and Human Health sub-disciplines at this level. Once data evaluation has been completed, references will be tagged according to their "*Acceptable*" or "*Uninformative*" quality designation.

- [ ] Systematic Review
  - [ ] Engineering
    - [ ] Title & Abstract Review
      - [ ] Included
      - [ ] Excluded
      - [ ] Supplemental
    - [ ] Full Text Review
      - [ ] Included
      - [ ] Excluded
      - [ ] Supplemental
    - [ ] Data Evaluation
      - [ ] Acceptable
      - [ ] Unacceptable
  - [ ] Exposure
    - [ ] Title & Abstract Review
      - [ ] Included
      - [ ] Excluded
      - [ ] Supplemental
    - [ ] Full Text Review
      - [ ] Included
      - [ ] Excluded
      - [ ] Supplemental
    - [ ] Data Evaluation
      - [ ] Acceptable
      - [ ] Unacceptable
  - [ ] Fate
    - [ ] Title & Abstract Review
      - [ ] Included
      - [ ] Excluded
      - [ ] Supplemental
    - [ ] Full Text Review
      - [ ] Included
      - [ ] Excluded
      - [ ] Supplemental
    - [ ] Data Evaluation
      - [ ] Acceptable
      - [ ] Unacceptable
  - [ ] Hazard
    - [ ] Title & Abstract Review
      - [ ] Included
      - [ ] Excluded
      - [ ] Supplemental
    - [ ] Full Text Review
      - [ ] Included
      - [ ] Excluded
      - [ ] Supplemental
    - [ ] Human Health: Data Evaluation
      - [ ] Acceptable
      - [ ] Unacceptable
    - [ ] Ecotoxicology: Data Evaluation
      - [ ] Acceptable
      - [ ] Unacceptable

- [ ] PChem
  - [ ] Title & Abstract Review
    - [ ] Included
    - [ ] Excluded
    - [ ] Supplemental
  - [ ] Full Text Review
    - [ ] Included
    - [ ] Excluded
    - [ ] Supplemental
  - [ ] Data Evaluation
    - [ ] Acceptable
    - [ ] Unacceptable

Appendix K DATA QUALITY CRITERIA FOR PHYSICAL AND CHEMICAL PROPERTY DATA

K.1 Types of Physical and Chemical Property Data Sources

Physical and chemical property data include physical state/form, melting point, boiling point, density, vapor pressure, vapor density, water solubility, octanol:water partition coefficient, Henry's Law constant, flash point, auto-flammability, and viscosity, among others. Both experimental and modeled physical and chemical property data sources will be evaluated. Generally, experimental physical and chemical property data are preferred over modeled data. Definitions for the two data types are shown in Table_Apx K-1. Because the availability of information varies considerably for different chemicals, it is anticipated that some study types will not be available while others may be identified beyond those listed in Table_Apx K-1.

Table_Apx K-1. Types of Physical and Chemical Property Data Sources

Data Source Type	Definition
Trusted sources	Data obtained from peer-reviewed databases (*e.g.*, CRC Handbook of Chemistry & Physics, Merck Index).
Experimental data	Data obtained from experimental studies conducted in a controlled environment with standardized testing protocols or pre-defined testing conditions. Examples include data from laboratory studies or tests such as those conducted for melting point (*e.g.*, OECD TG 102) or water solubility (*e.g.*, OECD TG 105), among others.
Modeled data	Calculated values derived from computational models for estimating physical and chemical property data.

K.1.1 Trusted Sources

Trusted sources are databases of curated, peer-reviewed data that can be considered to have high quality data. Because of this, data extracted from trusted sources can be used without further systematic review of the underlying studies. Table_Apx K-2 below lists those databases that are considered trusted sources with a description of the data they contain, and their quality control processes. Table_Apx K-3 is also included as a reference for additional databases that are still useful, but where the underlying studies may need to be examined to determine data quality.

Table_Apx K-2. Trusted Source Databases for Physical and Chemical Property Data and their Curation and Quality Control Processes

Source	Description of the Data/Information Contained within the Source	Summary of Curation and Quality Control Processes
CRC Handbook of Chemistry and Physics	• This handbook is a comprehensive resource of property data on chemical compounds and their physical and chemical properties that have been reported in literature. EPA uses both the online and hard copy. • The data are derived from many sources including primary literature	• Manual data curation reported for several physical and chemical property data or endpoints. • Normal melting and boiling point values for many compounds have been critically evaluated using expert-system software from NIST, ThermoData Engine (www.nist.gov/srd/nist103b.cfm). This

Source	Description of the Data/Information Contained within the Source	Summary of Curation and Quality Control Processes
	and curated collections of data. Original references are listed but not distinctly assigned to specific values or chemicals.	software generates recommended values based on analysis of available data and uncertainties. • Hard and electronic copies are available, highly interactive comprehensive scientific resource, containing over 700 tables in over 450 documents, regularly updated. • Carefully reviewed by subject matter experts.
Merck Index	• The Merck Index is a comprehensive resource of chemistry information about chemical substances, drugs and biological molecules. EPA uses both the online and hard copy. Primary sources are only provided for isolation, preparation or synthesis, patent information and structural studies; primary sources are not cited for physical and chemical property data.	• The Merck Index reports data as found in literature. • Evaluates multiple sources of data/information and presents representative selections. • Published by the Royal Society of Chemistry, curated by subject matter experts.
ChemSpider	• ChemSpider seeks data from original sources for greater certainty about the data's provenance and accuracy. • Most experimental property data sources are secondary sources, Safety Data Sheets (SDS) or other sources with limited details on the test method or study measuring the physical and chemical properties.	• New entries to the database are run through a series of automated filters to pick out unsuitable structures (incorrect valences, unbalanced charges, or missing stereochemistry). • Basic name and synonym filtering are applied and regularly reviewed to continuously improve filters. • Data/information are curated on an ongoing basis by ChemSpider staff and users to ensure data integrity and data quality. Any user can post comments regarding erroneous data on the website.
Hazardous Substances Data Bank (HSDB)	• HSDB is a toxicology database providing information on human exposure, hazards, industrial hygiene, emergency handling procedures, environmental fate, regulatory requirements, nanomaterials, and related areas of chemical substances. • It typically contains experimental physical and chemical property data sources from recognized, publicly available chemistry handbooks and indexes.	• Assessed by the HSDB Scientific Review Panel • Data has been incorporated in PubChem

Table_Apx K-3. Other Databases for Physical and Chemical Property Data and their Curation and Quality Control Processes

Source	Description of the Data/Information Contained within the Source	Summary of Curation and Quality Control Processes
OECD QSAR Toolbox	• The OECD QSAR Toolbox is a software application that incorporates data and tools from various sources to identify and fill toxicological data gaps for the hazard assessment of chemical substances, including physical and chemical property information. • It contains both experimental and predicted physical and chemical property data on the target chemical substance or analogues, as well as bibliographic citations.	• There are 57 databases containing 2.5 million measured data points in the toolbox. • There are 11 database inventories for substances without experimental data: Canada DSL, CosIng, EPA DSSTOX, ECHA PR, EINECS, HPVC OECD, METI Japan, NICNAS, REACH ECB, TSCA, U.S. HPV Challenge Program. The donated databases are incorporated into the Toolbox as they have been received with no quality assurance or peer review of data within the Toolbox.

Chemistry Dashboard	• EPA's Chemistry Dashboard is a compilation of data, including physical and chemical properties, sourced from many sources of chemical information.
	• Most experimental physical and chemical property data sources are secondary sources, SDS or other sources with limited details on the test method or study measuring the physical and chemical properties.
	• It links EPA's data sources and public domain online resources.
		• The database aggregates data over the past 15 years by both manual and auto-curation techniques. Expansion, curation and validation of the content is ongoing.
		• The data in the dashboard are of varying quality and include:
		  ○ Expert curated: highest confidence in accuracy and consistency of unique chemical identifiers that are confirmed using multiple public sources.
		  ○ Programmatically curated from high quality EPA source(s) and unique chemical identifiers have no conflicts in ChemIDPlus and PubChem
		• Programmatically curated from ACToR or PubChem. Unique chemical identifiers have low confidence and have a single public source.

NIST Chemistry WebBook	• The NIST Chemistry WebBook is a compilation of data including UV/VIS spectra, thermodynamic data, and other chemical and physical property data.	• The data provided in the site are from collections maintained by the NIST Standard Reference Data Program and outside contributors.

Source	Description of the Data/Information Contained within the Source	Summary of Curation and Quality Control Processes
Reaxys	• Reaxys provides experimentally derived chemistry data and information for chemical substances. • It cites primary sources including journal articles, books, patents, reviews, conference proceedings, letters, reports, and handbooks.	• Expert life scientists are involved in the evaluation of the information before posting it to the database. • Chemistry journals, textbooks and patents are carefully selected for database inclusion. • Manual indexing and data extraction are performed on the journals, textbooks, and patents. • Automated processes are used secondarily for content enrichment to chemistry-related periodicals.
STN/CAS	• The STN/CAS database compiles scientific information on chemical substances related to their chemistry and related sciences, including both experimental and predicted property data and spectra. • EPA has a subscription to the database. Bibliographic information could be obtained for a per chemical substance and time fee basis.	• Indexes and summarizes articles from thousands of scientific journals, patents, conferences and other reputable sources of chemical information. • Scientists collect and analyze published literature, extracting and verifying data that is included in the database.

K.2 Data Quality Evaluation Domains

The quality of physical and chemical property data sources is evaluated against metrics and criteria grouped into three domains: Substance, Test and Outcome Reliability, and Other. These domains, as defined in Table_Apx K-4, address elements of the TSCA Science Standards 26(h)(1) through 26(h)(5). Certain domains, metrics, and criteria may not apply to all study types. For example, the Models metric does not apply to studies reporting measured data.

Table_Apx K-4. Types of Physical and Chemical Property Data Sources

Evaluation Domain	Definition
Substance	Metrics in this domain evaluate whether the information provided in the study provides a reliable confirmation that the test substance used in a study has the same (or sufficiently similar) identity and properties as the test substance of interest.
Test reliability	Metrics in this domain assess the reliability and possible bias of methods used to measure or characterize test substance behavior.
Other	Metrics in this domain are added and applied as needed to incorporate chemical-, study-, and reference-specific evaluations (*e.g.*, databases and QSAR models).

K.3 Data Quality Evaluation Metrics

The quality of physical and chemical property data sources is evaluated against six metrics. These metrics, as defined in Table_Apx K-5, address elements of the TSCA Science Standards 26(h)(1) through 26(h)(5). The evaluation strategies are intended to apply to all experimental physical and chemical property data, although certain metrics and criteria may not apply to all studies. Estimated data from QSARs is evaluated using the approach described in Appendix C.1.24 in combination with the appropriate metrics described in this appendix. As with all evaluation criteria, EPA may modify the metrics used for physical and chemical property data as more experience is acquired with the evaluation tools, to support fit-for-purpose TSCA risk evaluations. Any modifications will be documented.

Table_Apx K-5. Data Evaluation Metrics and Definitions for Physical and Chemical Property Data

Evaluation Domain	Evaluation Metric	Definition
Substance	Representativeness	This metric evaluates how the data relate to the chemical substance type.
	Appropriateness	This metric evaluates whether the information or data are relevant and consistent based on known physical and chemical properties, structural features or behaviors.
Test reliability	Reliability/unbiased (method objectivity)	This metric evaluates whether the method for producing the data/information is not biased towards a particular product or outcome.
	Reliability/analytical method	This metric evaluates whether the information or data reported are from a reliable method.
Other	Databases	This metric evaluates whether the information or data reported in databases have undergone reliable review.
	Models	This metric evaluates the applicability and appropriateness of the model for estimating physical and chemical properties of the chemical substance.

K.4 Ranking Method and Determination of Overall Data Quality Level

This section provides details about the ordinal ranking system applied to physical and chemical property data and information.

K.4.1 Determination of Overall Study Rank

To determine the overall study rank, the average of the metric ranking is determined, as shown in Table_Apx K-6, to obtain an overall rank. The metric ranks are then summed and divided by the count of metrics evaluated to obtain an overall study rank between 1 and 3. The equation for calculating the overall rank is shown below:

$$Overall\ Rank\ (range\ of\ 1\ to\ 3) = \sum(Metric\ Rankings) / (Number\ of\ metrics)$$

Ranking examples for physical and chemical property data studies are given in Table_Apx K-7 for measured data.

Studies with any single metric ranked as critically deficient (Ranking = 4) are automatically assigned an overall quality rank of 4 (uninformative). A critically deficient rank means that serious flaws are noted in the metric that consequently make the data unusable (or invalid). EPA plans to use data with an overall quality level of *High, Medium, or Low* quality to quantitatively or qualitatively support the risk evaluations but does not plan to use data rated as *Uninformative*.

Any metrics that are *not rated/not applicable* to the study under evaluation will not be considered in the numerator or calculation of the study's overall quality rank. These metrics will not be included in the numerator or denominator of the overall rank equation. The overall rank is calculated using only those metrics that receive a numerical rank. In addition, if a publication reports more than one study or endpoint, each study and, as needed, each endpoint is evaluated separately.

A detailed table showing quality criteria for the metrics is provided in Table_Apx K-8.

Table_Apx K-6. Range of Metric Ranks for the Quality of Physical and Chemical Property Data

Evaluation Domain	Metric	Range of Metric Rankings
Substance	1. Representativeness	1 to 3[b] or N/A[c]
	2. Appropriateness	
Test reliability	3. Reliability/Unbiased (Method Objectivity)	
	4. Reliability/Analytical Method	
Other	5. Databases	
	6. Models	
Sum (of all metric rankings)[a]		6 to 18
Range of overall rankings, where Overall Ranking = ∑(Metric Rankings) / (Number of metrics being evaluated)		1 to 3[b]

[a] The count of metrics evaluated will differ if some metrics are not ranked (not applicable).
[b] A rank of 4 for critically deficient study data is not presented.
[c] Not applicable or not rated. Metrics assigned N/A are not included in calculations of the sum or average ranks.

Table_Apx K-7. Ranking Example for Physical and Chemical Property Data (*i.e.*, Water Solubility Data) in Peer-Reviewed Literature with All Applicable Metrics Ranked

Evaluation Domain	Metric	Metric Rankings
Substance	1. Representativeness	1
	2. Appropriateness	1
Test reliability	3. Reliability/unbiased (method objectivity)	2
	4. Reliability/analytical method	1

Evaluation Domain	Metric	Metric Rankings
Other	5. Databases	N/A
	6. Models	N/A
Sum (Metric Rankings)		5
Overall ranking, where Overall ranking[a] = ∑(Metric Rankings) / (Number of Metrics Evaluated)		1.25 (High)

High	Medium	Low
≥1 and <1.7	≥1.7 and <2.3	≥2.3 and ≤3

[a] The cutoffs between categories were defined by calculating the difference between the highest possible ranking of 3 and the lowest possible ranking of 1 (*i.e.*, 3 – 1 = 2) and dividing it into three equal parts (2 ÷ 3 = 0.67). This results in a range of approximately 0.7 for each overall study data quality ranking, which is used to estimate the transition points (cut-off values) in the scale between high and medium rankings, and medium and low rankings. These transition points between the ranges of 1 and 3 are determined as follows:

- cut-off values between high and medium: 1 + 0.67 = 1.67, rounded to 1.7 (rankings lower than 1.7 are assigned an overall quality level of high); and
- cut-off values between medium and low: 1.67 + 0.67 = 2.34, rounded to 2.3 (rankings between 1.7 and lower than 2.3 are assigned an overall quality level of medium).

K.5 Data Quality Criteria

Table_Apx K-8 describes the general approach that EPA uses to assess the quality of experimentally derived physical and chemical property data.

Table_Apx K-8. Evaluation Metrics and Ratings for Physical and Chemical Property Data

Quality Level (Ranking)	Description
Domain 1. Substance	
Metric 1. Representativeness This metric evaluates how the data relate to the chemical substance type.	
High (Ranking = 1)	Data are measured or estimated for the subject chemical substance.
Medium (Ranking = 2)	Data are measured for a structural analogue of the subject chemical substance.
Metric 2. Appropriateness Are the information or data relevant and consistent based on known physical and chemical structural properties, features, or behaviors?	
High (Ranking = 1)	Measured data are consistent with the subject chemical substance structural features (*e.g.*, presence of certain functional groups) or other physical and chemical properties (*e.g.*, if the physical state is described as a liquid, the substance should have a melting point below 25 °C and a boiling point above 25 °C) or behaviors.

Quality Level (Ranking)	Description
Medium (Ranking = 2)	Data measured for a structural analogue of the subject chemical substance are consistent with what is expected for the subject chemical substance structural properties, features or behaviors.
Low (Ranking = 3)	Data measured for a structural analogue of the subject chemical substance are not consistent with the subject chemical substance structural properties, features or behaviors, or the structural features or behaviors of the subject chemical substance are uncertain.
Critically Deficient (Ranking = 4)	Measured data for a structural analogue of the subject chemical substance are not appropriate because the analogue is not appropriate (*e.g.*, analogue is a neutral molecule and the subject chemical substance is a salt).
Not rated	Rating of this factor is not applicable to this kind of information.
Domain 2. Test reliability	
Metric 3. Reliability/unbiased (method objectivity). The method for producing the data/information is not biased towards a particular product or outcome.	
High (Ranking = 1)	The methodology for producing the information is designed to answer a specific question, and the methodology's objective is clear.
Medium (Ranking = 2)	There is no indication that the methodology for producing the information was biased towards a particular product or outcome.
Low (Ranking = 3)	The methodology indicates that method bias is likely.
Critically Deficient (Ranking = 4)	Method bias is so severe as to be critically deficient.
Not rated	Rating of this factor is not applicable to this kind of information.
Metric 4. Reliability/analytical method The information or data reported are from a reliable method	
High (Ranking = 1)	Data are obtained by accepted standard analytical methods, including, but not limited to OECD guidelines for physical and chemical properties or other developed standard.
Medium (Ranking = 2)	The analytical method is non-standard but is expected to be appropriate OR the analytical method is unknown but is likely to be appropriate based on the data's inclusion in a peer-reviewed/recognized database or other secondary source.
Low (Ranking = 3)	The analytical method is unknown and there is no indication that a reliable method was used.
Critically Deficient (Ranking = 4)	The analytical method described is not appropriate.

Quality Level (Ranking)	Description
Not rated	Rating of this factor is not applicable to this kind of information.
Domain 3. Other	
Metric 5. Databases The information or data reported in databases have undergone reliable review.	
High (Ranking = 1)	The information or data is from a recognized data collection/repository where data are peer-reviewed by experts in the field, are broadly available to the public for review and use OR includes references to the original sources.
Medium (Ranking = 2)	The data are from a source that is known but is missing elements required for *High* designation such as peer-review, public availability, or the inclusion of references to original sources.
Low (Ranking = 3)	The data are from a primary source without expert peer-review or an unknown secondary source without peer-review and references to the original sources.
Critically Deficient (Ranking = 4)	The data are from an unknown source or there are concerns regarding the source of the data.
Not rated/ Not applicable	Rating of this factor is not applicable to this kind of information.
Metric 6. Models. Did the model have a defined, unambiguous endpoint and appropriate measures of goodness-of-fit, robustness and predictivity, defined by $r^2 > 0.7$, $q^2 > 0.5$ and SE < 0.3, where r^2 is the correlation coefficient, q^2 is the cross-validated correlation coefficient, and SE is the standard error (ECHA, 2016)?	
High (Ranking = 1)	The model had a defined, unambiguous endpoint AND the model performance was known and $r^2 > 0.7$, $q^2 > 0.5$, and SE < 0.3 (ECHA, 2016).
Medium (Ranking = 2)	The model endpoint is broad (*e.g.*, overall persistence) AND/OR non-transparent or difficult-to-reproduce methods were used to build the (Q)SAR model (*e.g.*, artificial neural networks using many structural descriptors).
Low (Ranking = 3)	The algorithm is not publicly available to verify or reproduce the predictions AND/OR statistics on the external validation set are unavailable.
Critically Deficient (Rank = 4)	The model performance was either not known or $r^2 < 0.7$, $q^2 < 0.5$ or SE > 0.3 (ECHA, 2016). These are serious flaws that make the study unusable.
Not rated	Rating of this factor is not applicable to this kind of information.

Appendix L DATA QUALITY CRITERIA FOR FATE DATA

L.1 Types of Fate Data Sources

The quality of fate data, which includes mass transport, chemical partitioning, and chemical or biological transformations in soil, surface waters, groundwater, and air (*e.g.*, biodegradation, hydrolysis, photolysis), is evaluated for four different data sources: experimental data, field studies, modeling data, and monitoring data. Generally experimental fate data is preferred over modeled data; however, fate data from all data sources are evaluated using the data criteria in this section. Definitions for these data types are shown in Table_Apx L-1. Because the availability of information varies considerably for different chemicals, it is anticipated that some study types will not be available while others may be identified beyond those listed in Table_Apx L-1.

Table_Apx L-1. Types of Fate Data

Type of Data Source	Definition
Experimental data	Data obtained from experimental studies conducted in a controlled environment with pre-defined testing conditions. Examples include data from laboratory tests such as those conducted for ready biodegradation (*e.g.*, MITI test) or hydrolysis (*i.e.*, following OECD TG 111), among others.
Field studies	Data collected from incidental sampling of environmental media, especially to provide information on partitioning, bioconcentration, or long-term environmental fate.
Modeling data	Calculated values derived from computational models for estimating environmental fate and property data including degradation, bioconcentration, and partitioning.
Monitoring data	Measured chemical concentration(s) obtained from systematic sampling of environmental media (*e.g.*, air, water, soil, and biota) to observe and study the effect of environment conditions on the fate of chemicals. Monitoring data may include studies of chemical(s) after a known exposure/release of test substance as well as measured chemical concentrations over a period of time to provide direct evidence about fate in environment.

L.2 Data Quality Evaluation Domains

The quality of fate data sources will be evaluated against metrics and criteria grouped into eight evaluation domains: Test Substance; Test Design; Test Conditions; Test Organisms (does not apply to abiotic studies); Outcome Assessment; Confounding/Variable Control; Data Presentation and Analysis; and Other. These domains, as defined in Table Table_Apx L-2, address elements of the TSCA Science Standards 26(h)(1) through 26(h)(5). The evaluation strategies are intended to apply to all fate data, although certain domains, metrics, and criteria may not apply to all studies. For example, there are evaluation strategy considerations for organisms in biodegradation, bioconcentration, or bioaccumulation studies that do not apply to abiotic studies.

Table_Apx L-2. Data Evaluation Domains and Definitions for Fate Data

Evaluation Domain	Definition
Test substance	Metrics in this domain evaluate whether the information provided in the study provides a reliable[a] confirmation that the test substance used in a study has the same

Evaluation Domain	Definition
	(or sufficiently similar) identity, purity, and properties as the test substance of interest.
Test design	Metrics in this domain evaluate whether the experimental design enables the study to distinguish the behavior of the test substance from other factors. This domain includes metrics related to the use of control groups.
Test conditions	Metrics in this domain assess the reliability of methods used to measure or characterize test substance behavior. These metrics evaluate whether presence of the test substance was characterized using method(s) that provide reliable results over the duration of the experiment.
Test organisms	Metrics in this domain pertain to some fate studies.[b] These metrics assess the appropriateness of the population or organism(s) to assess the outcome of interest.
Outcome assessment	Metrics in this domain assess the reliability of methods, including sensitivity, that are used to measure or otherwise characterize outcomes. Outcomes may include physical and chemical properties or fate parameters.
Confounding/ variable control	Metrics in this domain assess the potential impact of factors other than presence of test substance that may affect the outcome. The metrics evaluate whether studies identify and account for factors that are related to presence of the test substance and independently related to outcome (confounding factors) and whether appropriate experimental or analytical (statistical) methods are used to control for factors unrelated to the presence of test substance that may affect the risk of outcome (variable control).
Data presentation and analysis	Metrics in this domain assess whether appropriate experimental or analytical methods were used and if all outcomes are presented.
Other	Metrics in this domain are added as needed to incorporate chemical- or study-specific evaluations (*i.e.*, QSAR models).

[a] Reliability is defined as "the inherent property of a study or data, which includes the use of well-founded scientific approaches, the avoidance of bias within the study or data collection design and faithful study or data collection conduct and documentation" (ECHA, 2011b).
[b] This domain does not apply to abiotic studies.

L.3 Data Quality Evaluation Metrics

Table_Apx L-3 lists the data evaluation domains and metrics for fate studies. Each domain has between two and four metrics; however, some metrics may not apply to all fate data. A general domain for other considerations is available for metrics that are specific to a given test substance or study type (*i.e.*, QSAR models).

As with all evaluation criteria, EPA may modify the metrics used for fate data as more experience is acquired with the evaluation tools, to support fit-for-purpose TSCA risk evaluations. Any modifications will be documented.

Table_Apx L-3. Summary of Metrics for the Fate Data Evaluation Domains

Evaluation Domain	Number of Metrics Overall	Metrics (Metric Number and Description)
Test substance	2	Metric 1: Test Substance Identity Metric 2: Test Substance Purity
Test design	2	Metric 3: Study Controls Metric 4: Test Substance Stability
Test conditions	4	Metric 5: Test Method Suitability Metric 6: Testing Conditions Metric 7: Testing Consistency Metric 8: System Type and Design
Test organisms[a]	2	Metric 9: Test Organism – Degradation Metric 10: Test Organism – Partitioning
Outcome assessment	2	Metric 11: Outcome Assessment Methodology Metric 12: Sampling Methods
Confounding/ variable control	2	Metric 13: Confounding Variables Metric 14: Outcomes Unrelated to Exposure
Data presentation and analysis	2	Metric 15: Data Presentation Metric 16: Statistical Methods & Kinetic Calculations
Other	2	Metric 17: Verification or Plausibility of Results Metric 18: QSAR Models
[a] This domain does not apply to abiotic studies.		

L.4 Ranking Method and Determination of Overall Data Quality Level

This section provides details about the criteria for ordinal ranking of fate data/information for each domain.

L.4.1 Determination of Overall Study Ranking

Ranking examples for fate studies are given in Table_Apx L-4 to Table_Apx L-7. Studies with any single metric ranked as *critically deficient* (Ranking = 4) are automatically assigned an overall quality ranking of 4 (*uninformative*) and further evaluation of the remaining metrics is not necessary. A *critically deficient* ranking means that serious flaws are noted in the domain metric that consequently make the data unusable (or invalid). EPA plans to use data with an overall quality level of *High*, *Medium*, or *Low* to quantitatively or qualitatively support the risk evaluations but does not plan to use data rated as *Uninformative*.

Any metrics that are *not rated/not applicable* to the study under evaluation will not be considered in the numerator or calculation of the study's overall quality ranking. These metrics will not be included in the nominator or denominator of the *overall ranking* determination. The overall ranking is determined using

only those metrics that receive a numerical ranking. In addition, if a publication reports more than one study or endpoint, each study and, as needed, each endpoint is evaluated separately.

Detailed tables showing quality criteria for the metrics are provided in Table_Apx L-8, including serious flaws that would make the metric-specific data *critically deficient* and unfit for use in the environmental fate assessment.

Table_Apx L-4. Rankings for Determining the Quality of Environmental Fate Data

Domain Number/ Description	Metric Number/Description	Range of Metric Rankings[a]
1. Test substance	1. Test Substance Identity	1 to 3
	2. Test Substance Purity	1 to 3
2. Test design	3. Study Controls	1 to 3
	4. Test Substance Stability	1 to 3
3. Test conditions	5. Test Method Suitability	1 to 3
	6. Testing Conditions	1 to 3
	7. Testing Consistency	1 to 3
	8. System Type and Design	1 to 3
4. Test organisms[b]	9. Test Organism – Degradation	1 to 3
	10. Test Organism – Partitioning	1 to 3
5. Outcome assessment	11. Outcome Assessment Methodology	1 to 3
	12. Sampling Methods	1 to 3
6. Confounding/ variable control	13. Confounding Variables	1 to 3
	14. Outcomes Unrelated to Exposure[b]	1 to 3
7. Data presentation and analysis	15. Data Reporting	1 to 3
	16. Statistical Methods & Kinetic Calculations	1 to 3
8. Other	17. Verification or Plausibility of Results	1 to 3
	18. QSAR Models	1 to 3
	Total number of metrics (up to 18)	**Sum = 18 to 54**
Overall Ranking[c] = Σ (Metric Rankings) / (Number of metrics)		
18/18 = 1; 54/18 =3 Range of overall study ranking = 1 to 3		

Domain Number/ Description	Metric Number/Description	Range of Metric Rankings[a]
High ≥1 and <1.7	Medium ≥1.7 and <2.3	Low ≥2.3 and <3.0

[a] For the purposes of calculating an overall study ranking, the range of possible metric rankings is 1 to 3 for each metric, corresponding to high and low quality. No calculations are conducted if a study receives an "critically deficient" rating (Ranking of "4") for any metric.

[b] This metric does not apply to abiotic studies.

[c] The cutoffs between categories were defined by calculating the difference between the highest possible ranking of 3 and the lowest possible ranking of 1 (*i.e.*, 3 – 1 = 2) and dividing it into three equal parts (2 ÷ 3 = 0.67). This results in a range of approximately 0.7 for each overall study data quality ranking, which is used to estimate the transition points (cut-off values) in the scale between high and medium rankings, and medium and low rankings. These transition points between the ranges of 1 and 3 are determined as follows:

- cut-off values between high and medium: 1 + 0.67 = 1.67, rounded to 1.7 (rankings lower than 1.7 are assigned an overall quality level of high); and
- cut-off values between medium and low: 1.67 + 0.67 = 2.34, rounded to 2.3 (rankings between 1.7 and lower than 2.3 are assigned an overall quality level of medium).

Table_Apx L-5. Ranking Example for Abiotic Fate Data (*i.e.*, Hydrolysis Data) with All Applicable Metrics Ranked

Domain	Metric	Metric Ranking
1. Test substance	1. Test Substance Identity	1
	2. Test Substance Purity	2
2. Test design	3. Study Controls	1
	4. Test Substance Stability	3
3. Test conditions	5. Test Method Suitability	1
	6. Testing Conditions	1
	7. Testing Consistency	1
	8. System Type and Design	1
4. Test organisms	9. Test Organism – Degradation	N/A
	10. Test Organism – Partitioning	N/A
5. Outcome assessment	11. Outcome Assessment Methodology	2
	12. Sampling Methods	1
6. Confounding/variable control	13. Confounding Variables	1
	14. Outcomes Unrelated to Exposure	N/A
7. Data presentation and analysis	15. Data Reporting	2

Domain	Metric	Metric Ranking
	16. Statistical Methods & Kinetic Calculations	1
8. Other	17. Verification or Plausibility of Results	1
	18. QSAR Models	N/A
	Sum	19
	Overall Study Ranking[a]	**19/14 = 1.4**
High ≥1 and <1.7	Medium ≥1.7 and <2.3	Low ≥2.3 and <3.0

[a] The cutoffs between categories were defined by calculating the difference between the highest possible ranking of 3 and the lowest possible ranking of 1 (*i.e.*, 3 – 1 = 2) and dividing it into three equal parts (2 ÷ 3 = 0.67). This results in a range of approximately 0.7 for each overall study data quality ranking, which is used to estimate the transition points (cut-off values) in the scale between high and medium rankings, and medium and low rankings. These transition points between the ranges of 1 and 3 are determined as follows:

- cut-off values between high and medium: 1 + 0.67 = 1.67, rounded to 1.7 (rankings lower than 1.7 are assigned an overall quality level of high); and
- cut-off values between medium and low: 1.67 + 0.67 = 2.34, rounded to 2.3 (rankings between 1.7 and lower than 2.3 are assigned an overall quality level of medium).

Table_Apx L-6. Ranking Example for Abiotic Fate Data (*i.e.*, hydrolysis data) with Some Metrics Not Rated/Not Applicable

Domain	Metric	Metric Ranking
1. Test substance	1. Test Substance Identity	1
	2. Test Substance Purity	2
2. Test design	3. Study Controls	1
	4. Test Substance Stability	3
3. Test conditions	5. Test Method Suitability	1
	6. Testing Conditions	1
	7. Testing Consistency	NR
	8. System Type and Design	NR
4. Test organisms	9. Test Organism – Degradation	N/A
	10. Test Organism – Partitioning	N/A
5. Outcome assessment	11. Outcome Assessment Methodology	2
	12. Sampling Methods	1
6. Confounding/variable control	13. Confounding Variables	N/A

Domain	Metric	Metric Ranking
	14. Outcomes Unrelated to Exposure	NR
7. Data presentation and analysis	15. Data Reporting	2
	16. Statistical Methods & Kinetic Calculations	1
8. Other	17. Verification or Plausibility of Results	1
	18. QSAR Models	N/A
NR = not rated N/A = not applicable to abiotic data	Sum	16
	Overall Study Ranking[a]	**16/11 = 1.5**
Overall Ranking[a] = ∑ (Metric Rankings)/(Number of Metrics)		
High ≥1 and <1.7	Medium ≥1.7 and <2.3	Low ≥2.3 and <3

[a] The cutoffs between categories were defined by calculating the difference between the highest possible ranking of 3 and the lowest possible ranking of 1 (*i.e.*, 3 – 1 = 2) and dividing it into three equal parts (2 ÷ 3 = 0.67). This results in a range of approximately 0.7 for each overall study data quality ranking, which is used to estimate the transition points (cut-off values) in the scale between high and medium rankings, and medium and low rankings. These transition points between the ranges of 1 and 3 are determined as follows:

- cut-off values between high and medium: 1 + 0.67 = 1.67, rounded to 1.7 (rankings lower than 1.7 are assigned an overall quality level of high); and
- cut-off values between medium and low: 1.67 + 0.67 = 2.34, rounded to 2.3 (rankings between 1.7 and lower than 2.3 are assigned an overall quality level of medium).

Table_Apx L-7. Ranking Example for QSAR Data

Domain Number/ Description	Metric Number/Description	Metric Ranking[a]
1. Test substance	1. Test Substance Identity	NR
	2. Test Substance Purity	NR
2. Test design	3. Study Controls	NR
	4. Test Substance Stability	NR
3. Test conditions	5. Test Method Suitability	NR
	6. Testing Conditions	NR
	7. Testing Consistency	NR
	8. System Type and Design	NR
4. Test organisms[c]	9. Test Organism – Degradation	NR
	10. Test Organism – Partitioning	NR

Domain Number/ Description	Metric Number/Description	Metric Ranking[a]
5. Outcome assessment	11. Outcome Assessment Methodology	NR
	12. Sampling Methods	NR
6. Confounding/variable control	13. Confounding Variables	NR
	14. Outcomes Unrelated to Exposure[c]	NR
7. Data presentation and analysis	15. Data Reporting	NR
	16. Statistical Methods & Kinetic Calculations	NR
8. Other	17. Verification or Plausibility of Results	2
	18. QSAR Models	1
	Sum (of all metrics evaluated)[b]	**3**
Overall Study Ranking	3/2=1.5 1.5 (High)	
Overall Ranking[c] = ∑ (Metric Rankings)/ (Number of metrics)		
High ≥1 and <1.7	Medium ≥1.7 and <2.3	Low ≥2.3 and <3

[a] For the purposes of calculating an overall study rank, the range of possible metric rank is 1 to 3 for each metric, corresponding to high and low quality. No calculations are conducted if a study receives a *critically deficient* rating (Rank of "4") for any metric.

[b] Not applicable to abiotic studies.

[c] The cutoffs between categories were defined by calculating the difference between the highest possible ranking of 3 and the lowest possible ranking of 1 (*i.e.*, 3 – 1 = 2) and dividing it into three equal parts (2 ÷ 3 = 0.67). This results in a range of approximately 0.7 for each overall study data quality ranking, which is used to estimate the transition points (cut-off values) in the scale between high and medium rankings, and medium and low rankings. These transition points between the ranges of 1 and 3 are determined as follows:

- cut-off values between high and medium: 1 + 0.67 = 1.67, rounded to 1.7 (rankings lower than 1.7 are assigned an overall quality level of high); and
- cut-off values between medium and low: 1.67 + 0.67 = 2.34, rounded to 2.3 (rankings between 1.7 and lower than 2.3 are assigned an overall quality level of medium).

L.5 Data Quality Criteria

Table_Apx L-8. Data Quality Criteria for Fate Data

Data Quality Level	Description
Domain 1. Test substance	
Metric 1. Test substance identity Was the test substance identified definitively?	
High (Ranking = 1)	The test substance was identified definitively (*i.e.*, established nomenclature, CASRN, or structure reported, including information on the specific form tested [particle characteristics for solid-state materials, salt or base, valence state, isomer, etc.] for materials that may vary in form, or submitting company's code name with supporting confirmatory documentation) and the specific form characterized, where applicable.
Medium (Ranking = 2)	The test substance was identified by trade name or other internal designation, but characterization details were omitted that could affect interpretation of study results; however, the omission was not likely to have a substantial impact on the study results.
Low (Ranking = 3)	The test substance was identified; however, it lacked specific characteristics such as stereochemistry or valence state OR there were some uncertainties or conflicting information regarding test substance identification or characterization that were likely to have a substantial impact on the study results.
Critically Deficient (Ranking = 4)	The test substance identity could not be determined from the information provided (*e.g.*, nomenclature was unclear and CASRN or structure was not reported). This is a serious flaw that makes the study unusable.
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. Test substance purity Was the source of the test substance reported? If the test substance was synthesized or extracted (as part of the synthesis or from a substrate), was the test substance identity verified by analytical methods? Were the purity, grade or hydration state (*e.g.*, analytical, technical) of the test substance reported? If the test substance was tested as part of a finished or formulated product, was the full chemical composition of the formulation reported?	
High (Ranking = 1)	The source or purity of the test substance was reported or the test substance identity and purity were verified by analytical means (chemical analysis, etc.) OR if the test substance was tested as part of a finished or formulated product, the full chemical composition of the formulation was reported AND

Data Quality Level	Description
	any observed effects were likely due to the nominal test substance itself (*e.g.*, pure, analytical grade, technical grade test substance, or other substances in the formulation were inert, or the other components were inert under the test conditions).
Medium (Ranking = 2)	The test substance source was not reported AND/OR the test substance purity was low or not reported (*e.g.*, lack of information on hydration state of a compound introduces uncertainty into concentration calculations); however, the omissions or identified impurities were not likely to have a substantial impact on the study results.
Low (Ranking = 3)	The source and purity of the test substance were not reported or verified by analytical means OR The test substance was synthesized or extracted and its identity was not verified by analytical means (*i.e.*, chemical analysis, etc.) OR identified impurities were likely to have a substantial impact on study results.
Critically Deficient (Ranking = 4)	The nature and quantity of reported impurities were such that study results were unduly influenced by one or more of the impurities. These are serious flaws that make the study unusable.
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. Test design	
Metric 3. Study controls Was a concurrent negative control or blank group included? Were positive and toxicity controls included? If a vehicle was used, was the control group exposed to the vehicle? Is the selected vehicle unlikely to influence the study results, stability, bioavailability or/toxicity of the test substance?	
High (Ranking = 1)	A concurrent negative control, or blank group, toxicity control, and positive control were included (where applicable) AND results from controls were within the ranges specified for test validity (or validity criteria for equivalent or similar tests, if not a guideline test) AND a concurrent blank with vehicle (*e.g.*, oil or carrier solvent) was included and the vehicle was not likely to influence the study results (where applicable).
Medium (Ranking = 2)	Some concurrent control group details were not included; however, the lack of data was not likely to have a substantial impact on study results AND the vehicle was not likely to influence the study results (where applicable).
Low (Ranking = 3)	Reported results from control group(s) were outside the ranges specified for test validity (or validity criteria for equivalent or similar tests, if not a guideline test)

Data Quality Level	Description
	OR the vehicle was likely to have a substantial impact on study results.
Critically Deficient (Ranking = 4)	The study did not include or report crucial control groups that consequently made the study unusable (*e.g.*, no positive control for a biodegradation study reporting 0% removal) OR the vehicle used in the study was likely to unduly influence the study results. These are serious flaws that make the study unusable.
Not rated/not applicable	The study did not require concurrent control groups.
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. Test substance stability Did the study characterize and accommodate the test substance stability, homogeneity, preparation, and storage conditions? Were the frequency of preparation and storage conditions appropriate to the test substance stability?	
High (Ranking = 1)	The test substance stability, homogeneity, preparation, and storage conditions were reported (*e.g.*, mixing temperature, stock concentration, stirring methods, centrifugation or filtration), and were appropriate for the study (*e.g.*, a test substance known to degrade in light was stored in dark or amber bottles).
Medium (Ranking = 2)	The test substance stability, homogeneity, preparation or storage conditions were not reported; however, these factors were not likely to influence the test substance or were not likely to have a substantial impact on study results.
Low (Ranking = 3)	The test substance stability, homogeneity, preparation, and storage conditions were not reported and these factors likely influenced the test substance or are likely to have a substantial impact on the study results.
Critically Deficient (Ranking = 4)	There were problems with test substance stability, homogeneity, preparation, or storage conditions that had an impact on concentration or dose estimates and interfered with interpretation of study results. These are serious flaws that make the study unusable.
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. Test conditions	
Metric 5. Test method suitability Was the test method reported and suitable for the test material? Was the target chemical tested at concentrations below its aqueous solubility?	
High (Ranking = 1)	The test method was suitable for the test substance AND the target chemical was tested at concentrations below its aqueous solubility (when applicable).

Data Quality Level	Description
Medium (Ranking = 2)	The test method was suitable for the test substance with minor deviations AND/OR nominal estimates of media concentrations were provided, but the levels were not measured or suitable to the study type or outcome(s) of interest AND these deviations or omissions were not likely to have a substantial impact on study results.
Low (Ranking = 3)	Applied target chemical concentrations were greater than the aqueous solubility AND the deviations were likely to have a substantial impact on the results.
Critically Deficient (Ranking = 4)	The test method was not reported or not suitable for the test substance. These deviations or lack of information resulted in serious flaws that make the study unusable.
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. Testing conditions Were the test conditions monitored, reported, and appropriate for the study method (*e.g.*, the temperature range reported, dissolved organic matter, aeration, total organic matter, pH or water hardness reported and maintained throughout the test)?	
High (Ranking = 1)	Testing conditions were monitored, reported, and appropriate for the method. For example, depending on the study, the following conditions were reported: aerobic/anaerobic conditions reported dissolved oxygen (DO) measured redox/electron activity (pE) parameters listed and/or anaerobic conditions otherwise identified (*e.g.*, sulfate reducing, methanogenic, etc.) pH buffer for studies on the fate of a substance that may exist in ionized form(s) in the pH range of environmental relevance For studies in aquatic environments, conditions reported separately for both the water and sediment column For studies in soil, soil type (location if available), moisture level, soil particle size distribution, background SOM (soil organic matter) or OC (organic carbon) content, CEC (cation exchange capacity) or soil pH, soil name (*e.g.*, USDA series)
Medium (Ranking = 2)	There were reported deviations or omissions in testing conditions (*e.g.*, temperature was not constant or was not in a standard range for the test but, results can be extrapolated to approximate appropriate temperatures); however, sufficient data were reported to determine that the deviations and omissions were not likely to have a substantial impact on study results.
Low (Ranking = 3)	Inappropriate test conditions for the study method (*e.g.*, temperature fluctuations) and the deviations were likely to have a substantial impact on the results.

Data Quality Level	Description
Critically Deficient (Ranking = 4)	Testing conditions were not reported and data provided were insufficient to interpret results OR testing conditions were not appropriate for the method (*e.g.*, a biodegradation study at temperatures that inhibit the microorganisms) resulting in serious flaws that make the study unusable.
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. Testing consistency Were test conditions established to be consistent across samples or study groups? Were multiple exposures evaluated, where applicable?	
High (Ranking = 1)	Test conditions were consistent across samples or study groups (*i.e.*, same exposure method and timing, comparable particle size characteristics). The conditions of the exposure were documented.
Medium (Ranking = 2)	There were minor inconsistencies in test conditions across samples or study groups OR some test conditions across samples or study groups were not reported, but these discrepancies were not likely to have a substantial impact on study results.
Low (Ranking = 3)	There were inconsistencies in test conditions across samples or study groups that are likely to have a substantial impact on results.
Critically Deficient (Ranking = 4)	Critical exposure details across samples or study groups were not reported and these omissions resulted in serious flaws that had a substantial impact on the overall quality, consequently making the study unusable.
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 8. System type and design[a] Was equilibrium established? Were the system type and design capable of appropriately maintaining substance concentrations for experimental studies?	
High (Ranking = 1)	Equilibrium was established. The system type and design (*i.e.*, static, semi-static, and flow-through; sealed, open) were capable of appropriately maintaining substance concentrations.
Medium (Ranking = 2)	Equilibrium was not established or reported but this was not likely to have a substantial impact on study results OR the system type and design (*i.e.*, static, semi-static, and flow-through; sealed, open) were not capable of appropriately maintaining substance concentrations or not described but the deviation was not likely to have a substantial impact on study results.

Data Quality Level	Description
Low (Ranking = 3)	
Critically Deficient (Ranking = 4)	Equilibrium was not established or reported preventing meaningful interpretation of study results OR the system type and design (*i.e.*, static, semi-static, and flow-through; sealed, open) were not capable of appropriately maintaining substance concentrations preventing meaningful interpretation of study results. These are serious flaws that make the study unusable.
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. Test organisms (does not apply to all fate studies)	
Metric 9. Test organism – degradation Was information about the test organism, species or inoculum reported? Were inoculum source, concentration or number of microorganisms, and any pre-conditioning or pre-adaptation procedures reported? Are the test organism, species or inoculum source routinely used for similar study types or outcome(s)[b] of interest? Were the chosen organisms or inoculum appropriate for the study method or route?	
High (Ranking = 1)	The test organism information or inoculum source were reported AND the test organism, species, or inoculum are routinely used for similar study types and appropriate (*e.g.*, aerobic microorganisms used for anaerobic biodegradation study) for the study method or route.
Medium (Ranking = 2)	The test organism, species, or inoculum source were reported, but are not routinely used for similar study types; however, the deviation was not likely to have a substantial impact on study results.
Low (Ranking = 3)	The test organism, species, or inoculum source are not routinely used for similar study types or were not appropriate for the evaluation of the specific outcome(s) of interest or route (*e.g.*, genetically modified strains uniquely susceptible or resistant to one or more outcome of interest). In practice, this manifests as using an inappropriate inoculum for the study method (*e.g.*, polyseed capsules instead of activated sludge from a publicly owned treatment works [POTW] for a ready biodegradability test). OR an inoculum that was pre-adapted to the test substance was used for a biodegradation rate study AND no justification for selection of the test organism was provided. The deviation was likely to have a substantial impact on study results.
Critically Deficient (Ranking = 4)	The test organism, species, or inoculum source were not reported.

Data Quality Level	Description
Not rated/not applicable	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Metric 10. Test organism – partitioning Was information about the test organism reported? Was the test organism source known? Is the test organism or species routinely used for similar study types or outcome(s)[a] of interest?	
High (Ranking = 1)	Test organism information was reported, including species or sex, age, and starting body weight (where applicable) OR the test organism was obtained from a reliable or commercial source AND the test organism or species is routinely used for similar study types.
Medium (Ranking = 2)	The test organism was obtained from a reliable or commercial source OR the test organism or species is routinely used for similar study types; however, one or more additional characteristics of the organisms were not reported (*i.e.*, sex, health status, age, or starting body weight), but these omissions were not likely to have a substantial impact on study results.
Low (Ranking = 3)	The test organism was not obtained from a reliable or commercial source OR the test organism or species is not routinely used for similar study types or was not appropriate (*i.e.*, species, life-stage) for the evaluation of the specific outcome(s) of interest (*e.g.*, genetically modified organisms, strain was uniquely susceptible or resistant to one or more outcome of interest) AND no justification for selection of the test organism was provided. The deviations were likely to have a substantial impact on study results.
Critically Deficient (Ranking = 4)	The test organism information was not reported**.**
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 5. Outcome assessment	
Metric 11. Outcome[c] assessment methodology Did the outcome assessment methodology address and report the outcome(s)[c] of interest?	
High (Ranking = 1)	The outcome assessment methodology addressed or reported the intended outcome(s) of interest.

Data Quality Level	Description
Medium (Ranking = 2)	There were minor differences between the assessment methodology and the intended outcome assessment (*i.e.*, biodegradation rate not reported; however, degradation products and a degradation pathway were determined) OR there was incomplete reporting of outcome assessment methods; however, such differences or absence of details were not likely to be severe or have a substantial impact on the study results.
Low (Ranking = 3)	Deficiencies in the outcome assessment methodology of the assessment or reporting were likely to have a substantial impact on results.
Critically Deficient (Ranking = 4)	The assessment methodology did not address or report the outcome(s) of interest. This is a serious flaw that makes the study unusable.
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 12. Sampling adequacy Were the sampling methods, including timing and frequency, adequate, for the outcome(s)[c] of interest?	
High (Ranking = 1)	The study reported the use of sampling methods that address the outcome(s) of interest, and used widely accepted methods/approaches for the chemical and media being analyzed (*e.g.*, sampling equipment, sample storage conditions) AND no notable uncertainties or limitations were expected to influence results.
Medium (Ranking = 2)	Minor limitations were identified in sampling methods of the outcome(s) of interest were reported (*i.e.*, the sampling intervals were such that a half-life or other rate could be determined and/or pathways could be defined); however, the limitations were not likely to have a substantial impact on results.
Low (Ranking = 3)	Details regarding sampling methods of the outcome(s) were not fully reported, and the omissions were likely to have a substantial impact on study results AND/OR an accepted method/approach for the chemical and media being analyzed was not used (*e.g.*, inappropriate sampling equipment, improper storage conditions).
Critically Deficient (Ranking = 4)	Serious uncertainties or limitations were identified in sampling methods of the outcome(s) of interest and these were likely to have a substantial impact on the results, resulting in serious flaws which make the study unusable.
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 Level	Description
Domain 6. Confounding/variable control	
Metric 13. Confounding variables Were sources of variability or uncertainty noted in the study? Did confounding differences among the study groups influence the outcome[c] assessment?	
High (Ranking = 1)	Sources of variability and uncertainty in the measurements, and statistical techniques and between study groups (if applicable) were considered and accounted for in data evaluation AND all reported variability or uncertainty was not likely to influence the outcome assessment.
Medium (Ranking = 2)	Sources of variability and uncertainty in the measurements and statistical techniques and between study groups (if applicable) were reported in the study AND the differences in the measurements and statistical techniques and between study groups were considered or accounted for in data evaluation with minor deviations or omissions AND the minor deviations or omissions were not likely to have a substantial impact on study results.
Low (Ranking = 3)	Sources of variability and uncertainty in the measurements and statistical techniques and between study groups (if applicable) were not considered or accounted for in data evaluation resulting in some uncertainty AND there is concern that variability or uncertainty was likely to have a substantial impact on the results.
Critically Deficient (Ranking = 4)	There were sources of variability and uncertainty in the measurements and statistical techniques or between study groups resulting in serious flaws that make the study unusable.
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 14. Outcomes unrelated to exposure Were there differences among the study groups in organism attrition or health outcomes unrelated to exposure to the test substance that influenced the outcome[d] assessment?	
High (Ranking = 1)	There were multiple study groups, and there were no differences among the study groups in organism attrition or health outcomes (*i.e.*, unexplained mortality) that influenced the outcome assessment.
Medium (Ranking = 2)	Attrition or health outcomes were not reported; however, this omission was not likely to have a substantial impact on study results.
Low (Ranking = 3)	

Data Quality Level	Description
Critically Deficient (Ranking = 4)	Attrition or health outcomes were not reported, and this omission was likely to have a substantial impact on study results OR one or more study groups experienced disproportionate organism attrition or health outcomes that influenced the outcome assessment (*e.g.*, pH drastically decreased for one treatment and resulted in pH effects vs. effects from the chemical being tested). This is a serious flaw that makes the study unusable.
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 7. Data presentation and analysis	
Metric 15. Data reporting Were the target chemical and transformation product(s) concentrations reported? Was the extraction efficiency, percent recovery, and/or mass balance reported? Was the analytical method used suitable for detection and capable of identifying or quantifying the parent and transformation products? Was sufficient evidence presented to confirm that the disappearance of the parent compound was not due to some other process (*e.g.*, sorption)?	
High (Ranking = 1)	The target chemical and transformation product(s) concentrations (if required), extraction efficiency, percent recovery, or mass balance were reported AND analytical methods used were suitable for detection and quantification of the target chemical and transformation product(s) (if required) AND for degradation studies, sufficient evidence was presented to confirm that parent compound disappearance was not likely due to some other process AND the lipid content or the lipid-normalized bioconcentration factor (BCF) was reported for BCF studies AND detection limits were sensitive enough to follow decline of parent and formation of the metabolites; structures of metabolites were given. Volatile products were trapped and identified.
Medium (Ranking = 2)	The target chemical and transformation product(s) concentrations, extraction efficiency, percent recovery, or mass balance were not reported; however, these omissions were not likely to have a substantial impact on study results OR the lipid content or lipid normalized BCF was not reported for BCF studies, but these deficiencies or omissions were not likely to have a substantial impact on study results.
Low (Ranking = 3)	There was insufficient evidence presented to confirm that parent compound disappearance was not likely due to some other process OR

Data Quality Level	Description
	concentrations of the target chemical or transformation product(s), extraction efficiency, percent recovery, or mass balance were not measured or reported, preventing meaningful interpretation of study results OR lipid normalized BCF and lipid content were not measured or reported, preventing meaningful interpretation of study results AND these omissions were likely to have a substantial impact on study results.
Critically Deficient (Ranking = 4)	The analytical method used was not suitable for detection of the test substance.
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 16. Statistical methods & kinetic calculations. Were statistical methods or kinetic calculations clearly described and consistent?	
High (Ranking = 1)	Statistical methods or kinetic calculations were clearly described and address the dataset(s).
Medium (Ranking = 2)	Statistical analysis used an outdated, unusual, or non-robust method; however, the study results were likely to be similar to those obtained using a current/more robust method OR kinetic calculations were not clearly described AND these differences were not likely to have a substantial impact on study results. OR No statistical analyses were conducted; however, sufficient data were provided to conduct an independent statistical analysis.
Low (Ranking = 3)	Statistical analysis or kinetic calculations were not conducted or were not described clearly AND the lack of information was likely to have a substantial impact on study results.
Critically Deficient (Ranking = 4)	Statistical methods or kinetic calculations used were likely to provide biased results. These are serious flaws that make the study unusable.
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 8. Other	

Data Quality Level	Description
Metric 17. Verification or plausibility of results. Were the study results reasonable? Was anything not covered in the evaluation questions?	
High (Ranking = 1)	Reported values were within expected range as defined by reference substance(s) OR reported values were consistent with related physical and chemical properties (*e.g.*, considering K_{OW}, pKa, vapor pressure, etc.).
Medium (Ranking = 2)	The study results were reasonable AND the reported value was outside expected range, as defined by reference substance(s) or in relation to related physical and chemical properties (*e.g.*, considering K_{OW}, vapor pressure, etc.); however, no serious study deficiencies were identified, and the value was plausible.
Low (Ranking = 3)	Due to limited information, evaluation of the reasonableness of the study results was not possible (*i.e.*, reference substance(s) not used or physical and chemical properties unknown and unable to be estimated).
Critically Deficient (Ranking = 4)	Reported value was completely inconsistent with reference substance data, related physical and chemical properties, analogue data, or otherwise implausible, suggesting that an unidentified serious study deficiency exists. These are serious flaws that make the study unusable.
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 18. QSAR models. Did the QSAR model have a defined, unambiguous endpoint and appropriate measures of goodness-of-fit, robustness and predictivity, defined by $r^2 > 0.7$, $q^2 > 0.5$ and SE < 0.3, where r^2 is the correlation coefficient, q^2 is the cross-validated correlation coefficient and SE is the standard error (ECHA, 2016)?	
High (Ranking = 1)	The QSAR model had a defined, unambiguous endpoint AND the model performance was known and $r^2 > 0.7$, $q^2 > 0.5$, and SE < 0.3 (ECHA, 2016).
Medium (Ranking = 2)	Model endpoint is broad (*i.e.*, overall persistence) AND/OR non-transparent and difficult to reproduce methods were used to build the (Q)SAR model (*e.g.*, artificial neural networks using many structural descriptors).
Low (Ranking = 3)	Algorithm is not publicly available to verify or reproduce the predictions AND/OR statistics on the external validation set are unavailable.
Critically Deficient (Ranking = 4)	The model performance was either not known or $r^2 < 0.7$, $q^2 < 0.5$ or SE > 0.3 (ECHA, 2016). These are serious flaws that make the study unusable.

Data Quality Level	Description
Not rated/not applicable	A QSAR model was not reported.
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*
Optimization of the list of serious flaws may occur after pilot calibration exercises. [a] For studies of partitioning [b] For studies of degradation [c] For all fate studies (*i.e.*, degradation, partitioning, etc.) [d] For studies of partitioning in organisms	

Appendix M DATA QUALITY CRITERIA FOR ENVIROMENTAL RELEASE AND OCCUPATIONAL EXPOSURE DATA

M.1 Types of Environmental Release and Occupational Exposure Data Sources

Environmental release and occupational exposure data and information may be found in various sources, and most are not found in controlled studies. Therefore, the evaluation of these data and information requires approaches that differ from the evaluation of controlled studies. The tables inherently cover these differences for the different sources (*e.g.*, all tables in the Engineering and Occupational Exposure portion of Appendix H). In these tables, some metrics are shown *as not applicable* and will not be ranked. Other metrics may have criteria that reflect differences in the documentation of background information about the data or information, especially if the data or information are not collected from a controlled study that is fully documented.

The data quality will be evaluated for five different types of data sources that contain the environmental release and occupational exposure data: (1) monitoring data from various sources (*e.g.*, journal articles, government reports, public databases); (2) release data from various sources; (3) published models for exposures or releases; (4) completed exposure or risk assessments; and (5) and reports for data or information other than exposure or release data. Definitions for these data types are shown below in Table_Apx M-1; note that these data types do not include epidemiology sources that lack occupational exposure data.

Table_Apx M-1. Types of Environmental Release and Occupational Exposure Data Sources

Type of Data Source	Definition
Monitoring data	Measured occupational exposures, which include, but not limited to, personal inhalation exposure monitoring, area/stationary airborne concentration monitoring, and surface wipe sampling.
Environmental release data	Measured or calculated quantities of chemical or chemical substance released across a facility fence line into an environmental media or waste management/disposal method.
Published models for exposures or releases	Published models used to calculate occupational exposures or environmental releases.
Completed exposure or risk assessments	Completed exposure or risk assessments containing a broad range of data types (*i.e.*, exposure concentrations, doses, estimated values, exposure factors). Examples: ATSDR assessments, risk assessments completed by other countries.
Reports for data or information other than exposure or release data	Data sources used for data or information other than exposure or release data, such as process description information. Example: Kirk-Othmer Encyclopedia of Chemical Technology

M.2 Data Quality Evaluation Domains

The data sources will be evaluated against the following four data quality evaluation domains: (1) reliability; (2) representativeness; (3) accessibility/clarity; (4) and variability and uncertainty. These domains, as defined in Table_Apx M-2, address elements of TSCA Science Standards 26(h)(1) through 26(h)(5).

Table_Apx M-2. Data Evaluation Domains and Definitions

Evaluation Domain	Definition
Reliability	The inherent property of a study or data, which includes the use of well-founded scientific approaches, the avoidance of bias within the study or data collection design and faithful study or data collection conduct and documentation (ECHA, 2011b).
Representativeness	The data reported address exposure scenarios (*e.g.*, sources, pathways, routes, receptors) that are relevant to the assessment.
Accessibility/clarity	The data and supporting information are accessible and clearly documented.
Variability and uncertainty	The data describe variability and uncertainty (quantitative and qualitative) or the procedures, measures, methods, or models are evaluated and characterized.

M.3 Data Quality Evaluation Metrics

Table_Apx M-3 provides a summary of the quality metrics for each data type. EPA may adjust these quality metrics as more experience is acquired with the evaluation tools to support fit-for-purpose TSCA risk evaluations. If this happens, EPA will document the changes to the evaluation tool.

Table_Apx M-3. Summary of Quality Metrics for the Five Types of Data Sources

Type of Data Source	Overall Number of Metrics[a]	Metric Names
Monitoring data	7	Sampling and analytical methodology; Geographic Scope; Applicability; Temporal representativeness; Sample size; Metadata[b] completeness informing the Accessibility and Clarity domain; Metadata completeness informing the Variability and Uncertainty domain
Environmental release data	7	Methodology; Geographic Scope; Applicability; Temporal representativeness; Sample size; Metadata completeness informing the Accessibility and Clarity domain; Metadata completeness informing the Variability and Uncertainty domain
Published models for exposures or releases	Up to 6	Methodology; Geographic Scope; Applicability; Temporal representativeness; Metadata completeness informing the Accessibility and Clarity domain; Metadata completeness informing the Variability and Uncertainty domain
Completed exposure or risk assessments	Up to 7	Methodology; Geographic Scope; Applicability; Temporal representativeness; Sample Size; Metadata completeness informing

Type of Data Source	Overall Number of Metrics[a]	Metric Names
		the Accessibility and Clarity domain; Metadata completeness informing the Variability and Uncertainty domain
Reports for data or information other than exposure or release data	Up to 7	Methodology; Geographic Scope; Applicability; Temporal representativeness; Sample size; Metadata completeness informing the Accessibility and Clarity domain; Metadata completeness informing the Variability and Uncertainty domain

[a] Overall number of metrics indicates the number of metrics across evaluation domains.
[b] Metadata are data that provide descriptive information about other data. Examples include the date of the data, the author and author's affiliation of a report or study, and the type of exposure monitoring sample (*e.g.*, personal breathing zone sample).

M.4 Ranking Method and Determination of Overall Data Quality Level

Section 5 provides information about the evaluation method applied across the various data/information sources being assessed to support TSCA risk evaluations. In addition, this section provides details about the ranking system that will be applied to release and occupational exposure data/information.

Table_Apx M-4 summarizes the range of possible ranking for each metric, and the range of overall ranking if all the metrics are ranked for a particular data type.

Table_Apx M-4. Metric Ranking and the Range Metric Ranking for Ranking the Quality of Environmental Release and Occupational Exposure Data

Domain	Metric	Metric Ranking (range of possible values)
Reliability	Methodology	1 to 3
Representativeness	Applicability	1 to 3
	Geographic scope	1 to 3
	Temporal representativeness	1 to 3
	Sample size	1 to 3
Accessibility/clarity	Metadata completeness	1 to 3
Variability and uncertainty	Metadata vompleteness	1 to 3
Sum (if all metrics included)[a]		7 to 21
Range of overall ranking, where overall ranking = ∑(metric ranking) / ∑(metric factors)		**7/7=1; 21/7=3 Range of overall ranking = low to high**
High	Medium	Low

[a] The sum of all metric ranking will differ if some metrics are not ranked (not applicable).

M.4.1 Determination of Overall Study Ranking

To determine the overall study ranking, the first step is to sum the ranking for each metric (1, 2, or 3 for high, medium, or low, respectively), as shown in Table_Apx M-5. Then divided by the sum of the metric factors (for all metrics that are ranked) to obtain an overall study ranking between 1 and 3. The equation for calculating the overall ranking is shown below:

$$\textit{Overall Ranking (range of 1 to 3)} = \sum \textit{(Metric Ranking)} / \sum \textit{(Metric Factors)}$$

EPA plans to use data with an overall quality rating of High, Medium, or Low to support the risk evaluations quantitatively or qualitatively but does not plan to use data rated uninformative. If any single metric for a data source has a ranking of critically deficient, then the overall quality of the data is automatically rated with an overall quality ranking of uninformative. A critically deficient ranking means that serious flaws are noted in the domain metric that consequently make the data unusable (or invalid).

If any metric is not applicable to a data set, that metric is not rated. In that case, the metric is not included in the ranking. In the case that the source type contains more than one data set or information element, the reviewer provides an overall quality ranking for each data set or information element that is found in the source. Therefore, it is possible that a source may have more than one overall quality ranking.

Table_Apx M-5 provides an example of ranking when a particular metric is not rated. In this example, the sample size metric under the representativeness domain is not applicable for published models. Detailed tables showing quality criteria for the metrics are provided in Table_Apx H-10 through Table_Apx H-19 for each data type, including separate tables which summarize the serious flaws which would make the data uninformative for use in the environmental release and occupational exposure assessment.

Table_Apx M-5. Ranking Example for Published Models where Sample Size Is Not Applicable

Domain	Metric	Metric Factor	Metric Ranking
Reliability	Methodology	1	2
Representativeness	Applicability	1	1
	Geographic scope	1	2
	Temporal representativeness	1	1
	Sample size	N/A	N/A
Accessibility/clarity	Metadata completeness	1	2
Variability and uncertainty	Metadata completeness	1	3
		Sum= 6	**Sum=11**

Domain	Metric	Metric Factor	Metric Ranking
Range of overall ranking, where overall ranking[a] = ∑(metric ranking) / ∑(metric factors)			**11/6=1.8** **Medium**
High	Medium	Low	

[a] The cutoffs between categories were defined by calculating the difference between the highest possible ranking of 3 and the lowest possible ranking of 1 (*i.e.*, 3 – 1 = 2) and dividing it into three equal parts (2 ÷ 3 = 0.67). This results in a range of approximately 0.7 for each overall study data quality ranking, which is used to estimate the transition points (cut-off values) in the scale between high and medium rankings, and medium and low rankings. These transition points between the ranges of 1 and 3 are determined as follows:

- cut-off values between high and medium: 1 + 0.67 = 1.67, rounded to 1.7 (rankings lower than 1.7 are assigned an overall quality level of high); and
- cut-off values between medium and low: 1.67 + 0.67 = 2.34, rounded to 2.3 (rankings between 1.7 and lower than 2.3 are assigned an overall quality level of medium).

M.5 Data Sources Frequently Used in Environmental Release and Occupational Exposure Assessments

A key component in many of the metric criteria is if the methodology is sound and widely accepted (*i.e.*, from a source generally using sound methods and/or approaches). Table_Apx M-6 provides examples of data sources that EPA frequently uses to support the data needs of release and occupational exposure assessments. EPA notes that some data sources may use or include data or information that are not of high quality but are still acceptable (*e.g.*, medium or low quality) for use in risk evaluation. The methodologies in the individual studies under review will still be assessed in relation to chemical- and scenario- specific considerations. Thus, the data source may still receive quality rankings ranging from Critically deficient to High even though the data source used a methodology from a source commonly known to use sound methods and/or approaches. EPA may determine standard quality ratings for some of these sources as more experience is acquired with TSCA risk evaluations.

Table_Apx M-6. Examples of Data Sources Frequently Used in Environmental Release and Occupational Exposure Data

Data Source	
U.S. EPA	Chemical Data Reporting (CDR)
	High Production Volume (HPV) Challenge Submissions
	Extra HPV Program Submissions
	EPA Existing Chemicals Engineering Files
	EPA Generic Scenarios
	Toxics Release Inventory (TRI)
	National Emissions Inventory (NEI)

Data Source	
	Office of Water
	Office of Air
	Office of Enforcement and Compliance Assistance Sector Notebooks
	AP-42
	Other EPA Programs (*e.g.*, Design for Environment)
Occupational Safety and Health Administration (OSHA)	
National Institute of Occupational Safety and Health (NIOSH)	
American Conference of Governmental Industrial Hygienists (ACGIH)	
Agency for Toxic Substances and Disease Registry (ATSDR)	
Other federal agencies (*e.g.*, Department of Defense, Department of Energy)	
Organisation for Economic Co-operation and Development (OECD)	Screening Information Dataset (SIDS)
	Emission Scenario Documents (ESDs)
	Other Programs
Environment Canada	Canadian Pollution Prevention Information Clearinghouse
	Other Programs
U.S. Census Bureau	North American Industry Classification System (NAICS) Definitions
	County Business Patterns
	Annual Survey of Manufacturers
	Current Industrial Reports
	Economic Census
Bureau of Labor Statistics (BLS)	
States (*e.g.*, North Carolina Division of Pollution Prevention and Environmental Assistance)	
Kirk-Othmer Encyclopedia of Chemical Technology	
National Library of Medicine's PubChem	
Risk Evaluation from other countries	European Chemicals Agency (ECHA)
National Library of Medicine's HazMap	
This list is not intended to be comprehensive, but to show examples used by EPA in the past.	

M.6 Data Quality Criteria

This section presents tables showing quality criteria for the metrics for each data type, including separate tables which summarize the serious flaws which would make the data critically deficient for use in the environmental release and occupational exposure assessment. The overall data quality ranking is automatically rated as *uninformative* if any single metric for a data set has a ranking of critically deficient, or serious flaws that would make the data unusable (or invalid) for the environmental release and occupational exposure assessment. If the source type contains more than one data set or information element, the review provides an overall quality ranking for each data set or information element that is found in the source. Therefore, it is possible that a source may have more than one overall quality ranking.

M.6.1 Monitoring Data

The general approach for setting the criteria for a critically deficient rating is to only assign a critically deficient rating when EPA can confirm that the data or information is critically deficient. If the data source lacks documentation of needed metadata, EPA will not rate the metric as critically deficient but will rate it as low. The reason for this approach is to avoid omitting potentially valid data or information because release and occupational exposure data are often sparse. EPA will not use data/information that exhibit serious flaws as described in Table_Apx M-7.

Table_Apx M-7. Serious Flaws that Would Make Monitoring Data Critically Deficient for Use in the Environmental Release and Occupational Exposure Assessment

Domain	Metric	Description of Serious Flaw(s) in Data
Reliability	Sampling and analytical methodology	Sampling or analytical methodology is specified, and EPA has information that indicates the methodology is critically deficient.
Representativeness	Geographic scope	This metric does not have a critically deficient criterion because no geographic location is known to have critically deficient data.
	Applicability	The data are from an occupational or non-occupational scenario that does not apply to any occupational scenario within the scope of the risk evaluation.
	Temporal representativeness	Known factors (*e.g.*, new and completely different process or equipment) are so different as to make outdated information critically deficient.
	Sample size	This metric does not have a critically deficient criterion.
Accessibility /clarity	Metadata completeness	Monitoring data do not include any needed metadata to understand what the data represent and are not usable in the risk evaluation.
Variability and uncertainty	Metadata completeness	This metric does not have a critically deficient criterion.
Optimization of the list of serious flaws may occur after pilot calibration exercises.		

Table_Apx M-8. Evaluation Criteria for Monitoring Data

Data Quality Ranking	Description	
Domain 1. Reliability		
Metric 1. Sampling and analytical methodology		
High (ranking = 1)	Sampling or analytical methodology is an approved OSHA or NIOSH method or is well described and found to be equivalent to approved OSHA or NIOSH methods.	
Medium (ranking = 2)	Sampling or analytical methodology is not equivalent to an approved OSHA or NIOSH method and EPA review of information indicates the methodology is acceptable. Differences in methods are not expected to lead to lower quality data.	
Low (ranking = 3)	Sampling or analytical methodology is not specified.	
Critically deficient (ranking = 4)	Sampling or analytical methodology is specified, and EPA has information that indicates the methodology is critically deficient.	
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 2. Geographic scope		
High (ranking = 1)	The data are from the United States and are representative of the industry being evaluated.	
Medium (ranking = 2)	The data are from an OECD country. other than the U.S., and locality-specific factors (*e.g.*, potential differences in regulatory occupational exposure limits, industry/process technologies) may impact exposures relative to the U.S.	
Low (ranking = 3)	The data are from a non-OECD country, and locality-specific factors (*e.g.*, potentially greater differences in regulatory occupational exposure limits, industry/process technologies) may impact exposures relative to the U.S., or the country of origin is not specified.	
Critically deficient (ranking = 4)	This metric does not have a critically deficient criterion because no geographic location is known to have critically deficient data.	
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. Applicability		
High (ranking = 1)	The data are for an occupational scenario within the scope of the risk evaluation.	

Data Quality Ranking	Description	
Medium (ranking = 2)	The data are for an occupational scenario that is similar to an occupational scenario within the scope of the risk evaluation, in terms of the type of industry, operations, and work activities.	
Low (ranking = 3)	The data are for a non-occupational scenario that is similar to an occupational scenario within the scope of the risk evaluation, such as a consumer DIY scenario that is similar to a worker scenario.	
Critically deficient (ranking = 4)	The data are from an occupational or non-occupational scenario that does not apply to any occupational scenario within the scope of the risk evaluation.	
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 representativeness		
High (ranking = 1)	The operations, equipment, and worker activities associated with the data are expected to be representative of current operations, equipment, and activities. The monitoring data were collected after the most recent PEL establishment or update or are generally, no more than 10 years old, whichever is shorter. If no PEL is established, the data are no more than 10 years old. Metadata on the operations, equipment, and worker activities associated with the data show that the data should be representative of current operations, equipment, and activities.	
Medium (ranking = 2)	Operations, equipment, and worker activities are expected to be reasonably representative of current conditions. The monitoring data were collected after the most recent PEL establishment or update but are generally more than 10 years old. If no PEL is established, the data are more than 10 years but generally, no more than 20 years old.	
Low (ranking = 3)	Metadata on the operations, equipment, and worker activities associated with the data show that the data agree representative of outdated operations, equipment, and activities rather than current operations, equipment, and worker activities. The data were collected before the most recent PEL establishment or update or are more than 20 years old if no PEL is established.	
Critically deficient (ranking = 4)	Known factors (*e.g.*, new and completely different process or equipment) are so different as to make outdated information critically deficient.	
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		
High (ranking = 1)	Statistical distribution of samples is fully characterized.	
Medium	Distribution of samples is characterized by a range with uncertain statistics.	

Data Quality Ranking	Description	
(ranking = 2)		
Low (ranking = 3)	Distribution of samples is qualitative or characterized by no statistics.	
Critically deficient (ranking = 4)	This metric does not have a critically deficient criterion.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 3. Accessibility/clarity		
Metric 6. Metadata completeness		
High (ranking = 1)	Monitoring data include all associated metadata, including sample types, exposure types, sample durations, exposure durations worker activities, and exposure frequency.	
Medium (ranking = 2)	Monitoring data include most critical metadata, such as sample type and exposure type, but lacks additional metadata, such as sample durations, exposure durations, exposure frequency, and/or worker activities.	
Low (ranking = 3)	Monitoring data include sample type (*e.g.*, personal breathing zone) but no other metadata.	
Critically deficient (ranking = 4)	Monitoring data do not include any needed metadata to understand what the data represent and are not usable in the risk evaluation.	
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 7. Variability and uncertainty		
High (ranking = 1)	The monitoring study addresses variability in the determinants of exposure for the sampled site or sector. The monitoring study addresses uncertainty in the exposure estimates or uncertainty can be determined from the sampling and analytical method.	
Medium (ranking = 2)	The monitoring study provides only limited discussion of the variability in the determinants of exposure for the sampled site or sector. The monitoring study provides only limited discussion of the uncertainty in the exposure estimates.	
Low (ranking = 3)	The monitoring study does not address variability or uncertainty.	

Data Quality Ranking	Description	
Critically deficient (ranking = 4)	This metric does not have a critically deficient criterion.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

M.6.2 Environmental Release Data

The general approach for setting the criteria for a critically deficient rating is to only assign a critically deficient rating when EPA can confirm that the data or information is critically deficient. If the data source lacks documentation of needed metadata, EPA will not rate the metric as critically deficient but will rate it as low. The reason for this approach is to avoid omitting potentially valid data or information because release and occupational exposure data are often sparse. EPA will not use data/information from data sources that exhibit serious flaws as described in Table_Apx M-9.

Table_Apx M-9. Serious Flaws that Would Make Environmental Release Data Critically Deficient for Use in the Environmental Release Assessment

Domain	Metric	Description of Serious Flaw(s) in Data Source
Reliability	Methodology	The release data methodology is specified, and EPA has information that indicates the methodology is critically deficient.
Representativeness	Geographic scope	This metric does not have a critically deficient criterion because no geographic location is known to have critically deficient data.
	Applicability	The release data are from an occupational or non-occupational scenario that does not apply to any occupational scenario within the scope of the risk evaluation.
	Temporal representativeness	Known factors (*e.g.*, new and completely different process or equipment) are so different as to make outdated information critically deficient.
	Sample size	EPA has information that indicates the samples are not expected to represent the assessed release.
Accessibility/ clarity	Metadata completeness	Release data do not include any needed metadata to understand what the data represent and are not usable in the risk evaluation.
Variability and uncertainty	Metadata completeness	This metric does not have a critically deficient criterion.
Optimization of the list of serious flaws may occur after calibrating evaluation tool during pilot exercise.		

Table_Apx M-10. Evaluation Criteria for Environmental Release Data

Data Quality Ranking	Description	
Domain 1. Reliability		
Metric 1. Methodology		
High (ranking = 1)	The release data methodology is known or expected (see Table_Apx M-6) to be accurate and is known to cover all release sources at the site.	
Medium (ranking = 2)	The release data methodology is known or expected to be accurate (see Table_Apx M-6) but may not cover all release sources at the site.	
Low (ranking = 3)	The release data methodology is not specified.	
Critically deficient (ranking = 4)	The release data methodology is specified, and EPA has information that indicates the methodology is critically deficient.	
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 2. Geographic scope		
High (ranking = 1)	The data are from the United States and are representative of the industry being evaluated.	
Medium (ranking = 2)	The data are from an OECD country other than the U.S., and locality-specific factors (*e.g.*, potential differences in regulatory emission limits, industry/process technologies) may impact releases relative to the U.S.	
Low (ranking = 3)	The data are from a non-OECD country, and locality-specific factors may impact (*e.g.*, potentially greater differences in regulatory emission limits, industry/ process technologies) releases relative to the U.S., or the country of origin is not specified.	
Critically deficient (ranking = 4)	This metric does not have a critically deficient criterion because no geographic location is known to have critically deficient data.	
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. Applicability		
High (ranking = 1)	The release data are for an occupational scenario within the scope of the risk evaluation.	

Data Quality Ranking	Description	
Medium (ranking = 2)	The release data are for an occupational scenario that is similar to an occupational scenario within the scope of the risk evaluation, in terms of the type of industry, operations, and work activities.	
Low (ranking = 3)	The release data are for a non-occupational scenario that is similar to an occupational scenario within the scope of the risk evaluation, such as a consumer DIY scenario that is similar to a worker scenario.	
Critically deficient (ranking = 4)	The release data are from an occupational or non-occupational scenario that does not apply to any occupational scenario within the scope of the risk evaluation.	
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 representativeness		
High (ranking = 1)	The operations, equipment, and worker activities associated with the data indicate that the data should be representative of current operations, equipment, and activities. The release data were collected after the most recent federal regulatory action (*e.g.*, NESHAP for air release or effluent limit guideline (ELG) for water release) or update or are no more than 10 years old, whichever is shorter. If no federal regulation is established, the data are generally no more than 10 years old.	
Medium (ranking = 2)	The release data were collected after the most recent federal regulatory action or update but are generally, more than 10 years old. If no federal regulation is established, the data are more than 10 years but no more than 20 years old. However, operations, equipment, and worker activities are expected to be reasonably representative of current conditions.	
Low (ranking = 3)	The data were collected before the most recent federal regulatory action or update or are more than 20 years old if no federal regulation is established. The operations, equipment, and worker activities are not available or indicate that the associated data are expected to be outdated.	
Critically deficient (ranking = 4)	Known factors (*e.g.*, new and completely different process or equipment) are so different as to make outdated information critically deficient.	
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		
High (ranking = 1)	Statistical distribution of samples is fully characterized. Sample size is sufficiently representative.	
Medium (ranking = 2)	Distribution of samples is characterized by a range with uncertain statistics. It is unclear if analysis is representative.	

Data Quality Ranking	Description	
Low (ranking = 3)	Distribution of samples is qualitative or characterized by no statistics.	
Critically deficient (ranking = 4)	EPA has information that indicates the samples are not expected to represent the assessed release.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 3. Accessibility/clarity		
Metric 6. Metadata completeness		
High (ranking = 1)	Release data include all associated metadata, including release media; process, unit operation, or activity that is the source of the release; and release frequency.	
Medium (ranking = 2)	Release data include most critical metadata, including release media and release frequency, but lacks additional metadata, such as process, unit operation, and/or activity that is the source of the release.	
Low (ranking = 3)	Release data include release media but no other metadata.	
Critically deficient (ranking = 4)	Release data do not include any needed metadata to understand what the data represent and are not usable in the risk evaluation.	
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 7. Variability and uncertainty		
High (ranking = 1)	The release data study addresses variability in the determinants of release. The release data study addresses uncertainty in the release results.	
Medium (ranking = 2)	The release data study provides only limited discussion of the variability in the determinants of release. The release data study provides only limited discussion of the uncertainty in the release results.	
Low (ranking = 3)	The release data study does not address variability or uncertainty.	
Critically deficient (ranking = 4)	This metric does not have a critically deficient criterion.	

Data Quality Ranking	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]*	

M.6.3 Published Models for Environmental Release or Occupational Exposure

The general approach for setting the criteria for a critically deficient rating is to only assign a critically deficient rating when EPA can confirm that the data or information is critically deficient. If the data source lacks documentation of needed metadata, EPA will not rate the metric as critically deficient but will rate it as low. The reason for this approach is to avoid omitting potentially valid data or information because release and occupational exposure data are often sparse. EPA will not use data/information from data sources that exhibit serious flaws as described in Table_Apx M-11.

Table_Apx M-11. Serious Flaws that Would Make Published Models Critical Deficient for Use in the Environmental Release and Occupational Exposure Assessment

Domain	Metric	Description of Serious Flaw(s) in Data Source
Reliability	Methodology	Mathematical equations of the model have significant errors, parameters use erroneous values, or the model is based on flawed logic.
Representativeness	Geographic scope	This metric does not have a critically deficient criterion because no geographic location is known to have critically deficient data.
	Applicability	The model is not applicable and cannot be adapted to any occupational scenario within the scope of the risk evaluation.
	Temporal representativeness	Known factors (*e.g.*, new and completely different process or equipment) are so different as to make outdated information critically deficient.
Accessibility/ clarity	Metadata completeness	The model is a "black box" and provides no documentation or clarity of its approaches, equations, and parameter values.
Variability and uncertainty	Metadata completeness	This metric does not have a critically deficient criterion.
Optimization of the list of serious flaws may occur after pilot calibration exercises.		

Table_Apx M-12. Evaluation Criteria for Published Models

Data Quality Rankin	Description	
Domain 1. Reliability		
Metric 1. Methodology		
High	The model is free of mathematical errors and is based on scientifically sound approaches or methods. Equations and choice of parameter values are	

Data Quality Rankin	Description	
(ranking = 1)	appropriate for the model's application (note: peer review may address appropriate application).	
Medium (ranking = 2)	The model is free of mathematical errors and is based on scientifically sound approaches or methods. However, equations and choice of parameter values are not fully described and some equations and/or parameter values may not be appropriate for the model's application.	
Low (ranking = 3)	The model is free of mathematical errors. However, the model makes assumptions or uses parameter values that lead to significant uncertainties.	
Critically deficient (ranking = 4)	Mathematical equations of the model have significant errors, parameters use erroneous values, or the model is based on flawed logic.	
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 2. Geographic scope		
High (ranking = 1)	The data are from the United States and are representative of the industry being evaluated.	
Medium (ranking = 2)	The data are from an OECD country other than the U.S., and locality-specific factors (*e.g.*, potential differences in regulatory occupational exposure or emission limits, industry/process technologies) may impact exposures or releases relative to the U.S.	
Low (ranking = 3)	The data are from a non-OECD country, and locality-specific factors (*e.g.*, potentially greater differences in regulatory occupational exposure or emission limits, industry/process technologies) may impact exposures or releases relative to the U.S., or the country of origin is not specified.	
Critically deficient (ranking = 4)	This metric does not have a critically deficient criterion because no geographic location is known to have critically deficient data.	
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. Applicability		
High (ranking = 1)	The model can be appropriately applied to an occupational scenario within the scope of the risk evaluation.	
Medium (ranking = 2)	Not applicable: this domain is dichotomous: applicable or not applicable.	

Data Quality Rankin	Description	
Low (ranking = 3)	Not applicable: this domain is dichotomous: applicable or not applicable. Can a poor fit model be used?	
Critically deficient (ranking = 4)	The model is not applicable and cannot be adapted to any occupational scenario within the scope of the risk evaluation.	
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 representativeness		
High (ranking = 1)	The model is based on operations, equipment, and worker activities expected to be representative of current conditions. The model is based on data that are generally no more than 10 years old.	
Medium (ranking = 2)	The model is based on data that are generally more than 10 years but no more than 20 years old. However, the model is based on operations, equipment, and worker activities are expected to be reasonably representative of current conditions.	
Low (ranking = 3)	The model is based on data that are more than 20 years old. The model is based on operations, equipment, and worker activities that are expected to be outdated.	
Critically deficient (ranking = 4)	Known factors (*e.g.*, new and completely different process or equipment) are so different as to make outdated information critically deficient.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 3. Accessibility/clarity		
Metric 6. Metadata completeness		
High (ranking = 1)	Model approach, equations, and choice of parameter values are transparent and clear and can be evaluated. Rationale for selection of approach, equations, and parameter values is provided.	
Medium (ranking = 2)	Model approach, equations, and choice of parameter values are transparent. However, rationale for selection of approach, equations, and parameter values is not provided.	
Low (ranking = 3)	The model documentation describes the approach and parameters, but the equations and/or selection of parameter values are not provided. Rationale for modeling approach and parameter value selection is not provided.	
Critically deficient (ranking = 4)	The model is a "black box" and provides no documentation or clarity of its approaches, equations, and parameter values.	

Data Quality Rankin	Description	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 4. Variability and uncertainty		
Metric 7. Variability and uncertainty		
High (ranking = 1)	The model characterizes variability and uncertainty in the results.	
Medium (ranking = 2)	The model has limited characterization of the variability of parameter values. The model has limited characterization of the uncertainty in the results.	
Low (ranking = 3)	The model does not characterize variability or uncertainty.	
Critically deficient (ranking = 4)	This metric does not have a critically deficient criterion.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
EPA will consult with the *Guidance on the Development, Evaluation, and Application of Environmental Models* (U.S. EPA, 2009) when evaluating models and modeling data types.		

M.6.4 Data/Information from Completed Exposure or Risk Assessments

The general approach for setting the criteria for a critically deficient rating is to only assign a critically deficient rating when EPA can confirm that the data or information is critically deficient. If the data source lacks documentation of needed metadata, EPA will not rate the metric as critically deficient but will rate it as low. The reason for this approach is to avoid omitting potentially valid data or information because release and occupational exposure data are often sparse. EPA will not use data/information from data sources that exhibit serious flaws as described in Table_Apx M-13.

Table_Apx M-13. Serious Flaws that Would Make Data/Information from Completed Exposure or Risk Assessments Critically Deficient for Use in the Environmental Release and Occupational Exposure Assessment

Domain	Metric	Description of Serious Flaw(s) in Data Source
Reliability	Methodology	The assessment or report uses data or techniques or methods that are not consistent with the best available science. Assumptions, extrapolations, measurements, and models are not appropriate. There appears to be mathematical errors or errors in logic.
Representativeness	Geographic scope	This metric does not have a critically deficient criterion because no geographic location is known to have critically deficient data.

Domain	Metric	Description of Serious Flaw(s) in Data Source
	Applicability	The assessment is from an occupational or non-occupational scenario that does not apply to any occupational scenario within the scope of the risk evaluation.
	Temporal representativeness	Known factors (*e.g.*, new and completely different process or equipment) are so different as to make outdated information critically deficient.
	Sample size	This metric does not have a critically deficient criterion.
Accessibility/ clarity	Metadata completeness	Assessment or report does not document its data sources, assessment methods, and assumptions.
Variability and uncertainty	Metadata completeness	This metric does not have a critically deficient criterion.
Optimization of the list of serious flaws may occur after pilot calibration exercises.		

Table_Apx M-14. Evaluation Criteria for Data/Information from Completed Exposure or Risk Assessments

Data Quality Ranking	Description	
Domain 1. Reliability		
Metric 1. Methodology		
High (ranking = 1)	The assessment or report uses high quality data and/or techniques or sound methods that are from a frequently used source (*e.g.*, European Union or OECD reports, NIOSH HHEs, journal articles, Kirk-Othmer; see Table_Apx M-6) and are generally accepted by the scientific community, and associated information does not indicate flaws or quality issues.	
Medium (ranking = 2)	The assessment or report uses high quality data and/or techniques or sound methods that are not from a frequently used source, and associated information does not indicate flaws or quality issues.	
Low (ranking = 3)	The data, data sources, and/or techniques or methods used in the assessment or report are not specified.	
Critically deficient (ranking = 4)	The assessment or report uses data or techniques or methods that are not consistent with the best available science. Assumptions, extrapolations, measurements, and models are not appropriate. There appears to be mathematical errors or errors in logic.	
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 2. Geographic scope		

Data Quality Ranking	Description	
High (ranking = 1)	The data are from the United States and are representative of the industry being evaluated.	
Medium (ranking = 2)	The data are from an OECD country other than the U.S., and locality-specific factors (*e.g.*, potential differences in regulatory occupational exposure or emission limits, industry/process technologies) may impact exposures or releases relative to the U.S.	
Low (ranking = 3)	The data are from a non-OECD country, and locality-specific factors (*e.g.*, potentially greater differences in regulatory occupational exposure or emission limits, industry/process technologies) may impact exposures or releases relative to the U.S. or the country of origin is not specified.	
Critically deficient (ranking = 4)	This metric does not have a critically deficient criterion because no geographic location is known to have critically deficient data.	
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. Applicability		
High (ranking = 1)	The assessment is for an occupational scenario within the scope of the risk evaluation.	
Medium (ranking = 2)	The assessment is for an occupational scenario that is similar to an occupational scenario within the scope of the risk evaluation, in terms of the type of industry, operations, and work activities.	
Low (ranking = 3)	The assessment is for a non-occupational scenario that is similar to an occupational scenario within the scope of the risk evaluation, such as a consumer DIY scenario that is similar to a worker scenario.	
Critically deficient (ranking = 4)	The assessment is from an occupational or non-occupational scenario that does not apply to any occupational scenario within the scope of the risk evaluation.	
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 representativeness		
High (ranking = 1)	The assessment captures operations, equipment, and worker activities expected to be representative of current conditions. EPA has no reason to believe exposures have changed. The completed exposure or risk assessment is generally no more than 10 years old.	
Medium (ranking = 2)	The assessment captures operations, equipment, and worker activities that are expected to be reasonably representative of current conditions. The completed	

Data Quality Ranking	Description	
	exposure or risk assessment is generally, more than 10 years but no more than 20 years old.	
Low (ranking = 3)	The completed exposure or risk assessment is more than 20 years old. The assessment captures operations, equipment, and worker activities that are expected to be outdated.	
Critically deficient (ranking = 4)	Known factors (*e.g.*, new and completely different process or equipment) are so different as to make outdated information critically deficient.	
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		
High (ranking = 1)	Statistical distribution of samples is fully characterized. Sample size is sufficiently representative.	
Medium (ranking = 2)	Distribution of samples is characterized by a range with uncertain statistics. It is unclear if analysis is representative.	
Low (ranking = 3)	Distribution of samples is qualitative or characterized by no statistics.	
Critically deficient (ranking = 4)	This metric does not have a critically deficient criterion.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 3. Accessibility/clarity		
Metric 6. Metadata completeness		
High (ranking = 1)	Assessment or report clearly documents its data sources, assessment methods, results, and assumptions.	
Medium (ranking = 2)	Assessment or report clearly documents results, methods, and assumptions. Data sources are generally described but not fully transparent.	
Low (ranking = 3)	Assessment or report provides results, but the underlying methods, data sources, and assumptions are not fully transparent.	
Critically deficient (ranking = 4)	Assessment or report does not document its data sources, assessment methods, and assumptions.	

Data Quality Ranking	Description	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 4. Variability and uncertainty		
Metric 7. Variability and uncertainty		
High (ranking = 1)	The assessment addresses variability and uncertainty in the results. Uncertainty is well characterized.	
Medium (ranking = 2)	The assessment provides only limited discussion of the variability and uncertainty in the results.	
Low (ranking = 3)	The assessment does not address variability or uncertainty.	
Critically deficient (ranking = 4)	This metric does not have a critically deficient criterion.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

M.6.5 Data/Information from Reports Containing Other than Exposure or Release Data

The general approach for setting the criteria for a critically deficient rating is to only assign a critically deficient rating when EPA can confirm that the data or information is critically deficient. If the data source lacks documentation of needed metadata, EPA will not rate the metric as critically deficient but will rate it as low. The reason for this approach is to avoid omitting potentially valid data or information because release and occupational exposure data are often sparse. EPA will not use data/information from data sources that exhibit serious flaws as described in Table_Apx M-15.

Table_Apx M-15. Serious Flaws that Would Make Data/Information from Reports Containing Other than Release or Exposure Data Critically Deficient for Use in the Environmental Release and Occupational Exposure Assessment

Domain	Metric	Description of Serious Flaw(s) in Data Source
Reliability	Methodology	The assessment or report uses data or techniques or methods that are not consistent with the best available science. Assumptions, extrapolations, measurements, and models are not appropriate. There appears to be mathematical errors or errors in logic.
Representativeness	Geographic scope	This metric does not have a critically deficient criterion because no geographic location is known to have critically deficient data.
	Applicability	The report is from an occupational or non-occupational scenario that does not apply to any occupational scenario within the scope of the risk evaluation

Domain	Metric	Description of Serious Flaw(s) in Data Source
	Temporal representativeness	Known factors (*e.g.*, new and completely different process or equipment) are so different as to make outdated information critically deficient.
	Sample size	This metric does not have a critically deficient criterion.
Accessibility/ clarity	Metadata completeness	Assessment or report does not document its data sources, assessment methods, and assumptions.
Variability and uncertainty	Metadata completeness	This metric does not have a critically deficient criterion.
Optimization of the list of serious flaws may occur after pilot calibration exercises.		

Table_Apx M-16. Evaluation Criteria for Data/Information Reports Containing Other than Exposure or Release Data

Data Quality Ranking	Description	
Domain 1. Reliability		
Metric 1. Methodology		
High (ranking = 1)	The assessment or report uses high quality data and/or techniques or sound methods that are from frequently used sources (*e.g.*, European Union or OECD reports, NIOSH HHEs, journal articles, Kirk-Othmer) and are generally accepted by the scientific community, and associated information does not indicate flaws or quality issues.	
Medium (ranking = 2)	The assessment or report uses high quality data and/or techniques or sound methods that are not from a frequently used source and associated information does not indicate flaws or quality issues.	
Low (ranking = 3)	The data, data sources, and/or techniques or methods used in the assessment or report are not specified.	
Critically deficient (ranking = 4)	The assessment or report uses data or techniques or methods that are not high quality or not consistent with the best available science. Assumptions, extrapolations, measurements, and models are not appropriate. There appears to be mathematical errors or errors in logic.	
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 2. Geographic scope		
High (ranking = 1)	The data are from the United States and are representative of the industry being evaluated.	

Data Quality Ranking	Description	
Medium (ranking = 2)	The data are from an OECD country other than the U.S., and locality-specific factors (*e.g.*, potential differences in regulatory occupational exposure or emission limits, industry/process technologies) may impact exposures or releases relative to the U.S.	
Low (ranking = 3)	The data are from a non-OECD country, and locality-specific factors (*e.g.*, potentially greater differences in regulatory occupational exposure or emission limits, industry/process technologies) may impact exposures or releases relative to the U.S., or the country of origin is not specified.	
Critically deficient (ranking = 4)	This metric does not have a critically deficient criterion because no geographic location is known to have critically deficient data.	
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. Applicability		
High (ranking = 1)	The report is for an occupational scenario within the scope of the risk evaluation.	
Medium (ranking = 2)	The report is for an occupational scenario that is similar to an occupational scenario within the scope of the risk evaluation, in terms of the type of industry, operations, and work activities.	
Low (ranking = 3)	The report is for a non-occupational scenario that is similar to an occupational scenario within the scope of the risk evaluation, such as a consumer DIY scenario that is similar to a worker scenario.	
Critically deficient (ranking = 4)	The report is from an occupational or non-occupational scenario that does not apply to any occupational scenario within the scope of the risk evaluation.	
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 representativeness		
High (ranking = 1)	The report captures operations, equipment, and worker activities expected to be representative of current conditions. The report is generally no more than 10 years old.	
Medium (ranking = 2)	The report captures operations, equipment, and worker activities that are expected to be reasonably representative of current conditions. The report is generally more than 10 years but no more than 20 years old.	
Low (ranking = 3)	The report is more than 20 years old. The report captures operations, equipment, and worker activities that are expected to be outdated.	

Data Quality Ranking	Description	
Critically deficient (ranking = 4)	Known factors (*e.g.*, new and completely different process or equipment) are so different as to make outdated information critically deficient.	
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		
High (ranking = 1)	Statistical distribution of samples is fully characterized. Sample size is sufficiently representative.	
Medium (ranking = 2)	Distribution of samples is characterized by a range with uncertain statistics. It is unclear if analysis is representative.	
Low (ranking = 3)	Distribution of samples is qualitative or characterized by no statistics.	
Critically deficient (ranking = 4)	This metric does not have a critically deficient criterion.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 3. Accessibility/clarity		
Metric 6. Metadata completeness		
High (ranking = 1)	Assessment or report clearly documents its data sources, assessment methods, results, and assumptions.	
Medium (ranking = 2)	Assessment or report clearly documents results, methods, and assumptions. Data sources are generally described but not fully transparent.	
Low (ranking = 3)	Assessment or report provides results, but the underlying methods, data sources, and assumptions are not fully transparent.	
Critically deficient (ranking = 4)	Assessment or report does not document its data sources, assessment methods, and assumptions.	
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 7. Variability and uncertainty		

Data Quality Ranking	Description	
High (ranking = 1)	The report addresses variability and uncertainty in the results. Uncertainty is well characterized.	
Medium (ranking = 2)	The report provides only limited discussion of the variability and uncertainty in the results.	
Low (ranking = 3)	The report does not address variability or uncertainty.	
Critically deficient (ranking = 4)	This metric does not have a critically deficient criterion.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

Appendix N DATA QUALITY CRITERIA FOR STUDIES ON CONSUMER, GENERAL POPULATION, AND ENVIRONMENTAL EXPOSURE

N.1 Types of Consumer, General Population and Environmental Exposure Data Sources

The data quality of consumer, general population, and environmental exposure data sources will be evaluated for seven different types of data sources: monitoring data, modeling data, survey-based data, epidemiological based data, experimental data, completed exposure assessments and risk characterizations, and database sources not unique to a chemical. Definitions for these data types are shown below in Table_Apx N-1.

Table_Apx N-1. Types of Exposure Data Sources

Type of Data Source	Definition
Monitoring data	Measured chemical concentration(s) obtained from sampling of environmental media (*e.g.*, air, water, soil, and biota) to observe and study conditions of the environment. Monitoring data also include measured concentrations of chemicals or their metabolites in biological matrices (*i.e.*, blood, urine, breastmilk, breath, hair, and organs) that provide direct evidence about exposure of environmental contaminants in humans and wildlife, as well as measured chemical concentrations obtained from personal exposure monitoring (*i.e.*, breathing zone, skin patch samples).
Modeling data	Calculated values derived from computational models for estimation of environmental concentrations (*i.e.*, indoor, outdoor, microenvironments) and uptakes (*e.g.*, ADD, lifetime average daily dose [LADD], C_{max}, or AUC) associated with relevant exposure scenarios and routes (*i.e.*, inhalation, oral, dermal).
Survey-based data	Data collected from survey questionnaires about activity and use patterns (*e.g.*, habits, practices, food intake) to evaluate exposure to an individual, a population segment or a population.
Epidemiological data	Exposure data obtained from epidemiological studies collected as part of the examination of the association between chemical exposure and the occurrence and causes of health effects in human populations. The data may also come from case study reports which characterize exposures to one person.
Experimental data	Data obtained from experimental studies conducted in a controlled environment with pre-defined testing conditions. Examples include data from laboratory/chamber tests such as those conducted for product testing, source characterization, emissions testing, and migration testing. Experimental data may also include chemical concentrations from personal exposure or biomonitoring studies conducted in laboratory/chamber test settings.
Completed exposure Assessments and risk characterizations	Data reported in completed exposure assessments and risk characterizations containing a broad range of exposure data types (*e.g.*, media concentrations, doses, estimated values, exposure factors). Examples: ATSDR assessments, risk assessments completed by other countries.
Database sources not unique to a chemical	Data obtained from large databases which collate information for a wide variety of chemicals using methods that are reasonable and consistent with sound scientific

Type of Data Source	Definition
	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: NHANES, STORET.
ADD = Average daily dose; AUC = Area under the curve; C_{max} = maximum concentration in plasma.	

In general, the studies will inform the following basic data needs for exposures assessment (NRC, 1991):

- measures or estimates of the chemical;
- the source of the chemical exposure;
- environmental media of exposure;
- specific populations exposed, including PESS;
- intensity and frequency of contact; and
- spatial and temporal concentration patterns.

Some data sources identified as *on-topic*[21] for consumer, general population, and environmental exposure will also be identified as *on-topic* for the other disciplines (Engineering, Fate, Human Health Hazard, Environmental Hazard) supporting the development of the TSCA risk evaluations. In these cases, each discipline will consider different aspects of the same study. This is the case for epidemiological studies which examine disease patterns among populations during a specific duration of time. While the human health assessors are primarily interested in the hazards and effects that exposure to pollutants have on key biological, chemical, and physical processes affecting human health, exposure assessors are primarily interested in estimating exposure via direct measurements (*e.g.*, media concentrations coupled with uptake rates, biomonitoring concentrations) or modeling. EPA anticipates that many epidemiological studies will need to be assessed by both the exposure and the human health assessors.

N.2 Data Quality Evaluation Domains

The data sources will be evaluated against the following four data quality evaluation domains: reliability, representativeness, accessibility/clarity, and variability and uncertainty. These domains, as defined in Table_Apx N-2, address elements of TSCA Science Standards 26(h)(1) through 26(h)(5).

Table_Apx N-2. Data Evaluation Domains and Definitions

Evaluation Domain	Definition
Reliability	The inherent property of a study, which includes the use of well-founded scientific approaches, the avoidance of bias within the study design and faithful study conduct and documentation (ECHA, 2011a).
Representativeness	The data reported address exposure scenarios (*e.g.*, sources, pathways, routes, receptors) that are relevant to the assessment.
Accessibility/clarity	The data and supporting information are accessible and clearly documented.

[21] For the scoping phase, EPA developed specific criteria to determine which references should be tagged as "on-topic" (inclusion criteria) and "off-topic" (exclusion criteria). Refer to the literature search strategies and bibliographies developed for each of the 10 existing chemicals under evaluation.

Evaluation Domain	Definition
Variability and uncertainty	The data describe variability and uncertainty (quantitative and qualitative) or the procedures, measures, methods, or models are evaluated and characterized.

N.3 Data Quality Evaluation Metrics

The data quality evaluation domains will be evaluated by assessing unique metrics that have been developed for each data type. A summary of the number of metrics and metric name for each data type is provided in Table_Apx N-3.

EPA may adjust these metrics as more experience is acquired with the evaluation tools to support fit-for-purpose TSCA risk evaluations. If this happens, EPA will document the changes to the evaluation tool.

Table_Apx N-3. Summary of Metrics for the Seven Data Types

Type of Data Source	Overall Number of Metrics[a]	Metric Types
Monitoring data	10	Sampling Methodology; Analytical Methodology; Selection of Biomarker of Exposure; Geographic Area; Temporality; Spatial and Temporal Variability; Exposure Scenario; Reporting of Results; Quality Assurance; Variability and Uncertainty
Modeling data	6	Mathematical Equations; Model Evaluation; Exposure Scenario; Model and Model Documentation Availability; Model Inputs and Defaults; Variability and Uncertainty
Survey-based data	8	Data Collection Methodology; Data Analysis Methodology, Geographic Area; Sampling/Sampling Size; Response Rate; Reporting of Results; Quality Assurance; Variability and Uncertainty
Epidemiological data	18	Measurement or Exposure Characterization; Reporting Bias; Exposure Variability and Misclassification; Sample Contamination; Method Requirements; Matrix Adjustment; Method Sensitivity; Stability; Use of Biomarker of Exposure; Relevance; Population; Participant Selection; Comparison Group; Attrition; Documentation; QA/QC; Variability; Uncertainties
Experimental data	9	Sampling Methodology and Conditions; Analytical Methodology; Selection of Biomarker of Exposure; Testing Scenario, Sample Size and Variability; Temporality; Reporting of Results; Quality Assurance; Variability and Uncertainty
Completed exposure assessments and characterizations	4	Methodology; Exposure Scenario; Documentation of References; Variability and Uncertainty

Type of Data Source	Overall Number of Metrics[a]	Metric Types
Database sources not unique to a chemical	8	Sampling Methodology; Analytical Methodology; Geographic Area; Temporal; Exposure Scenario; Availability of Database and Supporting Documents; Reporting of Results; Variability and Uncertainty
[a] Number of metrics across evaluation domains.		

N.4 Ranking Method and Determination of Overall Data Quality Level

N.4.1 Determination of Overall Study Ranking

To determine the overall study ranking, the metric rankings are summed and divided by the number of metrics that are evaluated to obtain an overall study ranking between 1 and 3. The equation for calculating the overall ranking is shown below.

$$\textit{Overall Ranking (range of 1 to 3)} = \sum \textit{(Metric Rankings) / (Number of Metrics)}$$

Table_Apx N-4 provides a ranking example for monitoring data.

Studies with any single metric ranking of 4 will be automatically assigned an overall quality ranking of *uninformative* and further evaluation of the remaining metrics is not necessary. An *uninformative* ranking means that serious flaws are noted in a critical metric that consequently make the data unusable (or invalid) for exposure assessment. EPA plans to use studies or information with an overall quality level of *high*, *medium*, or *low* to quantitatively or qualitatively support the risk evaluations but does not plan to use studies rated as *uninformative*.

Any metrics that are *not rated/not applicable* to the study under evaluation will not be considered in the calculation of the study's overall quality ranking. These metrics will not be included in the nominator or denominator of the overall ranking equation. The overall ranking will be calculated using only those metrics that receive rankings of *high*, *medium* or *low*. In addition, if a publication reports more than one study or endpoint, each study and, as needed, each endpoint, will be evaluated separately. Detailed tables showing quality criteria for the metrics are provided in Table_Apx N-6 through Table_Apx N-14, including a table that summarizes the serious flaws that would make the data uninformative for use in the exposure assessment.

Table_Apx N-4. Ordinal Ranking Example for Monitoring Data

Metric/Description	Metric Ranking
Metric 1: Sampling Methodology	1
Metric 2: Analytical Methodology	2
Metric 3: Selection of biomarker of Exposure	2
Metric 4: Geographic area	1
Metric 5: Temporality	1

<table>
<tr><th>Metric/Description</th><th colspan="3">Metric Ranking</th></tr>
<tr><td>Metric 6: Spatial and Temporal Variability</td><td colspan="3">1</td></tr>
<tr><td>Metric 7: Exposure Scenario</td><td colspan="3">3</td></tr>
<tr><td>Metric 8: Reporting of Results</td><td colspan="3">1</td></tr>
<tr><td>Metric 9: Quality Assurance</td><td colspan="3">2</td></tr>
<tr><td>Metric 10: Variability and Uncertainty</td><td colspan="3">2</td></tr>
<tr><td colspan="3">Sum = 10</td><td rowspan="3">Sum = 16

=16/10=1.6
1.6
(High)</td></tr>
<tr><td colspan="3">Overall Ranking[a] = ∑(Metric Ranking)/ (Number of Metrics)</td></tr>
<tr><td>High
≥1 and <1.7</td><td>Medium
≥1.7 and <2.3</td><td>Low
≥2.3 and <3</td></tr>
<tr><td colspan="4">[a] The cutoffs between categories were defined by calculating the difference between the highest possible ranking of 3 and the lowest possible ranking of 1 (i.e., 3 – 1 = 2) and dividing it into three equal parts (2 ÷ 3 = 0.67). This results in a range of approximately 0.7 for each overall study data quality ranking, which is used to estimate the transition points (cut-off values) in the scale between high and medium rankings, and medium and low rankings. These transition points between the ranges of 1 and 3 are determined as follows:
• cut-off values between high and medium: 1 + 0.67 = 1.67, rounded to 1.7 (rankings lower than 1.7 are assigned an overall quality level of high); and
• cut-off values between medium and low: 1.67 + 0.67 = 2.34, rounded to 2.3 (rankings between 1.7 and lower than 2.3 are assigned an overall quality level of medium).</td></tr>
</table>

N.5 Data Sources Frequently Used in Consumer, General Population and Environmental Exposure Assessments

Many of the metric criteria definitions for the quality levels (*i.e.*, *high*, *medium*, *low*, and *critically deficient*) examine if the methodology used was sound and widely accepted. Table_Apx N-5 provides examples of data sources that EPA frequently uses to support the data needs of consumer, general population and environmental exposure assessments. EPA notes that some data sources in Table_Apx N-5 may use or include data or information that are not of high quality but are still acceptable (*e.g.*, *medium* or *low* quality) for use in risk evaluation. The methodologies in the individual studies under review will still be assessed in relation to chemical- and scenario-specific considerations, thus the study may still receive study quality rankings ranging from *uninformative* to *high* even though the study used a methodology from a source commonly known to use sound methods and/or approaches. EPA may determine standard quality ratings for some of these sources as more experience is acquired with TSCA risk evaluations.

Table_Apx N-5. Examples of Data Sources Frequently Used for Consumer, General Population and Environmental Exposure Assessments

Agency/Organization	Source
U.S. EPA	Chemical Data Reporting (CDR)
	High Production Volume (HPV) Challenge Submissions
	Extra HPV Program Submissions
	EPA Existing Chemicals Engineering Files
	EPA Generic Scenarios
	Toxics Release Inventory (TRI)
	National Emissions Inventory (NEI)
	Office of Water
	Office of Air
	Office of Enforcement and Compliance Assistance Sector Notebooks
	AP-42
	Other EPA Programs (*e.g.*, Design for Environment)
Occupational Safety and Health Administration (OSHA)	
National Institute of Occupational Safety and Health (NIOSH)	
American Conference of Governmental Industrial Hygienists (ACGIH)	
Agency for Toxic Substances and Disease Registry (ATSDR)	
Organisation for Economic Co-operation and Development (OECD)	Screening Information Dataset (SIDS)
	Emission Scenario Documents (ESDs)
	Other Programs
Environment Canada	Canadian Pollution Prevention Information Clearinghouse
	Other Programs
U.S. Census Bureau	North American Industry Classification System (NAICS) Definitions
	County Business Patterns
	Annual Survey of Manufacturers
	Current Industrial Reports

Agency/Organization	Source
	Economic Census
Bureau of Labor Statistics (BLS)	
North Carolina Division of Pollution Prevention and Environmental Assistance	
	Kirk-Othmer Encyclopedia of Chemical Technology
Hazardous Substances Data Bank (HSDB)	
National Library of Medicine's HazMap	

N.6 Data Quality Criteria

N.6.1 Monitoring Data

Table_Apx N-6. Serious Flaws that Would Make Sources of Monitoring Data Uninformative for Use in the Exposure Assessment

Domain	Metric	Description of Serious Flaw(s) in Data Source
Reliability	Sampling Methodology	The sampling methodology is not discussed in the data source or companion source.
		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).
		There are numerous inconsistencies in the reporting of sampling information, resulting in high uncertainty in the sampling methods used.
	Analytical Methodology	Analytical methodology is not described, including analytical instrumentation (*i.e.*, high pressure liquid chromatography [HPLC])
		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).
		There are numerous inconsistencies in the reporting of analytical information, resulting in high uncertainty in the analytical methods used.
	Selection of Biomarker of Exposure	This metric does not have a critically deficient criterion.
Representative	Geographic Area	Geographic location is not reported, discussed, or referenced.
	Currency	Timing of sample collection for monitoring data is not reported, discussed, or referenced.
		Sample size is not reported.
		Single sample collected per data set.

Domain	Metric	Description of Serious Flaw(s) in Data Source
	Spatial and Temporal Variability	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.
	Exposure Scenario	If reported, the exposure scenario discussed in the monitored study does not represent the exposure scenario of interest for the chemical.
Accessibility/ Clarity	Reporting of Results	There are numerous inconsistencies or errors in the calculation and/or reporting of results, resulting in highly uncertain reported results.
	Quality Assurance	QA/QC issues have been identified which significantly interfere with the overall reliability of the study.
Variability and Uncertainty	Variability and Uncertainty	Estimates are highly uncertain based on characterization of variability and uncertainty.
Optimization of the list of serious flaws may occur after pilot calibration exercises.		

Table_Apx N-7. Evaluation Criteria for Sources of Monitoring Data

Quality level (ranking)	Description	
Domain 1. Reliability		
Metric 1. Sampling methodology		
High (Ranking = 1)	Samples were collected according to publicly available SOPs that are scientifically sound and widely accepted (*i.e.*, from a source generally using sound methods and/or approaches) for the chemical and media of interest. Example SOPs include USGS's "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 from a source generally 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/regime sample storage conditions/duration performance/calibration of sampler study site characteristics matrix characteristics	
Medium (Ranking = 2)	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**	

Quality level (ranking)	Description	
	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 (Ranking = 3)	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 (Ranking = 4)	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]*	
<u>Metric 2</u>. Analytical methodology		
High (Ranking = 1)	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	

Quality level (ranking)	Description	
	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 (Ranking = 2)	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 (Ranking = 3)	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.	
Critically Deficient (Ranking= 4)	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	

Quality level (ranking)	Description	
	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 (Ranking = 1)	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 (Ranking = 2)	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 (Ranking = 3)	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 (Ranking = 4)	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		

Quality level (ranking)	Description	
High (Ranking = 1)	Geographic location(s) is reported, discussed, or referenced.	
Medium (Ranking = 2)	Not applicable. This metric is dichotomous (*i.e.*, high vs. critically deficient).	
Low (Ranking = 3)	Not applicable. This metric is dichotomous (*i.e.*, high vs. critically deficient).	
Critically Deficient (Ranking = 4)	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 (Ranking = 1)	Timing of sample collection for monitoring data is consistent with current or recent exposures **(within 5 years)** may be expected.	
Medium (Ranking = 2)	Timing of sample collection for monitoring data **is less consistent** with current or recent exposures **(>5 to 15 years)** may be expected.	
Low (Ranking = 3)	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 (Ranking = 4)	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 (Ranking = 1)	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 samples for a single scenario). Use of replicate samples. Use of systematic or continuous monitoring methods.	

Quality level (ranking)	Description	
	Sampling over a sufficient period of time to characterize trends. For urine, 24-hr 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.	
Medium (Ranking = 2)	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 (Ranking = 3)	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 doesn't include all periods of time or locations, or For urine, un-pooled spot samples.	
Critically Deficient (Ranking = 4)	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 (Ranking = 1)	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 (Ranking = 2)	The data likely represent the relevant exposure scenario (*i.e.*, population/scenario/media of interest). **One or more key pieces of information**	

Quality level (ranking)	Description	
	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 (Ranking = 3)	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 (Ranking = 4)	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 (Ranking = 1)	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 (Ranking = 2)	Supplementary or raw data (*i.e.*, individual data points) are not reported, and therefore summary statistics cannot be reproduced.	

Quality level (ranking)	Description	
	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 (Ranking = 3)	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 (Ranking = 4)	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 (Ranking = 1)	The study applied quality assurance/quality control measures and all pertinent quality assurance 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 quality control issues were identified, or any identified issues were minor and adequately addressed (*i.e.*, correction for low recoveries, correction for completeness).	
Medium (Ranking = 2)	The study applied and documented quality assurance/quality control 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 quality control issues were identified, or any identified issues were minor and addressed (*i.e.*, correction for low recoveries, correction for completeness).	

Quality level (ranking)	Description	
Low (Ranking = 3)	Quality assurance/quality control techniques and results were not directly discussed but can be implied through the study's use of standard field and laboratory protocols. AND/OR Deficiencies were noted in quality assurance/quality control measures that are likely to have a substantial impact on results. AND/OR There are some inconsistencies in the quality assurance measures reported, resulting in low confidence in the quality assurance/control measures taken and results (*e.g.*, differences between text and tables in data source).	
Critically Deficient (Ranking = 4)	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 10. Variability and uncertainty		
High (Rating = 1)	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 (Rating = 2)	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 (Rating = 3)	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	

Quality level (ranking)	Description	
Critically Deficient (Ranking = 4)	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]*	

N.6.2 Modeling Data[22]

Table_Apx N-8. Serious Flaws that Would Make Sources of Modeling Data Uninformative for Use in the Exposure Assessment

Domain	Metric	Description of Serious Flaw(s) in Data Source
Reliability	Mathematical equations	For widely accepted models from a source generally known to use sound methods and/or approaches, the module used is not germane to the scenario being assessed. For other (non-public/non-authoritative) models, key mathematical equations and/or theory are not provided in the data source or in a companion reference. Key mathematical equations are not based on scientifically sound approaches. Key mathematical equations are incorrect.
	Model evaluation	The model used in the data source has not undergone evaluation. It is unknown whether the model has undergone evaluation. Evaluation efforts indicate that the model results do not correctly estimate concentrations or uptakes. Model has no acceptance among the scientific or regulatory community.
Representative	Exposure scenario	Model inputs do not reflect relevant conditions for the scenario of interest, or insufficient information is provided to make a determination.
Accessibility/ Clarity	Model and model documentation availability	This metric does not have a critically deficient criterion.
	Model inputs and defaults	There is at most a very limited description of model inputs/defaults and their associated data sources.
Variability and Uncertainty	Variability and uncertainty	Estimates are highly uncertain based **on** characterization of uncertainty.

[22] Evaluation of models and modeling data types will largely follow guidance from (U.S. EPA, 2009).

Domain	Metric	Description of Serious Flaw(s) in Data Source
Optimization of the list of serious flaws may occur after pilot calibration exercises.		

Table_Apx N-9. Evaluation Criteria for Sources of Modeling Data

Data Quality Level	Description	
Domain 1. Reliability		
Metric 1. Mathematical equations/theory		
High (Rating = 1)	The model is scientifically sound and widely accepted (*i.e.*, from a source generally using sound methods and/or approaches) for the scenario being assessed. OR For other (non-public/non-authoritative) models, key mathematical equations to calculate concentrations or uptakes are provided in the data source or in a companion reference. Equations are described in detail and correctness can be assessed.	
Medium (Rating = 2)	For other (non-public/authoritative) models, key mathematical equations to calculate concentrations or uptakes are not available in the data source, but the scientific and mathematical theory (*i.e.*, conceptual model) is described in detail.	
Low (Rating = 3)	For other (non-public/authoritative) models, key mathematical equations or theory to calculate concentrations or uptakes are unclear or not detailed enough to thoroughly assess.	
Critically Deficient (Rating = 4)	For widely accepted models from a source generally known to use sound methods and/or approaches, the module used is not germane to the scenario being assessed. AND/OR For other (non-public/non-authoritative) models, key mathematical equations and/or theory are not provided in the data source or in a companion reference. AND/OR Key mathematical equations are not based on scientifically sound approaches. AND/OR Key mathematical equations are incorrect.	
Not Rated/ Applicable		
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 2. Model evaluation		
High (Rating = 1)	The model used in the data source has undergone extensive evaluation. The evaluation methodology and results are either discussed in the data source or provided in a companion source. Example evaluation methods include: formal peer review	

Data Quality Level	Description	
	quantitative corroboration of model results with monitoring data directly relevant for the scenario of interest benchmarking against other models quality assurance checks during model development.	
Medium (Rating = 2)	The model used in the data source has undergone only targeted/limited evaluation. For example: informal peer review at most limited evaluation with monitoring data qualitative corroboration of model results through expert elicitation evaluation via other model predictions quality assurance checks during model development. AND/OR There is only limited discussion on the evaluation methodology and results in either the data source or other references. AND/OR Model has wide acceptance among the scientific and regulatory community, but has not have been validated for the scenario of interest, peer-reviewed, or well documented.	
Low (Rating = 3)	Model evaluation was conducted according to the author; however, there is no information provided regarding model peer review, corroboration, or quality assurance checks. AND/OR Model has only limited acceptance among the scientific and regulatory community.	
Critically Deficient (Rating = 4)	The model used in the data source has not undergone evaluation. AND/OR It is unknown whether the model has undergone evaluation. AND/OR Evaluation efforts indicate that the model results do not correctly estimate concentrations or uptakes. AND/OR Model has no acceptance among the scientific and regulatory community.	
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. Exposure scenario		
High (Rating = 1)	The modeled scenario closely represents current exposures (within 5 years) and/or relevant conditions (*e.g.*, environmental conditions, consumer products, exposure factors, geographical location).	

Data Quality Level	Description	
Medium (Rating = 2)	The modeled scenario is less representative of current exposures (>5 to 15 years) and/or relevant conditions for the scenario of interest (*e.g.*, environmental conditions, consumer products, exposure factors, geographical location).	
Low (Ranking = 3)	The modeled scenario is not consistent with when current exposures are expected (>15 years) and/or with relevant conditions (*e.g.*, environmental conditions, consumer products, exposure factors, geographical location); inconsistencies are likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	Model inputs do not reflect relevant conditions for the scenario of interest, or insufficient information is provided to make a determination.	
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 4. Model and model documentation availability		
High (Ranking = 1)	The model and documentation (user guide, documentation manual) are publicly available or there is sufficient documentation in the data source or in a companion reference.	
Medium (Ranking = 2)	Not applicable. This metric is dichotomous (*i.e.*, high vs. low).	
Low (Ranking = 3)	The model and documentation (user guide, documentation manual) are not available, or there is insufficient documentation in the data source or in a companion reference.	
Critically Deficient (Ranking = 4)	Not applicable. This metric is dichotomous (*i.e.*, high vs. low).	
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. Model inputs and defaults		
High (Ranking = 1)	Key model inputs (*e.g.*, chemical mass released, release pattern over time, receptor uptake rates and locations over time) and defaults are identified, referenced and clearly described. AND	

Data Quality Level	Description	
	Model inputs meet data quality acceptance criteria specified by the authors or are standard or commonly accepted inputs (*e.g.*, from Exposure Factors Handbook).	
Medium (Ranking = 2)	Key model inputs and defaults and associated data sources are generally identified, referenced and clearly described, but the descriptions are not detailed. AND/OR Data quality acceptance criteria specified by the author are not discussed, but inputs appear appropriate.	
Low (Ranking = 3)	Numerous key model inputs and defaults and associated data sources are not identified, referenced or clearly described; AND/OR There are some inconsistencies in the reporting of inputs and defaults and their associated data sources (*e.g.*, differences between text and tables in data source, differences between standard method and actual procedures reported to have been used) that lead to a low confidence in the inputs and defaults used. AND/OR Data quality acceptance criteria specified by the author are not discussed and some inputs appear inappropriate.	
Critically Deficient (Ranking = 4)	There is at most a very limited description of model inputs/defaults and their associated data sources.	
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 6. Variability and uncertainty		
High (Ranking = 1)	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 (Ranking = 2)	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.	

Data Quality Level	Description	
(Ranking = 3)	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 (Ranking = 4)	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]*	
EPA will consult with the *Guidance on the Development, Evaluation, and Application of Environmental Models* (U.S. EPA, 2009) when evaluating models and modeling data types.		

N.6.3 Survey Data

Table_Apx N-10. Serious Flaws that Would Make Sources of Survey Data Uninformative for Use in the Exposure Assessment

Domain	Metric	Description of Serious Flaw(s) in Data Source
Reliability	Data Collection Methodology	Data collection methods are not described. Data collection methods used are not appropriate (*i.e.*, scientifically sound) for the target population, the intended purpose, data requirements of the survey, or the target response rate. There are numerous inconsistencies in the reporting of data collection information resulting in high uncertainty in the data collection methods used.
	Data Analysis Methodology	Data analysis methodology is not described. Data analysis methodology is not appropriate (*i.e.*, scientifically sound) for the intended purpose of the survey and the data/information collected. There are numerous inconsistencies in the reporting of analytical information resulting in high uncertainty in the data analysis methods used.
Representative	Geographic Area	Geographic location is not reported, discussed, or referenced.
	Sampling/ Sampling Size	Sampling procedures (*e.g.*, stratified sampling, cluster sampling, multi-stage sampling, non-probability sampling, etc.) are not documented in the data source or companion source.
		Sample size is not reported.

Domain	Metric	Description of Serious Flaw(s) in Data Source
	Response Rate	This metric does not have a critically deficient criterion.
Accessibility/ Clarity	Reporting of Results	There are numerous inconsistencies or errors in the calculation and/or reporting of results, resulting in highly uncertain reported results.
	Quality Assurance	QA/QC issues have been identified which significantly interfere with the overall reliability of the survey results.
Variability and Uncertainty	Variability and Uncertainty	Estimates are highly uncertain based on characterization of variability and uncertainty.
Optimization of the list of serious flaws may occur after pilot calibration exercises.		

Table_Apx N-11. Evaluation Criteria for Source of Survey Data

Data Quality Level	Description	
Domain 1. Reliability		
Metric 1. Data collection methodology		
High (Ranking = 1)	Survey data were collected using a standard or validated data collection methods (*e.g.*, mail, phone, personal interview, online surveys, etc.) that are appropriate (*i.e.*, scientifically sound) given the characteristics of the target population, the intended purpose, data requirements of the survey, and the target response rate. AND All pertinent information regarding data collection methodology is provided in the data source or companion source. Examples include: data collection instrument (*e.g.*, questionnaire, diaries, etc.) data collection protocols for field personnel date of data collection description of target population	
Medium (Ranking = 2)	Survey data were collected using standard or validated data collection methods appropriate given the characteristics of the target population, the intended purpose and data requirements of the survey, and the target response rate. However, one or more pieces of pertinent information regarding data collection is not described. The missing information is unlikely to have a substantial impact on results.	
Low (Ranking = 3)	Data collection methods are only briefly discussed, therefore most data collection information is missing and likely to have a substantial impact on results. AND/OR There are some inconsistencies in the reporting of data collection information (*e.g.*, differences between text and tables in data source) which lead to a low confidence in the data collection methodology used.	
Critically Deficient (Ranking = 4)	Data collection methods are not described. AND/OR	

Data Quality Level	Description	
	Data collection methods used are not appropriate (*i.e.*, scientifically sound) for the target population, the intended purpose, data requirements of the survey, or the target response rate. AND/OR There are numerous inconsistencies in the reporting of data collection information resulting in high uncertainty in the data collection 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. Data analysis methodology		
High (Ranking = 1)	Data analysis methodology is discussed in detail and is clear and appropriate (*i.e.*, scientifically sound) for the intended purpose of the survey and the data/information collected. Methods employed are standard/widely accepted. AND All pertinent analytical methodology information is provided in the data source or companion source. Examples include: information on statistical and weighting methods (if applicable) discussion regarding treatment of missing data Identification of sources of error, including coverage error, nonresponse error, measurement error, and data processing error (*e.g.*, keying, coding, editing, and imputation error) Methods for measuring sampling and nonsampling errors	
Medium (Ranking = 2)	Data analysis methodology is discussed and is clear and appropriate for the intended purpose of the survey and the data/information collected. Methods employed are standard/widely accepted; however, one or more pieces of analytical information is not described. The missing information is unlikely to have a substantial impact on results.	
Low (Ranking = 3)	Data analysis methodology is only briefly discussed in the data source or companion source, therefore most analytical information is missing and likely to have a substantial impact on results. AND/OR Methods for data analysis are not standard/widely accepted. AND/OR There are some inconsistencies in the reporting of analytical information which lead to a low confidence in the data analysis methodology used.	
Critically Deficient (Ranking = 4)	Data analysis methodology is not described in the data source or companion source. OR Data analysis methodology is not appropriate (*i.e.*, scientifically sound) for the intended purpose of the survey and the data/information collected. OR	

Data Quality Level	Description	
	There are numerous inconsistencies in the reporting of analytical information resulting in high uncertainty in the data analysis 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]*	
Domain 2. Representative		
Metric 3. Geographic area		
High (Ranking = 1)	Geographic location(s) is reported, discussed, or referenced.	
Medium (Ranking = 2)	Not applicable. This metric is dichotomous (*i.e.*, high vs. critically deficient).	
Low (Ranking = 3)	Not applicable. This metric is dichotomous (*i.e.*, high vs. critically deficient).	
Critically Deficient (Ranking = 4)	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. Sampling/sampling size		
High (Ranking = 1)	Sampling procedures are documented (*e.g.*, stratified sampling, cluster sampling, multi-stage sampling, non-probability sampling, etc.). AND Sample size and method of calculation is reported. AND Sample size is large enough to be reasonably assured that the samples represent the population of interest. For example, sample size has a margin of error of <10% and a quality level of >90%.	
Medium (Ranking = 2)	Sampling procedures are documented (*e.g.*, stratified sampling, cluster sampling, multi-stage sampling, non-probability sampling, etc.). AND Sample size is reported, but the sample size calculation method is not reported. AND/OR	

Data Quality Level	Description	
	Sample size is small, indicating that the survey results are less likely to represent the target population. For example, sample size has a margin of error of >10% and a quality level of <90%.	
Low (Ranking = 3)	Sampling procedures are documented (*e.g.*, stratified sampling, cluster sampling, multi-stage sampling, non-probability sampling, etc.). AND Sample size is reported, but the sample size calculation method is not reported. AND/OR Adequacy of sample size is not discussed or cannot be determined from information in the study.	
Critically Deficient (Ranking = 4)	Sampling procedures (*e.g.*, stratified sampling, cluster sampling, multi-stage sampling, non-probability sampling, etc.) are not documented in the data source or companion source. AND/OR Sample size is not reported.	
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. Response rate		
High (Ranking = 1)	The survey response rate is documented and is high enough (*i.e.*, >70%) to reasonably ensure that the survey results are representative of the target population.	
Medium (Ranking = 2)	The survey response rate is documented and the response rate is >40–70%, indicating that the survey results will likely represent the target population.	
Low (Ranking = 3)	The survey response rate is documented, and the response rate is <40%, indicating that the survey results are less likely to represent the target population. OR The survey response rate is not documented in the data source or companion source.	
Critically Deficient (Ranking = 4)	This metric does not have a critically deficient criterion.	
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		

Data Quality Level	Description	
Metric 6. Reporting of results		
High (Ranking = 1)	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 Number of samples in data set Range or percentiles Measure of variation (coefficient of variation [CV], standard deviation) Measure of central tendency (mean, geometric mean, median) Test for outliers (if applicable)	
Medium (Ranking = 2)	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).	
Low (Ranking = 3)	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 (Ranking = 4)	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 7. Quality assurance		
High (Ranking = 1)	Survey quality assurance/control measures were employed during each phase of the survey and are documented. Examples may include: training staff in protocols monitoring interviewers conducting response analysis surveys contingencies to modify the survey procedures monitoring of data collection activities AND No quality control issues were identified OR	

Data Quality Level	Description	
	any identified issues were minor and were addressed.	
Medium (Ranking = 2)	The study applied and documented quality assurance/quality control 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 quality control issues were identified OR any identified issues were minor and addressed.	
Low (Ranking = 3)	Quality assurance/quality control techniques and results were not directly discussed but can be implied through the study's use of standard survey protocols. AND/OR Deficiencies were noted in quality assurance/quality control measures that are likely to have a substantial impact on results. AND/OR There are some inconsistencies in the quality assurance measures reported, resulting in low confidence in the quality assurance/control measures taken and results (*e.g.*, differences between text and tables in data source).	
Critically Deficient (Ranking = 4)	QA/QC issues have been identified which significantly interfere with the overall reliability of the survey 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]*	
Domain 4. Variability and uncertainty		
Metric 8. Variability and uncertainty		
High (Ranking = 1)	The variability in the population and data collected in the survey is characterized (*e.g.*, sampling and non-sampling errors). AND Key uncertainties, limitations, and data gaps have been identified. AND The uncertainties are minimal and have been characterized.	
Medium (Ranking = 2)	The study has limited characterization of variability in the population studied and data collected in the survey. 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.	

Data Quality Level	Description	
Low (Ranking = 3)	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 (Rating = 4)	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]*	

N.6.4 Epidemiology Data to Support Exposure Assessment

EPA will not use data/information from data sources that exhibit serious flaws as described in Table_Apx N-12.

Table_Apx N-12. Serious Flaws that Would Make Sources of Epidemiology Data Uninformative for Use in the Exposure Assessment

Domain	Metric	Description of Serious Flaw(s) in Data Source
Reliability (All Study Types)	Measurement or Exposure Characterization	Exposure misclassification (*e.g.*, differential recall of self-reported exposure) is present, but no attempt is made to address it.
	Reporting Bias	This metric does not have a critically deficient criterion.
Reliability (Applicable to Study Types with Direct Exposure Measurements Only)	Exposure Variability and Misclassification	Exposure based on a single sample and error is known to be so large that the results are too uncertain to be useful.
	Sample Contamination	There are known contamination issues and the issues were not addressed.
	Method Requirements	The method used is known to produce unreliable or invalid results.
	Matrix Adjustment	This metric does not have a critically deficient criterion.
	Method Sensitivity	This metric does not have a critically deficient criterion.
	Stability	This metric does not have a critically deficient criterion.

Domain	Metric	Description of Serious Flaw(s) in Data Source
Reliability (Applicable to Study Types with Biomarker Measurements Only)	Use of Biomarker of Exposure	This metric does not have a critically deficient criterion.
Representativeness	Relevance	This metric does not have a critically deficient criterion.
	Geographic Area	Geographic location is not reported, discussed, or referenced.
	Participant Selection	This metric does not have a critically deficient criterion.
	Attrition	***For cohort studies:*** The loss of subjects (*i.e.*, incomplete exposure data) was both large and unacceptably handled (as described in the low quality category). ***For case-control and cross-sectional studies:*** The exclusion of subjects from analyses was both large and unacceptably handled (as described in the low quality category).
	Comparison Group	Subjects in all groups were not similar, recruited within very different time frames, or had very different participation/ response rates.
Accessibility/ Clarity	Documentation	There are numerous inconsistencies or errors in the calculation and/or reporting of information and results, resulting in highly uncertain reported results.
	QA/QC	QA/QC issues have been identified which significantly interfere with the overall reliability of the study and are not addressed.
Variability and Uncertainty	Variability	This metric does not have a critically deficient criterion.
	Uncertainties	This metric does not have a critically deficient criterion.
Optimization of the list of serious flaws may occur after pilot calibration exercises.		

Table_Apx N-13. Evaluation Criteria for Sources of Epidemiology Data to Support the Exposure Assessment

Data Quality Level	Metric Description	
Domain 1. Reliability		
Metric 1. Measurement or exposure characterization[a]		
High (Ranking = 1)	Exposure was consistently assessed (*i.e.*, under the same method and time frame across cases, controls or the entire cohort) using well-established	

Data Quality Level	Metric Description	
	methods that directly measure exposure (*e.g.*, measurement of the chemical in air or measurement of the chemical in blood, plasma, urine, etc.). OR Exposure was consistently assessed using less-established methods that directly measure exposure and are validated against well-established methods.	
Medium (Ranking = 2)	Exposure was assessed using indirect measures (*e.g.*, questionnaire or occupational exposure assessment by a certified industrial hygienist) that have been validated or empirically shown to be consistent with methods that directly measure exposure (*i.e.*, inter-methods validation: one method vs. another)	
Low (Ranking = 3)	Exposure was assessed using direct or indirect measures that have not been validated or have poor validity. OR If using indirect methods, they have not empirically shown to be consistent with methods that directly measure exposure (*e.g.*, a job-exposure matrix or self-report without validation). OR There is insufficient information provided about the exposure assessment, including validity and reliability, but no evidence for concern about the method used.	
Critically Deficient (Ranking = 4)	Exposure misclassification (*e.g.*, differential recall of self-reported exposure) is present and likely to impact results, but no attempt is made to address it.	
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. Reporting bias[a]		
High (Ranking = 1)	All of the study's measured exposures outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) are reported.	
Medium (Ranking = 2)	Not applicable. This metric is dichotomous (*i.e.*, high vs. low)	
Low (Ranking = 3)	All of the study's measured exposures outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have not been reported.	
Critically Deficient (Ranking = 4)	Not applicable. This metric is dichotomous (*i.e.*, high vs. low).	

Data Quality Level	Metric Description	
Not rated/not applicable		
Reviewer's Comments: *[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*		
Metric 3. Exposure variability and misclassification[b]		
High (Ranking = 1)	There are a sufficient number of samples per individual to estimate exposure over the appropriate duration, or through the use of adequate long-term sampling data. A "sufficient" number is dependent upon the chemical and the research question. AND Error is considered by calculating measures of accuracy (*e.g.*, sensitivity and specificity) and reliability (*e.g.*, intra-class correlation coefficient [ICC]).	
Medium (Ranking = 2)	One sample is used per individual, and there is stated evidence that errors from a single measurement are negligible.	
Low (Ranking = 3)	More than one sample collected per individual, but without evaluation of error. OR Exposure based on a single sample without consideration or recognition of error	
Critically Deficient (Ranking = 4)	Exposure based on a single sample and error is known to be so large that the results are too uncertain to be useful.	
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. Sample contamination[b]		
High (Ranking = 1)	Samples are contamination-free from the time of collection to the time of measurement (*e.g.*, by use of certified analyte free collection supplies and reference materials, and appropriate use of blanks both in the field and lab). AND Documentation of the steps taken to provide the necessary assurance that the study data are reliable is included.	
Medium (Ranking = 2)	Samples are stated to be contamination-free from the time of collection to the time of measurement. AND	

Data Quality Level	Metric Description	
	There is incomplete documentation of the steps taken to provide the necessary assurance that the study data are reliable.	
Low (Ranking = 3)	Samples are known to have contamination issues, but steps have been taken to address and correct contamination issues. OR Samples are stated to be contamination-free from the time of collection to the time of measurement, but there is no use or documentation of the steps taken to provide the necessary assurance that the study data are reliable.	
Critically Deficient (Ranking = 4)	There are known contamination issues and the issues were not addressed.	
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. Method requirements[b]		
High (Ranking = 1)	Study uses instrumentation that provides *unambiguous* identification and quantitation of the biomarker or chemical in media at the required sensitivity (*e.g.*, gas chromatography-high-resolution mass spectrometry (GC-HRMS), gas chromatography-tandem mass spectrometry (GC-MS/MS), liquid chromatography-tandem mass spectrometry (LC-MS/MS)).	
Medium (Ranking = 2)	Study uses instrumentation that allows for identification of the biomarker or chemical in media with confidence and the required sensitivity (*e.g.*, gas chromatography-mass spectrometry (GC-MS), gas chromatography-electron capture detector (GC-ECD)).	
Low (Ranking = 3)	Study uses instrumentation that only allows for possible quantification of the biomarker or chemical in media but the method has known interferants (*e.g.*, gas chromatography-flame ionization detector (GC-FID)). OR Study uses a semi-quantitative method to assess the biomarker or chemical in media (*e.g.*, fluorescence).	
Critically Deficient (Ranking = 4)	The method used is known to produce unreliable or invalid 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 Level	Metric Description	
Metric 6. Matrix adjustment[b]		
High (Ranking = 1)	If applicable for the biomarker under consideration, study provides results, either in the main publication or as a supplement, for adjusted and unadjusted matrix concentrations (*e.g.*, creatinine-adjusted or SG-adjusted and non-adjusted urine concentrations) and reasons are given for adjustment approach.	
Medium (Ranking = 2)	If adjustments are needed, study only provides results using one method (matrix adjusted or not).	
Low (Ranking = 3)	If applicable for the biomarker under consideration, no established method for matrix adjustment was conducted.	
Critically Deficient (Ranking = 4)	Not applicable. A study will not be deemed critically deficient based on matrix adjustment.	
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. Method sensitivity[b]		
High (Ranking = 1)	Limits of detection/quantification are reported and low enough to detect chemicals in a sufficient percentage of the samples to address the research questions (*e.g.*, 50–60% detectable values if the research hypothesis requires estimates of both central tendencies and upper tails of the population concentrations). OR All samples are above the LOD/LOQ.	
Medium (Ranking = 2)	Not applicable. This metric is dichotomous (*i.e.*, high vs. low).	
Low (Ranking = 3)	Frequency of detection too low to address the research question OR There are samples below the LOD/LOQ, and LOD/LOQ are not stated.	
Critically Deficient (Ranking = 4)	Not applicable. This metric is dichotomous (*i.e.*, high vs. low).	
Not rated/not applicable		
Reviewer's Comments:		

Data Quality Level	Metric Description	
[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]		
Metric 8. Stability[b]		
High (Ranking = 1)	Samples with a known history and documented stability data or those using real-time measurements.	
Medium (Ranking = 2)	Samples have known losses during storage but the difference between low and high exposures can be qualitatively assessed.	
Low (Ranking = 3)	Samples with either unknown history and/or no stability data for analytes of interest.	
Critically Deficient (Ranking = 4)	Not applicable. A study will not be deemed critically deficient based on stability.	
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. Use of biomarker of exposure[c]		
High (Ranking = 1)	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 (Ranking = 2)	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 (Ranking = 3)	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	

Data Quality Level	Metric Description	
	Biomarker in a specified matrix is a poor surrogate (low accuracy and precision) for exposure/dose.	
Critically Deficient (Ranking = 4)	Not applicable. A study will not be deemed critically deficient based on the use of biomarker of exposure.	
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. Representativeness		
Metric 10. Relevance		
High (Ranking = 1)	The study represents current exposures (within 5 years) and relevant conditions (*e.g.*, environmental conditions, consumer products, exposure factors, geographical location).	
Medium (Ranking = 2)	The study is less representative of current exposures (>5 to 15 years) and/or relevant conditions for the scenario of interest (*e.g.*, environmental conditions, consumer products, exposure factors, geographical location).	
Low (Ranking = 3)	The study is not consistent with current exposures (>15 years) and/or with relevant conditions (*e.g.*, environmental conditions, consumer products, exposure factors, geographical location); inconsistencies are likely to have a substantial impact on results. OR Insufficient information is provided to determine whether the study represents current relevant conditions for the scenario of interest.	
Critically Deficient (Ranking = 4)	Not applicable. A study will not be deemed critically deficient based on relevance.	
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 11. Geographic area		
High (Ranking = 1)	Geographic location(s) is reported, discussed, or referenced.	
Medium (Ranking = 2)	Not applicable. This metric is dichotomous (*i.e.*, high vs. critically deficient).	

Data Quality Level	Metric Description	
Low (Ranking = 3)	Not applicable. This metric is dichotomous (*i.e.*, high vs. critically deficient).	
Critically Deficient (Ranking = 4)	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 12. Participant selection		
High (Ranking = 1)	The participants selected are representative of the larger population from which they were sampled. OR Approaches (*e.g.*, survey weights, inverse probability weighting) were applied to ensure representativeness.	
Medium (Ranking = 2)	Not applicable. This metric is dichotomous (*i.e.*, high vs. low).	
Low (Ranking = 3)	The participants selected do not appear to be representative of the larger population from which they were sampled. OR There is insufficient information to determine whether participants selected are representative of the population from which they were sampled.	
Critically Deficient (Ranking = 4)	Not applicable. This metric is dichotomous (*i.e.*, high vs. low).	
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 13. Attrition		
High (Ranking = 1)	*For cohort studies:* There was minimal subject attrition during the study (or exclusion from the analysis sample) and exposure data were largely complete. OR	

Data Quality Level	Metric Description	
	Any loss of subjects (*i.e.*, incomplete exposure data) was adequately* addressed (as described above) and reasons were documented when human subjects were removed from a study. OR Missing data have been imputed using appropriate methods (*e.g.*, random regression imputation), and characteristics of subjects lost to follow up or with unavailable records are described in identical way and are not significantly different from those of the study participants. *For case-control studies and cross-sectional studies*: There was minimal subject withdrawal from the study (or exclusion from the analysis sample) and exposure data were largely complete. OR Any exclusion of subjects from analyses was adequately* addressed (as described above), and reasons were documented when subjects were removed from the study or excluded from analyses. **NOTE for all study types:* Adequate handling of subject attrition includes: very little missing exposure data; missing exposure data balanced in numbers across study groups, with similar reasons for missing data across groups.	
Medium (Ranking = 2)	*For cohort studies:* There was moderate subject attrition during the study (or exclusion from the analysis sample). AND Any loss or exclusion of subjects was adequately addressed (as described in the acceptable handling of subject attrition in the high quality category) and reasons were documented when human subjects were removed from a study. *For case-control studies and cross-sectional studies*: There was moderate subject withdrawal from the study (or exclusion from the analysis sample), but exposure data were largely complete. AND Any exclusion of subjects from analyses was adequately addressed (as described above), and reasons were documented when subjects were removed from the study or excluded from analyses.	
Low (Ranking = 3)	*For cohort studies:* There was large subject attrition during the study (or exclusion from the analysis sample), but it was adequately addressed (*i.e.*, missing exposure data was balanced in numbers across groups and reasons for missing data were similar across groups). OR Subject attrition was not large, but it was inadequately addressed. Inadequate handling of subject attrition: reason for missing exposure data likely to be related to true exposure, with either imbalance in numbers or reasons for missing data across study groups; or potentially inappropriate application of imputation. OR Numbers of individuals were not reported at each stage of study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible,	

Data Quality Level	Metric Description	
	included in the study or analysis sample, completing follow-up, and analyzed). Reasons were not provided for non-participation at each stage. *For case-control and cross-sectional studies*: There was large subject withdrawal from the study (or exclusion from the analysis sample), but it was adequately addressed (*i.e.*, missing exposure data was balanced in numbers across groups and reasons for missing data were similar across groups). OR Subject attrition was not large, but it was inadequately addressed. Inadequate handling of subject attrition: reason for missing exposure data likely to be related to true exposure, with either imbalance in numbers or reasons for missing data across study groups; or potentially inappropriate application of imputation. OR Numbers of individuals were not reported at each stage of study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study or analysis sample, and analyzed). Reasons were not provided for non-participation at each stage.	
Critically Deficient (Ranking = 4)	*For cohort studies*: The loss of subjects (*i.e.*, incomplete exposure data) was both large and unacceptably handled (as described above in the low quality category). *For case-control and cross-sectional studies*: The exclusion of subjects from analyses was both large and unacceptably handled (as described above in the low quality category).	
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 14. Comparison group[d]		
High (1)	Key elements of the study design are reported (*i.e.*, setting, inclusion and exclusion criteria, and methods of participant selection), and indicate that subjects (in all groups) were similar (*e.g.*, recruited with the same method of ascertainment and within the same time frame using the same inclusion and exclusion criteria, and were of similar age and health status) OR Baseline characteristics of groups differed *but* these differences were considered as potential confounding or stratification variables and were thereby controlled by statistical analysis.	
Medium (2)	There is indirect evidence (*i.e.*, stated by the authors without providing a description of methods) that subjects (in all groups) were similar (as described above for the high quality ranking). AND	

Data Quality Level	Metric Description	
	Baseline characteristics for subjects (in all groups) reported in the study were similar.	
Low (3)	There is indirect evidence (*i.e.*, stated by the authors without providing a description of methods) that subjects (in all groups) were similar (as described above for the high quality ranking). AND Baseline characteristics for subjects (in all groups) were not reported.	
Critically Deficient (Ranking 4)	Subjects in all groups were not similar, recruited within very different time frames, or had very different participation/ response rates.	
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 15. Documentation		
High (Ranking = 1)	Study clearly states aims, methods, assumptions and limitations. AND Study clearly states the time frame over which exposures were estimated and what the exposure level represents (*e.g.*, spot measurement, peak, or average over a specified time frame). AND Discussion of sample collection requirements, relevant participant characteristics, and matrix treatment is provided. AND Supplementary data is included, allowing summary statistics to be reproduced.	
Medium (Ranking = 2)	Study clearly states aims, methods, assumptions and limitations. AND Study clearly states the time frame over which exposures were estimated and what the exposure level represents (*e.g.*, spot measurement, peak, or average over a specified time frame). AND Discussion of sample collection requirements, relevant participant characteristics, and matrix treatment is provided. AND Supplementary data is not included; summary statistics cannot be reproduced.	

Data Quality Level	Metric Description	
Low (Ranking = 3)	Aims, methods, assumptions and limitations are not clear or not completely reported. OR The time frame over which exposures were estimated and/or what the exposure level represents (*e.g.*, peak, average over a specified time frame) are not clear (*e.g.*, spot measurement, peak, average over a specified time frame). OR Discussion of sample collection requirements, relevant participant characteristics, and matrix treatment is not provided.	
Critically Deficient (Ranking = 4)	There are numerous inconsistencies or errors in the calculation and/or reporting of information and 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 16. Quality assurance/quality control		
High (Ranking = 1)	The study applied quality assurance/quality control measures and all pertinent quality assurance 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 quality control issues were identified or, if they were identified, were appropriately addressed (*i.e.*, correction for low recoveries, correction for completeness).	
Medium (Ranking = 2)	It is stated that quality assurance/quality control measures were used, but no details were provided. AND No quality control issues were identified OR any identified issues were minor and addressed (*i.e.*, correction for low recoveries, correction for completeness).	
Low (Ranking = 3)	Information on quality assurance/quality control was absent. OR	

Data Quality Level	Metric Description	
	Quality assurance/quality control measures were applied and documented; however, minor quality control issues have been identified but not addressed, or there may be some reporting inconsistencies.	
Critically Deficient (Ranking = 4)	QA/QC issues have been identified which significantly interfere with the overall reliability of the study and are not addressed.	
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 17. Variability		
High (Ranking = 1)	Study summarizes mean and variation in exposure levels for one or more groups. AND Study presents discussion of sources of variability.	
Medium (Ranking = 2)	Not applicable. This metric is dichotomous (*i.e.*, high vs. low).	
Low (Ranking = 3)	Study does not summarize mean and variation in exposure levels for any groups. AND/OR Study does not present discussion of sources of variability.	
Critically Deficient (Ranking = 4)	Not applicable. This metric is dichotomous (*i.e.*, high vs. low).	
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 18. Uncertainties		
High (Ranking = 1)	Key uncertainties, limitations, and data gaps are recognized and discussed (*e.g.*, those related to inherent variability in environmental and exposure-related parameters or possible measurement errors). AND The uncertainties are minimal.	

Data Quality Level	Metric Description	
Medium (Ranking = 2)	Not applicable. This metric is dichotomous (*i.e.*, high vs. low).	
Low (Ranking = 3)	Key uncertainties, limitations, or data gaps are not recognized or discussed. AND/OR Estimates are highly uncertain.	
Critically Deficient (Ranking = 4)	Not applicable. This metric is dichotomous (*i.e.*, high vs. low).	
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]*		
[a] Applicable to all study types. [b] Applicable only to study types with direct exposure measurements (*i.e.*, measurement of chemical in specific media or biomarker measurement). [c] Only applicable to studies with biomarker measurements. [d] Only applicable to studies that compare exposure in different groups.		

N.6.5 Experimental Data

Table_Apx N-14. Serious Flaws that Would Make Sources of Experimental Data Uninformative for Use in the Exposure Assessment

Domain	Metric	Description of Serious Flaw(s) in Data Source
Reliability	Sampling Methodology and Conditions	The sampling methodology is not discussed in the data source or companion source. 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). There are numerous inconsistencies in the reporting of sampling information, resulting in high uncertainty in the sampling methods used.
	Analytical Methodology	Analytical methodology is not described, including analytical instrumentation (*i.e.*, High pressure liquid chromatography (HPLC), GC). 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). There are numerous inconsistencies in the reporting of analytical information, resulting in high uncertainty in the analytical methods used.

Domain	Metric	Description of Serious Flaw(s) in Data Source
	Selection of Biomarker of Exposure	Biomarker in a specified matrix is a poor surrogate (low accuracy and precision) for exposure/dose.
Representative	Testing Scenario	Testing conditions are not relevant to the exposure scenario of interest for the chemical.
	Sample Size and Variability	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.
	Temporality	Temporality of tested items is not reported, discussed, or referenced.
Accessibility/ Clarity	Reporting of Results	There are numerous inconsistencies or errors in the calculation and/or reporting of results, resulting in highly uncertain reported results.
	Quality Assurance	QA/QC issues have been identified which significantly interfere with the overall reliability of the study.
Variability and Uncertainty	Variability and Uncertainty	Estimates are highly uncertain based on characterization of variability and uncertainty.
Optimization of the list of serious flaws may occur after pilot calibration exercises.		

Table_Apx N-15. Evaluation Criteria for Sources of Experimental Data

Data Quality Level	Metric Description	
Domain 1. Reliability		
Metric 1. Sampling Methodology and Conditions		
High (Ranking = 1)	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 Level	Metric Description	
Medium (Ranking = 2)	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 (Ranking = 3)	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 (Ranking = 4)	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		
High (Ranking = 1)	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	

Data Quality Level	Metric Description	
	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 LOQ, LOD, detection limits, and/or reporting limits recovery samples biomarker used (if applicable) matrix-adjustment method (*i.e.*, creatinine, lipid, moisture)	
Medium (Ranking = 2)	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 (Ranking = 3)	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.	
Critically Deficient (Ranking = 4)	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	

Data Quality Level	Metric Description	
	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 (Ranking = 1)	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 (Ranking = 2)	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 (Ranking = 3)	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.	
Critically Deficient (Ranking = 4)	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]*	
Domain 2. Representative		
Metric 4. Testing scenario		
High (Ranking = 1)	Testing conditions closely represent relevant exposure scenarios (*i.e.*, population/scenario/media of interest). Examples include:	

Data Quality Level	Metric Description	
	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 (Ranking = 2)	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 (Ranking = 3)	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.	
Critically Deficient (Ranking = 4)	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 (Ranking = 1)	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 Level	Metric Description	
Medium (Ranking = 2)	Sample size is moderate (*i.e.*, 5 to 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 (Ranking = 3)	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 (Ranking = 4)	Sample size is not reported. AND/OR Single sample collected per data set. 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 (Rating = 1)	Source(s) of tested items appears to be current (within 5 years).	
Medium (Rating = 2)	Source(s) of tested items is less consistent with when current or recent exposures (>5 to 15 years) are expected.	
Low (Rating = 3)	Source(s) of tested items is not consistent with when current or recent exposures (>15 years) are expected or is not identified.	
Critically Deficient (Rating = 4)	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]*	
Domain 3. Accessibility/clarity		
Metric 7. Reporting of results		

Data Quality Level	Metric Description	
High (Rating = 1)	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 (Rating = 2)	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 (Ranking = 3)	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 (Ranking = 4)	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 8. Quality assurance		
High (Ranking = 1)	The study applied quality assurance/quality control measures and all pertinent quality assurance information is provided in the data source or companion source. Examples include: Laboratory, and/or storage recoveries. Laboratory control samples.	

Data Quality Level	Metric Description	
	Baseline (pre-exposure) samples. Biomarker stability Completeness of sample (*i.e.*, creatinine, specific gravity, osmolality for urine samples) AND No quality control issues were identified OR any identified issues were minor and adequately addressed (*i.e.*, correction for low recoveries, correction for completeness).	
Medium (Ranking = 2)	The study applied and documented quality assurance/quality control 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 quality control issues were identified OR any identified issues were minor and addressed (*i.e.*, correction for low recoveries, correction for completeness).	
Low (Ranking = 3)	Quality assurance/quality control techniques and results were not directly discussed but can be implied through the study's use of standard field and laboratory protocols. AND/OR Deficiencies were noted in quality assurance/quality control measures that are likely to have a substantial impact on results. AND/OR There are some inconsistencies in the quality assurance measures reported, resulting in low confidence in the quality assurance/control measures taken and results (*e.g.*, differences between text and tables in data source).	
Critically Deficient (Ranking = 4)	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 (Ranking = 1)	The study characterizes variability in the population/media studied. AND Key uncertainties, limitations, and data gaps have been identified. AND	

Data Quality Level	Metric Description	
	The uncertainties are minimal and have been characterized.	
Medium (Ranking = 2)	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 (Ranking = 3)	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 (Ranking = 4)	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]*	

N.6.6 Database Data

Table_Apx N-16. Serious Flaws that Would Make Sources of Database Data Uninformative for Use in the Exposure Assessment

Domain	Metric	Description of Serious Flaw(s) in Data Source
Reliability	Sampling methodology	The sampling methodologies used were not appropriate for the chemical/media of interest in the database (*e.g.*, inappropriate sampling equipment, improper storage conditions).
	Analytical methodology	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).
Representative	Geographic area	Geographic location of sampling data within database is not reported, discussed, or referenced.
	Temporal	Timing of sample data is not reported, discussed, or referenced.
	Exposure scenario	Data provided in the database are not representative of the media or population of interest.

Domain	Metric	Description of Serious Flaw(s) in Data Source
Accessibility/ Clarity	Availability of database and supporting documents	No information is provided on the database source or availability to the public.
	Reporting results	There are numerous inconsistencies or errors in the calculation and/or reporting of results, resulting in highly uncertain reported results.
		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.
Variability and Uncertainty	Variability and uncertainty	Estimates are highly uncertain based on characterization of variability and uncertainty.
Optimization of the list of serious flaws may occur after pilot calibration exercises.		

Table_Apx N-17. Evaluation Criteria for Sources of Database Data

Data Quality Level	Description	
Domain 1. Reliability		
Metric 1. Sampling methodology		
High (Ranking = 1)	Widely accepted sampling 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 USGS's "National Field Manual for the Collection of Water-Quality Data", EPA's "Ambient Air Sampling" (SESDPROC-303-R5), etc.	
Medium (Ranking = 2)	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 (Ranking = 3)	The sampling methodology was not reported in data source or companion data source.	
Critically Deficient (Ranking = 4)	The sampling methodologies used were not appropriate for the chemical/media of interest in the database (*e.g.*, inappropriate sampling equipment, improper storage conditions).	
Not Rated/Not Applicable		
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 2. Analytical methodology		

Data Quality Level	Description	
High (Ranking = 1)	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 (Ranking = 2)	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 (Ranking = 3)	The analytical methodology was not reported in data source or companion data source.	
Critically Deficient (Rating = 4)	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 (Ranking = 1)	Geographic location(s) is reported, discussed, or referenced.	
Medium (Ranking = 2)	Not applicable. This metric is dichotomous (*i.e.*, high vs. critically deficient).	
Low (Ranking = 3)	Not applicable. This metric is dichotomous (*i.e.*, high vs. critically deficient).	
Critically Deficient (Rating = 4)	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 (Ranking = 1)	The data reflect current conditions (within 5 years) AND/OR	

Data Quality Level	Description	
	Database contains robust historical data for spatial and temporal analyses (if applicable).	
Medium (Ranking = 2)	The data are less consistent with current or recent exposures (>5 to 15 years) AND/OR Database contains sufficient historical data for spatial and temporal analyses (if applicable).	
Low (Ranking = 3)	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 (Ranking = 4)	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 (Ranking = 1)	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 (Ranking = 2)	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 (Ranking = 3)	The data lack multiple key pieces of information and the deficiencies are likely to have a substantial impact on the characterization of the exposure scenario. AND/OR There are **some inconsistencies or possible errors** in the reporting of scenario information (*e.g.*, differences between text and tables in data source, differences between standard method and actual procedures reported to have been used, etc.) which leads to a lower confidence in the scenario assessed. AND/OR	

Data Quality Level	Description	
	If surrogate data, activities have lesser similarity but are still potentially applicable to the activities within scope.	
Critically Deficient (Ranking = 4)	If reported, the exposure scenario discussed in the monitored study does not represent the exposure scenario of interest for the chemical.	
Not Rated/Not Applicable		
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 3. Accessibility/clarity		
Metric 6. Availability of database and supporting documents		
High (Ranking = 1)	Database is widely accepted and/or from a source generally known to use sound methods and/or approaches (*e.g.*, NHANES, STORET).	
Medium (Ranking = 2)	The database may not be widely known or accepted (*e.g.*, state-maintained databases), but the database is adequately documented with the following information: Within the database, metadata is present (sample identifiers, annotations, flags, units, matrix descriptions, etc.) and data fields are generally clear and defined. A user manual 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 (Ranking = 3)	The database may not be widely known or accepted, and only limited database documentation is available (see the medium rating).	
Critically Deficient (Rating = 4)	No information is provided on the database source or availability to the public.	
Not Rated/ Applicable		
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 7. Reporting of results		
High (Ranking = 1)	The information source reporting the analysis of the database data is well organized and understandable by the target audience. AND	

Data Quality Level	Description	
	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 (Ranking = 2)	The information source reporting the analysis of the database data is well organized and understandable by the target audience. AND Summary statistics are missing one or more parameters (see description for high).	
Low (Ranking = 3)	The information source reporting the analysis of the database data is unclear or not well organized. AND/OR Summary statistics are missing most parameters (see description for high) AND/OR There are some inconsistencies or errors in the results reported, resulting in low confidence in the results reported (*e.g.*, differences between text and tables in data source, less appropriate statistical methods).	
Critically Deficient (Rating = 4)	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 (Ranking = 1)	Key uncertainties, limitations, and data gaps have been identified. AND The uncertainties are minimal and have been characterized.	
Medium (Ranking = 2)	The study has limited discussion of key uncertainties, limitations, and data gaps. AND/OR	

Data Quality Level	Description	
	Multiple uncertainties have been identified but are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	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 (Rating = 4)	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]*	

N.6.7 Completed Exposure Assessments and Risk Characterizations

Table_Apx N-18. List of Serious Flaws that Would Make Completed Exposure Assessments and Risk Characterizations Uninformative for Use in the Exposure Assessment

Domain	Metric	Description of Serious Flaw(s) in Data Source
Reliability	Methodology	The assessment uses techniques that are not appropriate (*e.g.*, inappropriate assumptions, models not within domain of the exposure scenario, etc.). Assumptions, extrapolations, measurements, and models are not described. There appears to be mathematical errors or errors in logic which significantly interfere with the overall reliability of the study.
Representative	Exposure scenario	If reported, the exposure scenario discussed in the monitored study does not represent the exposure scenario of interest for the chemical. Surrogate data, if available, are not similar enough to the chemical and use of interest to be used.
Accessibility/ Clarity	Documentation of references	The reported data, inputs, and defaults are not documented or only sparsely documented.
Variability and Uncertainty	Variability and uncertainty	Estimates are highly uncertain based on characterization of variability and uncertainty.
Optimization of the list of serious flaws may occur after pilot calibration exercises.		

Table_Apx N-19. Evaluation Criteria for Completed Exposure Assessments and Risk Characterizations

Data Quality Level	Description	
Domain 1. Reliability		
Metric 1. Methodology		
High (Ranking = 1)	The assessment uses technical approaches that are generally accepted by the scientific community. AND Assumptions, extrapolations, measurements, and models have been documented and described. AND There are no mathematical errors or errors in logic.	
Medium (Ranking = 2)	The assessment uses techniques that are from reliable sources and are generally accepted by the scientific community; however, a discussion of assumptions, extrapolations, measurements, and models is limited.	
Low (Ranking = 3)	The assessment uses techniques that may not be generally accepted by the scientific community. AND/OR There is only a brief discussion of assumptions, extrapolations, measurements, and models, or some components may be missing. AND/OR There are some mathematical errors or errors in logic.	
Critically Deficient (Rating = 4)	The assessment uses techniques that are not appropriate (*e.g.*, inappropriate assumptions, models not within domain of the exposure scenario, etc.) AND/OR Assumptions, extrapolations, measurements, and models are not described. AND/OR There appears to be mathematical errors or errors in logic 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 2. Representative		
Metric 2. Exposure scenario		
High (Ranking = 1)	The data (media concentrations, doses, estimated values, exposure factors) closely represent exposure scenarios of interest. Examples include: • Geography • Temporality • Chemical/use of interest	

Data Quality Level	Description	
Medium (Ranking = 2)	The exposure activity assessed likely represents the population/scenario/media of interest; however, one or more key pieces of information may not be described. OR If surrogate data, activities seem similar to the activities within scope.	
Low (Ranking = 3)	The study lacks 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 (Rating = 4)	If reported, the exposure scenario discussed in the monitored study does not represent the exposure scenario of interest for the chemical. AND/OR Surrogate data, if available, are not similar enough to the chemical and use of interest to be 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*	
Domain 3. Accessibility/clarity		
Metric 3. Documentation of references		
High (Ranking = 1)	References are available for all reported data, inputs, and defaults. AND References generally appear to be from publicly available and peer-reviewed sources.	
Medium (Ranking = 2)	References are available for all reported data, inputs, and defaults; however, some references may not be publicly available or are not from peer-reviewed sources (*i.e.*, professional judgment, personal communication).	
Low (Ranking = 3)	Numerous references for reported data, inputs, and defaults appear to be missing or there are discrepancies with the references. AND/OR Numerous references may not be publicly available or are not from peer-reviewed sources (*i.e.*, professional judgment or personal communication).	

Data Quality Level	Description	
Critically Deficient (Rating = 4)	The reported data, inputs, and defaults are not documented or only sparsely documented.	
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 4. Variability and uncertainty		
High (Ranking = 1)	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 (Ranking = 2)	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 (Ranking = 3)	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 (Rating = 4)	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]*	

Appendix O DATA QUALITY CRITERIA OF EXPOSURE MODELS

When evaluating exposure assessment models to be used in draft risk evaluations, EPA will consult with EPA's *Guidance on the Development, Evaluation, and Application of Environmental Models* (U.S. EPA, 2009). The following information is excerpted from Chapter 4 of EPA (2009). Model evaluation provides information to help answer four main questions (Beck, 2002 as cited in U.S. EPA, 2009)

- How have the principles of sound science been addressed during model development?
- How is the choice of model supported by the quantity and quality of available data?
- How closely does the model approximate the real system of interest?
- How does the model perform the specified task while meeting the objectives set by quality assurance project planning?

In its *Models in Environmental Regulatory Decision Making* report, the NRC summarizes the key elements of a model evaluation (NRC, 2007 as cited in U.S. EPA, 2009).

- **Scientific basis.** The scientific theories that form the basis for models.
- **Computational infrastructure.** The mathematical algorithms and approaches used in executing the model computations.
- **Assumptions and limitations.** The detailing of important assumptions used in developing or applying a computational model, as well as the resulting limitations that will affect the model's applicability.
- **Peer review.** The documented critical review of a model or its application conducted by qualified individuals who are independent of those who performed the work, but who collectively have at least equivalent technical expertise to those who performed the original work. Peer review attempts to ensure that the model is technically adequate, competently performed, properly documented, and satisfies established quality requirements through the review of assumptions, calculations, extrapolations, alternate interpretations, methodology, acceptance criteria, and/or conclusions pertaining from a model or its application (modified from EPA 2006).
- **Quality assurance and quality control (QA/QC).** A system of management activities involving planning, implementation, documentation, assessment, reporting, and improvement to ensure that a model and its components are of the type needed and expected for its task and that they meet all required performance standards.
- **Data availability and quality.** The availability and quality of monitoring and laboratory data that can be used for both developing model input parameters and assessing model results.
- **Test cases.** Basic model runs where an analytical solution is available, or an empirical solution is known with a high degree of confidence to ensure that algorithms and computational processes are implemented correctly.
- **Corroboration of model results with observations.** Comparison of model results with data collected in the field or laboratory to assess the model's accuracy and improve its performance.
- **Benchmarking against other models.** Comparison of model results with other similar models.
- **Sensitivity and uncertainty analysis.** Investigation of the parameters or processes that drive model results, as well as the effects of lack of knowledge and other potential sources of error in the model.
- **Model resolution capabilities.** The level of disaggregation of processes and results in the model compared to the resolution needs from the problem statement or model application. The resolution includes the level of spatial, temporal, demographic, or other types of disaggregation.
- **Transparency.** The need for individuals and groups outside modeling activities to comprehend either the processes followed in evaluation or the essential workings of the model and its outputs.

The extent of model evaluation will vary and is related to many factors such as available data and intended application. EPA will use the list provided above in conjunction with the quality criteria for modeling data to guide the evaluation of models and modeling data types.

Appendix P DATA QUALITY CRITERIA FOR ENVIRONMENTAL HAZARD STUDIES

P.1 Types of Environmental Hazard Data Sources

The data quality will be evaluated for a variety of environmental hazard studies (Table_Apx P-1). Because the availability of information varies considerably on different chemicals, it is anticipated that some environmental hazard studies will not be available while others may be identified beyond those listed in Table_Apx P-1.

Table_Apx P-1. Types of Environmental Hazard Data Sources

Data Category	Types of Data Sources
Environmental Hazard	Acute and chronic toxicity to aquatic invertebrates and fish (*e.g.*, freshwater, saltwater, and sediment-based exposures); toxicity to algae, cyanobacteria, and other microorganisms; toxicity to terrestrial invertebrates; acute oral toxicity to birds; toxicity to reproduction of birds; toxicity to terrestrial plants; toxicity to mammalian wildlife

P.2 Data Quality Evaluation Domains

The methods for evaluation of study quality were developed after review of selected existing processes and references describing existing study quality and risk of bias evaluation tools for toxicity studies including Criteria for Reporting and Evaluating Ecotoxicity Data (CRED) and ECOTOX knowledgebase (ECOTOX) (EC, 2018; Cooper et al., 2016; Lynch et al., 2016; Moermond et al., 2016b; Samuel et al., 2016; NTP, 2015a; Hooijmans et al., 2014; Koustas et al., 2014; Kushman et al., 2013; Hartling et al., 2012; Hooijmans et al., 2010). These publications, coupled with professional judgment and experience, informed the identification of domains and metrics for consideration in the evaluation and ranking of study quality. The evaluation domains and criteria were developed by harmonizing criteria across existing processes including CRED and ECOTOX processes. Furthermore, the evaluation tool is intended to address elements of TSCA Science Standards 26(h)(1) through 26(h)(5) that EPA must address during the development process of the risk evaluations.

Environmental hazard studies will be evaluated for data quality by assessing the following seven domains: Test Substance, Test Design, Exposure Characterization, Test Organism, Outcome Assessment, Confounding/Variable Control, and Data Presentation and Analysis. The data quality within each domain will be evaluated by assessing unique metrics that pertain to each domain. For example, the Test Substance domain will be evaluated by considering the information reported by the study on the test substance identity, purity, and source. The domains are defined in Table_Apx P-2 and further information on evaluation metrics is provided in the subsequent section.

Table_Apx P-2. Data Evaluation Domains and Definitions

Evaluation Domain	Definition
Test Substance	Metrics in this domain evaluate whether the information provided in the study provides a reliable[a] confirmation that the test substance used in a study has the same (or sufficiently similar) identity, purity, and properties as the substance of interest.

Evaluation Domain	Definition
Test Design	Metrics in this domain evaluate whether the experimental design enables the study to distinguish the effect of exposure from other factors. This domain includes metrics related to the use of control groups and randomization in allocation to ensure that the effect of exposure is isolated.
Exposure Characterization	Metrics in this domain assess the validity and reliability of methods used to measure or characterize exposure. These metrics evaluate whether exposure to the test substance was characterized using a method(s) that provides valid and reliable results, whether the exposure remained consistent over the duration of the experiment, and whether the exposure levels were appropriate to the outcome of interest.
Test Organisms	These metrics assess the appropriateness of the population or organism(s), number of organisms used in the study, and the organism conditions to assess the outcome of interest associated with the exposure of interest.
Outcome Assessment	Metrics in this domain assess the validity and reliability of methods, including sensitivity of methods, that are used to measure or otherwise characterize the outcome (*e.g.*, immobilization as a measure of mortality in aquatic invertebrates)
Confounding/Variable Control	Metrics in this domain assess the potential impact of factors other than exposure that may affect the risk of outcome. The metrics evaluate whether studies identify and account for factors that are related to exposure and independently related to outcome (confounding factors) and whether appropriate experimental or analytical (statistical) methods are used to control for factors unrelated to exposure that may affect the risk of outcome (variable control).
Data Presentation and Analysis	Metrics in this domain assess whether appropriate statistical methods were used and if data for all outcomes are presented.
Other	Metrics in this domain are added as needed to incorporate chemical- or study-specific evaluations.
[a] Reliability is defined as "the inherent property of a study or data, which includes the use of well-founded scientific approaches, the avoidance of bias within the study or data collection design and faithful study or data collection conduct and documentation" (ECHA, 2011b).	

P.3 Data Quality Evaluation Metrics

The data quality evaluation domains will be evaluated by assessing unique metrics that have been developed for environmental hazard studies. Each metric will be binned into a quality level of *high*, *medium*, *low*, or *critically deficient*. Each quality level which is based on professional judgement is assigned an ordinal ranking (*i.e.*, 1 through 4) that is used in the method of assessing the overall quality of the study as *high*, *medium*, *low*, or *uninformative*. This approach to derive an overall study ranking provides a method to objectively, consistently, and transparently determine how a study compares to others for a given chemical and across chemicals.

Table_Apx P-3 lists the data evaluation domains and metrics for environmental hazard studies. Each

domain has between two and six metrics; however, some metrics may not apply to all study types. A general domain for other considerations is available for metrics that are specific to a given test substance or study type. EPA may modify the metrics used for environmental hazard studies as the Agency acquires experience with the evaluation tool. Any modifications will be documented.

Data Quality ranking specifications for each metric are provided in Table_Apx P-4. Table_Apx P-7 summarizes the serious flaws that would make environmental hazard studies uninformative for use in the assessment.

Table_Apx P-3. Data Evaluation Domains and Metrics for Environmental Hazard Studies

Evaluation Domain	Number of Metrics Overall	Metrics (Metric Number and Description)
Test Substance	3	Metric 1: Test Substance Identity
		Metric 2: Test Substance Source
		Metric 3: Test Substance Purity
Test Design	3	Metric 4: Negative Controls
		Metric 5: Negative Control Response
		Metric 6: Randomized Allocation
Exposure Characterization	6	Metric 7: Experimental System/Test Media Preparation
		Metric 8: Consistency of Exposure Administration
		Metric 9: Measurement of Test Substance Concentration
		Metric 10: Exposure Duration and Frequency
		Metric 11: Number of Exposure Groups and Spacing of Exposure Levels
		Metric 12: Testing at or Below Solubility Limit
Test Organisms	4	Metric 13: Test Organism Characteristics
		Metric 14: Acclimatization and Pretreatment Conditions
		Metric 15: Number of Organisms and Replicates per Group
		Metric 16: Adequacy of Test Conditions
Outcome Assessment	2	Metric 17: Outcome Assessment Methodology
		Metric 18: Consistency of Outcome Assessment
Confounding/ Variable Control	2	Metric 19: Confounding Variables in Test design and Procedures
		Metric 20: Outcomes Unrelated to Exposure
	3	Metric 21: Statistical Methods

Evaluation Domain	Number of Metrics Overall	Metrics (Metric Number and Description)
Data Presentation and Analysis		Metric 22: Reporting of Data
		Metric 23: Explanation of Unexpected Outcomes

P.4 Ranking Method and Determination of Overall Data Quality Level

This section provides details about the ranking system that will be applied to environmental hazard studies.

P.4.1 Determination of Overall Study Ranking

A data quality ranking (1, 2, or 3 for *high*, *medium*, or *low*, respectively) is assigned for each relevant metric within each domain. If a publication reports more than one study or endpoint/health effect, each study and each endpoint/health effect will be evaluated separately. For studies that have only metrics with *high*, *medium*, or *low* (1, 2, or 3, respectively), the overall study ranking is determined by summing the individual metric rankings and then dividing by the total number of metrics to obtain an overall study ranking between 1 and 3. The equation for calculating the overall ranking is shown below:

$$\textit{Overall Ranking (range of 1 to 3)} = \sum \textit{(Metric Ranking)} / \textit{(Number of Metrics)}$$

Some metrics may not be applicable to all study types (and are identified as *N/A, not ranked/applicable*). These metrics will not be included in the numerator or denominator of the equation above. Also, metrics with serious flaws will be ranked as *critically deficient* (ranking = 4) and the study/endpoint/health effect will then be assigned an overall data quality ranking of 4 in DistillerSR (*uninformative for dose-response*). Study/endpoint/health effect combinations with an overall data quality level of *high*, *medium*, or *low* data quality ranking may be used to quantitatively or qualitatively support the risk evaluations, while studies ranked as *uninformative for dose-response* may be considered during the hazard identification and in the weight of the scientific evidence but will not be considered for dose-response.

Detailed tables showing quality criteria for the metrics are provided in Table_Apx P-4 through Table_Apx P-8 for environmental hazard studies.

Table_Apx P-4. Range of Metric Rankings for Environmental Hazard Studies

Domain Number/ Description	Metric Number/Description	Range of Metric Rankings[a]
1. Test substance	1. Test substance identity	1 to 3
	2. Test substance source	
	3.Test substance purity	
2. Test design	4. Negative controls	
	5. Negative control response	
	6. Randomized allocation	
	7. Experimental system/test media preparation	

Domain Number/ Description	Metric Number/Description	Range of Metric Rankings[a]
3. Exposure characterization	8. Consistency of exposure administration	
	9. Measurement of Test Substance Concentration	
	10. Exposure duration and frequency	
	11. Number of exposure groups and dose spacing	
	12. Testing at or Below Solubility Limit	
4. Test organisms	13. Test organism characteristics	
	14. Acclimatization and pretreatment conditions	
	15. Number of organisms and replicates per group	
	16. Adequacy of test conditions	
5. Outcome assessment	17. Outcome assessment methodology	
	18. Consistency of outcome assessment	
6.Confounding/ variable control	19. Confounding variables in test design and procedures	
	20. Outcomes unrelated to exposure	
7. Data presentation and analysis	21. Statistical methods	
	22. Reporting of data	
	23. Explanation of unexpected outcomes	
	Range of sums (if all metrics evaluated)[b]	23–69
	Range of overall rankings (if all metrics evaluated)[b]	1 to 3 (23/23 to 69/23)
High ≥1 and <1.7	Medium ≥1.7 and <2.3	Low ≥ 2.3 and 3

[a] For the purposes of calculating an overall study ranking, the range of possible metric rankings is 1 (high) to 3 (low) for each metric. No calculations will be conducted if a study receives an "uninformative for dose-response" ranking (= "4") for any metric.
[b] The sum of rankings will differ if some metrics are not ranked (*i.e.*, they are *not applicable*).

Table_Apx P-5. Ranking Example for an Environmental Hazard Study with all Metrics Ranked

Domain	Metric	Metric Ranking
Test substance	1. Test substance identity	2

Domain	Metric	Metric Ranking
	2. Test substance source	3
	3.Test substance purity	2
Test design	4. Negative controls	1
	5. Negative control response	2
	6. Randomized allocation	3
Exposure characterization	7. Experimental system/test media preparation	2
	8. Consistency of exposure administration	1
	9. Measurement of test substance concentration	1
	10. Exposure duration and frequency	1
	11. Number of exposure groups and dose spacing	1
	12. Testing at or Below Solubility Limit	1
Test organisms	13. Test organism characteristics	2
	14. Acclimatization and pretreatment conditions	2
	15. Number of organisms and replicates per group	1
	16. Adequacy of test conditions	1
Outcome assessment	17. Outcome assessment methodology	1
	18. Consistency of outcome assessment	1
Confounding/ variable control	19. Confounding variables in test design and procedures	2
	20. Outcomes unrelated to exposure	2
Data presentation and analysis	21. Statistical methods	2
	22. Reporting of data	1
	23. Explanation of unexpected outcomes	2
	Sum of Ranks	37
	Overall Ranking[a]	High 37/23 = 1.61
High ≥1 and <1.7	Medium ≥1.7 and <2.3	Low ≥2.3 and < 3.0

[a] The cutoffs between categories were defined by calculating the difference between the highest possible ranking of 3 and the lowest possible ranking of 1 (*i.e.*, 3 – 1 = 2) and dividing it into three equal parts (2 ÷ 3 = 0.67). This results in a range of approximately 0.7 for each overall study data quality ranking, which is used to estimate the

Domain	Metric	Metric Ranking
transition points (cut-off values) in the scale between high and medium rankings, and medium and low rankings. These transition points between the ranges of 1 and 3 are determined as follows: • cut-off values between high and medium: 1 + 0.67 = 1.67, rounded to 1.7 (rankings lower than 1.7 are assigned an overall quality level of high); and • cut-off values between medium and low: 1.67 + 0.67 = 2.34, rounded to 2.3 (rankings between 1.7 and lower than 2.3 are assigned an overall quality level of medium).		

Table_Apx P-6. Ranking Example for an Environmental Hazard with Some Metrics Not Rated/Not Applicable

Domain	Metric	Metric Ranking
Test substance	1. Test substance identity	2
	2. Test substance source	3
	3.Test substance purity	2
Test design	4. Negative controls	1
	5. Negative control response	2
	6. Randomized allocation	3
Exposure characterization	7. Experimental system/test media preparation	2
	8. Consistency of exposure administration	1
	9. Measurement of test substance concentration	1
	10. Exposure duration and frequency	1
	11. Number of exposure groups and dose spacing	1
	12. Testing at or Below Solubility Limit	N/A
Test organisms	13. Test organism characteristics	3
	14. Acclimatization and pretreatment conditions	2
	15. Number of organisms and replicates per group	1
	16. Adequacy of test conditions	N/A
Outcome assessment	17. Outcome assessment methodology	1
	18. Consistency of outcome assessment	N/A
Confounding/variable control	19. Confounding variables in test design and procedures	3
	20. Outcomes unrelated to exposure	N/A
Data presentation and analysis	21. Statistical methods	2
	22. Reporting of data	1

Domain	Metric	Metric Ranking
	23. Explanation of unexpected outcomes	N/A
	Sum of ranks	32
	Overall ranking[a]	Medium 32/18 = 1.78
High ≥1 and <1.7	Medium ≥1.7 and <2.3	Low ≥2.3 and < 3.0

[a] The cutoffs between categories were defined by calculating the difference between the highest possible ranking of 3 and the lowest possible ranking of 1 (*i.e.*, 3 – 1 = 2) and dividing it into three equal parts (2 ÷ 3 = 0.67). This results in a range of approximately 0.7 for each overall study data quality ranking, which is used to estimate the transition points (cut-off values) in the scale between high and medium rankings, and medium and low rankings. These transition points between the ranges of 1 and 3 are determined as follows:

- cut-off values between high and medium: 1 + 0.67 = 1.67, rounded to 1.7 (rankings lower than 1.7 are assigned an overall quality level of high); and
- cut-off values between medium and low: 1.67 + 0.67 = 2.34, rounded to 2.3 (rankings between 1.7 and lower than 2.3 are assigned an overall quality level of medium).

P.4.2 Data Quality Criteria

Table_Apx P-7. Serious Flaws that Would Make Environmental Hazard Studies Uninformative

Domain	Metric	Description of Serious Flaw(s) in Data Source
Test substance	Test substance identity	The test substance identity and form (the latter if applicable) cannot be determined from the information provided (*e.g.*, nomenclature was unclear and CASRN or structure were not reported) OR for mixtures, the components and ratios were not characterized, or the chemical of interest is not specifically named as being part of the mixture.
	Test substance source	The test substance was not obtained from a manufacturer OR if synthesized or extracted, analytical verification of the test substance was not conducted.
	Test substance purity	The nature and quantity of reported impurities were such that study results were likely to be due to one or more of the impurities or no information was provided on purity of the chemical.
Test design	Negative controls	A concurrent negative control group was not included or reported OR

Domain	Metric	Description of Serious Flaw(s) in Data Source
		the reported negative control group was not appropriate (*e.g.*, age/weight of organisms differed between control and treated groups).
	Negative control response	The biological responses of the negative control groups were not reported OR there was unacceptable variation in biological responses between control replicates.
	Randomized allocation	The study reported using a biased method to allocate organisms to study groups (*e.g.*, each study group consists of organisms from a single brood and the broods differ among study groups).
Exposure characterization	Experimental system/test media preparation	The physical and chemical properties of the test substance required special considerations for preparation and maintenance of test substance concentrations, but no measures were taken to appropriately prepare test concentrations and/or minimize loss of test substance before and during the exposure and/or the use of such measures was not reported. In addition, the test substance concentrations were not measured, thereby preventing characterization of a concentration-response relationship.
	Consistency of exposure administration	Reported information indicated that critical exposure details were inconsistent across study groups and these differences are considered serious flaws that make the study unusable (*e.g.*, for a poorly soluble mixture, a solvent was used for some study groups while a water-accommodated fraction was used for others).
	Measurement of test substance concentration	For test substances that have poor water solubility or are volatile or unstable in test media: Exposure concentrations were not measured and nominal values are highly uncertain due to the nature of the test substance OR exposure concentrations were measured but analytical methods were not appropriate for the test substance resulting in serious uncertainties in measured concentrations (*e.g.*, recovery and/or repeatability were poor).
	Exposure duration and frequency	The duration of exposure and/or exposure frequency were not reported OR the reported duration of exposure and/or exposure frequency were not suited to the study type and/or outcome(s) of interest (*e.g.*, study intended to assess effects on reproduction did not expose organisms to test

Domain	Metric	Description of Serious Flaw(s) in Data Source
Exposure characterization		substance for an acceptable period of time prior to mating).
	Number of exposure groups and spacing of exposure levels	The number of exposure groups and spacing of exposure levels were not conducive to the purpose of the study (*e.g.*, the range of concentrations tested was either too high or too low to observe a concentration-response relationship, a LOAEC, NOAEC, LC_{50}, or EC_{50} could not be identified) OR no information is provided on the number of exposure groups and spacing of exposure levels.
	Testing at or below solubility limit	All exposure concentrations greatly exceeded the water solubility limit (or dispersibility limit if applicable) and the range of exposure concentrations tested was insufficient to characterize a concentration-response relationship AND/OR the solvent concentration exceeded an appropriate concentration and is likely to have influenced the biological response of the test organisms.
Test organisms	Test organism characteristics	The test organisms were not identified sufficiently or were not appropriate for the evaluation of the specific outcome(s) of interest or were not from an appropriate source (*e.g.*, collected from a polluted field site).
	Acclimatization and pretreatment conditions	There were serious differences in acclimatization acclimatization (*e.g.*, no acclimatization period) and/or pretreatment conditions between control and exposed groups OR organisms were previously exposed to the test substance or other unintended stressors.
	Number of organisms and replicates per group	The number of test organisms and/or replicates was insufficient to characterize toxicological effects and/or provided insufficient power for statistical analysis (*e.g.*, 1–2 organisms/group).
	Adequacy of test conditions	Organism housing and/or environmental conditions and/or food, water, and nutrients and/or biomass loading were not conducive to maintenance of health (*e.g.*, overt signs of handling stress are evident).
Outcome assessment	Outcome assessment methodology	The outcome assessment methodology was not reported OR the reported outcome assessment methodology was not sensitive for the outcome(s) of interest (*e.g.*, in the assessment of reproduction in a chronic daphnid test,

Domain	Metric	Description of Serious Flaw(s) in Data Source
		offspring were not counted and removed until the end of the test, rather than daily).
	Consistency of outcome assessment	There were large inconsistencies in the execution of study protocols for outcome assessment across study groups OR outcome assessments were not adequately reported for meaningful interpretation of results.
Confounding/ variable control	Confounding variables in test design and procedures	The study reported significant differences among the study groups with respect to environmental conditions (*e.g.*, differences in pH unrelated to the test substance) or other non-treatment-related factors and these prevent meaningful interpretation of the results.
	Outcomes unrelated to exposure	One or more study groups experienced serious test organism attrition or outcomes unrelated to exposure (*e.g.*, infection).
Data presentation and analysis	Statistical methods	Statistical methods used were not appropriate (*e.g.*, parametric test for non-normally distributed data) OR statistical analysis was not conducted AND data enabling an independent statistical analysis were not provided.
	Reporting of data	Data presentation was inadequate (*e.g.*, the report does not differentiate among findings in multiple treatment groups) OR major inconsistencies were present in reporting of results.
	Explanation of unexpected outcomes	The occurrence of unexpected outcomes, including, but not limited to, within-study variability and/or variation from historical measures, are considered serious flaws that make the study unusable.
Optimization of the list of serious flaws may occur after pilot calibration exercises.		

Table_Apx P-8. Data Quality Criteria for Environmental Hazard Studies

Data Quality Level	Description	
Domain 1. Test substance		
Metric 1. Test substance identity. Was the test substance identified definitively (*i.e.*, established nomenclature, CASRN, and/or structure reported, including information on the specific form tested (*e.g.*, particle characteristics for solid-state materials, salt or base, valence state, hydration state, isomer, radiolabel) for substances/materials that may vary in form? If test substance is a mixture, were mixture components and ratios characterized?		
High (Ranking = 1)	The test substance (*i.e.*, chemical of interest) was identified definitively (*e.g.*, nomenclature, CASRN, structure) and where applicable, the specific form (*e.g.*, particle characteristics for solid-state materials, salt or base, valence state, hydration state, isomer, radiolabel) was characterized. For mixtures, the amount of each component was characterized (*i.e.*, provided as concentration, ratio or percentage of the mixture or product).	
Medium (Ranking = 2)	The test substance *(i.e.*, chemical of interest) was identified and the specific form was characterized (where applicable). For mixtures, some components and ratios were identified and characterized but at least the chemical of interest has a percentage/concentration reported. There were minor uncertainties (*e.g.*, omission of minor characterization details) that were unlikely to have a substantial impact on results.	
Low (Ranking = 3)	The test substance and form (if applicable) were identified and components and ratios of mixtures were characterized, but there were uncertainties regarding test substance identification or characterization (*e.g.*, concentration range of the chemical of interest provided, omitted details regarding branched or straight chain structure).	
Critically deficient (Ranking = 4)	The test substance identity and form (if applicable) cannot be determined from the information provided (*e.g.*, nomenclature was unclear and CASRN or structure were not reported). OR For mixtures, the components and ratios were not characterized, or the chemical of interest is not specifically named as being part of the mixture. These are serious flaws that make the study unusable.	
Not rated/Not applicable[a]		
Reviewer's Comments	Mixtures should only be used if identified as the chemical of interest (*i.e.*, the chemical being evaluated for the TSCA risk evaluation) or if EPA has identified it as an appropriate analogue for the chemical of interest. *[In the comments section, document rationale for ranking by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	

Data Quality Level	Description	
Metric 2. Test substance source Was the source of the test substance reported, including manufacturer and batch/lot number for materials that may vary in composition? If synthesized or extracted, was the test substance identity verified by analytical methods?		
High (Ranking = 1)	The source of the test substance was reported, as a manufacturer or the production process was specifically identified. The batch/lot number was identified (for materials that may vary in composition), and the chemical identity was either certified by the source in the publication and/or verified by analytical methods (*e.g.*, melting point, chemical analysis, etc.). OR The test substance identity was analytically verified by the performing laboratory.	
Low (Ranking = 3)	The test substance was synthesized or extracted by a source other than the manufacturer (and no production process was identified). OR The source was not reported. AND The test substance identity was NOT analytically verified by the performing laboratory.	
Critically deficient (Ranking = 4)	None.	
Not rated/Not applicable[a]		
Reviewer's Comments	*[In the comments section, document rationale for ranking by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Metric 3. Test substance purity Was the purity or grade (*i.e.*, analytical and technical) of the (discrete and non-discrete) test substance reported and adequate to identify its toxicological effects? Were impurities identified? Were impurities present in quantities that could influence the results?		
High (Ranking = 1)	The test substance purity and composition were such that any observed effects were highly likely to be due to the nominal test substance itself (*e.g.*, highly pure at > 98% or analytical-grade test substance or a formulation of lower purity that contains what are considered to be inert ingredients, such as water). All components, including impurities, residual chemicals, were identified and the chemical of interest was the main component.	
Medium (Ranking = 2)	The nature and quantity of reported impurities are such that study results were not likely to be substantially impacted by the impurities (impurities not known to induce outcome of interest at low levels, impurities are inert or GRAS, etc.). AND	

Data Quality Level	Description	
	All components were provided, but not all were quantified (*e.g.*, only the main chemical of interest).	
Low (Ranking = 3)	Purity and/or grade of test substance were not reported.	
Critically deficient (Ranking = 4)	The nature and quantity of reported impurities were such that study results were likely to be due to one or more of the impurities or no information was provided on purity of the chemical. These are serious flaws that make the study unusable.	
Not rated/Not applicable[a]		
Reviewer's Comments	*[In the comments section, document rationale for ranking by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Domain 2. Test design		
Metric 4. Negative controls Was an appropriate concurrent negative control group tested? If a vehicle/solvent was used, was a vehicle (solvent) control tested in parallel?		
High (Ranking = 1)	Study authors reported using an appropriate concurrent negative control group (*i.e.*, all conditions equal except chemical exposure). There are no limitations that would result in a substantial impact on results.	
Low (Ranking = 3)	Study authors reported using a concurrent negative control (or solvent control) group, but there were minor limitations that are unlikely to have substantial impact on results and at least one vehicle control represents the highest concentration of the vehicle/solvent. OR There are aspects of the reported negative control group that differ between control and treated groups (*e.g.*, different organism used to base age/weight/etc.), however the details are provided so that data could be appropriately normalized.	
Critically deficient (Ranking = 4)	A concurrent negative control group was not included or reported. OR The lack of details is likely to have a substantial impact on results (*e.g.*, age/weight or other aspects of negative control groups differ between control and treated groups), resulting in a substantial impact on results.	
Not rated/Not applicable	In a field study, if a negative control and/or reference site is not reported, please select N/A.	
Reviewer's Comments	*[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional*	

Data Quality Level	Description	
	comments that may highlight study strengths or important elements such as relevance.]	
Metric 5. Negative control response Were the biological responses (*e.g.*, survival, growth, reproduction, etc.) of the negative control group(s) adequate? Is there an unusually high background incidence of the outcome of interest in concurrent controls?		
High (Ranking = 1)	The biological responses (*e.g.*, survival, growth, reproduction, etc.) of the negative control group(s) were adequate (*e.g.*, mortality of control fish ≤10% in an acute test). There are no limitations that would result in a substantial impact on results.	
Medium (Ranking = 2)	The biological responses of the negative control group(s) were reported, but there were minor uncertainties or limitations regarding the biological responses of the negative control group(s) (*e.g.*, differences in outcome between untreated and solvent controls) that are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	The biological response of the negative control groups was not reported.	
Critically deficient (Ranking = 4)	There were deficiencies regarding the control responses that are likely to have a substantial impact on results (*e.g.*, 30% mortality of control fish in an acute test). OR There was unacceptable variation in biological responses between control replicates. These are serious flaws that make the study unusable.	
Not rated/Not applicable	If N/A was selected for metric 4, select N/A for this metric.	
Reviewer's Comments	*[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Metric 6. Randomized allocation Did the study explicitly report randomized allocation of organisms to study groups?		
Medium (Ranking = 2)	The study reported that organisms were randomly allocated into study groups (including the control group). OR Allocation was performed with an unbiased method with a nonrandom component to ensure distribution across groups (*e.g.*, methods that account for body weight to ensure appropriate distribution across groups) that are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	Researchers did not report how organisms were allocated to study groups. OR There were minor limitations in the allocation method that are unlikely to have a substantial impact on results (*e.g.*, for algal studies, reporting of	

Data Quality Level	Description	
	random allocations could be limited. Algal studies should be reported as a low and not unacceptable if randomization details are not available).	
Critically deficient (Ranking = 4)	The study reported using a biased method to allocate organisms to study groups (*e.g.*, each study group consists of organisms from a single brood and the broods differ among study groups). This is a serious flaw that makes the study unusable. OR There were deficiencies regarding the allocation method that are likely to have a substantial impact on results (*e.g.*, allocation by animal number).	
Not rated/Not applicable[a]		
Reviewer's Comments	*[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Domain 3. Exposure characterization		
Metric 7. Experimental system/test media preparation Was the experimental system (*e.g.*, static, semi-static, or flow-through regime) described in adequate detail? Were methods for test media preparation appropriate for the test substance, taking into account its physical and chemical properties (*e.g.*, solubility, volatility) and reactivity (*e.g.*, hydrolysis, biodegradation, bioaccumulation, adsorption)? For reactive, volatile, and/or poorly soluble test substances, were adequate measures taken to prepare and maintain test substance concentrations and minimize loss of test substance before and during the exposure? Based on professional judgment, the reviewer may consider this metric to be Not Rated/Not Applicable for field and mesocosm studies.		
High (Ranking = 1)	The experimental system and methods for preparation of test media were described in adequate detail (*e.g.*, same stock solution was used for all exposure solutions) and appropriately accounted for the physical and chemical properties of the test substance (*e.g.*, use of closed, static systems with minimal headspace for volatile substances, use of water-accommodated fractions for multi-component substances that are only partially soluble in water, use of appropriate test experimental system as to not impact exposure concentration, etc.).	
Medium (Ranking = 2)	The experimental system and/or test media preparation methods were adequately reported but did not completely account for physical and chemical properties (*e.g.*, period between renewals was greater than the half-life of a test substance that degrades in the system, however measured concentrations were provided for the treatment groups before the next renewal). The identified limitations are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	The study provided only limited details on the measures taken to appropriately prepare test concentrations and/or minimize loss of test	

Data Quality Level	Description	
	substance before and during the exposure for reactive, volatile, and/or poorly soluble substances. AND Concentrations of test substance were not measured during the study. Therefore, the deficiencies are likely to have a substantial impact on results.	
Critically deficient (Ranking = 4)	The type of experimental system and/or test media preparation methods were not reported. OR The physical and chemical properties of the test substance required special considerations for preparation and maintenance of test substance concentrations, but no measures were taken to appropriately prepare test concentrations and/or minimize loss of test substance before and during the exposure and/or the use of such measures was not reported. In addition, the test substance concentrations were not measured, thereby preventing characterization of a concentration-response relationship. These are serious flaws that make the study unusable.	
Not rated/not applicable[a b]		
Reviewer's Comments	*[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Metric 8. Consistency of exposure administration Were exposures administered consistently across study groups (*e.g.*, same exposure protocol; same time of day)?		
High (Ranking = 1)	Details of exposure administration were reported, and exposures were administered consistently across study groups. If the study used solvents, the same solvent and solvent concentration were used across replicates and experiment groups for poorly soluble substances. Exposure solution volume or number of molecules of the test substance per container was the same across replicates and groups. There is unlikely any substantial impact on results.	
Medium (Ranking = 2)	Details of exposure administration were reported, but minor inconsistencies in administration of exposures among study groups were identified that are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	Details of exposure administration were reported, but inconsistencies in administration of exposures among study groups are considered deficiencies that are likely to have a substantial impact on results (*e.g.*, differing periods between renewal for an unstable test substance). OR Reporting omissions are likely to have a substantial impact on results.	
Critically deficient	Reported information indicated that critical exposure details were inconsistent across study groups and these differences are considered serious	

Data Quality Level	Description	
(Ranking = 4)	flaws that make the study unusable (*e.g.*, for a poorly soluble mixture, a solvent was used for some study groups while a water-accommodated fraction was used for others).	
Not rated/not applicable[a b]		
Reviewer's Comments	*[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Metric 9. Measurement of test substance concentration If test substance had poor water solubility, was it volatile or unstable in the test system (*e.g.*, hydrolyzed or biodegraded rapidly), was it bioaccumulated by biota, adsorbed to objects in the test system, or was otherwise subjected to factors that were likely to cause test concentrations to change during exposure? Additionally, were the test substance concentrations in the exposure medium measured analytically and were the appropriate analytical methods used (*i.e.*, recovery and repeatability were demonstrated)?		
High (Ranking = 1)	Exposure concentrations were measured using appropriate analytical technologies and methods. Analytical technologies used were highly sensitive (*e.g.*, LC-MS/MS or GC-MS). Analytical methodologies showed recovery, reproducibility, and measured concentrations were reported at the beginning, throughout, and end of the study. Endpoints were based on measured concentrations or analytically verified nominal concentrations.	
Medium (Ranking = 2)	Exposure concentrations were measured and are similar to nominal concentrations, but analytical technologies used were less sensitive (*e.g.*, HLPC) and the analytical methodologies included a measured verification of only once during the study. OR Analytical technologies and methods were not reported while measured concentrations were similar to nominal. OR Exposure concentrations were not measured but based on professional judgment of experimental design and nature of test substance, actual concentrations are likely to be similar to nominal concentrations. These minor uncertainties or limitations are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	Exposure concentrations were not measured, or measurements were not reported. AND Based on professional judgment of experimental design and nature of test substance, actual concentrations cannot be expected to be similar to nominal concentrations. This is likely to have a substantial impact on results.	
Critically deficient (Ranking = 4)	Exposure concentrations were not measured, and nominal values are highly uncertain due to the nature of the test substance. OR	

Data Quality Level	Description	
	Exposure concentrations were measured but analytical methods were not appropriate for the test substance resulting in serious uncertainties in measured concentrations (*e.g.*, recovery and/or repeatability were poor). These are serious flaws that make the study unusable.	
Not rated/not applicable[a,b]		
Reviewer's Comments	*[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Metric 10. Exposure duration and frequency Were the duration of exposure and/or exposure frequency reported and appropriate for the study type and/or outcome(s) of interest?		
High (Ranking = 1)	The duration of exposure and/or exposure frequency were reported and appropriate for the study type and/or outcome(s) of interest (*e.g.*, acute daphnid study of 48-hour duration).	
Medium (Ranking = 2)	Minor limitations in exposure frequency and duration of exposure were identified (*e.g.*, acute daphnid toxicity study of 24-hour duration) but are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	The duration of exposure and/or exposure frequency differed significantly from typical study designs (*e.g.*, acute daphnid toxicity study of 8-hour duration) but are unlikely to have a substantial impact on results.	
Critically deficient (Ranking = 4)	The duration of exposure and/or exposure frequency were not reported. OR The reported duration of exposure and/or exposure frequency were not suited to the study type and/or outcome(s) of interest (*e.g.*, study intended to assess effects on reproduction did not expose organisms to test substance for an acceptable period of time prior to mating). These are serious flaws that make the study unusable, and these deficiencies are likely to have a substantial impact on results.	
Not rated/not applicable[a,b]		
Reviewer's Comments	Refer to test guidelines for recommendations regarding the recommended exposure durations and frequency for specific test organism to evaluate whether the experiment(s) provide sufficient information for a dose response. EPA acknowledges the objectives of an experiment (*e.g.*, limit test vs. full test) will define the exposure durations and frequency. *[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	

Data Quality Level	Description	
Metric 11. Number of exposure groups and spacing of exposure levels Were the number of exposure groups and spacing of exposure levels justified by study authors (*e.g.*, based on range-finding studies) and adequate to address the purpose of the study? Did the range of concentrations/doses tested allow for identification of endpoint values (*i.e.*, LOAEC and NOAEC, LC_{50}, or EC_{50}, depending upon duration of study)?		
High (Ranking = 1)	The number of exposure groups and spacing of exposure levels were justified for a dose response by study authors, adequate to address the purpose of the study (*e.g.*, the selected doses produce a range of responses), and allowed for identification of endpoint values.	
Medium (Ranking = 2)	There were minor limitations regarding the number of exposure groups and/or spacing of exposure levels (*e.g.*, unclear if lowest concentration was low enough), but the number of exposure groups and spacing of exposure levels were adequate to show results relevant to the outcome of interest (*e.g.*, observation of a concentration-response relationship) and the concerns are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	There were deficiencies regarding the number of exposure groups and/or spacing of exposure levels (*e.g.*, narrow spacing between exposure levels with similar responses across groups), which may include the omission of some important details (*e.g.*, not all exposure levels are specified).	
Critically deficient (Ranking = 4)	The number of exposure groups and spacing of exposure levels were not conducive to the purpose of the study (*e.g.*, the range of concentrations tested was either too high or too low to observe a concentration-response relationship, a LOAEC, NOAEC, LC_{50}, or EC_{50} could not be identified). OR No information is provided on the number of exposure groups and spacing of exposure levels. These are serious flaws that make the study unusable, and these are likely to have a substantial impact on results.	
Not rated/not applicable[a,b]	If the study goal was not to have a dose-dependent effect and there is only one exposure concentration with an appropriate solvent concentration (*e.g.*, bioisomerization of HBCD).	
Reviewer's Comments	Refer to test guidelines for recommendations regarding number of exposure groups and spacing of exposure levels for specific test organisms. EPA acknowledges differences with different types of tests (*e.g.*, up/down, limit, and non-traditional test organisms). *[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Metric 12. Testing at or below solubility limit Were exposure concentrations at or below the limit of water solubility (or dispersibility limit if applicable)? If a solvent was used, was the solvent concentration appropriate (*i.e.*, no effects on biological responses were observed in the solvent control and no interactions were expected between the solvent and test substance)?		

Data Quality Level	Description	
High (Ranking = 1)	Exposure concentrations were at or below the water solubility limit (or dispersibility limit if applicable). OR The solvent concentration was appropriate (*i.e.*, no effects on biological responses were observed in the solvent control and no interactions were expected between the solvent and test substance).	
Medium (Ranking = 2)	A subset of the exposure concentrations exceeded the water solubility limit (or dispersibility limit if applicable) but a sufficient range of exposure concentrations was tested to characterize a concentration-response relationship. OR The solvent concentration slightly exceeded an appropriate concentration or was not reported, but the biological response of the solvent control was acceptable, and no interactions are expected between the solvent and test substance. These minor uncertainties or limitations are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	Reporting omissions prevented determination of whether exposure concentrations exceeded the water solubility limit (or dispersibility limit if applicable). OR Both the solvent concentration and biological response of the solvent control were not reported. These deficiencies are likely to have a substantial impact on results.	
Critically deficient (Ranking = 4)	All exposure concentrations greatly exceeded the water solubility limit (or dispersibility limit if applicable) and the range of exposure concentrations tested was insufficient to characterize a concentration-response relationship OR The solvent concentration exceeded an appropriate concentration affected the biological response of the test organisms (*e.g.*, significant difference between the solvent control and negative control). These are serious flaws that make the study unusable.	
Not rated/not applicable	Examples include, but are not limited to, citations on insoluble chemicals (*e.g.*, asbestos), and exposure that is via diet/sediment/soil.	
Reviewer's Comments	*[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	

Data Quality Level	Description	
Domain 4. Test organisms		
Metric 13. Test organism characteristics Were the species, strain, sex, age, size, life stage, and/or embryonic stage of the test organisms reported and appropriate for the evaluation of the specific outcome(s) of interest (*e.g.*, routinely used for similar study types or acceptable rationale provided for selection)? Were the test organisms from a reliable source?		
High (Ranking = 1)	The test organisms were adequately described and were obtained from a reliable source. The test organisms were appropriate for evaluation of the specific outcome(s) of interest (*e.g.*, routinely used for similar study types or acceptable rationale provided for selection).	
Medium (Ranking = 2)	There are minor reservations or uncertainties about the choice of test species, source of test organisms, or characteristics of test organisms (*e.g.*, age, size) that are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	The source (and sex if relevant) of the test animals was not reported. OR There were significant deficiencies or concerns regarding the choice of test species, source of test organisms, or characteristics of test organisms that are likely to have a substantial impact on study results.	
Critically decient (Ranking = 4)	The test organism species were not reported or appropriate for the evaluation of the specific outcome(s) of interest or were not from an appropriate source (*e.g.*, collected from a polluted field site, control organisms used in multiple studies (even as controls again)). There are major reservations or uncertainties (*e.g.*, lack of reporting) about the choice of species and characteristics of test organisms (*e.g.*, not reporting sex if the study is evaluating reproductive endpoints). These are serious flaws that make the study unusable.	
Not rated/not applicable[a,b]		
Reviewer's Comments	*[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Metric 14. Acclimatization and pretreatment conditions Were the test organisms acclimatized to test conditions? Were pretreatment conditions the same for control and exposed groups?		
High (Ranking = 1)	The test organisms were acclimatized to test conditions and all pretreatment conditions were the same for control and exposed organisms, such that the only difference was exposure to test substance.	
Medium (Ranking = 2)	Some acclimatization and/or pretreatment conditions differed between control and exposed populations, but the differences are unlikely to have a substantial impact on results or there are minor uncertainties or limitations in the details provided.	

Data Quality Level	Description	
Low (Ranking = 3)	The study did not report whether test organisms were acclimatized and/or whether pretreatment conditions were the same for control and exposed groups, but biological effects that were observed/not observed were consistent with other studies in the literature.	
Critically deficient (Ranking = 4)	There were serious differences in acclimatization (*e.g.*, for pretreatment conditions between control and exposed groups. OR Organisms were previously exposed to the test substance or other unintended stressors. These are serious flaws that make the study unusable.	
Not rated/not applicable[a,b]		
Reviewer's Comments	*[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Metric 15. Number of organisms and replicates per group Were the numbers of test organisms and replicates sufficient to characterize toxicological effects?		
Medium (Ranking = 2)	The numbers of test organisms and replicates were reported and sufficient to characterize toxicological effects. For example, see EPA Series 850 - Ecological Effects Test Guidelines. Please note, these guidelines should not be interpreted as absolutes.	
Low (Ranking = 3)	The numbers of test organisms and replicates were lower than the typical number used in studies of the same or similar type but sufficient for statistical analysis and sufficient to characterize toxicological effects. OR The number of test organisms and/or replicates was not reported.	
Critically deficient (Ranking = 4)	The number of test organisms and/or replicates was insufficient to characterize toxicological effects and/or provided insufficient power for statistical analysis (*e.g.*, 1-2 organisms/group). These are serious flaws that make the study unusable.	
Not rated/not applicable	Limit tests should receive a N/A for this metric.	
Reviewer's Comments	*[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Metric 16. Adequacy of test conditions Was organism housing, environmental conditions (*e.g.*, temperature, pH, dissolved oxygen, hardness, and salinity), food, water, and nutrients conducive to maintenance of health, both before and during exposure? Was the biomass loading of the organisms in the test system appropriate?		

Data Quality Level	Description	
High (Ranking = 1)	Organism housing, environmental conditions, food, water, and nutrients were conducive to maintenance of health and biomass loading was appropriate. For example, see EPA Series 850 - Ecological Effects Test Guidelines. Please note, guidelines should not be interpreted as absolutes.	
Medium (Ranking = 2)	Minor uncertainties or limitations were identified regarding organism housing, environmental conditions, food, water, nutrients, and/or biomass loading, but these are not likely to have a substantial impact on results.	
Low (Ranking = 3)	Reporting of housing and/or environmental conditions and/or food, water, and nutrients and/or biomass loading was not sufficiently reported to evaluate if adequate and whether differences occurred between control and exposed populations. These deficiencies or omitted details are likely to have a substantial impact on results.	
Critically deficient (Ranking = 4)	There were significant differences between control and exposed groups in organism housing and/or environmental conditions and/or food, water, and nutrients and/or biomass loading. OR Animal husbandry conditions deviated from customary practices in ways likely to impact study results (*e.g.*, injuries and stress due to overcrowding). OR These conditions were not conducive to maintenance of health (*e.g.*, overt signs of handling stress are evident). These are serious flaws that make the study unusable.	
Not rated/not applicable[a]		
Reviewer's Comments	*[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Domain 5. Outcome assessment		
Metric 17. Outcome assessment methodology Did the outcome[c] assessment methodology report the intended outcome(s) of interest? Was the outcome assessment methodology (including endpoints and timing of endpoint assessment) sensitive (*e.g.*, measured endpoints that were able to detect a true biological effect or hazard)?		
High (Ranking = 1)	The outcome assessment methodology addressed or reported the intended outcome(s) of interest and the assessment methodology was sensitive and appropriate for the outcomes(s) of interest.	
Medium (Ranking = 2)	The outcome assessment methodology partially addressed or reported the intended outcomes(s) of interest (*e.g.*, total number of offspring per group reported in the absence of data on fecundity per individual), but these are minor uncertainties or limitations that are unlikely to have a substantial impact on results.	

Data Quality Level	Description	
Low (Ranking = 3)	Significant deficiencies in the reported outcome assessment methodology were identified: Significant deficiencies in the implementation of the reported outcome assessment methodology were identified (*e.g.*, matrix/assay interference, assay yielded anomalous results, etc.). OR The outcome assessment methodology was not clearly reported (including if methods are cited to another publication); it was unclear whether methods were sensitive for the outcome of interest. This is likely to have a substantial impact on results.	
Critically deficient (Ranking = 4)	The reported measurement endpoint(s) or timing were not sensitive for the outcome(s) of interest (*e.g.*, evaluation of endpoints outside the appropriate age range). OR The reported outcome assessment methodology was not sensitive for the outcome(s) of interest. OR The reported outcome assessment methodology was not sensitive for the outcome(s) of interest (*e.g.*, in the assessment of reproduction in a chronic daphnid test, offspring were not counted and removed until the end of the test, rather than daily). These are serious flaws that make the study unusable.	
Not rated/not applicable[a,b]		
Reviewer's Comments	If outcome methods were cited to another publication, please review the relevant methods in the original publication and consider this information as you rate outcome assessment methodology. *[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Metric 18. Consistency of outcome assessment Was the outcome assessment carried out consistently (*i.e.*, using the same protocol) across study groups (*e.g.*, assessment at the same time after initial exposure in all study groups)?		
High (Ranking = 1)	Details of the outcome assessment protocol were reported, and outcomes were assessed consistently across study groups (*e.g.*, at the same time after initial exposure) using the same protocol in all study groups.	
Medium (Ranking = 2)	There were minor differences in the timing of outcome assessment across study groups, or incomplete reporting of minor details of outcome assessment protocol execution, but these uncertainties or limitations are unlikely to have substantial impact on results.	

Data Quality Level	Description	
Low (Ranking = 3)	Details regarding the execution of the study protocol for outcome assessment (*e.g.*, timing of assessment across groups) were confusing, limited, or not reported.	
Critically deficient (Ranking = 4)	There were large inconsistencies in the execution of study protocols for outcome assessment across study groups. These are serious flaws that make the study unusable.	
Not rated/not applicable[a]		
Reviewer's Comments	If outcome methods were cited to another publication, please review the relevant methods in the original publication and consider this information as you rate outcome assessment methodology. *[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Domain 6. Confounding/variable control		
Metric 19. Confounding variables in test design and procedures Were all variables consistent across experimental groups or appropriately controlled for in the analysis, including, but not limited to, size and age of test organisms, environmental conditions (*e.g.*, temperature, pH, and dissolved oxygen), and protective or toxic factors that could mask or enhance effects?		
High (Ranking = 1)	There were no reported differences among the study groups in environmental conditions or other factors that could influence the outcome assessment. There are no limitations that would result in a substantial impact on results.	
Medium (Ranking = 2)	The study reported minor differences among the study groups with respect to environmental conditions or other non-treatment-related factors, but these are unlikely to have a substantial impact on results. OR Data on attrition and/or outcomes unrelated to controlled variables for each study group were not reported because only substantial differences among groups were noted (as indicated by study authors), and it is unlikely there were any substantial impacts on results.	
Low (Ranking = 3)	The study did not provide enough information to allow a comparison of environmental conditions or other non-treatment-related factors across study groups.	
Critically deficient (Ranking = 4)	The study reported significant differences among the study groups with respect to environmental conditions (*e.g.*, differences in pH unrelated to the test substance) or other non-treatment-related factors and these prevent meaningful interpretation of the results. These are serious flaws that make the study unusable.	

Data Quality Level	Description	
Not rated/not applicable[a]		
Reviewer's Comments	*[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Metric 20. Outcomes unrelated to exposure Were there differences among the study groups in test organism attrition or outcomes unrelated to exposure (*e.g.*, infection) that could influence the outcome assessment?		
High (Ranking = 1)	Details regarding test organism attrition and outcomes unrelated to exposure (*e.g.*, infection) were reported for each study group and there were no differences among groups that could influence the outcome assessment.	
Medium (Ranking = 2)	There was no information in the study to suggest differences among groups in animal attrition or health outcomes unrelated to exposure (*e.g.*, infection) that could influence the outcome assessment.	
Low (Ranking = 3)	Reported information indicated that one or more study groups experienced disproportionate test organism attrition or outcomes unrelated to exposure (*e.g.*, infection). However, the remaining doses (concentrations) could be used to determine hazard identification and/or dose (concentration)-response.	
Critically deficient (Ranking = 4)	Reported information indicated that study groups experienced serious test organism attrition (*e.g.*, premature death) or outcomes unrelated to exposure (*e.g.*, infection) that would render the full study (*i.e.*, all dose/concentration groups) unusable.	
Not rated/not applicable[a]		
Reviewer's Comments	*[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Domain 7. Data presentation and analysis		
Metric 21. Statistical methods Were statistical methods clearly described and did the data meet assumptions of the test(s)?		
High (Ranking = 1)	Statistical methods (including any calculations or data transformations) were clearly described or had only minor omissions and were appropriate for dataset(s). OR Sufficient data were provided to conduct an independent statistical analysis.	
Low	Statistical analysis was performed but not described adequately.	

Data Quality Level	Description	
(Ranking = 3)		
Critically deficient (Ranking = 4)	Statistical analysis performed using an inappropriate method (*e.g.*, parametric test for non-normally distributed data). OR Statistical analysis was not conducted. AND Data enabling an independent statistical analysis were not provided. These are serious flaws that make the study unusable.	
Not rated/not applicable	Statistical analysis was not possible (n=1-2) or not necessary or typical (clearly negative findings across all groups; study focused on pathology findings; limit test.	
Reviewer's Comments	*[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Metric 22. Reporting of data Were the data for all outcomes presented? Were data reported for each treatment and control group? Were reported data sufficient to determine values for the endpoint(s) of interest (*e.g.*, LOEC, NOEC, LC_{50}, and EC_{50})?		
High (Ranking = 1)	Data for exposure-related findings were presented for each treatment and control group and were adequate to determine values for the endpoint(s) of interest. Negative findings were reported qualitatively or quantitatively.	
Medium (Ranking = 2)	Data for exposure-related findings were reported for most, but not all, outcomes by treatment and control group and/or data were not reported for outcomes with negative findings, but these minor uncertainties or limitations in outcome reporting are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	Data for exposure-related findings were not shown for each treatment and control group, but results were described in the text. OR Data were only reported for some outcomes (*i.e.*, less than half of the outcomes that were measured). OR Continuous data were presented without measures of variability or sample size of each group.	
Critically deficient (Ranking = 4)	Data presentation was inadequate (*e.g.*, the report does not differentiate among findings in multiple treatment groups). OR Major inconsistencies were present in reporting of results that render the findings uncertain regarding hazard identification or dose-response.	
Not rated/not applicable[a]		

Data Quality Level	Description	
Reviewer's Comments	*[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Metric 23. Explanation of unexpected outcomes Did the author provide a suitable explanation for unexpected outcomes (including excessive within-study variability)?		
High (Ranking = 1)	There were no unexpected outcomes, or unexpected outcomes were satisfactorily explained.	
Medium (Ranking = 2)	Minor uncertainties or limitations were identified in how the study characterized unexpected outcomes, including within-study variability and/or variation from historical measures, but those are not likely to have a substantial impact on results.	
Low (Ranking = 3)	The study did not report any measures of variability (*e.g.*, SE, SD, confidence intervals) and/or insufficient information was provided to determine if excessive variability or unexpected outcomes occurred. This is likely to have a substantial impact on results.	
Critically deficient (Ranking = 4)	The occurrence of unexpected outcomes, including, but not limited to, within-study variability and/or variation from historical measures, are considered serious flaws that make the study unusable.	
Not rated/not applicable[a]		
Reviewer's Comments	*[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	
Domain 8. Other (Apply as Needed)		
Metric		
High (Ranking = 1)		
Medium (Ranking = 2)		
Low (Ranking = 3)		
Critically deficient (Ranking = 4)		
Not Rated/Not Applicable		

Data Quality Level	Description	
Reviewer's Comments	*[In the comments section, document rationale for rating by describing concerns, uncertainties, limitations, and/or deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.]*	

[a] Not applicable is not selected for these metrics.

[b] These metrics should be ranked as *Not Rated/ Not Applicable* if the study cited a secondary literature source for the description of testing methodology; if the study is not classified as uninformative in the initial review, the secondary source will be reviewed during a subsequent evaluation step and the metric will be rated at that time.

[c] Outcome here refers to biological effects measured in an ecotoxicity study; *e.g.*, reproductive toxicity.

Appendix Q DATA QUALITY CRITERIA FOR STUDIES ON ANIMAL AND *IN VITRO* TOXICITY

Q.1 Types of Data Sources

The data quality will be evaluated for a variety of animal and *in vitro* toxicity studies. Table_Apx Q-1 provides examples of types of studies falling into these two broad categories. Because the availability of information varies considerably for different chemicals, it is anticipated that some study types will not be available while others may be identified beyond those listed in Table_Apx Q-1.

Table_Apx Q-1. Types of Animal and *In Vitro* Toxicity Data

Data Category	Type of Data Sources
Animal Toxicity	Oral, dermal, and inhalation routes: lethality, irritation, sensitization, reproduction, fertility, developmental, neurotoxicity, carcinogenicity, systemic toxicity, metabolism, pharmacokinetics, absorption, immunotoxicity, genotoxicity, mutagenicity, endocrine disruption
In Vitro Toxicity Studies	Irritation, corrosion, sensitization, genotoxicity, dermal absorption, phototoxicity, ligand binding, steroidogenesis, developmental, organ toxicity, mechanisms, high throughput, immunotoxicity, pharma/toxicokinetics

Mechanistic evidence is highly heterogeneous and may come from human, animal or *in vitro* toxicity studies. Mechanistic evidence may provide support for biological plausibility and help explain differences in tissue sensitivity, species, gender, life-stage or other factors (U.S. EPA, 2006). Although highly preferred, the availability of a fully elucidated mode of action (MOA) or adverse outcome pathway (AOP) is not required to conduct the human health hazard assessment for a given chemical. EPA plans to prioritize the evaluation of mechanistic evidence instead of evaluating all of the identified evidence upfront. This approach has the advantage of conducting a focused review of those mechanistic studies that are most relevant to the hazards under evaluation. The prioritization approach is generally initiated during the data screening step. For example, the hazard PECOs consider the mechanistic evidence as supplemental information during full-text screening. The assessor can eventually mine the supplemental information when specific questions or hypotheses arise related to the chemical's MOA/AOP.

Moreover, EPA anticipates that some chemicals undergoing TSCA risk evaluations may have physiologically based pharmacokinetic (PBPK) models that could be used for predicting internal dose at a target site as well as interspecies, intraspecies, route-to-route extrapolations or other types of extrapolations. These models should be carefully evaluated to determine if they can be used for risk assessment purposes, however currently there is not existing data quality criteria available for formally evaluating these studies.

Considerations for judging the suitability of a model are separated into two categories: scientific and technical. In summary, the scientific criteria focus on whether the biology, chemistry, and other information available for chemical mode(s) of action (MOA[s]) are appropriately represented by the model structure and equations. Significant to the overall efficiency of this process, the scientific criteria can be judged by reading the publication or report that describes the model, without requiring an evaluation of the computer code. Preliminary technical criteria include the availability of the computer

code and apparent completeness of parameter listing and documentation. The in-depth technical and scientific criteria focus on the accurate implementation of the conceptual model in the computational code, use of correct or biologically consistent parameters in the model, and reproducibility of model results reported in journal publications and other documents.

Although EPA is not including an evaluation strategy for PBPK models in this document, when necessary, it plans to document the model evaluation process based on the Quality Assurance Project Plan for PBPK models (U.S. EPA, 2018e). Also, EPA plans to use the evaluation strategies for animal and *in vitro* toxicity data to assess the quality of mechanistic and pharmacokinetic data supporting the model. EPA may tailor the criteria to capture the inherent characteristics of particular studies that are not captured in the current criteria (*e.g.*, optimization of criteria to evaluate the quality of new approach methodologies or NAMs). Similarly, certain toxicokinetic studies or other specialized investigations may also not be applicable to the existing data quality criteria. For each of these cases, EPA will evaluate and discuss the value of these studies based on expert judgement independent of the data evaluation forms.

Q.2 Data Quality Evaluation Domains

The methods for evaluation of study quality were developed after review of selected references describing existing study quality and risk of bias evaluation tools for toxicity studies (EC, 2018; Cooper et al., 2016; Lynch et al., 2016; Moermond et al., 2016b; Samuel et al., 2016; NTP, 2015a; Hooijmans et al., 2014; Koustas et al., 2014; Kushman et al., 2013; Hartling et al., 2012; Hooijmans et al., 2010). These publications, coupled with professional judgment and experience, informed the identification of domains and metrics for consideration in the evaluation and ranking of study quality. Furthermore, the evaluation tool is intended to address elements of TSCA Science Standards 26(h)(1) through 26(h)(5) that EPA must address during the development process of the risk evaluations.

The data quality of animal toxicity studies and *in vitro* toxicity studies is evaluated by assessing the following seven domains: Test Substance, Test Design, Exposure Characterization, Test Organism/Test Model, Outcome Assessment, Confounding/Variable Control, and Data Presentation and Analysis. The data quality within each domain will be evaluated by assessing unique metrics that pertain to each domain. The domains are defined in Table_Apx Q-2, and further information on evaluation metrics is provided in the subsequent section. Relevance of the studies will also be checked in continuance with relevance identification that began during the data screening process.

Table_Apx Q-2. Data Evaluation Domains and Definitions

Evaluation Domain	Definition
Test Substance	Metrics in this domain evaluate whether the information provided in the study provides a reliable[a] confirmation that the test substance used in a study has the same (or sufficiently similar) identity, purity, and properties as the substance of interest.
Test Design	Metrics in this domain evaluate whether the experimental design enables the study to distinguish the effect of exposure from other factors. This domain includes metrics related to the use of control groups and randomization in allocation to ensure that the effect of exposure is isolated.
Exposure Characterization	Metrics in this domain assess the validity and reliability of methods used to measure or characterize exposure. These metrics evaluate whether exposure to the test substance was characterized using a method(s) that provides valid and reliable results, whether the exposure remained consistent over the duration of the

Evaluation Domain	Definition
	experiment, and whether the exposure levels were appropriate to the outcome of interest.
Test Organism/Test Model	These metrics assess the appropriateness of the population or organism(s), group sizes used in the study (*i.e.*, number of organisms and/or number of replicates per exposure group), and the organism conditions to assess the outcome of interest associated with the exposure of interest.
Outcome Assessment	Metrics in this domain assess the validity and reliability of methods, including sensitivity of methods, that are used to measure or otherwise characterize the outcome(s) of interest.
Confounding/Variable Control	Metrics in this domain assess the potential impact of factors other than exposure that may affect the risk of outcome. The metrics evaluate whether studies identify and account for factors that are related to exposure and independently related to outcome (confounding factors) and whether appropriate experimental or analytical (statistical) methods are used to control for factors unrelated to exposure that may affect the risk of outcome (variable control).
Data Presentation and Analysis	Metrics in this domain assess whether appropriate statistical methods were used and if data for all outcomes are presented.
Other	Metrics in this domain are added as needed to incorporate chemical- or study-specific evaluations.

[a] Reliability is defined as "the inherent property of a study or data, which includes the use of well-founded scientific approaches, the avoidance of bias within the study or data collection design and faithful study or data collection conduct and documentation" (ECHA, 2011a).

Q.3 Data Quality Evaluation Metrics

The data quality evaluation domains are evaluated by assessing unique metrics that have been developed for animal and *in vitro* studies. Metric are binned into data quality ratings of *high*, *medium*, *low*, or *critically deficient* or a subset of these data quality rating levels. Each data quality level is assigned a ranking (*i.e.*, 1 through 4) that is used in the method of assessing the overall quality of the study.

Table_Apx Q-3 lists the data evaluation domains and metrics for animal toxicity studies including metrics that inform risk of bias and types of bias, and Table_Apx Q-4 lists the data evaluation domains and metrics for *in vitro* toxicity studies. Each domain has between 2 and 6 metrics; however, some metrics may not apply to all study types. A general domain for other considerations is available for metrics that are specific to a given test substance or study type.

EPA have modified the metrics used for animal toxicity and *in vitro* toxicity studies and may revise them further as the Agency acquires additional experience with the evaluation tool. Any modifications will be documented.

Table_Apx Q-3. Data Evaluation Domains and Metrics for Animal Toxicity Studies

Evaluation Domain	Number of Metrics	Metrics (Metric Number and Description, Type of Bias)
Test Substance	3	Metric 1: Test Substance Identity
		Metric 2: Test Substance Source
		Metric 3: Test Substance Purity (information bias[a c]) (detection bias[b c])
Test Design	3	Metric 4: Negative and Vehicle Controls (performance bias[b c])
		Metric 5: Positive Controls (information bias[a c])
		Metric 6: Randomized Allocation (selection bias[a b c])
Exposure Characterization	6	Metric 7: Preparation and Storage of Test Substance
		Metric 8: Consistency of Exposure Administration
		Metric 9: Reporting of Doses/Concentrations
		Metric 10: Exposure Frequency and Duration
		Metric 11: Number of Exposure Groups and Dose Spacing
		Metric 12: Exposure Route and Method
Test Organism	3	Metric 13: Test Animal Characteristics
		Metric 14: Adequacy and Consistency of Animal Husbandry Conditions
		Metric 15: Number per Group (missing data bias[a c])
Outcome Assessment	5	Metric 16: Outcome Assessment (information bias[a c]) (detection bias[b c])
		Metric 17: Consistency of Outcome Assessment
		Metric 18: Sampling Adequacy
		Metric 19: Blinding of (selection bias[a c]) (performance bias[b c]) Metric 20: Negative Control Response
Confounding/ Variable Control	2	Metric 21: Confounding Variables in Test Design and Procedures (other bias[b,c])
		Metric 22: Health Outcomes Unrelated to (attrition/exclusion bias[b c])
Data Presentation and Analysis	2	Metric 23: Statistical Methods (information bias[a c]) (other bias[b c])
		Metric 24: Reporting of Data (selective reporting bias[b c])

[a] National Academies of Sciences, Engineering, and Medicine. 2017. *Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals*. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/24758.

[b] National Toxicology Program, Office of Health Assessment and Translation (OHAT). 2015. OHAT Risk of Bias Rating Tool for Human and Animal Studies.

Evaluation Domain	Number of Metrics	Metrics (Metric Number and Description, Type of Bias)
[c] Can be used to assess internal validity/risk of bias.		

Table_Apx Q-4. Data Evaluation Domains and Metrics for *In Vitro* Toxicity Studies

Evaluation Domain	Number of Metrics	Metrics (Metric Number and Description, Type of Bias)
Test Substance	3	Metric 1: Test Substance Identity
		Metric 2: Test Substance Source
		Metric 3: Test Substance Purity
Test Design	4	Metric 4: Negative Controls[a]
		Metric 5: Positive Controls[a]
		Metric 6: Assay Procedures
		Metric 7: Standards for Test
Exposure Characterization	6	Metric 8: Preparation and Storage of Test Substance
		Metric 9: Consistency of Exposure Administration
		Metric 10: Reporting of Doses/Concentrations
		Metric 11: Exposure Duration
		Metric 12: Number of Exposure Groups and Dose Spacing
		Metric 13: Metabolic Activation
Test Model	2	Metric 14: Test Model
		Metric 15: Number per Group
Outcome Assessment	4	Metric 16: Outcome Assessment Methodology
		Metric 17: Consistency of Outcome Assessment
		Metric 18: Sampling Adequacy
		Metric 19: Blinding of Assessors
Confounding/ Variable Control	2	Metric 20: Confounding Variables in Test Design and Procedures
		Metric 21: Outcomes Unrelated to Exposure
Data Presentation and Analysis	4	Metric 22: Data Analysis
		Metric 23: Data Interpretation
		Metric 24: Cytotoxicity Data

Evaluation Domain	Number of Metrics	Metrics (Metric Number and Description, Type of Bias)
		Metric 25: Reporting of Data
[a] These are for the assay performance, not necessarily for the "validation" of extrapolating to a particular apical outcome (*i.e.*, assay performance vs. assay validation).		

Q.4 Ranking Method and Determination of Overall Data Quality Level

This section provides details about the ranking system that will be applied to animal and *in vitro* toxicity studies.

Q.4.1 Calculation of Overall Study Ranking

A data quality ranking is assigned for each relevant metric within each domain. If a publication reports more than one study or target organ and health effect, each study and each target organ and health effect will be evaluated separately. For studies that have only metrics with rankings of *high, medium,* or *low* (1, 2, or 3, respectively), the overall study ranking is determined by summing the individual metric rankings and dividing by the total number of metrics to obtain an overall study ranking between 1 and 3:

$$\textit{Overall Ranking (Range of 1 to 3)} = \sum \textit{(Metric Rankings) / (Number of Metrics)}$$

Some metrics may not be applicable to all study types (and are identified as N/A). These metrics will not be included in the numerator or denominator of the equation above. Also, metrics with serious flaws will be ranked as *critically deficient* (ranking = 4) and the study/target-organ/health effect will then be assigned an overall quality ranking of 4 in DistillerSR (*uninformative for dose-response*). Study /target organ/health effect combinations with an overall quality level of *high, medium, or low* data quality ranking may be used to quantitatively or qualitatively support the risk evaluations while studies rated as *uninformative for dose-response* may be considered during hazard identification and in the weight of the scientific evidence but will not be considered for dose-response.

Detailed tables showing quality criteria for the metrics are provided in Table_Apx Q-5 through Table_Apx Q-10 for animal toxicity and *in vitro* toxicity studies.

Table_Apx Q-5. Range of Metric Rankings for Animal Toxicity Studies

Domain Number/ Description	Metric Number/Description	Range of Metric Rankings[a]
1. Test Substance	1. Test Substance Identity	1 to 3
	2. Test Substance Source	
	3. Test Substance Purity	
2. Test Design	4. Negative and Vehicle Controls	
	5. Positive Controls	
	6. Randomized Allocation	
3. Exposure Characterization	7. Preparation and Storage of Test Substance	
	8. Consistency of Exposure Administration	

Domain Number/ Description	Metric Number/Description	Range of Metric Rankings[a]
	9. Reporting of Doses/Concentrations	1 to 3
	10. Exposure Frequency and Duration	
	11. Number of Exposure Groups and Dose Spacing	
	12. Exposure Route and Method	
4. Test Organisms	13. Test Animal Characteristics	
	14. Adequacy and Consistency of Animal Husbandry Conditions	
	15. Number per Group	
5. Outcome Assessment	16. Outcome Assessment Methodology	
	17. Consistency of Outcome Assessment	
	18. Sampling Adequacy	
	19. Blinding of Assessors	
	20. Negative Control Response	
6. Confounding/ Variable Control	21. Confounding Variables in Test Design and Procedures	
	22. Health Outcomes Unrelated to Exposure	
7. Data Presentation and Analysis	23. Statistical Methods	
	24. Reporting of Data	
	Range of sums (if all metrics ranked)[b]	24 to 72
	Range of overall rankings[c] (if all metrics ranked)	1 to 3 (24/24 to 72/24)

High	Medium	Low
≥1 and <1.7	≥1.7 and <2.3	≥ 2.3 and 3

[a] For the purposes of calculating an overall study ranking, the range of possible metric rankings is 1 (high) to 3 (low) for each metric. No calculations will be conducted if a study receives a "critically deficient" rating (= "4") for any metric.

[b] The sum of rankings will differ if some metrics are not ranked (*i.e.*, they are not applicable).

[c] The cutoffs between categories were defined by calculating the difference between the highest possible ranking of 3 and the lowest possible ranking of 1 (*i.e.*, 3 – 1 = 2) and dividing it into three equal parts (2 ÷ 3 = 0.67). This results in a range of approximately 0.7 for each overall study data quality ranking, which is used to estimate the transition points (cut-off values) in the scale between high and medium rankings, and medium and low rankings. These transition points between the ranges of 1 and 3 are determined as follows:

- cut-off values between high and medium: 1 + 0.67 = 1.67, rounded to 1.7 (rankings lower than 1.7 are assigned an overall quality level of high); and

Domain Number/ Description	Metric Number/Description	Range of Metric Rankings[a]
• cut-off values between medium and low: 1.67 + 0.67 = 2.34, rounded to 2.3 (rankings between 1.7 and lower than 2.3 are assigned an overall quality level of medium).		

Table_Apx Q-6. Range of Metric Rankings for *In Vitro* Toxicity Studies

Domain Number/ Description	Metric Number/Description	Range of Metric Rankings[a]
1. Test Substance	1. Test Substance Identity	1 to 3
	2. Test Substance Source	
	3. Test Substance Purity	
2. Test Design	4. Negative and Vehicle Controls	
	5. Positive Controls	
	6. Assay Procedures	
	7. Standards for Test	
3. Exposure Characterization	8. Preparation and Storage of Test Substance	
	9. Consistency of Exposure Administration	
	10. Reporting of Concentrations	
	11. Exposure Duration	
	12. Number of Exposure Groups and Dose Spacing	
	13. Metabolic Activation	
4. Test model	14. Test Model	
	15. Number per Group	
5. Outcome Assessment	16. Outcome Assessment Methodology	
	17. Consistency of Outcome Assessment	
	18. Sampling Adequacy	
	19. Blinding of Assessors	
6. Confounding/ Variable Control	20. Confounding Variables in Test design and Procedures	
	21. Outcomes Unrelated to Exposure	
	22. Data Analysis	
	23. Data Interpretation	

Domain Number/ Description	Metric Number/Description	Range of Metric Rankings[a]
7. Data Presentation and Analysis	24. Cytotoxicity Data	
	25. Reporting of Data	
	Range of sums (if all metrics ranked)[b]	25 to 75
	Range of overall rankings (if all metrics ranked)	1 to 3 (25/25 to 75/25)

High	Medium	Low
≥1 and <1.7	≥1.7 and <2.3	≥ 2.3 and 3.0

[a] For the purposes of calculating an overall study ranking, the range of possible metric rankings is 1 (high) to 3 (low) for each metric. No calculations will be conducted if a study receives an "critically deficient" rating (= "4") for any metric.
[b] The sum of rankings will differ if some metrics are not ranked (*i.e.*, they are not applicable).

Table_Apx Q-7. Ranking Example for Animal Toxicity Study with All Metrics Ranked

Domain	Metric	Metric Ranking
Test Substance	1. Test Substance Identity	2
	2. Test Substance Source	3
	3. Test Substance Purity	2
Test Design	4. Negative and Vehicle Controls	1
	5. Positive Controls	2
	6. Randomized Allocation	3
Exposure Characterization	7. Preparation and Storage of Test Substance	2
	8. Consistency of Exposure Administration	2
	9. Reporting of Doses/Concentrations	1
	10. Exposure Frequency and Duration	2
	11. Number of Exposure Groups and Dose Spacing	1
	12. Exposure Route and Method	1
Test Organisms	13. Test Animal Characteristics	2
	14. Consistency of Animal Conditions	2
	15. Number per Group	1
	16. Outcome Assessment Methodology	2

Domain	Metric	Metric Ranking
Outcome Assessment	17. Consistency of Outcome Assessment	3
	18. Sampling Adequacy	2
	19. Blinding of Assessors	3
	20. Negative Control Responses	2
Confounding/ Variable Control	21. Confounding Variables in Test Design and Procedures	2
	22. Health Outcomes Unrelated to Exposure	2
Data Presentation and Analysis	23. Statistical Methods	2
	24. Reporting of Data	2
	Sum of Ranks	47
	Overall Ranking	High 47/24 = 1.96

Table_Apx Q-8. Ranking Example for Animal Toxicity Study with Some Metrics Not Applicable

Domain	Metric	Metric Ranking
Test Substance	1. Test Substance Identity	2
	2. Test Substance Source	3
	3. Test Substance Purity	2
Test Design	4. Negative and Vehicle Controls	1
	5. Positive Controls	NR
	6. Randomized Allocation	3
Exposure Characterization	7. Preparation and Storage of Test Substance	2
	8. Consistency of Exposure Administration	NR
	9. Reporting of Doses/Concentrations	1
	10. Exposure Frequency and Duration	2
	11. Number of Exposure Groups and Dose Spacing	1
	12. Exposure Route and Method	1
Test Organisms	13. Test Animal Characteristics	2
	14. Consistency of Animal Conditions	2

Domain	Metric	Metric Ranking
	15. Number per Group	1
Outcome Assessment	16. Outcome Assessment Methodology	2
	17. Consistency of Outcome Assessment	NR
	18. Sampling Adequacy	2
	19. Blinding of Assessors	NR
	20. Negative Control Responses	2
Confounding/ Variable Control	21. Confounding Variables in Test Design and Procedures	2
	22. Health Outcomes Unrelated to Exposure	2
Data Presentation and Analysis	23. Statistical Methods	2
	24. Reporting of Data	2
	Sum of Ranks	37
	Overall Ranking	Medium 37/20 = 1.85

Q.4.2 Animal Toxicity Studies

Table_Apx Q-9. Data Quality Criteria for Animal Toxicity Studies

Data Quality Level	Description	
Domain 1. Test substance		
Metric 1. Test substance identity Was the test substance identified definitively (*i.e.*, established nomenclature, CASRN, and/or structure reported, including information on the specific form tested (*e.g.*, particle characteristics for solid-state materials, salt or base, valence state, hydration state, isomer, radiolabel, etc.) for materials that may vary in form)? If test substance is a mixture, were mixture components and ratios characterized?		
High (Ranking = 1)	The test substance (*i.e.*, chemical of interest) was identified definitively (*i.e.*, nomenclature, CASRN, structure) and, where applicable, the specific form (*e.g.*, particle characteristics for solid-state materials, salt or base, valence state, hydration state, isomer, radiolabel, etc.) was definitively and completely characterized. For mixtures, the components and ratios were characterized (*i.e.*, provided as concentration, ratio or percentage of the mixture or product).	
Medium (Ranking = 2)	The test substance (*i.e.*, chemical of interest) was identified and the specific form was characterized (where applicable). For mixtures, some components and ratios were identified and characterized but at least the chemical of interest has a percentage/concentration reported.	

Data Quality Level	Description	
	There were minor uncertainties (*e.g.*, omission of minor characterization details) that were unlikely to have a substantial impact on results.	
Low (Ranking = 3)	The test substance and form (if applicable) were identified, and components and ratios of mixtures were characterized, but there were uncertainties regarding test substance identification or characterization that are likely to have a substantial impact on results (*e.g.*, no information on isomer (or enantiomer) composition if differences could affect hazard properties, limited particle size information, omitted details regarding branched or straight chain structure).	
Critically Deficient (Ranking = 4)	The test substance identity and form (the latter if applicable) cannot be determined from the information provided (*e.g.*, nomenclature was unclear and CASRN or structure were not reported) **OR** for mixtures, the components and ratios were not characterized.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 2. Test substance source Was the source of the test substance reported, including manufacturer and batch/lot number for materials that may vary in composition? If synthesized or extracted, was test substance identity verified by analytical methods?		
High (Ranking = 1)	The source of the test substance was reported as a manufacturer or the production process was specifically identified. The batch/lot number was identified (for materials that may vary in composition), and the chemical identity was either certified by the source in the publication or could be verified on a manufacturer's website. **OR** The test substance identity was analytically verified by the laboratory that performed the toxicity study.	
Low (Ranking = 3)	The test substance was synthesized or extracted by a source other than the manufacturer (and no production process was identified). **OR** the source was not reported AND The test substance identity was NOT analytically verified by the performing laboratory.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

Data Quality Level	Description	
Metric 3. Test substance purity Was the purity or grade (*i.e.*, analytical, technical) of the test substance reported and adequate to identify its toxicological effects? Were impurities identified? Were impurities present in quantities that could influence the results?		
High (Ranking = 1)	For discrete substances, the test substance purity and composition were such that any observed effects were highly likely to be due to the nominal test substance itself (*e.g.*, highly pure at ≥ 98% or analytical-grade test substance or a formulation of lower purity that contains ingredients considered to be inert, such as water). **AND** All components, including impurities, residual chemicals, were identified and the chemical of interest was the main component.	
Medium (Ranking = 2)	The nature and quantity of reported impurities are such that study results were not likely to be substantially impacted by the impurities (impurities not known to induce outcome of interest at low levels, impurities are inert or GRAS, etc.). Regardless of the nature and purity, for discrete chemicals, the purity of the chemical of interest should be ≥ 70%, unless water is the only impurity.	
Low (Ranking = 3)	Purity and/or grade of test substance were not reported.	
Critically Deficient (Ranking = 4)	The nature and quantity of reported impurities were such that study results were likely to be due to one or more of the impurities. AND/OR For discrete chemicals, purity was < 70%.	
Not Rated/Not Applicable	Do not use for this metric when mixtures are specifically identified (a priori) as the test substance to be evaluated.	
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. Test design		
Metric 4. Negative and vehicle controls Was an appropriate concurrent negative control group included? If a vehicle was used, was the control group exposed to the vehicle? For inhalation and gavage studies, were controls sham-exposed?		
High (Ranking = 1)	Study authors reported using an appropriate, concurrent negative control group with all conditions equal except chemical exposure. If gavage or inhalation study, a vehicle and/or sham-treated control group was included. If each animal serves as its own control, appropriate control timepoints (baseline before exposure) are included and for any endpoints that may be sensitive to treatment protocols (*e.g.*, neurological or stress-related endpoints sensitive to the process of gavage or injection), a vehicle control group is also exposed to the same treatment method.	

Data Quality Level	Description	
Low (Ranking = 3)	Study authors reported using a concurrent negative control group, but all conditions were not equal to those of treated groups For example, study authors acknowledged using a concurrent negative control group, but the control group was not sham treated OR details regarding the negative control group were not reported (*e.g.*, if it is unclear whether the negative control was untreated vs. a vehicle or sham-exposed control), and the lack of details is likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	A concurrent negative control group was not included or controls were not reported OR the reported negative control group was not appropriate (*e.g.*, initial age or weight of animals differed significantly [for example, >20% body weight difference] between control and treated groups). This is a serious flaw that makes the study unusable.	
Not Rated/Not Applicable	Use for assays where no control is required (*e.g.*, acute lethality (LD50, LC50), skin and eye irritation, or DNA binding/adduct assays where measurement of radiolabeled test compound is the outcome).	
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. Positive controls Was an appropriate concurrent positive control group included if necessary based on study type (*e.g.*, when specifically required by OECD guidelines or for certain neurotoxicity studies)? This metric is Not Rated/Not Applicable if positive control was not indicated by study type.		
Medium (Ranking = 2)	When applicable, a concurrent (or historical, if appropriate based on test guidelines) positive control was used and a positive response was observed. If there are minor uncertainties (*e.g.*, minor details regarding control exposure or response were omitted) they are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	When applicable, an appropriate concurrent or historical positive control was used, but there were deficiencies regarding the control exposure or response that are likely to have a substantial impact on results (*e.g.*, the control response was not described) OR no positive control was used, but treatment-related positive responses were observed (demonstrating the laboratory is capable of detecting a positive response in the test)	
Critically Deficient (Ranking = 4)	When applicable, an appropriate positive control (*i.e.*, inducing a positive response) was not used and its omission is a serious flaw that makes the study unusable (*i.e.*, no treatment-related responses were observed, suggesting that the test may not be sensitive enough to detect a response) OR	

Data Quality Level	Description	
	positive controls were run and the lack of positive response indicates that the assay was not capable of detecting a positive response.	
Not Rated/Not Applicable	Select if study protocols or guidelines for the study type do not explicitly require a positive control.	
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. Randomized allocation of animals Did the study explicitly report randomized allocation of animals to study groups?		
Medium (Ranking = 2)	The study reported that animals were randomly allocated into study groups (including the control group) OR Allocation was performed with an unbiased method with a nonrandom component to ensure similar baseline characteristics across groups (*e.g.*, methods that account for body weight to ensure appropriate distribution across groups).	
Low (Ranking = 3)	The study did not report how animals were allocated to study groups, or there were deficiencies regarding the allocation method that are likely to have a substantial impact on results (*e.g.*, allocation by animal number).	
Critically Deficient (Ranking = 4)	The study reported using a biased method to allocate animals to study groups (*e.g.*, judgement of investigator). This is a serious flaw that makes the study unusable.	
Not Rated/Not Applicable	Select this metric for Drosophila or similar test species for which randomization is not practical	
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. Exposure characterization		
Metric 7. Preparation and storage of test substance Did the study characterize the test substance preparation and storage conditions (*e.g.*, test substance stability, homogeneity, mixing temperature, stock concentration, stirring methods, centrifugation/filtration)? Were the frequency of preparation and/or storage conditions appropriate to the test substance stability? For inhalation studies, was the aerosol/vapor generation method appropriate?		
High (Ranking = 1)	The test substance preparation/administration and storage conditions (*e.g.*, test substance stability, homogeneity, mixing temperature, stock concentration, stirring methods, centrifugation/filtration, aerosol/vapor generation method, storage conditions) were reported in detail and appropriate for the test substance (*e.g.*, test substance well-mixed in diet, volatile test substances prepared and stored in sealed containers, same stock solution for all exposure concentrations). For inhalation studies, the method and equipment used to generate the test substance	

Data Quality Level	Description	
	as a gas, vapor, or aerosol were reported and appropriate (*i.e.*, mixing with dry [for water-reactive substances] or humidified air for gases, elevated temperature or gas bubbler for vapor, atomization of nebulization for liquid aerosols, milling or sonication for solid aerosols).	
Medium (Ranking = 2)	The test substance preparation and storage conditions were reported, but there were only minor limitations in the test substance preparation and/or storage conditions were identified (*i.e.*, diet was not mixed fresh daily). For inhalation studies, the method and equipment used to generate the test substance were incomplete or confusing but there is no reason to believe there was an impact on animal exposure. OR There is an omission of details that are unlikely to have a substantial impact on results (*e.g.*, preparation/administration of test substance is described, but storage is not reported however the assay is a short-term study and therefore storage is unlikely to affect results).	
Low (Ranking = 3)	Deficiencies in reporting of test substance preparation and/or storage conditions are likely to have a substantial impact on results (*e.g.*, available information on physical and chemical properties suggested that stability and/or solubility of test substance in vehicle may be poor). For inhalation studies, there is reason to question the validity of the method used for generating the test substance. OR Information on preparation and storage was not reported and lack of details could substantially impact results (*e.g.*, storage for long-term studies, preparation for volatile or low-solubility chemicals). OR For inhalation studies, there was no mention of the method and equipment used to generate the test substance.	
Critically Deficient (Ranking = 4)	Serious flaws reported with test substance preparation and/or storage conditions will have critical impacts on dose/concentration estimates and make the study unusable (*e.g.*, instability of test substance in exposure medium was reported, or there was heterogeneous distribution of test substance in exposure matrix [*e.g.*, aerosol deposition in exposure chamber, insufficient mixing of dietary matrix]). For inhalation studies, the method used for preparation/generation of the test substance is inappropriate (see examples from High bin).	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 8. Consistency of exposure administration		

Data Quality Level	Description	
Were exposures administered consistently across study groups (*e.g.*, same exposure frequency; same time of day; consistent gavage volumes or diet compositions in oral studies; consistent chamber designs, animals/chamber, and comparable particle size characteristics in inhalation studies; consistent application methods and volumes in dermal studies)?		
High (Ranking = 1)	Details of exposure administration were reported and exposures were administered consistently across study groups in a scientifically sound manner (*e.g.*, gavage volume was not excessive (0.1 mL per 10g body weight is reasonable for most vehicles, 0.2mL per 10g body weight is reasonable when the vehicle is water)).	
Medium (Ranking = 2)	Details of exposure administration were reported, but minor limitations in administration of exposures (*e.g.*, small mistakes in dosing) were identified that are unlikely to have a substantial impact on results. OR Details of exposure administration are incompletely reported, but the missing information is unlikely to have a substantial impact on results	
Low (Ranking = 3)	Details of exposure administration were reported, but deficiencies in administration of exposures (*e.g.*, exposed at different times of day) are likely to have a substantial impact on results. OR Details of exposure administration are insufficiently reported (see examples in header) and the missing information is likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	Reported information indicated that exposures were not administered consistently across study groups (*e.g.*, differing particle size, varying exposure frequency), resulting in serious flaws that make the study unusable.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 9. Reporting of doses/concentrations Were doses/concentrations reported without ambiguity (*e.g.*, point estimate in addition to a range, analytical instead of nominal)? Note: Ambiguity also applies to doses/concentrations if values were only reported as points on a figure without numerical values. In oral studies, if doses were not reported, was information reported that enabled dose estimation (*e.g.*, test animal dietary intake and body weight monitoring data in dietary studies)? In inhalation studies, was test substance vapor/aerosol concentration measured analytically along with nominal and target concentrations?		
High (Ranking = 1)	For oral and dermal studies, administered doses/concentrations, or the information to calculate them (*i.e.*, body weight and intake data if doses reported as ppm), were reported without ambiguity (*e.g.*, point estimate instead of range, analytical/measured instead of nominal).	

Data Quality Level	Description	
	For inhalation studies, several specific considerations apply: Analytical, nominal and target chamber concentrations were all reported, with high confidence in the accuracy of the actual concentrations; the range of concentrations within a treatment group did not deviate widely (range should be within ±10% for gases and vapors and within ±20% for liquid and solid aerosols). The analytical method (HPLC, GC, IR spectrophotometry, etc.) used to measure chamber test substance and vehicle concentration was reported and appropriate. Actual chamber measurements using gravimetric filters are acceptable when testing dry aerosols and non-volatile liquid aerosols. The particle size distribution data, mass median aerodynamic diameter (MMAD), and geometric standard deviation were reported for all exposed groups (including vehicle controls, when used).	
Medium (Ranking = 2)	For oral and dermal studies, minor uncertainties in reporting of administered doses/concentrations occurred (*e.g.*, range instead of point estimate OR nominal instead of analytical/measured) but are unlikely to have a substantial impact on results. For inhalation studies, several specific considerations apply: With gases only, actual concentrations were not reported but there is high confidence that the animals were exposed at approximately the reported target concentrations. [There is no comparable medium result for aerosols and vapors if analytical concentrations are not reported.] For inhalation studies (gas, vapor, aerosol), the analytical method used was less than ideal or subject to interference but nevertheless yielded fairly reliable measurements of chamber concentrations. *Particle size distribution data were not reported, but mass median aerodynamic diameter (MMAD), and geometric standard deviation values were reported for all exposed groups (including vehicle controls, when used).*	
Low (Ranking = 3)	For oral and dermal studies, deficiencies in reporting of administered doses/concentrations occurred (*e.g.*, no information on animal body weight or intake were provided) that are likely to have a substantial impact on results. OR The exposure doses/concentrations or amounts of test substance were reported but with substantial ambiguity about precision (*e.g.*, only an estimated range AND only nominal instead of analytical measurements). For inhalation studies, several considerations apply: Using aerosols and vapors, a ranking of low is indicated if actual concentrations are not reported or the analytical method used, such as sampling tubes (*e.g.*, Draeger tubes) provided imprecise measurements. An MMAD or other particle size summary statistic is reported but no geometric standard deviation or particle size distribution data were reported.	

Data Quality Level	Description	
Critically Deficient (Ranking = 4)	The reported exposure levels could not be validated (*e.g.*, lack of food or water intake data for dietary or water exposures in conjunction with evidence of palatability differences, lack of body weight data in conjunction with qualitative evidence for body weight differences across groups, inconsistencies in reporting, etc.). This is a serious flaw that makes the study unusable. OR The exposure doses/concentrations or amounts of test substance were not reported resulting in serious flaws. For inhalation studies, actual concentrations were not reported, AND animal responses (or lack of responses) that indicate exposure problems due to faulty test substance generation were observed. Animals were exposed to an aerosol or particulate but MMAD/particle size data were not reported and no effects were observed at the highest dose.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 10. Exposure frequency and duration Were the exposure frequency (hours/day and days/week) and duration of exposure reported and appropriate for this study type and/or outcome(s) of interest?		
High (Ranking = 1)	The exposure frequency and duration of exposure were reported and appropriate for this study type and/or outcome(s) of interest (*e.g.*, inhalation exposure 6 hours/day, gavage 5 days/week, 2-year duration for cancer bioassays).	
Medium (Ranking = 2)	Minor limitations in exposure frequency and duration of exposure were identified (*e.g.*, inhalation exposure of 4 hours/day instead of 6 hours/day in a repeated exposure study) but are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	The duration of exposure and/or exposure frequency differed significantly from typical study designs (*e.g.*, gavage 1 day/week) and these deficiencies are likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	The exposure frequency or duration of exposure were not reported OR the reported exposure frequency and duration were not suited to the study type and/or outcome(s) of interest (*e.g.*, study length inadequate to evaluate tumorigenicity). These are serious flaws that make the study unusable.	
Not Rated/Not Applicable	Do not select for this metric.	

Data Quality Level	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 11. Number of exposure groups and dose/concentration spacing Were the number of exposure groups and dose/concentration spacing justified by study authors (*e.g.*, based on range-finding studies) and adequate to address the purpose of the study (*e.g.*, to evaluate dose-response relationships, identify points of departure, inform MOA/AOP, etc.)? Fewer dose groups may be acceptable for certain types of studies (*e.g.*, limit study, LD50).		
High (Ranking = 1)	The number of exposure groups and dose/concentration spacing were explicitly justified by study authors (*e.g.*, based on study type, based on data from another study) or despite no justification the selected range sufficiently covered the full range of responses (*i.e.*, both a NOAEL and LOAEL, with at least one dose above the LOAEL).	
Medium (Ranking = 2)	There were minor limitations regarding the number of exposure groups and/or dose/concentration spacing (*e.g.*, unclear if lowest dose was low enough or the highest dose was high enough), but the number of exposure groups and spacing of exposure levels were adequate to show results relevant to the outcome of interest (*e.g.*, observation of a dose-response relationship, selected based on results from another study) and the concerns are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	There were deficiencies regarding the number of exposure groups and/or dose/concentration spacing (*e.g.*, narrow spacing between doses with similar responses across groups, no effects for any outcome even at highest dose unless justified), and these are likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	The number of exposure groups or dosing were not reported (the number of exposure groups would be reported if the doses or concentrations used are provided). OR dose groups and spacing were not relevant for the assessment (*e.g.*, all doses in a developmental toxicity study produced overt maternal toxicity). These are serious flaws that make the study unusable.	
Not Rated/Not Applicable	If the study goal was not to have a dose-dependent effect and there is only one exposure concentration with an appropriate solvent concentration (*e.g.*, bioisomerization of HBCD).	
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 Level	Description	
Metric 12. Exposure route and method Were the route and method of exposure reported and suited to the test substance (*e.g.*, accounting for volatility, injection was not used for assays of liver metabolism, an appropriate vehicle was used when necessary)? For nose-only or head-only inhalation studies, were the animals appropriately acclimated or was the lack of acclimation controlled for?		
High (Ranking = 1)	The route and method of exposure were reported and were suited to the test substance (see above) For inhalation studies, a dynamic, nose-only or head-only chamber was used with greater than 10 or more air changes/hour. While dynamic nose- only (or head-only) studies are generally preferred, dynamic whole-body chambers are acceptable for gases.	
Medium (Ranking = 2)	There were minor limitations regarding the route and method of exposure, but the researchers took appropriate steps to mitigate the problem (*e.g.*, attempted to minimize headspace for volatile compounds in drinking water). These limitations are unlikely to have a substantial impact on results. For inhalation studies, a dynamic whole-body chamber was used for vapors that may condense (assume most will condense at high concentrations unless otherwise stated) or for aerosols, having 10 or more air changes/hour. A medium ranking can also be assigned if the study indicates a dynamic chamber but not the number of air changes.	
Low (Ranking = 3)	There were deficiencies regarding the route and method of exposure that are likely to have a substantial effect on results. Researchers may have attempted to correct the problem, but the success of the mitigating action was unclear. For inhalation studies, there are significant flaws in the design or operation of the inhalation chamber, such as uneven distribution of test substance in a whole-body chamber, having less than 10 air changes/hour in a whole-body chamber, or using a whole-body chamber that is too small for the number and volume of animals exposed. OR Only very minimal if any details about the methods for inhalation exposure administration (as described above) were reported, resulting in significant uncertainty about the true exposure parameters.	
Critically Deficient (Ranking = 4)	The route or method of exposure was not reported OR An inappropriate route or method (*e.g.*, administration of a volatile organic compound via the diet) was used for the test substance without taking steps to correct the problem (*e.g.*, mixing fresh diet). These are serious flaws that makes the study unusable. For inhalation studies, either a static chamber was used, there is no description of the inhalation chamber, or an atypical exposure method was used, such as allowing a container of test substance to evaporate in a room.	

Data Quality Level	Description	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 4. Test animals		
Metric 13. Test animal characteristics Were the test animal species, strain, sex, age, and starting body weight reported? Was the test animal from a commercial source or in-house colony? Was the test species and strain an appropriate animal model for the evaluation of the specific outcome(s) of interest (*e.g.*, routinely used for similar study types)?		
High (Ranking = 1)	The test animal species, strain, sex, age, and starting body weight were reported, and the test animal was obtained from a commercial source or laboratory-maintained colony. The test species and strain were an appropriate animal model for the evaluation of the specific outcome(s) of interest (*e.g.*, routinely used for similar study types).	
Medium (Ranking = 2)	Minor uncertainties in the reporting of test animal characteristics (*e.g.*, age, or starting body weight) are unlikely to have a substantial impact on results. The test animals were obtained from a commercial source or in-house colony, and the test species/strain/sex was an appropriate animal model for the evaluation of the specific outcome(s) of interest (*e.g.*, routinely used for similar study types).	
Low (Ranking = 3)	The source or sex of the test animal was not reported. These deficiencies are likely to have a substantial impact on results. OR the test animal (species, strain, sex, life-stage, source) was not the best choice for the evaluation of the specific outcome(s) of interest (*e.g.*, genetically modified animals, strain was uniquely susceptible or resistant to one or more outcome of interest, high background incidence). Note: Non-wild-type strains may be a suitable choice for mechanistic studies or evaluation of certain targeted outcomes that may be difficult to observe in standard models.	
Critically Deficient (Ranking = 4)	The test animal species was not reported OR the test animal (species, strain, sex, life-stage, source) was not relevant for the evaluation of the specific outcome(s) of interest (*e.g.*, developmental endpoints assessed in adult animals or at the wrong stage of development, species/sex does not contain the organ system of interest). These are serious flaws that make the study unusable.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

Data Quality Level	Description	
Metric 14. Adequacy and consistency of animal husbandry conditions Were all husbandry conditions (*e.g.*, housing, temperature) adequate and the same for control and exposed populations, such that the only difference was exposure to the test substance?		
High (Ranking = 1)	All husbandry conditions were reported (*e.g.*, temperature, humidity, light- dark cycle, diet, water availability) and were adequate and the same for control and exposed populations, such that the only difference was exposure.	
Medium (Ranking = 2)	Most husbandry conditions were reported (see High bin) and were adequate and similar for all groups. Some differences in conditions were identified among groups, but these differences were considered minor uncertainties or limitations that are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	Husbandry conditions were not sufficiently reported to evaluate if husbandry was adequate and whether differences occurred between control and exposed populations. These deficiencies are likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	There were significant differences in husbandry conditions between control and exposed groups (*e.g.*, temperature, humidity, light-dark cycle) OR Animal husbandry conditions deviated from customary practices in ways likely to impact study results (*e.g.*, injuries and stress due to cage overcrowding). These are serious flaws that makes the study unusable.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 15. Number of animals per group Was the number of animals per study group appropriate for the study type and outcome analysis?		
Medium (Ranking = 2)	The number of animals per study group was reported, appropriate for the study type and outcome analysis, and consistent with studies of the same or similar type (*e.g.*, 50/sex/group for rodent cancer bioassay, 10/sex/group for rodent subchronic study, 20 matings/group for reproductive study, etc.).	
Low (Ranking = 3)	The reported number of animals per study group was lower than the typical number used in studies of the same or similar type,, but sufficient for statistical analysis. OR The number of animals per study group was not reported.	
Critically Deficient (Ranking = 4)	The number of animals per study group was insufficient to characterize or observe toxicological effects (*e.g.*, 1–2 animals in each	

Data Quality Level	Description	
	group, highly variable numbers per group) and no effects were observed. These are serious flaws that makes the study unusable.	
Not Rated/Not Applicable	Not applicable for qualitative studies not requiring any statistics that do not have OECD guideline requirements (*e.g.*, certain acute studies such as limit tests).	
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. Outcome assessment		
Metric 16. Outcome assessment methodology. Did the outcome assessment methodology address or report the intended outcome(s) of interest? Was the outcome assessment methodology (including endpoints and timing of assessment) sensitive for the outcome(s) of interest (*e.g.*, measured endpoints that are able to detect a true health effect or hazard)? Note: Outcome, as addressed in this domain, refers to health effects measured in an animal study (*e.g.*, organ-specific toxicity, reproductive and developmental toxicity). Measurement endpoints, as addressed in this domain, refer to physiological changes that are measured to assess the outcome (*e.g.*, serum chemistry, liver weight, and histopathology for liver toxicity; litter size, sex ratio, and malformations for developmental toxicity). Assessment methodology, as addressed in this domain, refers to the techniques used to evaluate the measurement endpoints (*e.g.*, comet assay or γ-H2AX immunohistochemistry for DNA damage).		
High (Ranking = 1)	The outcome assessment methodology addressed the intended outcome(s) of interest AND the assessment methodology was sensitive and appropriate for the outcomes(s) of interest.	
Medium (Ranking = 2)	The outcome assessment methodology partially addressed the intended outcomes(s) of interest (*e.g.*, serum chemistry and organ weight evaluated in the absence of histology), but there are minor uncertainties are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	Significant deficiencies in the reported outcome assessment methodology were identified: Significant deficiencies in the implementation of the reported outcome assessment methodology were identified (*e.g.*, matrix/assay interference, assay yielded anomalous results, etc.) OR The outcome assessment methodology was not clearly reported and it was unclear whether methods were sensitive for the outcome of interest. This is likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	The reported outcome assessment methodology was not sensitive for the outcome(s) of interest. For example: if reported measurement endpoint(s) or timing were not sensitive for the outcome(s) of interest (*e.g.*, evaluation of developmental endpoints such as eye opening outside the appropriate age range, a systemic toxicity study that evaluated only grossly observable endpoints such as clinical signs and mortality) or if the reported outcome assessment methodology was not	

Data Quality Level	Description	
	sensitive for the outcome(s) of interest (*e.g.*, H&E staining for α2u-globulin pathology etc.). These are serious flaws that make the study unusable.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 17. Consistency of outcome assessment. Was the outcome assessment carried out consistently (*i.e.*, using the same protocol) across study groups (*e.g.*, assessment at the same time after initial exposure in all study groups)?		
High (Ranking = 1)	Details of the outcome assessment protocol were reported and outcomes were assessed consistently across study groups (*e.g.*, at the same time after initial exposure) using the same protocol in all study groups.	
Medium (Ranking = 2)	There were minor differences in the timing of outcome assessment across study groups, or incomplete reporting of minor details of outcome assessment protocol execution, but these uncertainties or limitations are unlikely to have substantial impact on results (*e.g.*, blood collected within 2-3 days across groups).	
Low (Ranking = 3)	Details regarding the execution of the study protocol for outcome assessment (*e.g.*, timing of assessment across groups) were confusing, limited, or not reported, and these deficiencies are likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	There were large inconsistencies in the execution of study protocols for outcome assessment across study groups. These are serious flaws that make the study unusable.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 18. Sampling adequacy. Was sampling adequate for the outcome(s) of interest, including experimental unit (*e.g.*, litter vs. individual animal weight), number of evaluations per dose group, and endpoint? Where guidelines are used, refer to information with the appropriate guideline (*e.g.*, OECD TG 421) to evaluate this metric.		
High (Ranking = 1)	Reported information indicates the study used adequate sampling for the outcome(s) of interest (*e.g.*, samples per litter provided for developmental studies; for confirming the effect).	
Medium (Ranking = 2)	Minor limitations were identified in the sampling of the outcome(s) of interest (*e.g.*, histopathology was performed for high-dose group and	

Data Quality Level	Description	
	controls only, and treatment-related changes were observed at the high dose) that are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	Details regarding sampling of outcomes were not reported and this deficiency is likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	Sampling was not adequate for the outcome(s) of interest (*e.g.*, histopathology was performed on exposed groups, but not controls). This is a serious flaw that makes the study unusable.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 19. Blinding of assessors Were investigators assessing subjective outcomes (*i.e.*, those evaluated using human judgment, including functional observational battery, qualitative neurobehavioral endpoints, histopathological re-evaluations) blinded to treatment group? If blinding was not applied, were quality control/quality assurance procedures for endpoint evaluation cited? Note that blinding is not required for initial histopathology review in accordance with Best Practices recommended by the Society of Toxicologic Pathology. This should be considered when rating this metric. Note that blinding is not required for initial histopathology review in accordance with Best Practices recommended by the Society of Toxicologic Pathology. This should be considered when rating this metric (Crissman et al. 2004). This metric is Not Rated/Not Applicable for initial histopathology review or if no subjective outcomes were assessed (*i.e.*, only automated measurements were included and/or human judgment was not applied).		
High (Ranking = 1)	The study explicitly reported that investigators assessing subjective outcomes (*i.e.*, those evaluated using human judgment, including functional observational battery, qualitative neurobehavioral endpoints, histopathological re-evaluations) were blinded to treatment group.	
Medium (Ranking = 2)	The study reported that blinding was not possible, but steps were taken to minimize bias (and this minor uncertainty is unlikely to have a substantial impact on results. Alternately, blinding was not reported; however, lack of blinding is not expected to have a substantial impact on results.	
Low (Ranking = 3)	The study did not report whether assessors were blinded to treatment group for subjective outcomes, and this deficiency is likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	Information in the study report suggested that the assessment of subjective outcomes (*e.g.*, functional observational battery, qualitative neurobehavioral endpoints, histopathological re-evaluations) was performed in a biased fashion (*e.g.*, assessors of subjective outcomes were aware of study groups). This is a serious flaw that makes the study unusable.	

Data Quality Level	Description	
Not Rated/Not Applicable	Select if outcomes are not subjective and blinding of assessors is not necessary (*e.g.*, OECD guidelines for the assay type do not specifically require blinding) or if outcomes were evaluated using automated methods	
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 20. Negative control response Were the biological responses (*e.g.*, histopathology, litter size, pup viability, etc.) of the negative control group(s) adequate? Is there an unusually high background incidence of the outcome of interest in concurrent controls?		
High (Ranking = 1)	The biological responses of the negative control group(s) were adequate (*e.g.*, no/low incidence of outcomes of interest in the study).	
Medium (Ranking = 2)	There were minor uncertainties or limitations regarding the biological responses of the negative control group(s) (*e.g.*, differences in response between untreated and solvent controls) that are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	The biological responses of the negative control group(s) were reported, but there were deficiencies regarding the control responses that are likely to have a substantial impact on results (*e.g.*, elevated incidence of histopathological lesions). OR The biological response of the negative control groups were not reported	
Critically Deficient (Ranking = 4)	There was unacceptable variation in biological responses between control replicates or the incidence of the outcome of interest is very high (*e.g.*, > 30%) in the control group, making it difficult to detect an effect of treatment. These are serious flaws that make the study unusable.	
Not Rated/Not Applicable	Use for assays where no control is required (*e.g.*, acute lethality (LD50, LC50), skin and eye irritation, or DNA binding/adduct assays where measurement of radiolabeled test compound is the outcome).	
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. Confounding/variable control		
Metric 21 Confounding variables in test design and procedures Were there confounding differences among the study groups in animal body weight changes or test substance palatability that could influence the outcome assessment (*e.g.*, did palatability issues lead to dehydration and/or malnourishment)? Did reflex bradypnea (*i.e.*, reduced respiration and reduced test substance exposure) induced by respiratory irritants influence outcome assessment? Were normal signs of reflex bradypnea misinterpreted as neurologic, behavioral, or developmental effects (*e.g.*, hypothermia, lethargy,		

Data Quality Level	Description	
unconsciousness, poor performance in behavioral studies, delayed pup development)? Some study designs may involve surgery (*e.g.*, tracheal installation of the test substance); these should not differ between groups (*e.g.*, use in treated groups but not in controls). There may also be additional items that could lead to confounding that are not covered by other metrics.		
High (Ranking = 1)	The study reported all information to determine whether confounding bias may exist (*e.g.*, body weight changes, respiratory rates with standard deviations) and there were no reported differences among the study groups in food or water intake, respiratory rate (for respiratory irritants), use of surgery or other factors not covered under other metrics that could influence the outcome assessment.	
Medium (Ranking = 2)	Although the study did not report all information to determine confounding, reported information did not identify differences (or identified only minor differences) among study groups in the above listed confounding factors.	
Low (Ranking = 3)	Reported information indicated moderate differences among the study groups with respect to body weight changes, drinking water and/or food consumption due to palatability issues, or respiratory rate due to reflex bradypnea (for respiratory irritants). OR body weight changes, food/water intake and differences in use of surgery were not reported. For respiratory irritants, respiratory rate was not reported.	
Critically Deficient (Ranking = 4)	Marked differences in drinking water/food intake due to palatability issues (≥20% difference from control) could have led to dehydration and/or malnourishment, or reflex bradypnea could have led to decreased oxygenation of the blood and decreased test substance distribution to tissues (for respiratory irritants). These issues could have confounded the assessment of systemic health outcomes.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 22. Health outcomes unrelated to exposure Were there differences among the study groups in animal attrition or health outcomes unrelated to exposure (*e.g.*, infection) that could influence the outcome assessment? Professional judgement should be used to determine whether or not signs of infection would invalidate the study.		
High (Ranking = 1)	Details regarding animal attrition and health outcomes unrelated to exposure (*e.g.*, infection) were reported for each study group and there were no differences among groups that could influence the outcome assessment.	
Medium (Ranking = 2)	There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition or health	

Data Quality Level	Description	
	outcomes unrelated to exposure (*e.g.*, infection) that could influence the outcome assessment. OR There were only minor differences among study groups (*e.g.*, 1–2 animal deaths at a low dose when no deaths occurred at higher doses).	
Low (Ranking = 3)	Reported information indicated that one or more study groups experienced disproportionate animal attrition or health outcomes unrelated to exposure (*e.g.*, infection, dosing errors). However, the remaining doses could be used to determine hazard identification and/or dose-response.	
Critically Deficient (Ranking = 4)	Reported information indicated that study groups experienced serious animal attrition (*e.g.*, premature death) or health outcomes unrelated to exposure (*e.g.*, infection) that would render the full study (*i.e.*, all dose groups) unusable.	
Not Rated/Not Applicable	Do not choose 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 7. Data presentation and analysis		
Metric 23. Statistical methods Were statistical methods clearly described and appropriate for dataset(s) (*e.g.*, parametric test for normally distributed data)?		
High (Ranking = 1)	Statistical methods (including any calculations or data transformations) were clearly described or had only minor omissions and were appropriate for the dataset(s). OR Sufficient data were provided to conduct an independent statistical analysis.	
Low (Ranking = 3)	Statistical analysis was performed but not described adequately.	
Critically Deficient (Ranking = 4)	Statistical analysis was performed using an inappropriate method (Statistical methods used were not appropriate (*e.g.*, parametric test for non-normally distributed data) OR Statistical analysis was not performed AND Data enabling an independent statistical analysis were not provided. These are serious flaws that make the study unusable.	
Not Rated/Not Applicable	Statistical analysis was not possible (n=1-2) or not necessary (clearly negative findings across all groups; Ames assay using 2-fold increase as benchmark; study focused on pathology findings).	

Data Quality Level	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 24. Reporting of data. Were the data for all outcomes presented? Were data reported by exposure group and sex (if applicable), with numbers of animals affected and numbers of animals evaluated (for quantal data) or group means and variance (for continuous data)? If severity rankings were used, was the scoring system clearly articulated?		
High (Ranking = 1)	Data for exposure-related findings were presented for all outcomes by exposure group and sex (if applicable) with quantal and/or continuous presentation and description of severity rankings if applicable. Negative findings were reported qualitatively or quantitatively.	
Medium (Ranking = 2)	Data for exposure-related findings were reported for most, but not all, outcomes by exposure group and sex (if applicable) with quantal and/or continuous presentation and description of severity Rankings if applicable. The minor uncertainties in outcome reporting are unlikely to have substantial impact on results (*e.g.*, outcomes without exposure-related effects are indicated as negative in text).	
Low (Ranking = 3)	Data for exposure-related findings were not shown for each study group, but results were described in the text OR data were only reported for some outcomes (*i.e.*, less than half of the outcomes that were measured). OR continuous data were presented without measures of variability or n/group OR severity rankings were not described.	
Critically Deficient (Ranking = 4)	Data presentation was inadequate (*e.g.*, the report does not differentiate among findings in multiple exposure groups) OR Major inconsistencies were present in reporting of results that render the findings uncertain regarding hazard identification or dose-response.	
Not Rated/Not Applicable	Do not use 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 8. Other (apply as needed)		
Metric:		
High (Ranking = 1)		
Medium (Ranking = 2)		

Data Quality Level	Description	
Low (Ranking = 3)		
Critically Deficient (Ranking = 4)		
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]*	

Q.4.3 *In Vitro* Toxicity Studies

Table_Apx Q-10. Data Quality Criteria for *In Vitro* Toxicity Studies

Data Quality Level	Description	
Domain 1. Test substance		
Metric 1. Test substance identity Was the test substance identified definitively (*i.e.*, established nomenclature, CASRN, physical nature, physical and chemical properties, and/or structure reported, including information on the specific form tested [*e.g.*, salt or base, valence state, isomer, if applicable] for materials that may vary in form)? If test substance was a mixture, were mixture components and ratios characterized?		
High (Ranking = 1)	The test substance (*i.e.*, chemical of interest) was identified definitively (*i.e.*, nomenclature, CASRN, structure) and where applicable the specific form (*e.g.*, particle characteristics for solid state materials, salt or base, valence state, hydration state, isomer, radiolabel, etc.) was definitively and completely characterized. For mixtures, the components and ratios were characterized (*I.e.*, provided as concentration, ratio of percentage of the mixture or	
Medium (Ranking = 2)	The test substance (*i.e.*, chemical of interest) was identified and the specific form was characterized (where applicable). For mixtures, some components and components and ratios were identified and characterized but at least the chemical of interest has a percentage/concentration reported. There were minor uncertainties (*e.g.*, minor characterization details were omitted) that were unlikely to have a substantial impact on results.	

Data Quality Level	Description	
Low (Ranking = 3)	The test substance and form (if applicable) were identified, and components and ratios of mixtures were characterized, but there were uncertainties regarding test substance identification or characterization that are likely to have a substantial impact on the results (*e.g.*, no information on isomer (or enantiomer) composition of differences could affect hazard properties, limited particle size information, omitted details regarding branched or straight chain structure).	
Critically Deficient (Ranking = 4)	The test substance identity and form (the latter if applicable) could not be determined from the information provided (*e.g.*, nomenclature was unclear and CASRN or structure were not reported) OR the components and ratios of mixtures were not characterized.	
Not Rated/Not	Do not select for this metric	
Guidance for reviewers	Mixtures should only be used if identified as the chemical of interest (*i.e.*, the chemical being evaluated for the TSCA risk evaluation) or if EPA has identified it as an appropriate analogue for the chemical of interest.	
Metric 2. Test substance source Was the source of the test substance reported, including manufacturer and batch/lot number for materials that may vary in composition? If synthesized or extracted, was test substance identity verified by analytical methods?		
High (Ranking = 1)	The source of the test substance was reported as a manufacturer or the production process was specifically identified. The batch/lot number was identified (for materials that may vary in composition), and the chemical identity was either certified by the source in the publication or could be verified on a manufacturer's website. OR The test substance identity was analytically verified by the laboratory that performed the toxicity study.	
Low (Ranking = 3)	The test substance was synthesized or extracted by a source other than the manufacturer [and no production process was identified] OR the source was not reported AND The test substance identity was NOT analytically verified by the performing laboratory.	
Not Rated/Not Applicable	Do not select for this metric	

Data Quality Level	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 3. Test substance purity Was the purity or grade (*i.e.*, analytical, technical) of the test substance reported and adequate to identify its toxicological effects? Were impurities identified? Were impurities present in quantities that could influence the results?		
High (Ranking = 1)	For discreet substances, the test substance purity and composition were such that any observed effects were highly likely to be due to the nominal test substance itself (*e.g.*, highly pure at >98% or analytical grade test substance or a formulation of lower purity that contains ingredients considered to be inert, such as water). All components, including impurities and residual chemicals, were identified and the chemical of interest was the main component.	
Medium (Ranking = 2)	The nature and quantity of reported impurities are such that study results were not likely to be substantially impacted by the impurities (impurities not known to induce outcome of interest at low levels, impurities are inert or GRAS, etc.). Regardless of the nature and purity, for discreet chemicals, the purity of the chemical of interest should be > 70%, unless water is the only impurity.	
Low (Ranking = 3)	Purity and/or grade of test substance were not reported.	
Critically Deficient (Ranking = 4)	The nature and quantity of reported impurities were such that study results were likely to be due to one or more of the impurities. This is a serious flaw that makes the study unusable.	
Not Rated/Not	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. Test design		
Metric 4. Negative controls Was a concurrent negative (untreated, sham-treated, and/or vehicle, as necessary) control group included?		
High (Ranking = 1)	Study authors reported using a concurrent negative control group (untreated and/or vehicle, as applicable) in which all conditions equal except exposure to test substance.	

Data Quality Level	Description	
Low (Ranking = 3)	Study authors reported using a concurrent negative control group, but all conditions were not equal to those of treated groups OR Study authors acknowledged using a concurrent negative control group, but details regarding the negative control group were not reported (*e.g.*, if its unclear whether the negative control was untreated vs. a vehicle or sham-exposed control), and the lack of details is likely to have a substantial impact on the results.	
Critically Deficient (Ranking = 4)	A concurrent negative control group was not included, or controls were not reported. OR the reported negative control group was not appropriate (*e.g.*, different cell lines used for controls and test substance exposure).	
Not Rated/Not Applicable	Use for DNA binding/adduct assays, where measurement of radiolabeled test compound is the outcome.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important*	
Guidance for reviewers	Differences in the vehicle used for control and treated groups (ethanol vs. DMSO) may be considered minor limitations (Medium rating). Factors to consider under this metric are those related to treatments of control vs. treated groups; use Metric 20 (confounding variables) to address underlying differences	
Metric 5. Positive controls Was a concurrent positive or proficiency control group included, *if applicable*, based on study type (*e.g.*, when specifically required by OECD guidelines or assay protocol), and was the response appropriate in this group (*e.g.*, induction of positive effect)? This metric is only applicable to studies that require a concurrent positive control (*e.g.*, genotoxicity).		
Medium (Ranking = 2)	When applicable, an appropriate concurrent or historical positive control or proficiency control was used, and a positive response was observed. If there are minor uncertainties (*e.g.*, minor details regarding control exposure or response were omitted or the positive control response was only reported qualitatively) they are unlikely to have a substantial impact on results.	

Data Quality Level	Description	
Low (Ranking = 3)	When applicable, an appropriate concurrent or historical positive control or proficiency control was used, but there were deficiencies regarding the control exposure or response that are likely to have a substantial impact on results (*e.g.*, the control response was not described). OR no positive control was used, but treatment-related positive responses were observed (demonstrating the test is capable of detecting a positive response in the rest).	
Critically Deficient (Ranking = 4)	When applicable an appropriate positive control or proficiency group (*i.e.*, inducing a positive response) was not used and its omission is a serious flaw that makes the study unusable (*i.e.*, no treatment-related responses were observed, suggesting that the test may not be sensitive enough to detect a response) OR positive controls were run, and the lack of positive response indicates that the assay was not capable of detecting a positive response.	
Not Rated/Not	Select if the study type does not explicitly require a positive control	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Guidance for reviewers	*This guidance is generally most applicable to genotoxicity studies but may also be applicable to other endpoints.* *Many OECD genotoxicity guidelines recommend use of a positive control but waive this requirement when the testing laboratory has demonstrated proficiency in the conduct of the test and has established a historical positive control range. For those study types:* • *If the study indicates that the laboratory has demonstrated proficiency in the assay through historical positive controls, rate this metric medium or low as appropriate based on the criteria.* • *If no concurrent or historical positive controls are reported, rate low if the study successfully identified treatment-related effects and rate critically deficient if no positive response was reported in the study (indicating that they assay may not be sufficiently sensitive to detect an effect).*	

Data Quality Level	Description	
Metric 6. Assay procedures Were assay methods and procedures (*e.g.*, test conditions, cell density culture media and volumes, pre- and post- incubation temperatures, humidity, reaction mix, washing/rinsing methods, incubation with amino acids, slide preparation, instrument used and calibration, wavelengths measured) described in detail and applicable to the study type?		
High (Ranking = 1)	Study authors described the methods and procedures (*e.g.*, test conditions, cell density culture media and volumes, pre- and post-incubation temperatures, humidity, reaction mix, washing/rinsing methods, incubation with amino acids, slide preparation, instrument used and calibration, wavelengths measured) used for the test in detail and they were applicable for the study type (*e.g.*, protocol for *in vitro* skin irritation test was reported).	
Medium (Ranking = 2)	Methods and procedures were partially described, but appeared to be appropriate (*e.g.*, reporting that "calculations were used for enumerating viable and mutant cells" in a mammalian cell gene mutation test using *Hprt* and *xprt* genes instead of inclusion of the equations) to the study type, so the omission of details is unlikely to have a substantial impact on results.	
Low (Ranking = 3)	The methods and procedures were not well described or deviated from customary practices (*e.g.*, post-incubation time was not stated in a mammalian cell gene mutation test using *Hprt* and *xprt* genes) and this is likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	Assay methods and procedures were not appropriate for the study type (*e.g.*, *in vitro* skin corrosion protocol used for *in vitro* skin irritation assay).	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Guidance for reviewers	If outcome methods were cited to another publication, please review the relevant methods in the original publication and consider this information as you rate assay procedures.	

Data Quality Level	Description	
Metric 7. Standards for tests For assays with established criteria, were the test validity, acceptability, reliability, and/or QC criteria reported and consistent with current standards and guidelines? For example, for assays that use a standard curve (ELISA, etc), results should be within the range of the standard curve; Other assay-specific standards established in guidelines (*e.g.,* OECD test guidelines) should be met. Example acceptability and QC criteria for an *in vitro* skin corrosion test using the EpiSkin™ (SM) model: Acceptability criteria: negative control OD values between ≥0.6 and ≤1.5, variability of the positive control replicates should be ≤20% of negative control, difference of viability between 2 tissue replicates should not exceed 30% in the range of 20–100% viability and for EDs≥0.3; QC criteria: Only QC-accepted tissue batches having an IC50 range of 1.0–3.0 mg/mL were used.) This metric is generally applicable to studies using reconstructed human cells and may not be applicable to other studies.		
Medium (Ranking = 2)	The test validity, acceptability, reliability, and/or QC criteria were reported and consistent with current standards and guidelines if applicable.[a]	
Critically Deficient (Ranking = 4)	QC criteria were not reported and/or inadequate data were provided to demonstrate validity, acceptability, and reliability of the test when compared with current standards and guidelines.	
Not Rated/Not Applicable	Select if the study type does not have established QC criteria and does not require indicators of test validity, acceptability or reliability	
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. Exposure characterization		
Metric 8. Preparation and storage of test substance Did the study characterize preparation of the test substance and storage conditions? Were the frequency of preparation and/or storage conditions appropriate to the test substance stability and solubility (if applicable)?		
High (Ranking = 1)	The test substance preparation and/or storage conditions (*e.g.,* test substance stability, homogeneity, mixing temperature, stock concentration, stirring methods, centrifugation/filtration, aerosol/vapor generation method, storage conditions) were reported and appropriate for the test substance (*e.g.,* stability in exposure media confirmed, volatile test substances prepared and stored in sealed containers, same stock solution for all exposure concentrations). For genotoxicity tests (*e.g.,* Ames assay), using the pre-incubation method (in sealed tubes with the bacteria, rather than direct plate incorporation) is sufficient to account for test substance volatility.	

Data Quality Level	Description	
Medium (Ranking = 2)	The test substance preparation and storage conditions were reported, but minor limitations in the test substance preparation and/or storage conditions were identified (*e.g.*, test substance formulations were stirred instead of centrifuged for a specific number of rotations per minute) OR There is an omission of details that are unlikely to have a substantial impact on results (*e.g.*, preparation/administration of test substance is described, but storage is not reported however the assay is a short-term study and therefore storage is unlikely to affect results, or the physical	
Low (Ranking = 3)	Deficiencies in reporting of test substance preparation, and/or storage conditions are likely to have a substantial impact on results (*e.g.*, available information on physical and chemical properties suggests that stability and/or solubility of test substance in vehicle or culture media may be poor). OR Information on preparation and storage was not reported and lack of details could substantially impact results (*e.g.*, storage for long-term studies, preparation for volatile or low-solubility chemicals).	
Critically Deficient (Ranking = 4)	Serious flaws reported with test substance preparation and/or storage conditions will have critical impacts on dose/concentration estimates and make the study unusable (*e.g.*, instability of test substance in exposure media, test substance volatilized rapidly from the open containers that were used as test vessels).	
Not Rated/Not Applicable	Do not select for this metric	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 9. Consistency of exposure administration Were exposures administered consistently across study groups (*e.g.*, consistent application methods and volumes, control for evaporation)?		
High (Ranking = 1)	Details of exposure administration were reported, and exposures were administered consistently across study groups in a scientifically sound manner (*e.g.*, consistent application methods and volumes, control for evaporation).	

Data Quality Level	Description	
Medium (Ranking = 2)	Details of exposure administration were reported or inferred from the text, but the minor limitations in administration of exposures (*e.g.*, accidental mistakes in dosing) that were identified are unlikely to have a substantial impact on results. OR Details of exposure administration are incompletely reported, but the missing information is unlikely to have a substantial impact on results.	
Low (Ranking = 3)	Details of exposure administration were reported, but deficiencies in administration of exposures (*e.g.*, non-calibrated instrument used to administer test substance) that were reported or inferred from the text are likely to have a substantial impact on results. OR Details of exposure administration are insufficiently reported, and the missing information is likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	Exposures were not administered consistently across and/or within study groups (*e.g.*, 75 mg/cm2 and 87 mg/cm2 administered to reconstructed corneas replicate 1 and replicate 2, respectively, in *in vitro* eye irritation test) resulting in serious flaws that make the study unusable.	
Not Rated/Not Applicable	Do not select for this metric	
Reviewer's Comments	[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance].	
Metric 10. Reporting of concentrations Were exposure doses/concentrations or amounts of test substance reported without ambiguity (*e.g.*, point estimate instead of range, analytical instead of nominal)? Note: Ambiguity also applies to doses/concentrations if values were only reported as points on a figure without numerical values.		
High (Ranking = 1)	The exposure doses/concentrations or amounts of test substance were reported without ambiguity (*e.g.*, point estimate instead of range, analytical/measured instead of nominal).	
Medium (Ranking = 2)	The exposure doses/concentrations or amounts of test substance were reported with some ambiguity (*e.g.*, range instead of point estimate OR nominal instead of analytical/measured).	
Low (Ranking = 3)	The exposure doses/concentrations or amounts of test substance were reported but with substantial ambiguity about precision (*e.g.*, only an estimated range AND Only nominal instead of analytical measurements).	

Data Quality Level	Description	
Critically Deficient (Ranking = 4)	The exposure doses/concentrations or amounts of test substance were not reported, resulting in serious flaws that make the study unusable.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 11. Exposure duration Was the exposure duration (*e.g.*, minutes, hours, days) reported and appropriate for this study type and/or outcome(s) of interest?		
High (Ranking = 1)	The exposure duration (*e.g.*, min, hours, days) was reported and appropriate for the study type and/or outcome(s) of interest (*e.g.*, 60-minute exposure for reconstructed epidermis in skin irritation test, 48 to 72-hour exposure for bacterial reverse mutation assay).	
Medium (Ranking = 2)	Duration(s) of exposure differed slightly from current standards and guidelines[a] for studies of this type (*e.g.*, 65 minutes for reconstructed epidermis in skin irritation test), but the differences are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	Duration(s) of exposure were not clearly stated (*e.g.*, exposure duration was described only in qualitative terms) OR duration(s) differed significantly from studies of the same or similar types. These deficiencies are likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	No information on exposure duration(s) was reported OR the exposure duration was not appropriate for the study type and/or outcome of interest (*e.g.*, 5 hours for reconstructed epidermis in skin irritation test, 24 hours exposure for bacterial reverse mutation test).	
Not Rated/Not Applicable	Do not select for this metric	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 12. Number of exposure groups and concentrations spacing Were the number of exposure groups and dose/concentration spacing justified by study authors (*e.g.*, based on study type [range-finding study, limit test, cytotoxicity studies]) and adequate to address the purpose of the study (*e.g.*, to evaluate dose-response relationships, inform MOA/AOP)?		

Data Quality Level	Description	
High (Ranking = 1)	The number of exposure groups and dose/concentration spacing were justified by study authors (*e.g.*, based on study type, based on data from another study) and considered adequate to address the purpose of the study (*e.g.*, to evaluate dose-response relationships, inform MOA/AOP, elicit a response).	
Medium (Ranking = 2)	There were minor limitations regarding the number of exposure groups and/or dose/concentration spacing (*e.g.*, unclear if lowest dose was low enough or the highest dose was high enough), but the number of exposure groups and spacing of exposure levels were adequate to show results relevant to the outcome of interest (*e.g.*, observation of a dose-response relationship, selected based on results from another study) and the concerns are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	There were deficiencies regarding the number of exposure groups and/or dose/concentration spacing (*e.g.*, only one bacterial strain exposed to only 2 concentrations of the test substance in bacterial reverse mutation assay, narrow spacing between doses with similar responses across groups, no effects for any outcome even at highest dose unless justified) and these concerns were likely had a substantial impact on interpretation of the results.	
Critically Deficient (Ranking = 4)	The number of exposure groups and dose/concentration spacing were not reported OR the number of exposure groups and dose/concentration spacing were not relevant for the assessment (*e.g.*, all concentrations used in an *in vitro* mammalian cell micronucleus test were cytotoxic).	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*.	
Metric 13. Metabolic activation (if applicable) Were exposures conducted in the presence and absence of a metabolic activation system (usually rat or mouse liver S9, but may also include host-mediated assays or organisms altered to include CYP or GST enzymes), if applicable, for the study type? Were the source, method of preparation, concentration or volume in final culture, and quality control information on the metabolic activation system reported?		
High (Ranking = 1)	Study authors reported exposures were conducted in the presence of metabolic activation; the type and source, method of preparation, composition mix, and concentration or volume in final culture for the metabolic activation system were described.	

Data Quality Level	Description	
Medium (Ranking = 2)	The presence of a commonly used metabolic activation system (*e.g.*, Aroclor-, ethanol-, or phenobarbitial/β-naphthoflavone-induced rat, hamster, or mice liver cells) was reported in the study; however, some details (see High bin) were not described. These omissions are unlikely to have a substantial impact on the results.	
Low (Ranking = 3)	The presence of a metabolic activation system was reported in the study, but the system described was not validated (*e.g.*, rigorous testing to ensure that it suitable for the purpose for which it is used) if novel and not comparable to commonly used systems (described above). OR The presence of a validated or commonly used metabolic activated system was reported in the study, but without any descriptive details (see High bin). OR	
Critically Deficient (Ranking = 4)	Not applicable for this metric.	
Not Rated/Not Applicable	Metabolic activation is not relevant for the assay performed.	
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. Test model		
Metric 14. Test model Were the test models (*e.g.*, cell types or lines, tissue models) and descriptive information (*e.g.*, tissue origin, number of passages, karyotype features, doubling times, donor information, biomarkers) reported? Was the test model from a commercial source or an in-house culture? Was the model routinely used for the outcome of interest (*e.g.*, Chinese hamster ovary cells for micronucleus formation)?		
High (Ranking = 1)	The test model (*e.g.*, cell types or lines, tissue models) and descriptive information (*e.g.*, tissue origin, number of passages, karyotype features, doubling times, donor information, biomarkers) were reported, the test model was obtained from a commercial source or laboratory-maintained culture, and the test model was routinely used for the outcome of interest (*e.g.*, Chinese hamster ovary cells for micronucleus formation).	
Medium (Ranking = 2)	The test model was reported along with limited descriptive information. The test model was routinely used for the outcome of interest. Reporting limitations are unlikely to have a substantial impact on results.	

Data Quality Level	Description	
Low (Ranking = 3)	The test model was reported but no additional details were reported for primary or non-standard immortalized cell lines. OR the test model was not routinely used for the outcome of interest (*e.g.*, feline cell line for micronucleus formation). This is likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	The test model and necessary descriptive information were not reported OR the test model was not appropriate for evaluation of the specific outcome of interest (*e.g.*, bacteria used to evaluate chromosome aberrations).	
Not Rated/Not Applicable	Do not select for this metric	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 15. Number/Replicates per group Was the number of organisms or tissues per study group and/or replicates per study group reported and appropriate for the study type and outcome analysis?		
Medium (Ranking = 2)	The number of organisms or tissues per study group and/or number of replicates per study group were reported and were appropriate for the study type and outcome analysis, and consistent with studies of the same or similar type (*e.g.*, at least two replicates/test substance/3 different exposure times for *in vitro* skin corrosion test, 3 replicates/strain of bacteria in bacterial reverse mutation assay, 3 replicates for most other assays).	
Low (Ranking = 3)	The number of organisms or tissues per study group and/or replicates per study group were reported but were less than recommended by current standards and guidelines or were lower than the typical number used in studies of the same or similar type (*e.g.*, one tissue/test concentration/exposure time for *in vitro* skin corrosion test, either no or only 2 replicates in bacterial reverse mutation assay). This is likely to have an impact on results. OR The number of organisms or tissues per study group and/or replicates per study group were not reported.	
Critically Deficient (Ranking = 4)	The number of organisms or tissues per study group and/or replicates per study group were insufficient to characterize toxicological effects (*e.g.*, one tissue/test concentration/one exposure time for *in vitro* skin corrosion test).	

Data Quality Level	Description	
Not Rated/Not Applicable	Not applicable for qualitative studies that do not require any statistics or that do not have OECD guideline requirements (*e.g.*, irritation test).	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance].*	
Guidance for reviewers	Note similarities and differences to Metric 18. Metric 15 accounts for number of technical/biological replicates, and Metric 18 accounts for statistical sample size within each replicate.	
Domain 5. Outcome assessment		
Metric 16. Outcome assessment methodology Did the outcome assessment methodology address or report the intended outcome(s) of interest? Was the outcome assessment methodology (including nature of endpoints evaluated, measurement technique, and timing of measurement[s]) sensitive for the outcome(s) of interest (*e.g.*, measured endpoints that are able to detect a true effect)?		
High (Ranking = 1)	The outcome assessment methodology addressed the intended outcome(s) of interest AND was sensitive for the outcome(s) of interest.	
Medium (Ranking = 2)	The outcome assessment methodology used partially addressed the intended outcomes(s) of interest (*e.g.*, mutation frequency evaluated in the absence of cytotoxicity in a gene mutation test), but minor uncertainties are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	Significant deficiencies in the implementation of the reported outcome assessment methodology were identified (*e.g.*, matrix/assay interference, assay yielded anomalous results, etc.) OR The outcome assessment methodology was not clearly reported, and it was unclear whether methods were sensitive for the outcome of interest. This is likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	The reported assessment methodology was not sensitive to the outcome(s) of interest. For example, the reported measurement endpoint(s) or timing were not sensitive for the outcome(s) of interest (*e.g.*, cells were evaluated for chromosomal aberrations immediately after exposure to the test substance instead of after post-exposure incubation period). These are serious flaws that make the study	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance].*	

Data Quality Level	Description	
Guidance for reviewers	If outcome assessment methods were cited to another publication, please review the relevant methods in the original publication and consider this information as you rate outcome assessment methodology.	
Metric 17. Consistency of outcome assessment Was the outcome assessment carried out consistently (*i.e.*, using the same protocol) across study groups (*e.g.*, assessment at the same time after initial exposure in all study groups)?		
High (Ranking = 1)	Details of the outcome assessment protocol were reported, and outcomes were assessed consistently across study groups (*e.g.*, at the same time after initial exposure) using the same protocol in all study groups.	
Medium (Ranking = 2)	There were minor differences in the timing of outcome assessment across study groups, or incomplete reporting of minor details of outcome assessment protocol execution, but these uncertainties or limitations are unlikely to have substantial impact on results.	
Low (Ranking = 3)	Details regarding the execution of the study protocol for outcome assessment (*e.g.*, timing of assessment across groups) were confusing, limited, or not reported (or cited to another publication with no description in the paper itself), and these deficiencies are likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	There were large inconsistencies in the execution of study protocols for outcome assessment across study groups. These are serious flaws that make the study unusable.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance].*	
Guidance for reviewers	If outcome methods were cited to another publication., please review the relevant methods in the original publication and consider this information as you rate outcome assessment	
Metric 18. Sampling adequacy Was the reported sampling size adequate for the outcome(s) of interest, including number of evaluations per exposure group, and endpoint (*e.g.*, number of slides/cells/metaphases evaluated per test concentration)?		
High (Ranking = 1)	The study reported adequate sampling for the outcome(s) of interest including number of evaluations per exposure group, and endpoint (*e.g.*, number of slides/cells/metaphases [at least 300 well-spread metaphases scored/concentration in a chromosome aberration test]).	

Data Quality Level	Description	
Medium (Ranking = 2)	Details regarding sampling for the outcome(s) of interest were reported, but minor limitations were identified in the reported sampling of the outcome(s) of interest, but those are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	Details regarding sampling of outcomes were not fully reported and the omissions are likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	Reported sampling was not adequate for the outcome(s) of interest and/or serious uncertainties or limitations were identified in how the study carried out the sampling of the outcome(s) of interest (*e.g.*, replicates from control and test concentrations were evaluated at different times).	
Not Rated/Not Applicable	NA should be used for assays/studies that do not require a certain number of slides/cells/metaphases etc. be sampled for scoring (*i.e.*, mutagenicity assays, mechanistic studies).	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance].*	
Guidance for reviewers	This metric was intended for assays that require a certain number of slides/cells/metaphases etc. be sampled for scoring following exposure (*e.g.*, chromosomal aberrations, micronuclei, sister chromatid exchange, single strand breaks). If sampling details were cited to another publication, please review the relevant methods in the original publication and consider this information as you rate outcome assessment methodology. Note similarities and differences to Metric 18. Metric 15 accounts for number of technical/biological replicates, and Metric 18	
Metric 19. Blinding of assessors Were investigators assessing subjective outcomes (*i.e.*, those evaluated using human judgment) blinded to treatment group? This metric is Not Rated/Not Applicable if no subjective outcomes were assessed (*i.e.*, only automated measurements were included, and human judgment was not applied).		
High (Ranking = 1)	The study explicitly reported that investigators assessing subjective outcomes (*i.e.*, those evaluated using human judgment) were blinded to treatment group.	
Medium (Ranking = 2)	The study reported that blinding was not possible, but steps were taken to minimize bias (*e.g.*, knowledge of study group was restricted to personnel not assessing subjective outcome) and this minor uncertainty is unlikely to have a substantial impact on results.	

Data Quality Level	Description	
Low (Ranking = 3)	The study did not report whether assessors were blinded to treatment group for subjective outcomes, and this deficiency is likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	Information in the study report suggested that the assessment of subjective outcomes was performed in a biased fashion (*e.g.*, assessors of subjective outcomes were aware of study groups).	
Not Rated/Not Applicable	Select if outcomes are not subjective and blinding of assessors is not explicitly required in test guidelines/assay protocols or if outcomes were evaluated using automated methods.	
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. Confounding/variable control		
Metric 20. Confounding variables in test design and procedures Were there confounding differences among the study groups in the size, and/or quality of tissues exposed that could influence the outcome assessment?		
High (Ranking = 1)	There were no differences reported among study group parameters (*e.g.*, test substance lot or batch, strain/batch/ lot number of organisms or models used per group or size, and/or quality of tissues exposed) that could influence the outcome assessment.	
Medium (Ranking = 2)	Minor differences were reported in initial conditions that are unlikely to have a substantial impact on results (*e.g.*, tissues from two different lots were used for *in vitro* skin corrosion test, and QC data were similar for both lots).	
Low (Ranking = 3)	Initial strain/batch/lot number of organisms or models used per group, size, and/or quality of tissues exposed was not reported. These deficiencies are likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	There were significant differences among the study groups with respect to the strain/batch/lot number of organisms or models used per group or size and/or quality of tissues exposed (*e.g.*, initial number of viable bacterial cells were different for each replicate [10^5 cells in replicate 1, 10^8 cell in replicate 2, and 10^3 cells in replicate 3], tissues from two different lots were used for *in vitro* skin corrosion test, but the control batch quality for one lot was outside of the acceptability range).	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance].*	

Data Quality Level	Description	
Guidance for reviewers	Select low if information on initial conditions for each study group and/or replicate is not reported. Use this metric to address underlying differences between control and exposed tissues (*e.g.*, differences in strain, lots number or tissue quality). Differences in treatment across groups (*e.g.*, failure to use a vehicle where appropriate) should be addressed under Metric 4 (negative and vehicle controls).	
Metric 21. Confounding variables in outcomes unrelated to exposure Were there differences among the study groups unrelated to exposure to test substance (*e.g.*, contamination) that could influence the outcome assessment? Did the test material interfere in the assay (*e.g.*, altering fluorescence or absorbance, signal quenching by heavy metals, altering pH, solubility or stability issues)?		
High (Ranking = 1)	There were no reported differences among the study replicates or groups in test model unrelated to exposure (*e.g.*, contamination) and the test substance did not interfere with the assay (*e.g.*, signal quenching by heavy metals).	
Medium (Ranking = 2)	Authors reported that one or more replicates or groups experienced disproportionate outcomes unrelated to exposure (*e.g.*, contamination), but data from the remaining exposure replicates or groups were valid and is unlikely to have a substantial impact on results OR the test material interfered in the assay, but the interference did not cause substantial differences among the groups.	
Low (Ranking = 3)	Data on outcome differences unrelated to exposure were not reported for each study replicate or group and the missing information is likely to have a substantial impact on results. OR Assay interference was present or inferred resulting in large variabilities among the groups.	
Critically Deficient (Ranking = 4)	One or more replicates or groups (*i.e.*, negative and positive controls experienced disproportionate growth or reduction in growth unrelated to exposure (*e.g.*, contamination), or assay interference occurred such that no outcomes could be assessed.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance].*	
Guidance for reviewers	Select medium if information is not reported and only choose high for the studies which mention that the strain/cells were free of fungal contamination etc.	

Data Quality Level	Description	
Domain 7. Data presentation and analysis		
Metric 22. Data analysis Were statistical methods, calculations methods, and/or data manipulation clearly described and appropriate for dataset(s)?		
High (Ranking = 1)	Statistical methods (including any calculations or data transformations) were clearly described or had only minor omissions and were appropriate for the dataset(s). OR Sufficient data were provided to conduct an independent statistical analysis.	
Low (Ranking = 3)	Statistical analysis was performed but not described adequately to understand what was performed or whether it was properly	
Critically Deficient (Ranking = 4)	Statistical analysis was performed using an inappropriate method (*e.g.*, parametric test for non-normally distributed data) OR Statistical analysis was not performed. AND Data enabling an independent statistical analysis were not provided. These are serious flaws that make the study unusable.	
Not Rated/Not Applicable	Statistical analysis was not possible (n=1-2) or not necessary (clearly negative findings across all groups; Ames assay using 2-fold increase as benchmark).	
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 23. Data interpretation Were the scoring and/or evaluation criteria reported and consistent with standards and guidelines?		
High (Ranking = 1)	Study authors reported the ranking and/or evaluation criteria (*e.g.*, for determining negative, positive, and equivocal outcomes) for the test and these were consistent with established practices.[a]	
Medium (Ranking = 2)	Ranking and/or evaluation criteria were partially reported (*e.g.*, evaluation criteria were reported following 3- and 60-minute exposures, but not for 240-minute exposure in *in vitro* skin corrosion test), but the omissions are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	Ranking and/or evaluation criteria were not reported, and the omissions are likely to have a substantial impact on interpretation of the results.	
Critically Deficient (Ranking = 4)	The reported ranking and/or evaluation criteria were inconsistent with established practices. resulting in the interpretation of data results that are seriously flawed.	

Data Quality Level	Description	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance].*	
Metric 24. Cytotoxicity data Were cytotoxicity endpoints defined, if necessitated by study type, and were methods for measuring cytotoxicity described and commonly used for assessment?[a]		
High (Ranking = 1)	Study authors defined cytotoxicity endpoints (*e.g.*, cell integrity, apoptosis, necrosis, color induction, cell viability, mitotic index, reduction in bacterial background lawn) and the methods for measuring cytotoxicity were clearly described and commonly used for assessment.	
Medium (Ranking = 2)	Cytotoxicity endpoints were defined, and methods of measurement were partially reported, but the omissions are unlikely to have substantial impact on study results.	
Low (Ranking = 3)	Cytotoxicity endpoints were defined, but the methods of measurements were not fully described or reported, and the omissions are likely to have a substantial impact on the study results. OR It could not be determined that cytotoxicity was accounted for in the interpretation of study results for non-Guideline assays in which cytotoxicity could be reasonably expected to have a confounding influence on results (*e.g.*, assays for cell proliferation, differentiation, or dysfunction, or some genotoxicity tests).	
Critically Deficient (Ranking = 4)	For genotoxicity or other cell-based assays with cytotoxicity required by Guideline methods, AND Genotoxicity/other outcomes (*e.g.*, cell proliferation, differentiation, or dysfunction) observed at higher doses, cytotoxicity endpoints were not defined, methods were not described, and it could not be determined that cytotoxicity was accounted for in the interpretation of study results.	
Not Rated/Not Applicable	Use for studies that do not require a separate cytotoxicity test for interpretation of results (*e.g.*, *ex vivo*, not a cell-based assay).	
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 25. Reporting of data Were the data for all outcomes presented? Were data reported by exposure group?		

Data Quality Level	Description	
High (Ranking = 1)	Data for exposure-related findings were presented for all outcomes by exposure group. Negative findings were reported qualitatively or quantitatively.	
Medium (Ranking = 2)	Data for exposure-related findings were reported for most, but not all, outcomes by exposure group (*e.g.*, sensitization percentages reported in the absence of incidence data). The minor uncertainties in outcome reporting are unlikely to have substantial impact on results. (*e.g.*, outcomes without exposure-related effects are indicated as negative in text).	
Low (Ranking = 3)	Data for exposure-related findings were not shown for each study group, but results were described in the text, OR Data were only reported for some outcomes, OR Continuous data were presented without measures of variability or n/group.	
Critically Deficient (Ranking = 4)	Data presentation was inadequate (*e.g.*, the report does not differentiate among findings in multiple exposure groups), OR Major inconsistencies were present in reporting of results that render the findings uncertain regarding hazard identification or dose-response.	
Not Rated/Not Applicable	Do not use 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].*	
Guidance for reviewers	The reporting of data in studies conducted by IBT during 1960-1978 is considered critically deficient due to concerns about the integrity of the lab (*i.e.*, discrepancies between raw data and study report, and gross deficiencies in study conduct were identified during an inspection by the FDA in 1976 and a follow-up audit by EPA and in collaboration with the Canadian Health and Welfare Department).	
Domain 8. Other (apply as needed)		
Metric:		
High (Ranking = 1)		
Medium (Ranking = 2)		
Low (Ranking = 3)		

Data Quality Level	Description	
Critically Deficient (Ranking = 4)		
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].*	
[a] For comparison purposes, current standards and guidelines may be reviewed in the Center for Food Safety and Applied Nutrition's Redbook 2000.		

Appendix R DATA QUALITY CRITERIA FOR EPIDEMIOLOGICAL STUDIES

R.1 Types of Data Sources

The data quality will be evaluated for the epidemiological studies listed in Table_Apx R-1.

Table_Apx R-1. Types of Epidemiological Studies

Data Category	Types of Data Sources
Epidemiological Studies	Controlled exposure, cohort, case-control, cross-sectional, case-crossover

R.2 Data Quality Evaluation Domains

The data sources will be evaluated against the following six data quality evaluation domains: study participation, exposure characterization, outcome assessment, potential confounding/variability control, analysis, and other. These domains, as defined in Table_Apx R-2, address elements of TSCA Science Standards 26(h)(1) through 26(h)(5).

Table_Apx R-2. Data Evaluation Domains and Definitions

Evaluation Domain	Definition
Study Participation	Study design elements characterizing the selection of participants in or out of the study (or analysis sample), which influence whether the exposure-outcome distribution among participants is representative of the exposure-outcome distribution in the overall population of eligible persons.
Exposure Characterization	Evaluation of exposure assessment methodology that includes consideration of methodological quality, sensitivity, and validation of the methods used, degree of variation in participants, and an established time order between exposure and outcome.
Outcome Assessment	Evaluation of outcome (effect) assessment methodology that includes consideration of diagnostic methods, training of interviewers, data sources including registries, blinding to exposure status or level, and reporting of all results.
Potential Confounding/ Variability Control	Valid and reliable methods to reduce research-specific bias, including standardization, matching, adjustment in multivariate models, and stratification. This includes control of potential co-exposures when it is known that there is potential for co-exposure to occur and the co-exposure could influence the outcome of interest.
Analysis	Appropriate study design chosen for the research question with evaluation of statistical power, reproducibility, and statistical or modeling approaches.
Other/Consideration for Biomarker Selection and Measurement	Measures of biomarker (exposure and/or effect) data reliability. This includes but is not limited to evaluations of storage, stability and contamination of samples, validity, and limits of detection of methods, method requirements, inclusion of matrix-specific considerations, and relationship of biomarker with external exposure, internal dose, or target dose.

R.3 Data Quality Evaluation Metrics

The data quality evaluation domains are evaluated by assessing two to seven unique metrics. Each metric is binned into a data quality level of *high*, *medium*, *low*, or *critically deficient*. Each data quality ranking is assigned a value (*i.e.*, 1 through 4) that is used in the method of assessing the overall quality of the study.

A summary of the number of metrics and metric name for each data type is provided in Table_Apx R-3. Each domain has between two and seven metrics. Metrics may be modified as EPA acquires experience with the evaluation tool to support fit-for-purpose TSCA risk evaluations. Any modifications will be documented.

Detailed tables showing data quality ranking specifications of the metrics are provided in Table_Apx R-4 through Table_Apx R-6 for each data type, including separate tables that summarize serious flaws that would make the data source *uninformative for dose-response* for the hazard assessment.

Table_Apx R-3. Summary of Metrics for the Seven Data Types

Evaluation Domain	Number of Metrics Overall	Metrics (Metric Number and Description)
Study Participation	3	Metric 1: Participant Selection Metric 2: Attrition Metric 3: Comparison Group
Exposure Characterization	3	Metric 4: Measurement of Exposure Metric 5: Exposure Levels Metric 6: Temporality
Outcome Assessment	2	Metric 7: Outcome Measurement or Characterization, Metric 8: Reporting Bias
Potential Confounding/ Variability Control	3	Metric 9: Covariate Adjustment Metric 10: Covariate Characterization Metric 11: Co-exposure Confounding/Moderation/Mediation
Analysis	4	Metric 12: Study Design and Methods Metric 13: Statistical Power Metric 14: Reproducibility of Analyses Metric 15: Statistical Models
Other/Consideration for Biomarker Selection and Measurement	7	Metric 16: Use of Biomarker of Exposure Metric 17: Effect Biomarker Metric 18: Method Sensitivity Metric 19: Biomarker Stability Metric 20: Sample Contamination Metric 21: Method Requirements Metric 22: Matrix Adjustment

R.4 Ranking Method and Determination of Overall Data Quality Level

A ranking system is used to assign the overall quality of the data source, as discussed in Section 5. Each data source is assigned an overall qualitative data quality level of *high*, *medium*, *low*, or *uninformative for dose-response*. This section provides details about the ranking system that will be applied to epidemiologic studies.

R.4.1 Determination of Overall Study Ranking

A data quality ranking is assigned for each relevant metric within each domain. If a publication reports more than one study or target organ and health effect, each study and each target organ and health effect will be evaluated separately. For studies that have only metrics with rankings of *high, medium,* or *low* (1, 2, or 3, respectively), the overall study ranking is determined by summing the individual metric rankings and dividing by the total number of metrics to obtain an overall study ranking between 1 and 3:

$$\textit{Overall Ranking (Range of 1 to 3)} = \sum \textit{(Metric Rankings)} / \textit{(Number of Metrics)}$$

Some metrics may not be applicable to all study types (and are identified as N/A). These metrics will not be included in the numerator or denominator of the equation above. Also, metrics with serious flaws will be ranked as critically deficient (ranking = 4) and the study/target-organ/health effect will then be assigned an overall quality ranking of 4 in DistillerSR (*uninformative for dose-response*). Study/target organ/health effect combinations with an overall quality level of *high, medium, or low* data quality ranking may be used to quantitatively or qualitatively support the risk evaluations while studies rated as *uninformative for dose-response* may be considered during hazard identification and in the weight of the scientific evidence but will not be considered for dose-response.

Detailed tables showing quality criteria for the metrics are provided in Table_Apx R-7 and Table_Apx R-8.

Table_Apx R-4. Summary of Domains, Metrics, and Range of Metric Rankings for Studies with Biomarkers

Domain	Metric	Range of Metric Rankings
Study Participation	Participant Selection	1 to 3
	Attrition	1 to 3
	Comparison Group	1 to 3
Exposure Characterization	Measurement of Exposure	1 to 3
	Exposure Levels	1 to 3
	Temporality	1 to 3
Outcome Assessment	Outcome Measurement or Characterization	1 to 3
	Reporting Bias	1 to 3
Potential Confounding/ Variable Control	Covariate Adjustment	1 to 3
	Covariate Characterization	1 to 3

Domain	Metric	Range of Metric Rankings
	Co-exposure Confounding/Moderation/Mediation	1 to 3
Analysis	Study Design and Methods	1 to 3
	Statistical Power	1 to 3
	Reproducibility of Analyses	1 to 3
	Statistical Models	1 to 3
Other (if applicable) Considerations for Biomarker Selection and Measurement (Lakind et al., 2014)	Use of Biomarker of Exposure	1 to 3
	Effect Biomarker	1 to 3
	Method Sensitivity	1 to 3
	Biomarker Stability	1 to 3
	Sample Contamination	1 to 3
	Method Requirements	1 to 3
	Matrix Adjustment	1 to 3
Range of sums (if all metrics ranked)[b]		22 to 66
Range of overall rankings[c] (if all metrics ranked)		1 to 3 (22/22 to 66/24)

High	Medium	Low
≥1 and <1.7	≥1.7 and <2.3	≥ 2.3 and 3

[a] For the purposes of calculating an overall study ranking, the range of possible metric rankings is 1 (high) to 3 (low) for each metric. No calculations will be conducted if a study receives an "critically deficient" rating (= "4") for any metric.

[b] The sum of rankings will differ if some metrics are not ranked (*i.e.,* they are not applicable).

[c] The cutoffs between categories were defined by calculating the difference between the highest possible ranking of 3 and the lowest possible ranking of 1 (*i.e.,* 3 – 1 = 2) and dividing it into three equal parts (2 ÷ 3 = 0.67). This results in a range of approximately 0.7 for each overall study data quality ranking, which is used to estimate the transition points (cut-off values) in the scale between high and medium rankings, and medium and low rankings. These transition points between the ranges of 1 and 3 are determined as follows:

- cut-off values between high and medium: 1 + 0.67 = 1.67, rounded to 1.7 (rankings lower than 1.7 are assigned an overall quality level of high); and
- cut-off values between medium and low: 1.67 + 0.67 = 2.34, rounded to 2.3 (rankings between 1.7 and lower than 2.3 are assigned an overall quality level of medium).

Table_Apx R-5. Summary of Domains, Metrics, and Range of Metric Rankings for Studies without Biomarkers

Domain	Metric	Range of Metric Rankings
Study Participation	Participant Selection	1 to 3
	Attrition	
	Comparison Group	
Exposure Characterization	Measurement of Exposure	
	Exposure Levels	
	Temporality	
Outcome Assessment	Outcome measurement or characterization	
	Reporting Bias	
Potential Confounding/ Variable Control	Covariate Adjustment	
	Covariate Characterization	
	Co-exposure Confounding/Moderation/ Mediation	
Analysis	Study Design and Methods	
	Statistical Power	
	Reproducibility of Analyses	
	Statistical Models	
Range of sums (if all metrics ranked)[b]		15 to 45
Range of overall rankings (if all metrics ranked)		1 to 3 (15/15 to 45/15)

High	Medium	Low
≥1 and <1.7	≥1.7 and <2.3	≥ 2.3 and 3

[a] For the purposes of calculating an overall study ranking, the range of possible metric rankings is 1 (high) to 3 (low) for each metric. No calculations will be conducted if a study receives an "critically deficient" rating (= "4") for any metric.

[b] The sum of rankings will differ if some metrics are not ranked (*i.e.*, they are not applicable).

[c] The cutoffs between categories were defined by calculating the difference between the highest possible ranking of 3 and the lowest possible ranking of 1 (*i.e.*, 3 – 1 = 2) and dividing it into three equal parts (2 ÷ 3 = 0.67). This results in a range of approximately 0.7 for each overall study data quality ranking, which is used to estimate the

Domain	Metric	Range of Metric Rankings
transition points (cut-off values) in the scale between high and medium rankings, and medium and low rankings. These transition points between the ranges of 1 and 3 are determined as follows: • cut-off values between high and medium: 1 + 0.67 = 1.67, rounded to 1.7 (rankings lower than 1.7 are assigned an overall quality level of high); and • cut-off values between medium and low: 1.67 + 0.67 = 2.34, rounded to 2.3 (rankings between 1.7 and lower than 2.3 are assigned an overall quality level of medium).		

Table_Apx R-6. Example of Ranking for Epidemiologic Studies where Sample Size Is Not Applicable

Domain	Metric	Metric Ranking
Study Participation	Participant Selection	1
	Attrition	3
	Comparison Group	2
Exposure Characterization	Measurement of Exposure	1
	Exposure Levels	1
	Temporality	1
Outcome Assessment	Outcome Measurement or Characterization	3
	Reporting Bias	2
Potential Confounding/ Variable Control	Covariate Adjustment	1
	Covariate Characterization	1
	Co-exposure/Confounding/Moderation/ Mediation	NR
Analysis	Study Design and Methods	1
	Statistical Power	2
	Reproducibility of Analyses	3
	Statistical Models	3
	Sum of Rankings	25
	Overall Ranking	Medium 25/14 = 1.79

R.5 Data Quality Criteria

Table_Apx R-7. Evaluation Criteria for Epidemiological Studies

Data Quality Level	Description	
Domain 1. Study participation		
Metric 1. Participant selection (selection, performance biases)		
High (Ranking = 1)	***For all study types:*** – All key elements of the study design are reported (*e.g.*, setting, participation rate described at all steps of the study, inclusion and exclusion criteria, and methods of participant selection or case ascertainment) AND – The reported information indicates that participant selection in or out of the study (or analysis sample) and participation was not likely to be biased (*i.e.*, the exposure-outcome distribution of the participants is likely representative of the exposure-outcome distributions in the population of persons eligible for inclusion in the study.)	
Medium (Ranking = 2)	***For all study types:*** – Some key elements of the study design were not present but available information indicates a low risk of selection bias (*i.e.*, the exposure-outcome distribution of the participants is likely representative of the exposure-outcome distributions in the population of persons eligible for inclusion in the study.)	
Low (Ranking = 3)	***For all study types:*** – Key elements of the study design and information on the population (*e.g.*, setting, participation rate described at most steps of the study, inclusion and exclusion criteria, and methods of participant selection or case ascertainment) are not reported [STROBE checklist 4, 5 and 6 (Von Elm et al., 2008)].	
Critically Deficient (Ranking = 4)	***For all study types:*** – The reported information indicates that selection in or out of the study (or analysis sample) and participation was likely to be significantly biased (*i.e.*, the exposure-outcome distribution of the participants is likely not representative of the exposure-outcome distribution of the population of persons eligible for inclusion in the study).	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.	
Metric 2. Attrition (missing data/attrition/exclusion, reporting biases)		
High	***For cohort studies:***	

Data Quality Level	Description	
(Ranking = 1)	– [There was minimal subject loss to follow up during the study (or exclusion from the analysis sample) and outcome and exposure data were largely complete. OR – Any loss of subjects (*i.e.*, incomplete outcome data) or missing exposure and outcome data were adequately* addressed (as described below) and reasons were documented when human subjects were removed from a study (NTP, 2015).] AND (applies to all bullets before/after) – [Missing data have been imputed using appropriate methods (*e.g.*, multiple imputation methods), and characteristics of subjects lost to follow up or with unavailable records are not significantly different from those of the study participants (NTP, 2015). ***For case-control studies and cross-sectional studies*:** – There was minimal subject withdrawal from the study (or exclusion from the analysis sample) and outcome data and exposure were largely complete. OR – Any exclusion of subjects from analyses was adequately* addressed (as described below), and reasons were documented when subjects were removed from the study or excluded from analyses (NTP, 2015).] ***NOTE for all study types:** Adequate handling of subject attrition can include: Use of imputation methods for missing outcome and exposure data; reasons for missing subjects unlikely to be related to outcome (for survival data, censoring was unlikely to introduce bias); missing outcome data balanced in numbers across study groups, with similar reasons for missing data across groups.	
Medium (Ranking = 2)	***For cohort studies:*** – There was moderate subject loss to follow up during the study (or exclusion from the analysis sample) or outcome and exposure data were nearly complete. AND – Any loss or exclusion of subjects was adequately addressed (as described in the acceptable handling of subject attrition in the high quality category) and reasons were documented when human subjects were removed from a study. ***For case-control studies and cross-sectional studies:*** – There was moderate subject withdrawal from the study (or exclusion from the analysis sample), but outcome and exposure data were largely complete AND	

Data Quality Level	Description	
	– Any exclusion of subjects from analyses was adequately addressed (as described above), and reasons were documented when subjects were removed from the study or excluded from analyses (NTP, 2015).	
Low (Ranking = 3)	***For cohort studies:*** – The loss of subjects (*e.g.*, loss to follow up, incomplete outcome or exposure data) was moderate and unacceptably handled (as described below in the critically deficient category) (NTP, 2015). **OR** – Numbers of individuals were not reported at important stages of study (*e.g.*, numbers of eligible participants included in the study or analysis sample, completing follow-up, and analyzed). Reasons were not provided for non-participation at each stage (Von Elm et al., 2008). ***For case-control and cross-sectional studies:*** – The exclusion of subjects from analyses was moderate and unacceptably handled (as described below in the critically deficient ranking category). OR – Numbers of individuals were not reported at important stages of study (*e.g.*, numbers of eligible participants included in the study or analysis sample, completing follow-up, and analyzed). Reasons were not provided for non-participation at each stage (Von Elm et al., 2008).	
Critically Deficient (Ranking = 4)	***For cohort studies:*** There was large subject attrition during the study (or exclusion from the analysis sample). OR – Unacceptable handling of subject attrition: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across study groups; or potentially inappropriate application of imputation (NTP, 2015). ***For case-control and cross-sectional studies:*** – There was large subject withdrawal from the study (or exclusion from the analysis sample). OR – Unacceptable handling of subject attrition: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across study groups; or potentially inappropriate application of imputation.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.	
Metric 3. Comparison group (selection, performance biases)		

Data Quality Level	Description	
High (Ranking = 1)	***For ALL study types:*** – Any differences in baseline characteristics of groups were considered as potential confounding or stratification variables and were thereby controlled by statistical analysis (NTP, 2015). OR ***For cohort and cross-sectional studies:*** – Key elements of the study design are reported (*i.e.*, setting, inclusion and exclusion criteria, and methods of participant selection), and indicate that subjects were similar (*e.g.*, recruited from the same eligible population with the same method of ascertainment and within the same time frame using the same inclusion and exclusion criteria, and were of similar age and health status) (NTP, 2015). ***For case-control studies:*** – Key elements of the study design are reported indicate that that cases and controls were similar (*e.g.*, recruited from the same eligible population with the number of controls described, and eligibility criteria and are recruited within the same time frame (NTP, 2015). ***For studies reporting Standardized Mortality Ratios (SMRs) or Standardized Incidence Ratios (SIRs):*** – Age, sex (if applicable), and race (if applicable) adjustment or stratification is described and choice of reference population (*e.g.*, general population) is reported.	
Medium (Ranking = 2)	***For cohort studies and cross-sectional studies:*** – There is only indirect evidence (*e.g.*, stated by the authors without providing a description of methods) that groups are similar (as described above for the high quality rating). ***For case-control studies:*** – There is indirect evidence (*i.e.*, stated by the authors without providing a description of methods) that cases and controls are similar (as described above for the high quality rating). ***For studies reporting SMRs or SIRs:*** – Age, sex (if applicable), and race (if applicable) adjustment or stratification is not specifically described in the text, but results tables are stratified by age and/or sex (*i.e.*, indirect evidence); choice of reference population (*e.g.*, general population) is reported.	
Low (Ranking = 3)	*Mark as low if:* ***For cohort and cross-sectional studies:*** – There is indirect evidence (*i.e.*, stated by the authors without providing a description of methods) that groups were not similar (as described above for the high quality rating).	

Data Quality Level	Description	
	AND – Control for differences in exposure groups is not adequately controlled for in the statistical analysis. ***For case-control studies:*** – There is indirect evidence (*i.e.*, stated by the authors without providing a description of methods) that cases and controls were not similar (as described above for the high quality rating). AND – The characteristics of cases and controls are not reported (NTP, 2015). AND – Control for differences in the case and control groups is not adequately controlled for in the statistical analysis. ***For studies reporting SMRs or SIRs:*** – Indirect evidence of a lack of adjustment or stratification for age or sex (if applicable); indirect evidence that choice of reference population (*e.g.*, general population) is appropriate.	
Critically Deficient (Ranking = 4)	***For cohort studies:*** – Subjects in all exposure groups were not similar. OR – Information was not reported to determine if participants in all exposure groups were similar [STROBE Checklist 6 (Von Elm et al., 2008)]. AND – Potential differences in exposure groups were not controlled for in the statistical analysis. OR – Subjects in the exposure groups had very different participation/ response rates (NTP, 2015). ***For case-control studies:*** – Controls were drawn from a very dissimilar population than cases or recruited within very different time frames (NTP, 2015). AND – otential differences in the case and control groups were not controlled for in the statistical analysis. OR – Rationale and/or methods for case and control selection, matching criteria including number of controls per case (if relevant) were not reported [STROBE Checklist 6 (Von Elm et al., 2008)]. ***For cross-sectional studies:*** – Subjects in all exposure groups were not similar, recruited within very different time frames, or had very different participation/response rates (NTP, 2015). AND – Potential differences in exposure groups were not controlled for in the statistical analysis.	

Data Quality Level	Description	
	OR – Sources and methods of selection of participants in all exposure groups were not reported [STROBE Checklist 6 (Von Elm et al., 2008)]. ***For studies reporting SMRs or SIRs:*** – Lack of adjustment or stratification for both age and sex (if applicable); choice of reference population (*e.g.*, general population) is not reported.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.	
Domain 2. Exposure characterization		
Metric 4. Measurement of exposure (Detection/measurement/information, performance biases)		
High (Ranking = 1)	***For all study types:*** – Exposure was consistently assessed (*i.e.*, using the same method and sampling time-frame) using well-established methods (*e.g.*, personal and/or industrial hygiene data used to determine levels of exposure, a frequently used biomarker of exposure) that directly measure exposure [*e.g.*, measurement of the chemical in the environment (air, drinking water, consumer product] or measurement of the chemical concentration in a biological matrix (*e.g.*, blood, plasma, urine) (NTP, 2015). OR – For an occupational population, contains detailed employment records which allows for construction of a job-matrix for entire work history of exposure (*i.e.*, cumulative or peak exposures, and time since first exposure).	
Medium (Ranking = 2)	***For all study types:*** – Exposure was directly measured and assessed using a method that is not well-established (*e.g.*, newly developed biomarker of exposure), ***but*** is validated against a well-established method and demonstrated a high agreement between the two methods OR – For an occupational study population, contains detailed employment records for only a portion of participant's work history (*i.e.*, only early years or later years), such that extrapolation of the missing years is required.	
Low (Ranking = 3)	***For all study types:*** – A less-established method (*e.g.*, newly developed biomarker of exposure) was used and no method validation was conducted against well-established methods, but there was little to no evidence that the method had poor validity and little to no evidence of significant exposure misclassification (*e.g.*, differential recall of self-reported exposure) (NTP, 2015).	

Data Quality Level	Description	
	OR – For an occupational study population, exposure was estimated solely using professional judgement.	
Critically Deficient (Ranking = 4)	***For all study types:*** – Methods used to quantify the exposure were not well defined, and sources of data and detailed methods of exposure assessment were not reported [STROBE Checklist 7 and 8]. OR – Exposure was assessed using methods known or suspected to have poor validity (NTP, 2015). OR – There is evidence of substantial exposure misclassification that would significantly bias the results.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.	
Metric 5. Exposure levels (detection/measurement/information biases)		
High (Ranking = 1)	Do not select for this metric	
Medium (Ranking = 2)	***For all study types:*** – The range and distribution of exposure is sufficient or adequate to develop an exposure-response estimate (Cooper et al., 2016). AND – Reports 3 or more levels of exposure (*i.e.*, referent group and 2 or more) or an exposure-response model using a continuous measure of exposure.	
Low (Ranking = 3)	***For all study types:*** – The range of exposure in the population is limited OR – Reports 2 levels of exposure (*e.g.*, exposed/unexposed)) (Cooper et al., 2016)	
Critically Deficient (Ranking = 4)	*For all study types:* – No description is provided on the levels or range of exposure OR – The description provided is inadequate to determine whether exposure is different between groups	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.	

Data Quality Level	Description	
Metric 6. Temporality (Detection/measurement/information biases):		
High (Ranking = 1)	***For all study types:*** – The study presents an appropriate temporality between exposure and outcome (*i.e.*, the exposure precedes the disease). AND – The interval between the exposure (or reconstructed exposure) and the outcome has an appropriate consideration of relevant exposure windows (Lakind et al., 2014).	
Medium (Ranking = 2)	***For all study types except cross-sectional studies:*** – Temporality is established, but it is unclear whether exposures fall within relevant exposure windows for the outcome of interest (Lakind et al., 2014). ***For cross-sectional studies:*** – The age of participants, timing of sample collection, fasted/fed status, and other temporal information are reported	
Low (Ranking = 3)	***For all study types except cross-sectional studies:*** – The temporality of exposure and outcome is uncertain ***For cross-sectional studies:*** – The study lacks adequate documentation of temporal information	
Critically Deficient (Ranking = 4)	***For all study types:*** – Study lacks an established time order, such that exposure is not likely to have occurred prior to outcome (LaKind et al., 2014). OR – There was inadequate follow-up of the cohort for the expected latency period. OR – Sources of data and details of methods of assessment were not sufficiently reported (e.g. duration of follow-up, periods of exposure, dates of outcome ascertainment, etc.) (Source: STROBE Checklist 8 (Von Elm et al., 2008)).	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.	
Domain 3. Outcome assessment		
Metric 7. Outcome measurement or characterization (detection/measurement/information, performance, reporting biases)		
High (Ranking = 1)	***For cohort studies:*** – The outcome was assessed using well-established methods (*e.g.*, the "gold standard").	

Data Quality Level	Description	
	For case-control studies: – The outcome was assessed in cases (*i.e.*, case definition) and controls using well-established methods (the gold standard). Subjects had been followed for the same length of time in all study groups (NTP, 2015). ***For cross-sectional studies:*** – There is direct evidence that the outcome was assessed using well-established methods (the gold standard) (NTP, 2015). ***Note:** Acceptable assessment methods will depend on the outcome, but examples of such methods may include: objectively measured with diagnostic methods, measured by trained interviewers, obtained from registries (NTP, 2015; Shamliyan et al., 2010).	
Medium (Ranking = 2)	***For all study types:*** – A less-established method was used and no method validation was conducted against well-established methods, but there was little to no evidence that that the method had poor validity and little to no evidence of outcome misclassification (*e.g.*, differential reporting of outcome by exposure status).	
Low (Ranking = 3)	***For cohort studies:*** – The outcome assessment method is an insensitive instrument or measure. OR – The length of follow up differed by study group (NTP, 2015). ***For case-control studies:*** – The outcome was assessed in cases (*i.e.*, case definition) using an insensitive instrument or measure (NTP, 2015). ***For cross-sectional studies:*** – The outcome assessment method is an insensitive instrument or measure (NTP, 2015). OR – Any self-reported information	
Critically Deficient (Ranking = 4)	*For all study types:* – Diagnostic criteria were not defined or reported [STROBE Checklist 15 (Von Elm et al., 2008)].	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.	
Metric 8. Reporting bias		

Data Quality Level	Description	
High (Ranking = 1)	***For all study types:*** – A description of measured outcomes is reported in the methods, abstract, and/or introduction. Effect estimates are reported with a confidence interval and/or standard errors; number of cases/controls or exposed/unexposed reported for each analysis, to be included in exposure-response analysis or fully tabulated during data extraction and analyses (NTP, 2015).	
Medium (Ranking = 2)	***For all study types:*** – All of the study's measured outcomes (primary and secondary) outlined in the methods, abstract, and/or introduction (that are relevant for the evaluation) are reported, but not in a way that would allow for detailed extraction (*e.g.*, results were discussed in the text but accompanying data were not shown).	
Low (Ranking = 3)	***For all study types:*** – All of the study's measured outcomes (primary and secondary) outlined in the methods, abstract, and/or introduction (that are relevant for the evaluation) have not been reported. ***Note:** In addition to not reporting outcomes, this would include reporting outcomes based on composite Ranking without individual outcome components or outcomes reported using measurements, analysis methods, or unplanned analyses were included that would appreciably bias results (NTP, 2015).	
Critically Deficient (Ranking = 4)	Do not select for this metric.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.	
Domain 4. Potential confounding/variable control		
Metric 9. Covariate adjustment (confounding)		
High (Ranking = 1)	***For all study types:*** – Appropriate adjustments or explicit considerations were made for potential confounders (*e.g.*, age, sex, socioeconomic status) (excluding co-exposures, which are evaluated in metric 11) in the final analyses through the use of statistical models to reduce research-specific bias, including matching, adjustment in multivariate models, stratification, or other methods that were appropriately justified (NTP, 2015). ***For studies reporting SMRs or SIRs:*** – Adjustments are described and results are age-, race-, and sex-adjusted (or stratified) if applicable.	
Medium	***For all study types:***	

Data Quality Level	Description	
(Ranking = 2)	– There is indirect evidence that appropriate adjustments were made [*i.e.*, considerations were made for potential confounders (excluding co-exposures)] without providing a description of methods. OR – The distribution of potential confounders (excluding co-exposures) did not differ significantly between exposure groups or between cases and controls. OR – The major potential confounders (excluding co-exposures) were appropriately adjusted (*e.g.*, SMRs, SIRs) and any not adjusted for are considered not to appreciably bias the results. ***For studies reporting SMRs or SIRs:*** – Indirect evidence that results are age- and sex-adjusted (or stratified) if applicable.	
Low (Ranking = 3)	***For all study types:*** – There is indirect evidence (*i.e.*, no description is provided in the study) that considerations were not made for potential confounders adjustment in the final analyses (NTP, 2015). AND – The distribution of primary covariates (excluding co-exposures) and potential confounders was not reported between the exposure groups or between cases and controls (NTP, 2015). ***For studies reporting SMRs or SIRs:*** – Results are age-, race-, OR sex-adjusted (or stratified) if applicable (*i.e.*, if both *should* have been adjusted).	
Critically Deficient (Ranking = 4)	***For all study types:*** – The distribution of potential confounders differed significantly between the exposure groups. AND – Confounding was demonstrated and was not appropriately adjusted for in the final analyses (NTP, 2015). ***For studies reporting SMRs or SIRs:*** – No discussion of adjustments. Results are not adjusted for both age and sex (or stratified) if applicable.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.	
Metric 10. Covariate characterization (measurement/information, confounding biases)		
High (Ranking = 1)	***For all study types:***	

Data Quality Level	Description	
	– Potential confounders (excluding co-exposures; *e.g.*, age, sex, SES) were assessed using valid and reliable methodology where appropriate (*e.g.*, validated questionnaires, biomarker).	
Medium (Ranking = 2)	***For all study types*:** – A less-established method was used to assess confounders (excluding co-exposures) and no method validation was conducted against well-established methods, but there was little to no evidence that that the method had poor validity and little to no evidence of confounding.	
Low (Ranking = 3)	***For all study types*:** – The confounder (excluding co-exposures) assessment method is an insensitive instrument or measure or a method of unknown validity.	
Critically Deficient (Ranking = 4)	***For all study types*:** – Confounders were assessed using a method or instrument known to be invalid.	
Not Rated/Not Applicable	***For all study types*:** Covariates were not assessed.	
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 11. Co-exposure confounding/moderation/mediation (measurement/information, confounding biases)		
High (Ranking = 1)	Do not select for this metric.	
Medium (Ranking = 2)	***For all study types*:** – Any co-exposures to pollutants that are not the target exposure that would likely bias the results were not likely to be present. OR – Co-exposures to pollutants were appropriately measured or either directly or indirectly adjusted for.	
Low (Ranking = 3)	***For cohort and cross-sectional studies*:** – There is direct evidence that there was an unbalanced provision of additional co-exposures across the primary study groups, which were not appropriately adjusted for. ***For case-control studies*:** – There is direct evidence that there was an unbalanced provision of additional co-exposures across cases and controls, which were not appropriately adjusted for, and significant indication a biased exposure-outcome association.	
Critically Deficient (Ranking = 4)	Do not select for this metric.	
Not Rated/Not Applicable	Enter "NA" and do not rank this metric.	

Data Quality Level	Description	
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.	
Domain 5. Analysis		
Metric 12. Study design and methods (reporting bias)		
High (Ranking = 1)	***For all study types:*** – The study design chosen was appropriate for the research question (e.g. assess the association between exposure levels and common chronic diseases over time with cohort studies, assess the association between exposure and rare diseases with case-control studies, and assess the association between exposure levels and acute disease with a cross-sectional study design). AND – The study uses an appropriate statistical method to address the research question(s) (*e.g.*, repeated measures analysis for longitudinal studies, logistic regression analysis for case-control studies, or mean, median for descriptive studies).	
Medium (Ranking = 2)	Do not select for this metric.	
Low (Ranking = 3)	***For all study types:*** – The study design chosen was not appropriate for the research question. OR – Inappropriate statistical analyses were applied to assess the research questions.	
Critically Deficient (Ranking = 4)	Do not select for this metric.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.	
Metric 13. Statistical power (sensitivity)		
High (Ranking = 1)	Do not select for this metric.	
Medium (Ranking = 2)	***For cohort and cross-sectional studies:*** – The number of participants are adequate to detect an effect in the exposed population and/or subgroups of the total population. OR – The paper reported statistical power is high enough (≥ 80%) to detect an effect in the exposure population and/or subgroups of the total population. ***For case-control studies:***	

Data Quality Level	Description	
	– The number of cases and controls are adequate to detect an effect in the exposed population and/or subgroups of the total population. OR – The paper reported statistical power is high enough (≥ 80%) to detect an effect in the exposure population and/or subgroups of the total population.	
Low (Ranking = 3)	***For cohort and cross-sectional studies:*** – The number of participants is inadequate to detect an effect in the exposed population and/or subgroups of the total population ***For case-control studies:*** – The number of cases and controls is inadequate to detect an effect in the exposed population and/or subgroups of the total population	
Critically Deficient (Ranking = 4)	Do not select for this metric.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.	
Metric 14. Reproducibility of analyses [adapted from Blettner et al. (2001)]		
High (Ranking = 1)	Do not select for this metric.	
Medium (Ranking = 2)	***For all study types:*** – The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible with access to the analytic data.	
Low (Ranking = 3)	***For all study types:*** – The description of the analysis is insufficient to understand what has been done and to be reproducible OR a description of analyses are not present (*e.g.*, statistical tests and estimation procedures were not described, variables used in the analysis were not listed, transformations of continuous variables (*e.g.*, logarithmic) were not explained, rules for categorization of continuous variables were not presented, exclusion of outliers was not elucidated and how missing values are dealt with was not mentioned).	
Critically Deficient (Ranking = 4)	Do not select for this metric.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.	

Data Quality Level	Description	
Metric 15. Statistical models (confounding bias)		
High (Ranking = 1)	***For all study types:*** – The model or method for calculating the risk estimates (*e.g.*, odds ratios, SMRs, SIR) is transparent (*i.e.*, it is stated how/why variables were included or excluded). AND – Model assumptions were met.	
Medium (Ranking = 2)	Do not select for this metric.	
Low (Ranking = 3)	***For all study types:*** – The statistical model building process is not fully appropriate OR model assumptions were not met OR a description of analyses/assumptions are not present [STROBE Checklist 12e (Von Elm et al., 2008)].	
Critically Deficient (Ranking = 4)	Do not select for this metric.	
Not Rated/Not Applicable	Enter "NA" if the study did not use a statistical model.	
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. Other (if applicable) considerations for biomarker selection and measurement (Lakind et al., 2014)		
Metric 16. Use of biomarker of exposure (detection/measurement/information biases)		
High (Ranking = 1)	– Biomarker in a specified matrix has accurate and precise quantitative relationship with external exposure, internal dose, or target dose. AND – Biomarker is derived from exposure to one parent chemical.	
Medium (Ranking = 2)	– 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.	
Low (Ranking = 3)	– Evidence exists for a relationship between biomarker in a specified matrix and external exposure, internal dose or target dose, but there has been no assessment of accuracy and precision or none was reported.	
Critically Deficient (Ranking = 4)	– Biomarker in a specified matrix is a poor surrogate (low accuracy, specificity, and precision) for exposure/dose.	

Data Quality Level	Description	
Not Rated/Not Applicable	Select "NA" if no human biological samples were assessed or if the only biomarkers assessed were biomarkers of effect or biomarkers of susceptibility.	
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 17. Effect biomarker (detection/measurement/information biases)		
High (Ranking = 1)	Effect biomarker measured is an indicator of a key event in an adverse outcome pathway (AOP).	
Medium (Ranking = 2)	Biomarkers of effect shown to have a relationship to health outcomes using well validated methods, but the mechanism of action is not understood.	
Low (Ranking = 3)	Biomarkers of effect shown to have a relationship to health outcomes, but the method is not well validated and mechanism of action is not understood.	
Critically Deficient (Ranking = 4)	Biomarker has undetermined consequences (*e.g.*, biomarker is not specific to a health outcome).	
Not Rated/Not Applicable	Select "NA" if no human biological samples were assessed or if the only biomarkers assessed were biomarkers of exposure or biomarkers of susceptibility.	
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 18. Method sensitivity (detection/measurement/information biases)		
High (Ranking = 1)	Do not select for this metric.	
Medium (Ranking = 2)	Limits of detection are low enough to detect chemicals in a sufficient percentage of the samples to address the research question. Analytical methods measuring biomarker are adequately reported. The limit of detection (LOD) and limit of quantification (LOQ) (value or %) are reported.	
Low (Ranking = 3)	Frequency of detection too low to address the research hypothesis. OR – LOD/LOQ (value or %) are not stated.	
Critically Deficient (Ranking = 4)	Do not select for this metric.	

Data Quality Level	Description	
Not Rated/Not Applicable	Do not select "NA" for this metric if the study assessed biomarkers. If LOD/LOQ are not stated then select Low. [If the study did not assess biomarkers, then this metric is automatically not rated].	
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 19. Biomarker stability (detection/measurement/information biases)		
High (Ranking = 1)	Samples with a known storage history and documented stability data or those using real-time measurements.	
Medium (Ranking = 2)	Samples have known losses during storage, but the difference between low and high exposures can be qualitatively assessed.	
Low (Ranking = 3)	Samples with either unknown storage history and/or no stability data for target analytes and high likelihood of instability for the biomarker under consideration.	
Critically Deficient (Ranking = 4)	Do not select for this metric.	
Not Rated/Not Applicable	Do not select "NA" for this metric if the study assessed biomarkers. [If the study did not assess biomarkers, then this metric is automatically not rated].	
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 20. Sample contamination (detection/measurement/information biases)		
High (Ranking = 1)	– Samples are contamination-free from the time of collection to the time of measurement (*e.g.*, by use of certified analyte free collection supplies and reference materials, and appropriate use of blanks both in the field and lab). AND – Documentation of the steps taken to provide the necessary assurance that the study data are reliable is included.	
Medium (Ranking = 2)	– Samples are stated to be contamination-free from the time of collection to the time of measurement. AND – There is incomplete documentation of the steps taken to provide the necessary assurance that the study data are reliable. OR – Samples are known to have contamination issues, but steps have been taken to address and correct contamination issues. OR – There is no information included about contamination (only allowed for biomarker samples not susceptible to contamination).	

Data Quality Level	Description	
Low (Ranking = 3)	– Samples are known to have contamination issues, but steps have been taken to address and correct contamination issues. OR – Samples are stated to be contamination-free from the time of collection to the time of measurement, but there is no use or documentation of the steps taken to provide the necessary assurance that the study data are reliable.	
Critically Deficient (4)	– There are known contamination issues (*e.g.*, phthalate study that used plastic sample collection vials) and no documentation that the issues were addressed.	
Not Rated/Not Applicable	Do not select "NA" for this metric if the study assessed biomarkers. [If the study did not assess biomarkers, then this metric is automatically not rated].	
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 21. Method requirements (detection/measurement/information biases)		
High (Ranking = 1)	– Instrumentation that provides unambiguous identification and quantitation of the biomarker at the required sensitivity [*e.g.*, gas chromatography/high-resolution mass spectrometry (GC–HRMS); gas chromatography with tandem mass spectrometry (GC–MS/MS); liquid chromatography with tandem mass spectrometry (LC–MS/MS)].	
Medium (Ranking = 2)	– Instrumentation that allows for identification of the biomarker with a high degree of confidence and the required sensitivity [*e.g.*, gas chromatography mass spectrometry (GC–MS), gas chromatography with electron capture detector (GC–ECD)].	
Low (Ranking = 3)	– Instrumentation that only allows for possible quantification of the biomarker, but the method has known interferants [*e.g.*, gas chromatography with flame-ionization detection (GC–FID), spectroscopy].	
Critically Deficient (Ranking = 4)	Do not select for this metric.	
Not Rated/Not Applicable	Do not select "NA" for this metric if the study assessed biomarkers. [If the study did not assess biomarkers, then this metric is automatically not rated].	
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 22. Matrix adjustment (detection/measurement/information biases)		
High (Ranking = 1)	– If applicable for the biomarker under consideration, study provides results, either in the main publication or as a supplement, for both adjusted and unadjusted matrix concentrations (*e.g.*, creatinine-adjusted	

Data Quality Level	Description	
	or specific gravity-adjusted and non-adjusted urine concentrations) and reasons are given for adjustment approach.	
Medium (Ranking = 2)	– If applicable for the biomarker under consideration, study only provides results using one method (matrix-adjusted or not).	
Low (Ranking = 3)	– If applicable for the biomarker under consideration, no established method for matrix adjustment was conducted.	
Critically Deficient (Ranking = 4)	– Do not select for this metric.	
Not Rated/Not Applicable	Select "NA" if matrix adjustment is not required for assessment of the biomarker.	
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.	

R.5.1 Data Quality Domains, Metrics, and Criteria for Epidemiology Data for Phthalates Based on Modified TSCA DistillerSR Forms to Facilitate the Use of IRIS Data in TSCA Risk Evaluations

As described in Appendix A.1.1.3, the IRIS Program has conducted systematic reviews for some of the same chemicals that are being assessed under TSCA, particularly phthalates and formaldehyde. A shortened TSCA form was developed to facilitate the use of these IRIS data. EPA may also choose to apply this form to additional chemical assessments where deemed more appropriate or practicable than the metrics in Appendix R.5.

IRIS domains are generally more collapsed than TSCA domains. For the IRIS phthalates epidemiology assessment, which was conducted using HAWC, each IRIS domain contains one metric, whereas each domain on the longer TSCA form contains several metrics. Crosswalks determined that most of the information captured in the expanded TSCA domains is captured in the collapsed IRIS domains. Each of the domains in the longer TSCA form for epidemiologic study evaluation has a corresponding domain in the IRIS form for phthalates, with the exception of the TSCA Other/Biomarkers domain. However, IRIS obtains information on biomarkers of exposure and biomarkers of effect in the IRIS Exposure Measurement domain and the IRIS Outcome Ascertainment domain, respectively. IRIS phthalates epidemiology domains correspond with TSCA domains as shown in Table_Apx R-8 below.

Table_Apx R-8. IRIS Phthalates Epidemiology Domains and Corresponding TSCA Domains

IRIS/HAWC Domain from Phthalates Epidemiology (2017)	Number of Metrics in IRIS/HAWC Domain	Corresponding TSCA/DistillerSR Domain	Corresponding TSCA/DistillerSR Metrics
1. Participant Selection	1	1. Study Participation	1,2,3
2. Exposure Measurement	1	2. Exposure Characterization	4,5,6

IRIS/HAWC Domain from Phthalates Epidemiology (2017)	Number of Metrics in IRIS/HAWC Domain	Corresponding TSCA/DistillerSR Domain	Corresponding TSCA/DistillerSR Metrics
3. Outcome Ascertainment	1	3. Outcome Assessment	7. Outcome Measurement or Characterization
4. Confounding	1	4. Potential Confounding/ Variability Control	9,10,11
5. Analysis	1	5. Analysis	12,14,15
6. Selective Reporting	1	3. Outcome Assessment	8. Reporting Bias
7. Sensitivity	1	5. Analysis	13. Statistical Power

Therefore, the modified TSCA DistillerSR form for phthalates includes the following domains and metrics:

- Domain 1. Study Participation
  - Metric 1A Participant Selection (Combines TSCA Long Form Metrics 1, 2, and 3)
- Domain 2. Exposure Characterization
  - Metric 2A Exposure Measurement (Combines TSCA Long Form Metrics 4, 5, and 6)
- Domain 3. Outcome Assessment
  - Metric 3A Outcome Ascertainment (Corresponds to TSCA Long Form Metric 7. Outcome Measurement or Characterization)
  - Metric 3B Selective Reporting (Corresponds to TSCA Long Form Metric 8. Reporting Bias)
- Domain 4. Potential Confounding/Variability Control
  - Metric 4A Confounding (Combines TSCA Long Form metrics 9,10, and 11)
- Domain 5. Analysis
  - Metric 5A Analysis (Combines TSCA Long Form Metrics 12, 14, and 15: Study Design and Methods, Reproducibility of Analyses, and Statistical Models)
  - Metric 5B Sensitivity (Corresponds to TSCA Long Form Metric 13. Statistical Power)

On the modified TSCA DistillerSR form for phthalates, each of the above metrics will be evaluated using the criteria from the IRIS Handbook (U.S. EPA, 2020) for the corresponding IRIS domain.

Appendix S DATA QUALITY CRITERIA FOR *IN VITRO* DERMAL ABSORPTION STUDIES

When evaluating *in vitro* dermal absorption data, EPA may accept non-guideline studies. However, EPA consulted OECD Test Guideline 428 (Skin Absorption; *In Vitro* Method) as well as OECD Series on Testing and Assessment document No. 28 (Guidance Document for the Conduct of Skin Absorption Studies) and No. 156 (Guidance Notes on Dermal Absorption) when developing many of the metrics in Table_Apx S-1 below. Assessors should also consult these documents when considering quality ratings for individual studies.

A single study may evaluate only a limited number of conditions (*e.g.*, use of only the neat compound). If all other methods and results are adequate, the study may be considered acceptable for certain conditions of use. However, the study may still be limited for use in the risk evaluation because it may not address other uses (*e.g.*, lower concentrations, certain solvents/diluents).

These metrics are undergoing further revision and a new version will be available for the final protocol.

Table_Apx S-1. Data Quality Criteria for *In Vitro* Dermal Absorption Studies

Data Quality Level	Description	
Domain 1. Test substance		
Metric 1. Test substance identity Was the test substance identified definitively (*i.e.*, established nomenclature, CASRN, physical nature, physical and chemical properties, and/or structure reported, including information on the specific form tested [*e.g.*, salt or base, valence state, isomer, if applicable] for materials that may vary in form)? If test substance was a mixture, were mixture components and ratios characterized?		
High (Ranking = 1)	The test substance (*i.e.*, chemical of interest) was identified definitively (*i.e.*, nomenclature, CASRN, structure) and where applicable the specific form (*e.g.*, particle characteristics for solid state materials, salt or base, valence state, hydration state, isomer, radiolabel, etc.) was definitively and completely characterized. For mixtures, the components and ratios were characterized (*i.e.*, provided as concentration, ratio of percentage of the mixture or product). Additionally, for radiolabeled substances, the location of the radiolabel within the substance should be indicated, ideally with ^{14}C in a metabolically stable position.	
Medium (Ranking = 2)	The test substance (*i.e.*, chemical of interest) was identified and the specific form was characterized (where applicable). For mixtures, some components and components and ratios were identified and characterized but at least the chemical of interest has a percentage/concentration reported. There were minor uncertainties (*e.g.*, minor characterization details were omitted, radiolabel details) that were unlikely to have a substantial impact on results.	

Data Quality Level	Description	
Low (Ranking = 3)	The test substance and form (if applicable) were identified, and components and ratios of mixtures were characterized, but there were uncertainties regarding test substance identification or characterization that are likely to have a substantial impact on the results (*e.g.*, no information on isomer (or enantiomer) composition of differences could affect hazard properties, limited particle size information, omitted details regarding branched or straight chain structure).	
Critically Deficient (Ranking = 4)	The test substance identity and form (the latter if applicable) could not be determined from the information provided (*e.g.*, nomenclature was unclear and CASRN or structure were not reported) OR The components and ratios of mixtures were not characterized.	
Not Rated/Not Applicable	Do not select for this metric	
Guidance for Reviewers	Mixtures should only be used if identified as the chemical of interest (*i.e.*, the chemical being evaluated for the TSCA risk evaluation) or if EPA has identified it as an appropriate analog for the chemical of interest.	
Metric 2. Test substance source Was the source of the test substance reported, including manufacturer and batch/lot number for materials that may vary in composition? If synthesized or extracted, was test substance identity verified by analytical methods?		
High (Ranking = 1)	The source of the test substance was reported as a manufacturer or the production process was specifically identified. The batch/lot number was identified (for materials that may vary in composition), and the chemical identity was either certified by the source in the publication or could be verified on a manufacturer's website. OR The test substance identity was analytically verified by the laboratory that performed the toxicity study.	
Low (Ranking = 3)	The test substance was synthesized or extracted by a source other than the manufacturer [and no production process was identified]. OR The source was not reported. AND The test substance identity was NOT analytically verified by the performing laboratory.	
Not Rated/Not Applicable	Do not select for this metric	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

Data Quality Level	Description	
Metric 3. Test substance purity Was the purity or grade (*i.e.*, analytical, technical) of the test substance (including the radiolabeled substance) reported and adequate? Were impurities identified? Were impurities present in quantities that could influence the results?		
High (Ranking = 1)	For discrete substances, the test substance purity and composition were such that any observed effects were highly likely to be due to the nominal test substance itself (*e.g.*, highly pure at >98% or analytical grade test substance or a formulation of lower purity that contains ingredients considered to be inert, such as water). All components, including impurities and residual chemicals, were identified and the chemical of interest was the main component.	
Medium (Ranking = 2)	The nature and quantity of reported impurities are such that study results were not likely to be substantially impacted by the impurities (impurities not known to induce outcome of interest at low levels, impurities are inert or GRAS, etc.). Regardless of the nature and purity, for discrete chemicals, the purity of the chemical of interest should be >70%, unless water is the only impurity.	
Low (Ranking = 3)	Purity and/or grade of test substance were not reported	
Critically Deficient (Ranking = 4)	The nature and quantity of reported impurities were such that study results were likely to be due to one or more of the impurities. This is a serious flaw that makes the study unusable.	
Not Rated/Not Applicable	Do not select for this metric	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 2. Test design		
Metric 4. Reference compounds Were the results of a reference compound (*e.g.*, caffeine, testosterone, benzoic acid) run concurrently or separately and recently by the same laboratory and reported in the study? Was the absorption response appropriate? [TBD: need to decide how important it is to have reference compounds]		
Medium (Ranking = 2)	When applicable, an appropriate concurrent or historical reference compound was used, and an appropriate response was observed. Any uncertainties (*e.g.*, omission of minor details regarding exposure or response) are minor.	

Data Quality Level	Description	
Low (Ranking = 3)	When applicable, an appropriate concurrent or historical reference compound was used, but there were deficiencies regarding the reference compound exposure or response (*e.g.*, the response was not described). OR No reference compound was used or reported.	
Critically Deficient (Ranking = 4)	Reference compounds were run but an inadequate response for the reference compounds (outside historical control results) indicates that the assay would not accurately measure absorption.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 5. Assay procedures Were assay methods and procedures (*e.g.*, diffusion cell set up, temperature, humidity, physiological conductivity of receptor fluid, volumes applied and surface area of skin, use/measurement of occlusion or carbon trap, materials and procedures used for tape stripping, capture of volatile compounds if required) described in detail and applicable? See other metrics for additional assay procedures (*e.g.*, metrics 1–3 for test substance information; metric 11 for exposure duration; metric 15 for replicates per group). OECD 428, OECD GD28 and OECD GD156 should be consulted and used to consider quality ratings.		
High (Ranking = 1)	Study authors described the methods and procedures (*e.g.*, diffusion cell set up, temperature, humidity, physiological conductivity of receptor fluid, volumes applied and surface area of skin, use/measurement of occlusion or carbon trap, materials and procedures used for tape stripping, capture of volatile compounds if required) used for the test in detail. Either a static cell or flow-through system was used, with either constant stirring (static cell) or an appropriate flow-rate (flow-through).	
Medium (Ranking = 2)	Methods and procedures were partially described but appeared to be appropriate (*e.g.*, TBD), so the omission of details is unlikely to have a substantial impact on results.	
Low (Ranking = 3)	The methods and procedures were not well described or deviated from customary practices (*e.g.*, TBD) and this is likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	Assay methods and procedures were not appropriate (*e.g.*, TBD).	
Not Rated/Not Applicable	Do not select for this metric	

Data Quality Level	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]*	
Guidance for reviewers	If outcome methods were cited to another publication, please review the relevant methods in the original publication and consider this information as you rate assay procedures.	
Metric 6. Standards for tests For assays with established criteria, were the test validity, acceptability, reliability, and/or QC criteria reported and consistent with current standards and guidelines? Example criteria: *Percent recovery:* 100±10% of the radioactivity as stated in OECD TG 428; 100±20% for volatile and unlabeled compounds as stated in OECD GD 28. *Skin integrity:* (1) Tritiated water – minimal flux threshold TBD (2) Electrical conductance - minimal threshold of 17 kilo-ohms (Fasano et al., 2002). OECD 428, OECD GD28, and OECD GD156 should be consulted; deviations should be explained.		
Medium (Ranking = 2)	The test validity, acceptability, reliability, and/or QC criteria (*e.g.*, threshold for skin integrity, percent recovery considered acceptable) were reported and consistent with current standards and guidelines, as/if applicable.	
Low (Ranking = 3)	Some QC criteria were not reported.	
Critically Deficient (Ranking = 4)	Inadequate data were provided to demonstrate validity, acceptability, and reliability of the test when compared with current standards and guidelines.	
Not Rated/Not Applicable	Do not select for this metric	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 3. Exposure characterization		
Metric 7. Preparation and storage of test substance (chemical) Did the study characterize preparation of the test substance and storage conditions? Were the frequency of preparation and/or storage conditions appropriate to the test substance stability and solubility (if applicable)?		

Data Quality Level	Description	
High (Ranking = 1)	The test substance preparation and/or storage conditions (*e.g.*, test substance stability, homogeneity, mixing temperature, stock concentration, stirring methods, storage conditions) were reported and appropriate for the test substance (*e.g.*, stability and solubility in diluents or solvents confirmed especially if they differ from what is used commercially; volatile test substances prepared and stored in sealed containers; same stock solution for all exposure concentrations).	
Medium (Ranking = 2)	The test substance preparation and storage conditions were reported, but minor limitations in the test substance preparation and/or storage conditions were identified (*e.g.*, TBD). OR There is an omission of details that are unlikely to have a substantial impact on results (*e.g.*, preparation/administration of test substance is described, but storage is not reported; however, storage is unlikely to affect results based on likely stability over the time frame of the test or the physical and chemical properties of the chemical make concerns about volatility or solubility unlikely).	
Low (Ranking = 3)	Deficiencies in reporting of test substance preparation, and/or storage conditions are likely to have a substantial impact on results (*e.g.*, available information on physical and chemical properties suggests that stability and/or solubility of test substance in diluent/solvent may be poor). OR Information on preparation and storage was *not* reported and lack of details could substantially impact results (*e.g.*, preparation for volatile or low-solubility chemicals).	
Critically Deficient (Ranking = 4)	Serious flaws reported regarding test substance preparation and/or storage conditions will have critical impacts on dose/concentration estimates and make the study unusable (*e.g.*, instability of test substance, test substance volatilized rapidly from storage containers).	
Not Rated/Not Applicable	Do not select for this metric	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 8. Consistency of exposure administration Were exposures administered consistently across study groups (*e.g.*, consistent volumes and area of skin surface for application)?		
High (Ranking = 1)	Details of exposure administration were reported and exposures were administered consistently across study groups in a scientifically sound manner (*e.g.*, consistent volumes, thickness and area of skin surface for application,).	

Data Quality Level	Description	
Medium (Ranking = 2)	Details of exposure administration were reported or inferred from the text, but the minor limitations in administration of exposures (*e.g.*, slight variation in volume, thickness, and area or skin surface used for application) that were identified are unlikely to have a substantial impact on results. OR Details of exposure administration are incompletely reported, but the missing information is unlikely to have a substantial impact on results.	
Low (Ranking = 3)	Details of exposure administration were reported, but deficiencies in administration of exposures (*e.g.*, moderate differences in volume, thickness, and area of skin surface used for application) that were reported or inferred from the text are likely to have a substantial impact on results. OR Details of exposure administration are insufficiently reported and the missing information is likely to have a substantial impact on results	
Critically Deficient (Ranking = 4)	Exposures were not administered consistently across and/or within study groups (*e.g.*, large differences in volume, thickness, and area of skin surface used for application) resulting in serious flaws that make the study unusable.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 9. Reporting of concentrations Were exposure doses/concentrations or amounts of test substance reported without ambiguity (*e.g.*, point estimate instead of range, analytical instead of nominal)? Note: Ambiguity also applies to doses/concentrations if values were only reported as points on a figure without numerical values.		
High (Ranking = 1)	The exposure doses/concentrations or amounts of test substance were reported without ambiguity (*e.g.*, point estimate instead of range, analytical/measured instead of nominal).	
Medium (Ranking = 2)	The exposure doses/concentrations or amounts of test substance were reported with some ambiguity (*e.g.*, range instead of point estimate OR nominal instead of analytical/measured).	
Low (Ranking = 3)	The exposure doses/concentrations or amounts of test substance were reported but with substantial ambiguity about precision (*e.g.*, only an estimated range AND only nominal instead of analytical measurements).	
Critically Deficient (Ranking = 4)	The exposure doses/concentrations or amounts of test substance were not reported, resulting in serious flaws that make the study unusable.	

Data Quality Level	Description	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 10. Exposure duration Was the exposure duration (*e.g.*, hours) reported and was it appropriate for this study type and/or outcome(s) of interest? [TBD: add text about human exposure relevancy].		
High (Ranking = 1)	The exposure duration (*e.g.*, hours) was reported and was appropriate for the study type and/or outcome(s) of interest (*e.g.*, at least 6 to 10 hours prior to washing and up to at least 24 hours post-washing). A shorter exposure duration may also be included but is less useful unless the substance is demonstrated to be volatile or the timepoint is used only for Kp/flux measurements.	
Low (Ranking = 3)	The duration(s) of exposure differed slightly from current standards and guidelines[a] for studies of this type (*e.g.*, <6 to 10 hours prior to washing and less than 24 hours post-washing), but the differences are unlikely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	No information on exposure duration(s) was reported OR the exposure duration was not appropriate OR Duration(s) differed significantly from studies of the same or similar types. These deficiencies are likely to have a substantial impact on results.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 11. Number of exposure groups and concentrations spacing Were the number of exposure groups and dose/concentration spacing justified by study authors (*e.g.*, to mimic a specific type of human exposure) and adequate for addressing the purpose of the study (*e.g.*, to evaluate dermal absorption)?		
High (Ranking = 1)	The number of exposure groups and dose/concentration spacing were justified by study authors (*e.g.*, to mimic a specific type of human exposure) and was adequate for addressing the purpose of the study.	
Low (Ranking = 3)	There were minor limitations regarding the number of exposure groups and/or applied dose/concentration spacing (*e.g.*, unclear if lowest dose was low enough or the highest dose was high enough), but the number of exposure groups and spacing of exposure levels were adequate and are unlikely to have a substantial impact on results.	

Data Quality Level	Description	
Critically Deficient (Ranking = 4)	The number of exposure groups and dose/concentration spacing were not reported OR the number of exposure groups and dose/concentration spacing were not adequate and did not mimic expected human exposures.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 4. Test model		
Metric 12. Test model Were the test models (*e.g.*, viable skin, cadaver/cosmetic surgery skin) and descriptive information (*e.g.*, tissue origin, anatomical site, tissue storage, integrity or viability) reported? What was the source of the test model? Was the model routinely used for the outcome of interest? For example, for human skin, split thickness (200–400µm), dermatomed skin is preferred.		
High (Ranking = 1)	The test model (*e.g.*, viable skin, cadaver skin, cosmetic surgery skin) and descriptive information (*e.g.*, tissue origin, anatomical site, tissue storage, integrity or viability) were reported and the test model was routinely used for the outcome of interest.	
Low (Ranking = 3)	The test model was reported along with limited descriptive information. OR The test model was routinely used for the outcome of interest. Reporting limitations are unlikely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	The test model and necessary descriptive information were not reported OR the test model was not appropriate for evaluation of the specific	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 13. Number/Replicates per group Was the number of replicates per dose/concentration group appropriate for the study type and outcome analysis?		
Medium (Ranking = 2)	The number of replicates per dose/concentration were reported and was appropriate (*e.g.*, acceptable data from a minimum of four replicates per test preparation).	

Data Quality Level	Description	
Low (Ranking = 3)	The number of replicates per dose/concentration was reported but was less than recommended by current standards and guidelines. This is likely to have an impact on results. OR The number of replicates per dose/concentration was not reported.	
Critically Deficient (Ranking = 4)	The number of organisms or tissues per study group and/or replicates per study group was insufficient to characterize dermal absorption (*e.g.*, less than four replicates per test preparation produced acceptable data).	
Not Rated/Not Applicable	Not applicable for qualitative studies not requiring any statistics.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Guidance for reviewers	Note similarities and differences to Metric 18. Metric 15 accounts for number of technical/biological replicates, and Metric 18 accounts for statistical sample size within each replicate.	
Domain 5. Outcome assessment		
Metric 14. Outcome assessment methodology Did the outcome assessment methodology address or report the intended outcome(s) of interest? Was the outcome assessment methodology (including nature of endpoints evaluated, measurement technique, and timing of measurement[s]) sensitive for the outcome(s) of interest (*e.g.*, measured endpoints that are able to detect a true effect)? OECD 428, OECD GD28 and OECD GD156 should be consulted, and deviations should be documented and explained.		
High (Ranking = 1)	The outcome assessment methodology addressed the intended outcome(s) of interest AND was sensitive for the outcome(s) of interest and followed OECD guidance documents. The dosing reflected a range of conditions of use (COUs) to which humans are exposed. The infinite dose scenario is optimum for Kp determinations while finite dosing is optimal for % absorption calculations. The dose in the skin should be considered to be the potentially absorbable dose to calculate the final % absorption. Recovery is 90±10% or 80±20%	
Medium (Ranking = 2)	The outcome assessment methodology used partially addressed the intended outcomes(s) of interest and deviations were explained (*e.g.*, mutation frequency evaluated in the absence of cytotoxicity in a gene mutation test), but minor uncertainties are unlikely to have a substantial impact on results.	

Data Quality Level	Description	
Low (Ranking = 3)	Significant deficiencies in the implementation of the reported outcome assessment methodology were identified (*e.g.*, matrix/assay interference, assay yielded anomalous results, etc.) OR The outcome assessment methodology was not clearly reported and it was unclear whether methods were sensitive for the outcome of interest. This is likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	The reported assessment methodology was not sensitive to the outcome(s) of interest. For example, the reported measurement endpoint(s) or timing were not sensitive for the outcome(s) of interest (*e.g.*, cells were evaluated for chromosomal aberrations immediately after exposure to the test substance instead of after post-exposure incubation period). These are serious flaws that make the study unusable.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Guidance for reviewers	If outcome assessment methods were cited to another publication, please review the relevant methods in the original publication and consider this information as you rate outcome assessment methodology	
Metric 15. Consistency of outcome assessment Was the outcome assessment carried out consistently (*i.e.*, using the same protocol) across study groups (*e.g.*, assessment at the same time after initial exposure in all study groups)?		
High (Ranking = 1)	Details of the outcome assessment protocol were reported and outcomes were assessed consistently across study groups (*e.g.*, at the same time after initial exposure) using the same protocol in all study groups. All study groups utilized the same blank formulation as a vehicle, the duration of exposure was the same across groups, the same receptor fluid composition was utilized for each group, the sampling period was consistent across groups, etc.	
Medium (Ranking = 2)	There were minor differences in the timing of outcome assessment across study groups, or incomplete reporting of minor details of outcome assessment protocol execution were explained, but these uncertainties or limitations are unlikely to have substantial impact on results.	
Low (Ranking = 3)	Details regarding the execution of the study protocol for outcome assessment (*e.g.*, timing of assessment across groups) were confusing, limited, or not reported nor deviations explained (or cited to another publication with no description in the paper itself), and these deficiencies are likely to have a substantial impact on results.	

Data Quality Level	Description	
Critically Deficient (Ranking = 4)	There were large inconsistencies in the execution of study protocols for outcome assessment across study groups. These are serious flaws that make the study unusable.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Guidance for reviewers	If outcome methods were cited to another publication., please review the relevant methods in the original publication and consider this information as you rate outcome assessment methodology	
Metric 16. Sampling adequacy Was the reported sampling size adequate for the outcome(s) of interest, including number of evaluations per exposure group, and endpoint (*e.g.*, number of slides/cells/metaphases evaluated per test concentration)? OECD 428, OECD GD28, and OECD GD156 should be consulted, deviations should be explained.		
High (Ranking = 1)	The study reported adequate sampling for the outcome(s) of interest including number of evaluations per exposure group, and endpoint (*e.g.*, scintillation counts/sample]). The sampling intervals should be adequate to allow accurately graphically representing the results of the receptor fluid content of the test article versus time.	
Medium (Ranking = 2)	Details regarding sampling for the outcome(s) of interest were reported, but minor limitations were identified in the reported sampling of the outcome(s) of interest and were explained. However, those limitations are unlikely to have a substantial impact on results.	
Low (Ranking = 3)	Details regarding sampling of outcomes were not fully reported nor explained and the omissions are likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	Reported sampling was not adequate for the outcome(s) of interest and/or serious uncertainties or limitations were identified in how the study carried out the sampling of the outcome(s) of interest (*e.g.*, replicates from control and test concentrations were evaluated at different times).	
Not Rated/Not Applicable	NA should be used for assays/studies that do not require a certain number of slides/cells/metaphases etc. be sampled for scoring (*i.e.*, mutagenicity assays, mechanistic studies).	
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 Level	Description	
Guidance for Reviewers	This metric was intended for assays that require a certain number of slides/cells/metaphases etc. be sampled for scoring following exposure (*e.g.*, chromosomal aberrations, micronuclei, sister chromatid exchange, single strand breaks). If sampling details were cited to another publication, please review the relevant methods in the original publication and consider this information as you rate outcome assessment methodology. Note similarities and differences to Metric 18. Metric 15 accounts for number of technical/biological replicates, and Metric 18 accounts for statistical sample size within each replicate.	
Domain 6. Confounding/variable control		
Metric 17. Confounding variables in test design and procedures Were there confounding differences among the study groups in the size, and/or quality of tissues exposed that could influence the outcome assessment? OECD 428, OECD GD28, and OECD GD156 should be consulted, and deviations should be explained. An adequate number of donors for skin samples should have compliance.		
High (Ranking = 1)	There were no differences reported among study group parameters (*e.g.*, test substance lot or batch, strain/batch/ lot number of organisms or models used per group or size, and/or quality of tissues exposed) that could influence the outcome assessment. Skin integrity was	
Medium (Ranking = 2)	Minor differences were reported and explained in initial conditions that are unlikely to have a substantial impact on results (*e.g.*, tissues from two different lots were used for *in vitro* skin corrosion test, and QC data were similar for both lots). Skin integrity had variability but were acceptable. Outliers were statistically evaluated.	
Low (Ranking = 3)	Initial strain/batch/lot number of organisms or models used per group, size, and/or quality of tissues exposed was not reported. These deficiencies are likely to have a substantial impact on results.	
Critically Deficient (Ranking = 4)	There were significant differences among the study groups with respect to the strain/batch/lot number of organisms or models used per group or size and/or quality of tissues exposed (*e.g.*, initial number of viable bacterial cells were different for each replicate [105 cells in replicate 1, 108 cell in replicate 2, and 103 cells in replicate 3], tissues from two different lots were used for *in vitro* skin corrosion test, but the control batch quality for one lot was outside of the acceptability range). Skin integrity results were below thresholds. Recovery was below guidance limits or not quantified. Exposures did not reflect	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

Data Quality Level	Description	
Guidance for Reviewers	Select low if information on initial conditions for each study group and/or replicate is not reported. Use this metric to address underlying differences between control and exposed tissues (*e.g.*, differences in strain, lots number or tissue quality). Differences in treatment across groups (*e.g.*, failure to use a vehicle where appropriate) should be addressed under Metric 4 (negative and vehicle controls).	
Metric 18. Confounding variables in outcomes unrelated to exposure Were there differences among the study groups unrelated to exposure to test substance (*e.g.*, contamination) that could influence the outcome assessment? Did the test material interfere in the assay (*e.g.*, altering fluorescence or absorbance, signal quenching by heavy metals, altering pH, solubility, or stability issues)?		
High (Ranking = 1)	There were no reported differences among the study replicates or groups in test model unrelated to exposure (*e.g.*, contamination) and the test substance did not interfere with the assay (*e.g.*, signal quenching by heavy metals). The test substance was demonstrated to be soluble in the receptor fluid.	
Medium (Ranking = 2)	Authors reported that one or more replicates or groups experienced disproportionate outcomes unrelated to exposure (*e.g.*, contamination), but data from the remaining exposure replicates or groups were valid and is unlikely to have a substantial impact on results. OR The test material interfered in the assay, but the interference did not cause substantial differences among the groups. OR Solubility in the receptor fluid was not demonstrated, but solubility is not likely to be an issue based on the expected concentration relative to the receptor fluid formulation.	
Low (Ranking = 3)	Data on outcome differences unrelated to exposure (including receptor fluid formulation) were not reported for each study replicate or group and the missing information is likely to have a substantial impact on results. OR Assay interference was present or inferred resulting in large variabilities among the groups.	
Critically Deficient (Ranking = 4)	There were indications of assay interference several replicates or groups or there is evidence of insolubility in the receptor fluid such that no outcomes could be assessed.	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

Data Quality Level	Description	
Guidance for Reviewers	Select medium if information is not reported and only choose high for the studies which mention that the strain/cells were free of fungal contamination, etc.	
Domain 7. Data presentation and analysis		
Metric 19. Data analysis Were statistical methods, calculations methods, and/or data manipulation clearly described and appropriate for dataset(s)?		
High (Ranking = 1)	Statistical methods (including any calculations or data transformations) were clearly described or had only minor omissions and were appropriate for the dataset(s). Percentage absorption estimates were presented across a time series for each compartment of the test system, and Kp/flux measurements were based on the linear/steady-state part of the absorption curve. Any selection of	
Low (Ranking = 3)	Statistical analysis was performed but not described adequately to understand what was performed or whether it was properly applied (*e.g.*, determination of outliers). OR Statistical analysis was inconsistently/inappropriately applied across replicates and datasets (*e.g.*, absorption not measured across time series, inconsistent exclusion of outliers across measurements, coefficient of variation for several replicates (SD relative to mean) was > 25%.	
Critically Deficient (Ranking = 4)	Statistical analysis was performed using an inappropriate method (*e.g.*, parametric test for non-normally distributed data), and/or coefficient of variation for several replicates (SD relative to mean) was >25% OR Statistical analysis was not performed. AND Data enabling an independent statistical analysis were not provided. These are serious flaws that make the study unusable.	
Not Rated/Not Applicable	Statistical analysis was not possible (n = 1−2) or not necessary (clearly negative findings across all groups; Ames assay using 2-fold increase as benchmark).	
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 20. Data interpretation Were the evaluation criteria reported and is the interpretation of results consistent with standards and guidelines? *E.g.*, Did reported absorption estimates account for sufficient recovery? Was the combined amount of test substance in the skin and receptor fluid counted in the overall estimate?		

Data Quality Level	Description	
High (Ranking = 1)	Study authors followed evaluation criteria for the test, and these were consistent with established practices [a]. Recovery of applied test substance was adequate (90% for occluded or non-volatile substance, 80% for non-occluded, volatile substance) AND Assay results were correctly interpreted relative to the properties of the test substance and the assay setup (sufficient duration to capture all absorption if not evaporated, proper interpretation of finite vs.infinite dose.	
Medium (Ranking = 2)	Absorption estimates were reported improperly (*e.g.*, skin compartment not included, values not normalized if recovery less than adequate), however simple independent data analysis is possible to overcome these issues.	
Low (Ranking = 3)	Complex reanalysis of the data is required in order to obtain usable interpretations (*e.g.*, external outlier analysis may be required, Kp determination must be recalculated from the time series).	
Critically Deficient (Ranking = 4)	The reported ranking and/or evaluation criteria were very inconsistent with established practices, resulting in the interpretation of data results that are seriously flawed and highly misleading relative to the properly interpreted results (*e.g.*, study author claims 5% absorption but correct analysis results in 40% absorption, only percentage absorption is reported from a finite dose).	
Not Rated/Not Applicable	Do not select for this metric.	
Reviewer's Comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 21. Reporting of data Were the data for all outcomes presented? Were data reported by exposure group?		
High (Ranking = 1)	Data for exposure-related findings were presented for all outcomes by exposure group. Negative findings were reported qualitatively or quantitatively.	
Medium (Ranking = 2)	Data for exposure-related findings were reported for most, but not all, outcomes by exposure group (*e.g.*, both short and long-term exposures). The minor uncertainties in outcome reporting are unlikely to have substantial impact on results (*e.g.*, outcomes without exposure-related effects are indicated as negative in text).	

Data Quality Level	Description	
Low (Ranking = 3)	Data for exposure-related findings were not shown for each study group, but results were described in the text. OR Data were only reported for some outcomes. OR Continuous data were presented without measures of variability or n/group.	
Critically Deficient (Ranking = 4)	Data presentation was inadequate (*e.g.*, the report does not differentiate among findings in multiple exposure groups) OR Major inconsistencies were present in reporting of results that render the findings uncertain regarding hazard identification or dose-response.	
Not Rated/Not Applicable	Do not use 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]*	
Guidance for Reviewers	The reporting of data in studies conducted by IBT during 1960-1978 is considered critically deficient due to concerns about the integrity of the lab (*i.e.*, discrepancies between raw data and study report, and gross deficiencies in study conduct were identified during an inspection by the FDA in 1976 and a follow-up audit by EPA in collaboration with the Canadian Health and Welfare Department (https://www.oecd.org/chemicalsafety/risk-assessment/49191960.pdf).	
Domain 8. Other (apply as needed)		
Metric:		
High (Ranking = 1)		
Medium (Ranking = 2)		
Low (Ranking = 3)		
Critically Deficient (Ranking = 4)		

Appendix T COMPARISON OF DATA QUALITY EVALUATION CRITERIA FOR HUMAN HEALTH (ANIMAL TOXICITY, EPIDEMIOLOGY), ENVIRONMENTAL HEALTH, AND *IN VITRO* DATA TYPES

To respond to SACC, NASEM, and public comments, EPA updated data quality criteria for *in vitro* studies, environmental health and human health hazards (animal toxicity and epidemiology studies) (as presented in Appendix O through Appendix R of the current document). Although there are necessary differences among these sub-disciplines, EPA strived to make the metrics and domains as consistent as possible. Table_Apx T-1 presents this comparison, and in particular and the choices that assessors have for data quality rankings for each discipline and metric. Some study metrics are not shown because they apply to only a single type of study or sub-discipline.

Table_Apx T-1. Comparison of Hazard Data Quality Criteria

Metric(s)	*In Vitro*	Environ Health	HH: Animal Tox	HH: Epi	Comments
Metric 1: Test substance identity (*in vitro*, environ health, animal tox) **Metric 21:** Method requirements (epi)	High, Med, Low, Critically Deficient	High, Med, Low, Critically Deficient	High, Med, Low, Critically Deficient	High, Med, Low, Not Rated	Similar language among disciplines except epi metric addresses biomarker measurements
Metric 2: Test substance source (*in vitro*, environ health, animal tox)	High, Low	High, Low	High, Low	NA	Similar language among disciplines
Metric 3: Test substance purity (*in vitro*, environ health, animal tox); **Metric 20:** Sample contamination (epi)	High, Med, Low, Critically Deficient	High, Med, Low, Critically Deficient	High, Med, Low, Critically Deficient	High, Med, Low, Critically Deficient, Not Rated	The *in vitro* and animal tox medium ranking identify a minimum purity threshold, but the environ health medium ranking does not
Metric 4: Negative controls (*in vitro*, environ health, animal tox)	High, Low, Critically Deficient, Not Rated	High, Low, Critically Deficient, Not Rated	High, Low, Critically Deficient, Not Rated	NA	Disciplines with this metric have similar language
Metric 5: Positive controls (*in vitro*, animal tox)	Med, Low, Critically Deficient, Not Rated	NA	Med, Low, Critically Deficient, Not Rated	NA	Environ health and epi studies generally do not have positive controls

Metric(s)	*In Vitro*	Environ Health	HH: Animal Tox	HH: Epi	Comments
Metric 6: Random allocation (environ health, animal tox); **Metric 1:** Participant selection (epi)	NA	Med, Low, Critically Deficient	Med, Low, Critically Deficient, Not Rated	High, Med, Low, Critically Deficient	Differences in allocation that result in substantial impacts on results are identified as critically deficient for environ health but low for animal tox
Metric 8/7: Preparation and storage of test substance (*in vitro*/animal tox); **Metric 7:** Experimental system/test media preparation (environ health); **Metric 19:** Biomarker stability (epi)	High, Med, Low, Critically Deficient	High, Med, Low, Critically Deficient	High, Med, Low, Critically Deficient	High, Med, Low, Not Rated	Differences generally reflect different types of studies
Metric 9/8: Consistency of exposure administration (*in vitro* (9), environ health and animal tox (8)); **Metric 4:** Measurement of exposure (epi)	High, Med, Low, Critically Deficient	High, Med, Low, Critically Deficient	High, Med, Low, Critically Deficient	High, Med, Low, Critically Deficient	Differences generally reflect differences among study types
Metric 10/9: Reporting of doses, concentrations (*in vitro* (10); animal tox (9); Measurement of test substance concentrations (environ health (9))	High, Med, Low, Critically Deficient	High, Med, Low, Critically Deficient	High, Med, Low, Critically Deficient	NA	Reporting omissions are considered low for environ health but in critically deficient for animal tox
Metric 11: Exposure Duration (*in vitro*); **Metric 10:** Exposure frequency and duration (environ health; animal tox)	High, Med, Low, Critically Deficient	High, Med, Low, Critically Deficient	High, Med, Low, Critically Deficient	NA	Differences between environ health and animal tox for some criteria levels
Metric 12/11: Number of exposure groups and dosing/ concentration/ exposure spacing (*in vitro* (12); environ health and animal tox (11); **Metric 5:** Exposure levels (epi)	High, Med, Low, Critically Deficient	High, Med, Low, Critically Deficient, Not Rated	High, Med, Low, Critically Deficient, Not Rated	Med, Low, Critically Deficient	Differences generally reflect differences among study types

Appendix U SOPs FOR IDENTIFICATION, ORGANIZATION, AND EVALUATION OF ADME AND PK STUDIES AND MODELS

Prepared by the U.S. Environmental Protection Agency, Office of Research and Development, PKWG QA Team
ORD QAPP ID Number:B-0030740-QP-1-1
This appendix contains excerpts from ORD's QAPP for PBPK models (U.S. EPA, 2018e), specifically Section B (SOP for Identification, Organization, and Evaluation of ADME and PK Studies and Models).

U.1 ADME Data Evaluation and Selection

This section describes the analytical process by which information from ADME studies is evaluated and selected for use in PK modeling. Uncertainty in PK modeling is reduced when the most relevant, reliable, and quantitatively valuable ADME studies are identified and given precedence over studies that provide limited information. It is important to identify all relevant, scientifically sound ADME data to provide the best possible basis for model calibration and evaluation. In particular, one would want to know how well a model describes any existing data, and the more data used in model evaluation and calibration, the lower the uncertainty in model predictions. On the other hand, for chemicals with very large available databases (there are hundreds of ADME studies for some chemicals), one will wish to identify a smaller, manageable set of PK studies that is representative of the larger database.

PBPK models serve to quantify inter- and intra-species PK differences, so are developed for specific animal species or humans. Therefore, the most relevant ADME studies are ones conducted in those species and it is generally acceptable to ignore studies from other species not being modeled. However, mechanistic information may be derived from other species, so a qualitative summary of those data can be helpful. ADME studies are used to: identify parent chemical and metabolite(s) found in test species and humans; demonstrate metabolic pathways; identify metabolizing enzymes and kinetic constants (*e.g.*, K_m, V_{max}); characterize metabolic competition (*i.e.*, when multiple chemicals compete for the same metabolic enzyme); characterize primary routes/methods of elimination; and identify data gaps toward which future research may be targeted. Given that nearly all PK reports have some level of intrinsic value, the considerations described below will help determine the level of detail at which these reports might be summarized.

For the purpose of PBPK modeling, optimal ADME studies are those that have been peer reviewed, have been conducted in humans or in the species/strain of animal being modeled, and have employed a range of doses that span those used in key toxicological studies or are relevant to human exposures. The most useful ADME studies report the time course for amounts or concentrations of a parent compound of interest and specifically identified metabolite(s), providing information on the overall fate and mass balance of the parent chemical. For human ADME studies, doses in the range of the point of departure (POD) are ideal for informing animal-to-human extrapolation. Other studies, including those that evaluate formation of a given metabolite by *in vitro* methods may also have value.

While there is no formally established approach to categorize ADME studies based on their data type and depth of detail, a conceptualized "tiered approach" may be a useful tool through which to consider the value of each study. For example, the initial evaluation may focus only on the primary features of a study such as the species, strain, sex, developmental stage, exposure route and regimen of administration, sample timing, extent to which metabolites are identified and distinguished analytically from the parent chemical, and the number of time-points evaluated. The most promising studies identified by applying filters to this first tier of information (*e.g.*, those conducted in the species, sex,

strain, and developmental stage being modeled, and which are dosed via the route(s) of interest) can then be evaluated more carefully in a second-tier review for aspects of study and data quality. The second tier review might identify the studies which quantify levels of the parent compound and key metabolites, demonstrate the relationship between exposure and internal dose, provide time-course data in target tissues or blood, and employ sound analytical and statistical methods. The points identified under the general considerations for *in vitro* and *in vivo* studies below should be used when evaluating study quality, whether or not a tiered approach is used.

It should be recognized that many chemicals produce multiple toxicities, through different MOAs, with different dose-response functions, and that a PBPK model may be used to help interpret results for multiple endpoints. It is recommended that ADME study and data selection focus not only on the apparent key effect (*i.e.*, based on external dose-response and severity considerations), but other endpoints that are triggered by exposures within an order of magnitude of the most sensitive one.

The extent to which ADME reports address the following questions impacts their value for PK modeling. While answers to all these questions are not strictly required, they are all valid and useful for ranking such studies. For chemicals with many ADME publications, greater application of these questions will aid in selecting the best data for modeling.

General considerations:

- Have toxicity studies identified a responsive test animal species (*e.g.*, Sprague-Dawley rat) and target organ or tissue (liver, thymus, kidney, brain)? Does the ADME investigation evaluate (tissues or samples from) the identified test species/strain or human? If not, to what extent can the species and tissue investigated be deemed an appropriate surrogate?
- Are the results based on chemical-specific identification and quantitation (*e.g.*, gas chromatographic, high-performance liquid chromatography [HPLC], or mass spectral identification) or on general measures of chemical distribution (*e.g.*, radiolabel quantitation)?
- For data from/in humans, is the characterization of exposure sufficient to inform qualitative or quantitative conclusions?
- To what extent can adverse outcome(s) be attributable to the parent chemical, metabolism of the parent chemical (via a specific pathway), or an identified metabolite? If the parent chemical or a key metabolite or pathway has been identified, to what extent does an ADME study inform the dosimetry of the parent chemical, specific metabolic pathway, or identified metabolite?
- To what extent can human data be used to characterize inter-individual PK variability?
- Are valid analytical methods utilized and described in sufficient detail to enable interpretation of the data; are limits of detection and/or quantification provided?
- To what extent has the report been subjected to a peer review? Is the document accessible in whole or in part?

For in vitro ADME investigations:

- To what extent has the concentration of the agent been localized (*e.g.*, measurement in cells versus media) and characterized (*e.g.*, parent chemical disappearance, metabolite formation)?
- Are non-biological sources of loss accounted for (*e.g.*, volatilization, solubility, binding to non-biological test system components)?
- To what extent does the range of concentrations studied enable an evaluation of events at non-saturating and saturating conditions of metabolism, binding, or transport?
- What evidence is available to determine whether *in vitro* concentrations have *in vivo* relevance, both in studies conducted in animal models and in human environmental exposures?

- What is the biological level of organization of the *in vitro* system? How much extrapolation is required to convert from units observed (*e.g.*, pmol product formed per minute per pmol enzyme) to values representative of the intact system? Do multiple bioprocessing steps or bifurcations in downstream or upstream metabolic process complicate the extrapolation?
- If metabolic rates have been determined using recombinantly expressed enzymes, has a relative activity factor been determined?
- If metabolic rate constants have been derived and presented by the authors, are the underlying data available for evaluation?

For in vivo ADME studies:

- Was the route and method (*e.g.*, inhalation, oral drinking water, oral bolus) of administration consistent with the route and method of exposure used in the toxicity evaluations?
- How likely is it that differences between the vehicle used in the toxicity study and the ADME study may have introduced PK differences between the two studies?
- Is it likely that manipulations of the animal have altered the underlying anatomy, physiology, or biochemistry related to related ADME processes (*e.g.*, could anesthesia have altered important functions like respiration and chemical metabolism)?
- Are time-course and/or exposure-dose PK data reported?
- What is the relationship of doses evaluated to the POD?
- Do the data demonstrate mass-balance? Or do they focus on a single pathway or step in a complex overall metabolic pathway?

After considering the set of available ADME studies against the various factors described above, it should be possible to sort the studies according to their relevance to the intended PBPK model development and application (*e.g.*, test species, route of exposure), type of information (studies that identify ADME mechanisms vs. those providing quantitative data useful for calibration and validation), and study quality. (which may enable ranking and selection of studies with apparently discordant results, or identification of those most useful for PK modeling).

In cases of apparently conflicting PK data sets, an analysis of the methods and details will be conducted to either resolve the discrepancy or decide which of the data sets is/are most likely to be correct. For example, there are sometimes significant strain- or gender-related differences in PK among laboratory animals. If apparent data discrepancies appear to be due to such differences, then a PBPK model would only be expected to fit a particular strain (or sex), and, for risk assessment application, this should be the one with critical dose-response data. Alternatively, model parameters might be identified for each strain, gender, life-stage, or other sub-population for which analysis is to be conducted. Discrepancies between data sets might also occur due to different analytical methods, in which case evaluation of the methods might lead to identification of certain data sets as unreliable. In each case, the rationale for selection or grouping of particular data sets will be recorded.

Once this is complete the qualitative information can be summarized (or used to evaluate the quality and completeness of an existing summary) and the studies from which data should be extracted for model calibration or validation identified. While it is beyond the scope of this QAPP to specify in detail how the summarization and study selection should be conducted, a written summary describing the approach used (*e.g.*, tiered evaluation, with selection process at each tier) and the rationale for study selection should be prepared, allowing for the process to be independently reviewed and possibly reproduced.

U.1.1 Extraction of Quantitative ADME Data and PK Model Parameters

All sources of data and parameters used for model calibration and evaluation will be documented in text tables and/or Excel workbooks, with a level of detail to allow easy validation. In particular, specific table numbers, figure numbers, or page and paragraph/line numbers should be provided. If multiple entries in a table report alternate values of a quantity (*e.g.*, measured by different techniques), then further detail shall be provided. If a model is obtained without documentation of ADME data and model parameters as described here, then such documentation shall be generated as part of the model QA evaluation.

Identifying the source of a PBPK model parameter as a publication describing a previous PBPK model where the parameter is in turn taken from an earlier source, is not sufficient, because that practice can lead to propagation of errors. The parameter value should be tracked back to and checked against the publication in which it is first reported or measured. This can include, however, articles and reports which comprehensively review and report physiological parameters, such as Brown et al. (1997) and ILSI (1994). However, for such comprehensive reviews, different values for the same parameter may be reported in different tables, hence it is particularly important to identify the specific table (and column/row) from which the parameter is taken.

Where calculations are used to convert reported parameters or data to values/units consistent with a model, sufficient detail to replicate the calculations shall be provided. Preferably, calculations and conversions are set up in computational scripts or Excel spreadsheets using embedded formulas. For example, if a tissue mass fraction is calculated from a reported tissue weight (TW) and body weight (BW), then the TW and BW are entered into adjacent columns, exactly as reported in the reference, and the resulting fraction (TW/BW) is calculated in a third column (*e.g.*, the entry is '= C1/B1'), rather than entered as a numerical value. Comment text (and column headers in spreadsheets) would identify the data source(s), as described above and provide details for more complex calculations.

When parameters are derived by more elaborate means, for example a regression analysis, details sufficient to replicate the result should be provided; this can be readily accomplished by embedding the analysis in a script. Simple regressions can also be performed directly in Excel plots, with the equations shown, allowing for easy validation. If a regression is performed by other means (*e.g.*, using the Solver function in Excel), then a plot of the resulting curve can be generated along with the data for visual comparison, which makes it immediately evident when a significant numerical error has occurred.

When data are received directly from the author, a copy of the data file shall be saved with "as received" and the date received or saved in the file name. Subsequent manipulations of the data file shall be done using copies of this original file, with that dependence documented in the copies or an accompanying text file.

If original data files are not available from the data authors (often the case for older data) then they should be validated against the published sources, with documentation generated in the process. Data provided in numerical form from an intermediate source (*e.g.*, a model author) can be plotted and compared to a published figure as described below to ensure accuracy.

All data and parameter extraction should be validating by having an individual other than the person who performed this initial extraction check the values against the original sources. If data were initially extracted by the authors of a publication, then a single reviewer (other than those authors) can perform the check. For data sets with less than 20 entries, all entries should be checked. For larger data sets a minimum of 20 entries or 20 percent of the entries should be checked, whichever is greater.

When data are digitized from a published figure, a preferred method of validation is to plot the data in Excel using identical axis types (*e.g.*, linear vs. log) and scales and a clear background for the plot. This generated plot can then be placed on top of a graphic image of the plot from the publication, stretched or compressed to give exact alignment of the axes, but smaller symbol sizes/alternate colors in the generated Excel plot. It can then be quickly seen that the reproduced plot points exactly match those in the digital image (to within a few percent precision). If the initial extractor creates such a plot, then a reviewer only needs to visually examine the plot and check that the data values in the spreadsheet cells used by the plot match the values in files read or otherwise used for the model – the reviewer does not need to re-create the plot to check its accuracy.

U.2 Review, Verification, and Validation of Existing Computational PBPK/PK Models

U.2.1 General Approach for Model Evaluation

Criteria for judging the quality of a model provided here are separated into two categories: scientific and technical, which are respectively described in Appendix U.2.2 and in Appendix U.2.3. In summary, the scientific criteria (primarily included in Criteria A) focus on whether or not the biology, chemistry, and other information available for chemical MOA(s) (or the subset of those being described by a specific model) are appropriately represented by the model structure and equations. The scientific criteria can be judged based on the (draft) publication or report that describes the model and do not require evaluation of the computer code. Criteria A also include preliminary technical criteria, such as availability of the computer code (if obtained from an outside source) and apparent completeness of parameter listing and documentation. The in-depth technical and remaining scientific criteria (Criteria B) focus on the accurate implementation of the conceptual model in the model code and scripts, use of correct or biologically consistent parameters in the model, and reproducibility of model results reported in journal publications and other documents. Any data sets incorporated into the model should be verified, and should be documented as described in Appendix U.1 for their accuracy and quality.

While the criteria presented here are in part a component of the current IRIS process, similar scientific criteria have also been successfully applied and are described in greater detail by Chiu et al. (2007), Mclanahan et al. (2012), IPCS (2010), and Clark et al. (2004). This approach stresses: (1) clarity in the documentation of model purpose, structure, and biological characterization; (2) validation of mathematical descriptions, parameter values, and computer implementation; and (3) evaluation of each plausible dose metric. Such transparency and documentation are important for compliance with the Agency's information quality guidelines (U.S. EPA, 2002a).

U.2.2 PBPK/PK Model Structure and Documentation (Criteria A)

It is assumed here that a journal article, report, or other scientific document describing the model structure, underlying science, and sources or methods for identifying all model parameters is available (need not be a peer-reviewed publication), and that a copy of the corresponding computer code has been obtained, along with permission for its use and subsequent public distribution. For QA evaluation, a brief report is prepared summarizing the key features of the PBPK model and its likely utility for use in a risk assessment. For example, one can quickly determine if a model has been calibrated for oral and/or inhalation exposures, and hence whether it is suitable for specific routes of exposure. This information is important for evaluating the potential applicability of a given PK or PBPK model. For example, if it is thought that a key toxic endpoint results from metabolism to a reactive metabolite in a target tissue, then a model that doesn't predict that rate (dose metric) would not be useful. The model QA report should evaluate the following criteria, based on the model description in publications or reports.

Scientific Criteria for PBPK/PK Models:

1. Biological basis for the model is accurate
2. Model equations are consistent with biochemical understanding and biological plausibility
3. Consistent with mechanisms that significantly impact dosimetry
4. Describes critical behavior, such as nonlinear kinetics in a relevant dose range
5. Predicts dose-metrics expected to be relevant and to be better correlated with toxicity or risk than applied doses
6. Applicable for relevant route(s) of exposure
7. Model should describe existing PK data reasonably well
8. Shape: matches curvature or nonlinearity, inflection points, peak concentration time, etc.
9. Quantitative value: model predictions preferably within a factor of 2 to 3 of the data
10. Validity of chemical-specific hypotheses:
11. Standard PBPK model compartments incorporate a limited number of hypotheses regarding ADME processes that have been tested and shown consistent with multiple data sets, for multiple chemicals, and therefore do not require in-depth consideration.
12. However, hypotheses specific to a particular chemical or chemical class, which are not supported by PBPK model agreement with data for other chemicals, should be evaluated more carefully, in particular when a hypothesis leads to prediction of much lower risk in humans than experimental animals.
13. For example, if it is hypothesized that a specific metabolic pathway operates in an experimental animal species (in a target tissue), making that species (tissue) particularly sensitive, then one should determine if there are ADME data for that metabolite (in the target tissue) in both sensitive and non-sensitive animal species demonstrating dosimetric differences commensurate with sensitivity, and dosimetric data in humans (or human tissues) demonstrating a lack of production.
14. Another example is the hypothesis that reactive metabolites formed in the liver will not have an impact on other tissues. But a moderately reactive metabolite with a half-life of minutes is sufficiently stable to be transported between tissues or cell types within a tissue, even if it is too reactive to measure in tissue samples from *in vivo* PK studies, so this hypothesis needs careful evaluation.
15. PBPK models which incorporate alternate hypotheses (*e.g.*, some systemic distribution for a metabolite vs. none) may be equally consistent with the ADME data, but lead to very different risk predictions, and the resulting range of uncertainty should be considered.

Technical Criteria for PBPK/PK Models (Evaluate if Scientific Criteria Are Met):

1. Well-documented model code
2. Parameters are clearly identified, including origin/derivation (validated as described in B1.2)
3. Parameters do not vary unpredictably with dose (*e.g.*, any dose-dependence in absorption constants is predictable across the dose ranges relevant for animal and human modeling)
4. For probabilistic human models, evaluate parameter distributions in the model vs. full human variability. For example, Bayesian calibration applied to human data taken from only healthy adults, and with physiological parameters representing that group, may not be sufficient to describe the entire population. When specific factors such as a genetic polymorphism are known to impact human variability, an analysis which fails to incorporate them would not be considered sufficient to replace default uncertainty factors. Generally, all segments of the population should be included when evaluating the distribution of the Human Equivalent Dose (HED) or Human Equivalent Concentration (HEC) but limiting the analysis to only the most sensitive group can be considered.

5. Sensitivity and uncertainty analysis has been conducted for relevant exposure levels (local sensitivity analysis is sufficient, although global sensitivity analysis is more informative)
6. If a sensitivity analysis was not conducted, then one should be performed as part of the QA evaluation
7. A sound explanation should be provided when sensitivity of the dose metric to model parameters differs from what is reasonably expected based on experience

U.2.3 PBPK/PK Model In-Depth Technical Evaluation (Criteria B)

The following technical criteria address the computational implementation, including checking the code versus published or implied equations, and attempting to reproduce published figures and tables.

1. Model equations and parameters specified in computer code match those published or implied[23] in the peer-reviewed manuscript or report
2. Published figures and tables of model simulations are reproducible to within 10 percent
3. The most rigorous approach to validating that a particular model implementation accurately represents the mathematical and conceptual model as described in a publication or report (or implied, if not all equations are explicitly listed) is to independently replicate coding of the model; *e.g.*, in a different programming language/environment. Such re-coding, while not necessary for acceptance and application of a PBPK model, may also facilitate transparency and communication of the model for internal and external scientific reviewers and other stakeholders and interested parties.
4. If errors in the model implementation (equations or parameters) are found and corrected, and the correction or change alters the evaluated model predictions (plots or tables showing model agreement with data) by less than 10 percent, the error is considered small enough to not invalidate the model or any other parameter value—*even if model predictions outside the range of the data change by more than 10 percent*.
5. Since model quality is judged by comparing model predictions to data, the impact of an error on model quality is evaluated only by determining the impact in the range of the data. The error is considered *de minimis*, hence acceptable, if the impact in the range of the data is less than 10 percent.
6. An impact greater than 10 percent outside the range of any data may indicate uncertainty in model extrapolation to that range but does not alter the evaluation of its technical quality.
7. If scientifically justified, a new version of the model equation or parameter may be documented and used in place of a published version (even if errors/corrections in the original version do not result in changes greater than 10 percent)
8. For corrections resulting in changes greater than 10 percent in the range of the data, or significant changes in model structure (vs. only revising parameters), the revised model should be evaluated as a new model version; key conclusions may be unchanged, but the quality cannot be judged based on results of the previous version.

U.2.4 Documentation of Model Evaluation

Documentation of a model evaluation, in particular the technical evaluation (Criteria B) should be generated and saved on a network drive/folder specific to the model being evaluated. A master checklist of items being evaluated (*e.g.*, model parameters, model data, model equations) should be created, to include summaries of the initial evaluation, corrective actions, and final decision with respect to overall model quality or acceptability. For sets of model parameters or data, which can be large in themselves,

[23] Some publications assume familiarity with the standard forms or equations for PBPK model compartments and may only describe them in the text and provide the associated parameters, without listing the specific equations. In this case the equations are implied.

dependent documents (checklists) can be generated. For example, the master check-list would identify "Model parameters" as one item, with a parameter check-list document identified therein. Evaluation of each parameter is then documented in the parameter check-list.

U.3 Development of New PBPK Models, Significant Revisions of Existing Models, and Other Computational Analyses

While the sections above specifically address the evaluation of existing PBPK models, development of new models, significant model revision, and other computational analysis (*e.g.*, estimation of exposure from biomarker levels) should be subject to the same scientific criteria and conducted in a way that satisfies the quality criteria, specifically

1. Parameters and data should be collected and documented, with a second individual checking the values/extraction for accuracy.
2. Complete details of unit conversions and other data manipulations, regressions, and the derivation of any non-typical model equations should be provided, with algebraic calculations embedded in Excel worksheets (using formulas) or in scripts (with comments).
3. Model equations should be described in complete detail in a text document (*e.g.*, a report or appendix), such that a reviewer can ascertain that the equations in the model code represent a correct mathematical translation of the model.
4. Comments should be provided within the code and scripts to facilitate review and QA (*i.e.*, describing what lines or sections of code do) and at the top of model scripts to summarize their function.
5. A second individual should check the model code and any accompanying scripts line-by-line to assure that the code matches the text description; or an accompanying "readme" file should be created to provide an overview and general directions for users. Instructions in this file should contain sufficient detail such that any person moderately experienced with programming and PBPK modeling can reproduce model results.
6. Documentation of the QA evaluation in the form of tables or checklists, listing all items checked, should be created and stored.

U.4 Model Environment Conversion

In order to support transparency and to facilitate external peer and stakeholder review of PBPK models, all such models should be made available in a freely available programming environment, such as R, MCSim, or Octave. If a model is already available in such an environment, then no conversion is required. However, when a model is converted from another environment it is expected that all numerical outputs (*e.g.*, results reported in tables) and graphical outputs (plots) should be matched between versions. Numerical results should match to at least three significant figures and there should be essentially no observable discrepancy in graphical output, beyond those that result from formatting choices. In the process of checking and assuring this level of consistency between software environments, errors in model equations or parameters may be found. Thus, software environment conversion facilitates QA evaluation. Therefore, it may be desirable to convert a highly influential model to an alternate environment, or independently code the model in the same environment, even when that is not needed for model sharing and review. All files defining the model equations and parameters, and any other scripts for each equivalent model version, should be made available for review and evaluation.