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Problem Formulation of the Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-)

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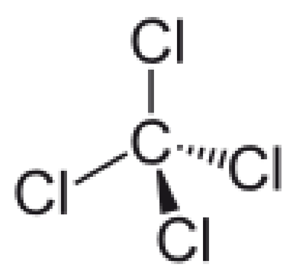

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Docket

Supporting information can be found in public docket: EPA-HQ-OPPT-2016-0733.

Disclaimer

ABBREVIATIONS

°C	Degrees Celsius
AAL	Allowable Ambient Levels
atm	Atmosphere(s)
ATSDR	Agency for Toxic Substances and Disease Registries
AWQC	Ambient Water Quality Criteria
BCF	Bioconcentration Factor
BUN	Blood Urea Nitrogen
CAA	Clean Air Act
CASRN	Chemical Abstract Service Registry Number
CBI	Confidential Business Information
CDR	Chemical Data Reporting
CEHD	Chemical Exposure Health Data
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act
CFC	Chlorofluorocarbon
cm^3	Cubic Centimeter(s)
CNS	Central Nervous System
COC	Concentration of Concern
CoRAP	Community Rolling Action Plan
CPSC	Consumer Product Safety Commission
CS_2	Carbon Disulfide
CSATAM	Community-Scale Air Toxics Ambient Monitoring
CSCL	Chemical Substances Control Law
CYP450	Cytochrome P450
CWA	Clean Water Act
DNA	Deoxyribonucleic Acid
DT50	Dissipation Time for 50% of the compound to dissipate
EC	European Commission
ECHA	European Chemicals Agency
EDC	Ethylene Dichloride
EPA	Environmental Protection Agency
EPCRA	Emergency Planning and Community Right-to-Know Act
ESD	Emission Scenario Document
EU	European Union
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug and Cosmetic Act
FHSA	Federal Hazardous Substance Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	Gram(s)
HAP	Hazardous Air Pollutant
HCFC	Hydrochlorofluorocarbons
HCl	Hydrochloric Acid
HFC	Hydrofluorocarbon
HFO	Hydrofluoroolefin
IDLH	Immediately Dangerous to Life and Health
IMAP	Inventory Multi-Tiered Assessment and Prioritisation
IRIS	Integrated Risk Information System
ISHA	Industrial Safety and Health Act

km	Kilometer(s)
L	Liter(s)
lb	Pound
log K_{oc}	Logarithmic Soil Organic Carbon:Water Partitioning Coefficient
log K_{ow}	Logarithmic Octanol:Water Partition Coefficient
m^3	Cubic Meter(s)
MACT	Maximum Achievable Control Technology
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	Milligram(s)
mmHg	Millimeter(s) of Mercury
MP	Montreal Protocol
mPa·s	Millipascal(s)-Second
NAICS	North American Industrial Classification System
NATA	National Air Toxics Assessment
NATTS	National Air Toxics Trends Stations
NEI	National Emissions Inventory
NESHAP	National Emission Standards
NHANES	National Health and Nutrition Examination Survey
NIOSH	National Institute of Occupational Safety and Health
NPDWR	National Primary Drinking Water Regulations
NTP	National Toxicology Program
NWQMC	National Water Quality Monitoring Council
OCSPP	Office of Chemical Safety and Pollution Prevention
ODS	Ozone Depleting Substance
OECD	Organisation for Economic Co-operation and Development
OELs	Occupational Exposure Limits
ONU	Occupational Non-Users
OPPT	Office of Pollution Prevention and Toxics
OSHA	Occupational Safety and Health Administration
OW	Office of Water
PCE	Perchloroethylene
PEL	Permissible Exposure Level
PESS	Potentially Exposed or Susceptible Subpopulations
POD	Point of Departure
POTW	Publicly Owned Treatment Works
ppm	Part(s) per Million
PDM	Probabilistic Dilution Model
QC	Quality Control
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RCRA	Resource Conservation and Recovery Act
RIE	Reactive Ion Etching
SDS	Safety Data Sheet
SDWA	Safe Drinking Water Act
SIAP	Screening Information Dataset Initial Assessment Profile
SIDS	Screening Information Dataset
STEL	Short-term Exposure Limit
STORET	STORage and RETrieval

SYR	Six-year Review
TCCR	Transparent, Clear, Consistent and Reasonable
TCLP	Toxicity Characteristic Leaching Procedure
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TURA	Toxic Use Reduction Act
TWA	Time-Weighted Average
UATMP	Urban Air Toxics Monitoring Program
U.S.	United States
USGS	United States Geological Survey
VOC	Volatile Organic Compounds
WHO	World Health Organisation
WQP	Water Quality Portal

EXECUTIVE SUMMARY

TSCA § 6(b)(4) requires the U.S. Environmental Protection Agency (EPA) to establish a risk evaluation process. In performing risk evaluations for existing chemicals, EPA is directed to "determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other non-risk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation by the Administrator under the conditions of use." In December of 2016, EPA published a list of 10 chemical substances that are the subject of the Agency's initial chemical risk evaluations (81 FR 91927), as required by TSCA § 6(b)(2)(A). Carbon tetrachloride was one of these chemicals.

TSCA § 6(b)(4)(D) requires that EPA publish the scope of the risk evaluation to be conducted, including the hazards, exposures, conditions of use and potentially exposed or susceptible subpopulations (PESS) that the Administrator expects to consider. In June 2017, EPA published the Scope of the Risk Evaluation for carbon tetrachloride. As explained in the scope document, because there was insufficient time for EPA to provide an opportunity for comment on a draft of the scope, as EPA intends to do for future scope documents, EPA is now publishing and taking public comment on a problem formulation document to refine the current scope, as an additional interim step prior to publication of the draft risk evaluation for carbon tetrachloride. Comments on this problem formulation document will inform the development of the draft risk evaluation.

This problem formulation document refines the conditions of use, exposures and hazards presented in the scope of the risk evaluation for carbon tetrachloride and presents refined conceptual models and analysis plans that describe how EPA expects to evaluate the risk for carbon tetrachloride.

Carbon tetrachloride is a high production volume solvent. The Montreal Protocol and Title VI of the Clean Air Act (CAA) Amendments of 1990 led to a phase-out of carbon tetrachloride production in the United States for most non-feedstock domestic uses in 1996 and the Consumer Product Safety Commission (CPSC) banned the use of carbon tetrachloride in consumer products (excluding unavoidable residues not exceeding 10 ppm atmospheric concentration) in 1970. Currently, carbon tetrachloride is used as a feedstock in the production of hydrochlorofluorocarbons (HCFCs), hydrofluorocarbons (HFCs) and hydrofluoroolefins (HFOs). EPA has identified information on the regulated use of carbon tetrachloride as a process agent in the manufacturing of petrochemicals-derived and agricultural products and other chlorinated compounds such as chlorinated paraffins, chlorinated rubber and others that may be used downstream in the formulation of solvents for degreasing and cleaning, adhesives, sealants, paints, coatings, rubber, cement and asphalt formulations. The use of carbon tetrachloride for non-feedstock uses (i.e., process agent, laboratory chemical) is regulated in accordance with the Montreal Protocol.

Recent data on environmental releases from the Toxics Release Inventory (TRI), indicate that approximately 153,000 pounds of carbon tetrachloride were released to the environment in 2015. Most of the reported environmental releases for carbon tetrachloride were air emissions (fugitive and point source air emissions).

This document presents the potential exposures that may result from the conditions of use of carbon tetrachloride. Exposure may occur through inhalation and oral and dermal pathways, due to carbon tetrachloride's widespread presence in a variety of environmental media such as air, drinking water, groundwater, and surface water. Exposures to the general population may occur from industrial, and/or commercial uses; industrial releases to air, water or land; and other conditions of use. Workers and

occupational non-users (ONU) may be exposed to carbon tetrachloride during a variety of conditions of use, such as manufacturing, processing and industrial and commercial uses, including manufacturing of refrigerants and other chlorinated compounds. EPA expects that the highest exposures to carbon tetrachloride generally involve workers in industrial and commercial settings. EPA considers workers and ONU to be PESS. EPA will evaluate whether groups of individuals may be exposed via pathways that are distinct due to unique characteristics (e.g., life stage, behaviors, activities, duration) that increase exposure, and whether groups of individuals have heightened susceptibility, and should therefore be considered PESS for purposes of the risk evaluation.

Carbon tetrachloride has been the subject of numerous health hazard reviews including EPA's Integrated Risk Information System (IRIS) Toxicological Review and Agency for Toxic Substances and Disease Registry's (ATSDR's) Toxicological Profile. EPA plans to evaluate all potential hazards for carbon tetrachloride, including any found in recent literature. Human health hazards of carbon tetrachloride that have been identified by EPA previously include liver toxicity, renal toxicity and cancer. Carbon tetrachloride hazards to fish, aquatic invertebrates, aquatic plants, sediment invertebrates and amphibians have previously been assessed by EPA or other organizations.

The revised conceptual models presented in this problem formulation identify conditions of use; exposure pathways (e.g., media); exposure routes (e.g., inhalation, dermal, oral); PESS; and hazards EPA expects to consider in the risk evaluation. The initial conceptual models provided in the scope document were revised during problem formulation based on evaluation of reasonably available information for physical and chemical properties, fate, exposures, hazards, and conditions of use, and based upon consideration of other statutory and regulatory authorities. In each problem formulation document for the first 10 chemical substances, EPA also refined the activities, hazards, and exposure pathways that will be included in and excluded from the risk evaluation.

EPA's overall objectives in the risk evaluation process are to conduct timely, relevant, high-quality, and scientifically credible risk evaluations within the statutory deadlines, and to evaluate the conditions of use that raise greatest potential for risk. 82 FR 33726, 33728 (July 20, 2017).

1 INTRODUCTION

This document presents for comment the problem formulation of the risk evaluation to be conducted for carbon tetrachloride under the Frank R. Lautenberg Chemical Safety for the 21st Century Act. The Frank R. Lautenberg Chemical Safety for the 21st Century Act amended the Toxic Substances Control Act (TSCA), the Nation's primary chemicals management law, on June 22, 2016. The new law includes statutory requirements and deadlines for actions related to conducting risk evaluations of existing chemicals.

In December of 2016, EPA published a list of 10 chemical substances that are the subject of the Agency's initial chemical risk evaluations (81 FR 91927), as required by TSCA § 6(b)(2)(A). These 10 chemical substances were drawn from the 2014 update of EPA's TSCA Work Plan for Chemical Assessments, a list of chemicals that EPA identified in 2012 and updated in 2014 (currently totaling 90 chemicals) for further assessment under TSCA. EPA's designation of the first 10 chemical substances constituted the initiation of the risk evaluation process for each of these chemical substances, pursuant to the requirements of TSCA § 6(b)(4).

TSCA § 6(b)(4)(D) requires that EPA publish the scope of the risk evaluation to be conducted, including the hazards, exposures, conditions of use and PESS that the Administrator expects to consider, within 6 months after the initiation of a risk evaluation. The scope documents for all first 10 chemical substances were issued on June 22, 2017. The first 10 problem formulation documents are a refinement of what was presented in the first 10 scope documents. TSCA § 6(b)(4)(D) does not distinguish between scoping and problem formulation, and requires EPA to issue scope documents that include information about the chemical substance, including the hazards, exposures, conditions of use, and the PESS that the Administrator expects to consider in the risk evaluation. In the future, EPA expects scoping and problem formulation to be completed prior to the issuance of scope documents and intends to issue scope documents that include problem formulation.

As explained in the scope document, because there was insufficient time for EPA to provide an opportunity for comment on a draft of the scope, as EPA intends to do for future scope documents, EPA is publishing and taking public comment on a problem formulation document to refine the current scope, as an additional interim step prior to publication of the draft risk evaluation for carbon tetrachloride. Comments received on this problem formulation document will inform development of the draft risk evaluation.

The Agency defines problem formulation as the analytical phase of the risk assessment in which "the purpose for the assessment is articulated, the problem is defined, and a plan for analyzing and characterizing risk is determined" (see Section 2.2 of the Framework for Human Health Risk Assessment to Inform Decision Making). The outcomes of problem formulation are a conceptual model(s) and an analysis plan. The conceptual model describes the linkages between stressors and adverse human health effects, including the stressor(s), exposure pathway(s), exposed life stage(s) and population(s), and endpoint(s) that will be addressed in the risk evaluation (U.S. EPA, 2014). The analysis plan follows the development of the conceptual model(s) and is intended to describe the approach for conducting the risk evaluation, including its design, methods and key inputs and intended outputs as described in the EPA Human Health Risk Assessment Framework (U.S. EPA, 2014). The problem formulation documents refine the initial conceptual models and analysis plans that were provided in the scope documents.

First, EPA has removed from the risk evaluation any activities and exposure pathways that EPA has concluded do not warrant inclusion in the risk evaluation. For example, for some activities that were listed as "conditions of use" in the scope document, EPA has insufficient information following the further investigations during problem formulation to find they are circumstances under which the chemical is actually "intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of."

Second, EPA also identified certain exposure pathways that are under the jurisdiction of regulatory programs and associated analytical processes carried out under other EPA-administered environmental statutes – namely, the Clean Air Act (CAA), the Safe Drinking Water Act (SDWA), the Clean Water Act (CWA), and the Resource Conservation and Recovery Act (RCRA) – and which EPA does not expect to include in the risk evaluation.

As a general matter, EPA believes that certain programs under other Federal environmental laws adequately assess and effectively manage the risks for the covered exposure pathways. To use Agency resources efficiently under the TSCA program, to avoid duplicating efforts taken pursuant to other Agency programs, to maximize scientific and analytical efforts, and to meet the three-year statutory deadline, EPA is planning to exercise its discretion under TSCA 6(b)(4)(D) to focus its analytical efforts on exposures that are likely to present the greatest concern and consequently merit a risk evaluation under TSCA, by excluding, on a case-by-case basis, certain exposure pathways that fall under the jurisdiction of other EPA-administered statutes.[1] EPA does not expect to include any such excluded pathways as further explained below in the risk evaluation. The provisions of various EPA-administered environmental statutes and their implementing regulations represent the judgment of Congress and the Administrator, respectively, as to the degree of health and environmental risk reduction that is sufficient under the various environmental statutes.

Third, EPA identified any conditions of use, hazards, or exposure pathways which were included in the scope document and that EPA expects to include in the risk evaluation but which EPA does not expect to further analyze in the risk evaluation. EPA expects to be able to reach conclusions about particular conditions of use, hazards or exposure pathways without further analysis and therefore plans to conduct no further analysis on those conditions of use, hazards or exposure pathways in order to focus the Agency's resources on more extensive or quantitative analyses. Each risk evaluation will be "fit-for-purpose," meaning not all conditions of use will warrant the same level of evaluation and the Agency may be able to reach some conclusions without comprehensive or quantitative risk evaluations. 82 FR 33726, 33734, 33739 (July 20, 2017).

EPA received comments on the published scope document for carbon tetrachloride and has considered the comments specific to carbon tetrachloride in this problem formulation document. EPA is soliciting public comment on this problem formulation document and when the draft risk evaluation is issued the Agency intends to respond to comments that are submitted. In its draft risk evaluation, EPA may revise the conclusions and approaches contained in this problem formulations, including the conditions of use and pathways covered and the conceptual models and analysis plans, based on comments received.

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[1] As explained in the final rule for chemical risk evaluation procedures, "EPA may, on a case-by case basis, exclude certain activities that EPA has determined to be conditions of use in order to focus its analytical efforts on those exposures that are likely to present the greatest concern, and consequently merit an unreasonable risk determination." [82 FR 33726, 33729 (July 20, 2017)]

1.1 Regulatory History

EPA conducted a search of existing domestic and international laws, regulations and assessments pertaining to carbon tetrachloride. EPA compiled this summary from data available from federal, state, international and other government sources, as cited in Appendix A. EPA evaluated and considered the impact of existing laws and regulations (e.g., regulations on landfill disposal, design, and operations) in the problem formulation step to determine what, if any, further analysis might be necessary as part of the risk evaluation. Consideration of the nexus between these existing regulations and TSCA conditions of use may additionally be made as detailed/specific conditions of use and exposure scenarios are developed in conducting the analysis phase of the risk evaluation.

Federal Laws and Regulations

Carbon tetrachloride is subject to federal statutes or regulations, other than TSCA, that are implemented by other offices within EPA and/or other federal agencies/departments. A summary of federal laws, regulations and implementing authorities is provided in Appendix A.

State Laws and Regulations

Carbon tetrachloride is subject to state statutes or regulations implemented by state agencies or departments. A summary of state laws, regulations and implementing authorities is provided in Appendix A.

Laws and Regulations in Other Countries and International Treaties or Agreements

Carbon tetrachloride is subject to statutes or regulations in countries other than the United States and/or international treaties and/or agreements. A summary of these laws, regulations, treaties and/or agreements is provided in Appendix A.

1.2 Assessment History

EPA has identified assessments conducted by other EPA Programs and other organizations (see Table 1-1). Depending on the source, these assessments may include information on conditions of use, hazards, exposures and PESS. Table 1-1 shows the assessments that have been conducted. EPA found an additional assessment for carbon tetrachloride by the National Industrial Chemicals Notification and Assessment Scheme (Australia) during the problem formulation and the assessment history table has been updated accordingly.

In addition to using this information, EPA intends to conduct a full review of the relevant data/information collected in the initial comprehensive search (see *Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document*, EPA-HQ-OPPT-2016-0733) following the literature search and screening strategies documented in the *Strategy for Conducting Literature Searches for Carbon Tetrachloride: Supplemental File for the TSCA Scope Document*, EPA-HQ-OPPT-2016-0733. This will ensure that EPA considers data/information that has been made available since these assessments were conducted.

Table 1-1. Assessment History of Carbon Tetrachloride

Authoring Organization	Assessment
EPA assessments	
U.S. EPA, Office of Water (OW)	Update of Human Health Ambient Water Quality Criteria: Carbon Tetrachloride 56-23-5, EPA-HQ-OW-2014-0135-0182 (2015b)
U.S. EPA, Integrated Risk Information System (IRIS)	Toxicological Review of Carbon Tetrachloride In Support of Summary Information on IRIS (2010)
U.S. EPA, Office of Drinking Water	Carbon Tetrachloride Health Advisory, Office of Drinking Water US Environmental Protection Agency (1987)
Other U.S.-based organizations	
Agency for Toxic Substances and Disease Registry (ATSDR)	Toxicological Profile for Carbon Tetrachloride (2005)
California Environment Protection Agency, Office of Environmental Health Hazard Assessment	Public Health Goal for Carbon Tetrachloride (2000)
International	
Health Canada	Guidelines for Canadian Drinking Water Quality, Guideline Technical Document, Carbon Tetrachloride (2010)
Organisation for Economic Co-operation and Development's Screening Information Dataset (OECD SIDS), Co-CAM, 10-12	SIDS SIAP for Carbon Tetrachloride (2011)
World Health Organisation (WHO)	Carbon Tetrachloride in Drinking Water, Background document for development of WHO Guidelines for Drinking -water Quality (2004)
National Industrial Chemicals Notification and Assessment Scheme (Australia)	Environment Tier II Assessment for Methane, Tetrachloro- (2017, last update)

1.3 Data and Information Collection

EPA/OPPT generally applies a systematic review process and workflow that includes: (1) data collection; (2) data evaluation; and (3) data integration of the scientific data used in risk evaluations developed under TSCA. Scientific analysis is often iterative in nature as new knowledge is obtained. Hence, EPA/OPPT expects that multiple refinements regarding data collection may occur during the process of risk evaluation.

Data Collection: Data Search

EPA/OPPT conducted chemical-specific searches for data and information on: physical and chemical properties; environmental fate and transport; conditions of use information; environmental exposures, human exposures, including potentially exposed or susceptible subpopulations (PESS) identified by virtue of greater exposure; ecological hazard; and human health hazard, including PESS identified by virtue of greater susceptibility.

EPA/OPPT designed its initial data search to be broad enough to capture a comprehensive set of sources containing data and/or information potentially relevant to the risk evaluation. Generally, the search was not limited by date and was conducted on a wide range of data sources, including but not limited to: peer-reviewed literature and gray literature (e.g., publicly-available industry reports, trade association resources, government reports). When available, EPA/OPPT relied on the search strategies from recent assessments, such as EPA IRIS assessments and the National Toxicology Program's (NTP) *Report on Carcinogens*, to identify relevant references and supplemented these searches to identify relevant information published after the end date of the previous search to capture more recent literature. The *Strategy for Conducting Literature Searches for Carbon Tetrachloride: Supplemental File for the TSCA Scope Document*, EPA-HQ-OPPT-2016-0733 provides details about the data sources and search terms that were used in the initial search.

Data Collection: Data Screening

Following the data search, references were screened and categorized using selection criteria outlined in the *Strategy for Conducting Literature Searches for Carbon Tetrachloride*: *Supplemental File for the TSCA Scope Document*, EPA-HQ-OPPT-2016-0733. Titles and abstracts were screened against the criteria as a first step with the goal of identifying a smaller subset of the relevant data to move into the subsequent data extraction and data evaluation steps. Prior to full-text review, EPA/OPPT anticipates refinements to the search and screening strategies, as informed by an evaluation of the performance of the initial title/abstract screening and categorization process.

The categorization scheme (or tagging structure) used for data screening varies by scientific discipline (i.e., physical and chemical properties; environmental fate and transport; use/conditions of use information; human and environmental exposures, including PESS identified by virtue of greater exposure; human health hazard, including PESS identified by virtue of greater susceptibility; and ecological hazard). However, within each data set, there are two broad categories or data tags: (1) o*n-topic* references or (2) *off-topic* references. *On-topic* references are those that may contain data and/or information relevant to the risk evaluation. O*ff-topic* references are those that do not appear to contain data or information relevant to the risk evaluation. The *Strategy for Conducting Literature Searches for Carbon Tetrachloride: Supplemental File for the TSCA Scope Document*, EPA-HQ-OPPT-2016-0733 discusses the inclusion and exclusion criteria that EPA/OPPT used to categorize references as *on-topic* or *off-topic*.

Additional data screening using sub-categories (or sub-tags) was also performed to facilitate further sorting of data/information - for example, identifying references by source type (e.g., published peer-reviewed journal article, government report); data type (e.g., primary data, review article); human health hazard (e.g., liver toxicity, cancer, reproductive toxicity); or chemical-specific and use-specific data or information. These sub-categories are described in the supplemental document, *Strategy for Conducting Literature Searches for Carbon Tetrachloride: Supplemental File for the TSCA Scope Document*, EPA-HQ-OPPT-2016-0733 and will be used to organize the different streams of data during the stages of data evaluation and data integration steps of systematic review.

Results of the initial search and categorization can be found in the *Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document*, EPA-HQ-OPPT-2016-0733. This document provides a comprehensive list (bibliography) of the sources of data identified by the initial search and the initial categorization for *on-topic* and *off-topic* references. Because systematic review is an iterative process, EPA/OPPT expects that some references may move from the *on-topic* to the *off-*

topic categories, and vice versa. Moreover, targeted supplemental searches may also be conducted to address specific needs for the analysis phase (e.g., to locate specific data needed for modeling); hence, additional *on-topic* references not initially identified in the initial search may be identified as the systematic review process proceeds.

1.4 Data Screening During Problem Formulation

EPA/OPPT is in the process of completing the full text screening of the on-topic references identified in the *Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document,* EPA-HQ-OPPT-2016-0733. Details about the screening process at the full-text level are provided in the *Application of Systematic Review in TSCA Risk Evaluations* document (U.S. EPA, 2018). Appendix H provides the inclusion and exclusion criteria applied at the full text screening. Since full text screening commenced right after the publication of the TSCA Scope document, the criteria were set to be broad to capture relevant information that would support the risk evaluation. Thus, the inclusion and exclusion criteria for full text screening do not reflect the refinements to the conceptual model and analysis plan resulting from problem formulation. As part of the iterative process, EPA is in the process of refining the results of the full text screening to incorporate the changes in information/data needs to support the risk evaluation.

These refinements include changes to the inclusion and exclusion criteria to better support the risk evaluation and will likely reduce the number of data/information sources that will undergo evaluation.

Following the screening process, the quality of the included studies will be assessed using the evaluation strategies that are described in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018). EPA/OPPT is in the process of completing the full text screening of the on-topic references identified in the *Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document,* EPA-HQ-OPPT-2016-0733. Details about the screening process and criteria at the full-text level are provided in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018). Following the screening process, the quality of the included studies will be assessed using the evaluation strategies that are described in the supplemental document on systematic review.

A review of the *on topic* human health references after the title and abstract screening revealed a large number of animal studies that were likely to be of limited use for the following reasons: (1) The aim of the study was to induce a disease state in an animal (e.g., cirrhosis, fibrosis, organ damage: liver, kidney, testes and others) rather than evaluate the effects of carbon tetrachloride exposure in animals and/or (2) Exposure was via injection. In order to refine the search results for full-text screening, the inclusion/exclusion criteria were revised to remove these studies from the “on topic” pool. Appendix B describes the process used to re-screen the references identified as “on topic” in the first screening round, including prioritizing the literature for screening and the re-categorization criteria applied during the re-screening and tagging.

2 PROBLEM FORMULATION

As required by TSCA, the scope of the risk evaluation identifies the conditions of use, hazards, exposures and PESS that the Administrator expects to consider. To communicate and visually convey the relationships between these components, EPA included in the scope document an initial life cycle diagram and initial conceptual models that describe the actual or potential relationships between carbon tetrachloride and human and ecological receptors. During the problem formulation, EPA has revised the life cycle diagram and conceptual models based on further data gathering and analysis as presented in this problem formulation document. A revised analysis plan is also included, which identifies, to the extent feasible, the approaches and methods that EPA may use to assess exposures, effects (hazards) and risks under the conditions of use of carbon tetrachloride.

2.1 Physical and Chemical Properties

Physical-chemical properties influence the environmental behavior and the toxic properties of a chemical, thereby informing the potential conditions of use, exposure pathways and routes and hazards that EPA intends to consider. For scope development, EPA considered the measured or estimated physical-chemical properties set forth in Table 2-1; EPA found no additional information during problem formulation that would change these values.

Table 2-1. Physical and Chemical Properties of Carbon Tetrachloride

Property	Value [a]	References
Molecular formula	CCl_4	
Molecular weight	153.82	
Physical form	Colorless liquid, sweet, aromatic and ethereal odor resembling chloroform	(Merck, 1996); (U.S. Coast Guard, 1985)
Melting point	-23°C	(Lide, 1999)
Boiling point	76.8°C	(Lide, 1999)
Density	1.46 g/cm^3 at 20°C	(Boublík et al., 1984)
Vapor pressure	115 mm Hg at 25°C	(Lide, 1999)
Vapor density	5.32 (relative to air)	(Boublík et al., 1984)
Water solubility	793 mg/L at 25°C	(Horvath, 1982)
Octanol:water partition coefficient (log K_{ow})	2.83[b]	(Hansch et al., 1995)
Henry's Law constant	0.0276 atm m^3/mole	(Leighton and Calo, 1981)
Flash point	None	(U.S. Coast Guard, 1985)
Autoflammability	Not readily available	
Viscosity	2.03 mPa·s at -23°C	(Daubert and Danner, 1989)
Refractive index	1.4607 at 20°C	(Merck, 1996)

Property	Value [a]	References
Diaelectric constant	2.24 at 20°C	(Norbert and Dean, 1967)
[a] Measured unless otherwise noted. [b] Estimated value based on modeling		

2.2 Conditions of Use

TSCA § 3(4) defines the conditions of use as ‘‘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.’’

2.2.1 Data and Information Sources

In the scope documents, EPA identified, based on reasonably available information, the conditions of use for the subject chemicals. As further described in the document, EPA searched a number of available data sources (e.g., *Use and Market Profile for Carbon Tetrachloride*, EPA-HQ-OPPT-2016-0733). Based on this search, EPA published a preliminary list of information and sources related to chemical conditions of use (see *Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: Carbon Tetrachloride*, EPA-HQ-OPPT-2016-0733-0003) prior to a February 2017 public meeting on scoping efforts for risk evaluations convened to solicit comment and input from the public. EPA also convened meetings with companies, industry groups, chemical users and other stakeholders to aid in identifying conditions of use and verifying conditions of use identified by EPA. The information and input received from the public and stakeholder meetings and public comments has been incorporated into this problem formulation document to the extent appropriate, as indicated in Table 2-3. Thus, EPA believes the identified manufacture, processing, distribution, use and disposal activities constitute the intended, known, and reasonably foreseeable activities associated with the subject chemical, based on reasonably available information.

2.2.2 Identification of Conditions of Use

To determine the current conditions of use of carbon tetrachloride and inversely, activities that do not qualify as conditions of use, EPA conducted extensive research and outreach. This included EPA’s review of published literature and online databases including the most recent data available from EPA’s Chemical Data Reporting program (CDR) and Safety Data Sheets (SDSs). EPA also reviewed Montreal Protocol’s (MP) directives and related reports (WCRP, 2016) with information on domestic and international regulation and monitoring of carbon tetrachloride use and emissions. EPA also received comments on the Scope of the Risk Evaluation for carbon tetrachloride (U.S. EPA, 2017e) that were used to determine the conditions of use. In addition, EPA convened meetings with companies, industry groups, chemical users, states, environmental groups, and other stakeholders to aid in identifying conditions of use and verifying conditions of use identified by EPA.

EPA has removed from the risk evaluation any activities that EPA has concluded do not constitute conditions of use – for example, because EPA has insufficient information to find certain activities are circumstances under which the chemical is actually “intended, known, or reasonably foreseen to be manufactured processed, distributed in commerce, used, or disposed of.” EPA has also identified any conditions of use that EPA does not expect to include in the risk evaluation. As explained in the final rule for Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act, TSCA section 6(b)(4)(D) requires EPA to identify "the hazards, exposures, conditions of use, and the PESS that the Administrator expects to consider in a risk evaluation," suggesting that EPA may exclude certain activities that EPA has determined to be conditions of use on a case-by-case basis. (82 FR 33736, 33729; July 20, 2017). For example, EPA may exclude conditions of use that the Agency has sufficient basis to conclude would present only de minimis exposures or otherwise insignificant risks (such as use in a closed system that effectively precludes exposure or use as an intermediate).

The activities that EPA no longer believes are conditions of use or that were otherwise excluded during problem formulation are described in Section 2.2.2.1. The conditions of use included in the scope of the risk evaluation are summarized in Section 2.2.2.2.

2.2.2.1 Categories and Subcategories Determined Not to be Conditions of Use or Otherwise Excluded During Problem Formulation

For carbon tetrachloride, EPA has conducted public outreach and literature searches to collect information about carbon tetrachloride's conditions of use and has reviewed reasonably available information obtained or possessed by EPA concerning activities associated with carbon tetrachloride. As a result of that analysis, EPA has identified activities not currently associated with carbon tetrachloride and therefore determined not to be conditions of use. In addition, there are conditions of use for which EPA has sufficient basis to conclude would present only de minimis exposures or otherwise insignificant risks and that do not warrant further evaluation. Consequently, EPA will not consider or evaluate these activities and conditions of use or associated hazards or exposures in the risk evaluation for carbon tetrachloride. These activities and conditions of use consist of incorporation of carbon tetrachloride into an article (activity that is not a condition of use), and industrial/commercial/consumer uses of carbon tetrachloride in commercially available aerosol and non-aerosol adhesives/sealants, paints/coatings, and cleaning/degreasing solvent products (conditions of use with de minimis exposure).

Domestic production and importation of carbon tetrachloride is currently prohibited under regulations implementing the Montreal Protocol (MP) and CAA Title VI, except when transformed (used and entirely consumed, except for trace quantities, in the manufacture of other chemicals for commercial purposes), destroyed (including destruction after use as a catalyst or stabilizer), or used for essential laboratory and analytical uses. *See* 40 CFR Part 82; *see also* 60 FR 24970, 24971 (May 10, 1995). Based on information obtained by EPA, there are no approved consumer uses for carbon tetrachloride. There are current regulatory actions that prohibit the direct use of carbon tetrachloride as reactant or additive in the formulation of commercially available products for industrial/commercial/consumer uses (including aerosol and non-aerosol adhesives/sealants, paints/coatings, and cleaning/degreasing solvent products), besides as a laboratory chemical. The use of carbon tetrachloride (and mixtures containing it) in household products has also been banned by CPSC since 1970, with the exception of "unavoidable manufacturing residues of carbon tetrachloride in other chemicals that under reasonably foreseen conditions of use do not result in an atmospheric concentration of carbon tetrachloride greater than 10 parts per million." 16 CFR 1500.17(a)(2).

The domestic and international use of carbon tetrachloride as a process agent is addressed under the Montreal Protocol (MP) side agreement, Decision X/14: Process Agents (UNEP/Ozone Secretariat, 1998). This decision lists a limited number of specific manufacturing uses of carbon tetrachloride as a process agent (non-feedstock use) in which carbon tetrachloride may not be destroyed in the production process. Based on the process agent applications, carbon tetrachloride is used in the manufacturing of other chlorinated compounds that may be subsequently added to commercially available products (i.e., solvents for cleaning/degreasing, adhesives/sealants, and paints/coatings). Given the high volatility of carbon tetrachloride and the extent of reaction and efficacy of the separation/purification process for purifying final products, EPA expects insignificant or unmeasurable concentrations of carbon tetrachloride in the manufactured chlorinated substances in the commercially available products. In its regulations on the protection of stratospheric ozone at 40 CFR part 82, EPA excludes from the definition of controlled substance the inadvertent or coincidental creation of insignificant quantities of a listed substance (including carbon tetrachloride) resulting from the substance's use as a process agent (40 CFR 82.3). These expectations and current regulations are consistent with public comments received by EPA, EPA-HQ-OPPT-2016-0733-0005 and EPA-HQ-OPPT-2016-0733-0017, stating that carbon tetrachloride may be present in a limited number of industrial products with chlorinated ingredients at a concentration of less than 0.003% by weight.

Based on the information identified by EPA, carbon tetrachloride is not a direct reactant or additive in the formulation of solvents for cleaning and degreasing, adhesives and sealants or paints and coatings. Because industrial, commercial, and consumer use of such products (solvents for cleaning/degreasing, adhesives/sealants, and paints/coatings) would present only de minimis exposure or otherwise insignificant risk, EPA has determined that these conditions of use do not warrant evaluation, and EPA does not expect to consider or evaluate these conditions of use or associated hazards or exposures in the risk evaluation for carbon tetrachloride. Based on information obtained by EPA and the household products ban at 16 CFR 1500.17(a)(2), there are no other approved consumer uses for carbon tetrachloride. Therefore, as a general matter, EPA does not expect to analyze consumer exposures or associated hazards in the risk evaluation for carbon tetrachloride, and accordingly the initial conceptual model for consumer activities and uses presented in the Scope of the Risk Evaluation for Carbon Tetrachloride (U.S. EPA, 2017e) does not appear in this problem formulation document.

In addition, EPA has determined that there is insufficient information to support the classification of one activity which was identified as a "condition of use" in the Scope document. TSCA defines a chemical's "conditions of use" as "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." 15 USC 2602(4). As explained in the final rule for Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act, TSCA grants EPA discretion to determine the circumstances that are appropriately considered to be "conditions of use." 82 FR at 33729. As noted above, EPA has conducted public outreach and literature searches to collect information about carbon tetrachloride's conditions of use and has reviewed reasonably available information obtained or possessed by EPA concerning activities associated with carbon tetrachloride. As a result of that analysis, EPA has determined there is insufficient information to support a finding that one activity which was listed as a condition of use in the Scope document for carbon tetrachloride actually constitutes a circumstance under which carbon tetrachloride "is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of." This activity consists of incorporation into articles. Incorporation into an article refers to processing in which the chemical becomes an integral component of an article (as defined at 40 CFR 704.3) that is distributed for industrial, trade or consumer use. EPA has not identified information during problem formulation indicating that carbon tetrachloride is incorporated into articles (see EPA-HQ-OPPT-2016-0733-0003). Consequently, EPA will not consider or evaluate incorporation into articles, or any associated hazards or exposures, in the risk evaluation for carbon tetrachloride.

Table 2-2. Categories and Subcategories Determined Not to be Conditions of Use or Otherwise Excluded During Problem Formulation

Life Cycle Stage	Category [a]	Subcategory [b]	References
Processing	Processing-Incorporation into Article	Incorporation into Article	(U.S. EPA, 2016b) * not confirmed as a current use

Life Cycle Stage	Category [a]	Subcategory [b]	References
Industrial/commercial/ consumer use	Solvents for Cleaning and Degreasing	Machinery cleaning	Use document, EPA-HQ-OPPT-2016-0733-0003; Public comment, EPAHQ-OPPT-2016-07330011 * de minimis exposure.
		Textile cleaning	Use document, EPA-HQhttps://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0733-0003OPPT-2016-0733-0003 * de minimis exposure
		Brake cleaning	Use document, EPA-HQhttps://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0733-0003OPPT-2016-0733-0003 * de minimis exposure
	Adhesives and Sealants	Rubber cement	Use document, EPA-HQhttps://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0733-0003OPPT-2016-0733-0003 * de minimis exposure
		Arts and crafts	Use document, EPA-HQ-OPPT-2016-0733-0003; Public comment, EPAHQ-OPPT-2016-07330015 * de minimis exposure
		Asphalt	Use document, EPA-HQhttps://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0733-0003OPPT-2016-0733-0003 * de minimis exposure
		Industrial adhesives	Use document, EPA-HQ-OPPT-2016-0733-0003; Public comments, EPA-HQ-OPPT-2016-0733-0011, EPA-HQ-OPPT2016-0733-0012, and EPA-HQ-OPPT-20160733-0015 * de minimis exposure
	Paints and Coatings	Paints and coatings	Use document, EPA-HQhttps://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0733-0003OPPT-2016-0733-0003 * de minimis exposure

2.2.2.2 Categories and Subcategories of Conditions of Use Included in the Scope of the Risk Evaluation

Table 2-3 summarizes each life cycle stage and the corresponding categories and subcategories of conditions of use for carbon tetrachloride that EPA expects to consider in the risk evaluation. Using the 2016 CDR, EPA identified industrial processing or use activities, industrial function categories and commercial and consumer use product categories. EPA identified the subcategories by supplementing CDR data with other published literature and information obtained through stakeholder consultations. For risk evaluations, EPA intends to consider each life cycle stage (and corresponding use categories and subcategories) and assess relevant potential sources of release and human exposure associated with that life cycle stage. Beyond the uses identified in the Scope of the Risk Evaluation for carbon tetrachloride (U.S. EPA, 2017e), EPA has received no additional information identifying additional current conditions of use for carbon tetrachloride from public comment and stakeholder meetings.

Table 2-3. Categories and Subcategories of Conditions of Use Included in the Scope of the Risk Evaluation

Life Cycle Stage	Category [a]	Subcategory [b]	References
Manufacture	Domestic Manufacture	Domestic manufacture	(U.S. EPA, 2016b)
	Import	Import	(U.S. EPA, 2016b)
Processing	Processing as a Reactant/ Intermediate	Hydrochlorofluorocarbons (HCFCs), Hydrofluorocarbon (HFCs) and Hydrofluoroolefin (HFOs)	Use document, EPA-HQ-OPPT-2016-0733-0003; Public comments, EPA-HQ-OPPT-2016-0733-0007, EPA-HQ-OPPT-2016-0733-0008, EPA-HQ-OPPT-2016-0733-0016 and EPA-HQ-OPPT-2016-0733-0064; (U.S. EPA, 2016b)
		Perchloroethylene (PCE)	Use document, EPA-HQ-OPPT-2016-0733-0003; Public comments, EPA-HQ-OPPT-2016-0733-0007 and EPA-HQ-OPPT-2016-0733-0008; (U.S. EPA, 2016b)
		Reactive ion etching (i.e., semiconductor manufacturing)	Use document, EPA-HQ-OPPT-2016-0733-0003; Public comment, EPA-HQ-OPPT-2016-0733-0063

Life Cycle Stage	Category [a]	Subcategory [b]	References
	Incorporation into Formulation, Mixture or Reaction Products	Petrochemicals-derived manufacturing; Agricultural products manufacturing; Other basic organic and inorganic chemical manufacturing.	(U.S. EPA, 2016b); Use document, EPA-HQ-OPPT-2016-0733-0003; (U.S. EPA, 2016a); (UNEP/Ozone Secretariat, 1998); Public comment, EPA-HQ-OPPT-2016-0733-0064
	Processing - repackaging	Laboratory Chemicals	(U.S. EPA, 2016a)
	Recycling	Recycling	(U.S. EPA, 2016b), (U.S. EPA, 2016a)
Distribution in commerce	Distribution	Distribution in commerce	(U.S. EPA, 2016a); Use document, EPA-HQ-OPPT-2016-0733-0003.
Industrial/commercial use	Petrochemicals-derived Products Manufacturing	Processing aid	Use document, EPA-HQ-OPPT-2016-0733-0003; (U.S. EPA, 2016b); (UNEP/Ozone Secretariat, 1998)
		Additive	Use document, EPA-HQ-OPPT-2016-0733-0003; Public comment, EPA-HQ-OPPT-2016-0733-0012; (U.S. EPA, 2016a); (UNEP/Ozone Secretariat, 1998)
	Agricultural Products Manufacturing	Processing aid	(U.S. EPA, 2016b), Use document, EPA-HQ-OPPT-2016-0733-0003; Public comments, EPA-HQ-OPPT-2016-0733-0007 and EPA-HQ-OPPT-2016-0733-0008; (UNEP/Ozone Secretariat, 1998)

Life Cycle Stage	Category [a]	Subcategory [b]	References
	Other Basic Organic and Inorganic Chemical Manufacturing	Manufacturing of chlorinated compounds used in solvents for cleaning and degreasing	Use document, EPA-HQ-OPPT-2016-0733-0003; Public comments, EPA-HQ-OPPT-2016-0733-0011, EPA-HQ-OPPT-2016-0733-0012 and EPA-HQ-OPPT-2016-0733-0015; (UNEP/Ozone Secretariat, 1998)
		Manufacturing of chlorinated compounds used in adhesives and sealants	Use document, EPA-HQ-OPPT-2016-0733-0003; Public comments, EPA-HQ-OPPT-2016-0733-0011, EPA-HQ-OPPT-2016-0733-0024, EPA-HQ-OPPT-2016-0733-0012, and EPA-HQ-OPPT-2016-0733-0015; (UNEP/Ozone Secretariat, 1998)
		Manufacturing of chlorinated compounds used in paints and coatings	Use document, EPA-HQ-OPPT-2016-0733-0003 Public comment, EPA-HQ-OPPT-2016-0733-0024; (UNEP/Ozone Secretariat, 1998)
		Manufacturing of inorganic chlorinated compounds (i.e., elimination of nitrogen trichloride in the production of chlorine and caustic)	Public comment, EPA-HQ-OPPT-2016-0733-0027; (UNEP/Ozone Secretariat, 1998)
		Manufacturing of chlorinated compounds used in asphalt	Use document, EPA-HQ-OPPT-2016-0733-0003; (UNEP/Ozone Secretariat, 1998)
		Manufacturing of Pharmaceuticals	(UNEP/Ozone Secretariat, 1998)
	Other Uses	Processing aid (i.e., metal recovery).	Use document, EPA-HQ-OPPT-2016-0733-0003

Life Cycle Stage	Category [a]	Subcategory [b]	References
		Specialty uses (i.e., aerospace industry)	Public comment, EPA-HQ-OPPT-2016-0733-0063
	Laboratory Chemicals	Laboratory chemical	Use document, EPA-HQ-OPPT-2016-0733-0003; (U.S. EPA, 2016b), Public comments, EPA-HQ-OPPT-2016-0733-0007; EPA-HQ-OPPT-2016-0733-0013 and EPA-HQ-OPPT-2016-0733-0063
Disposal	Disposal	Industrial pre-treatment	U.S. EPA, 2017d
		Industrial wastewater treatment	U.S. EPA, 2017d
		Publicly owned treatment works (POTW)	U.S. EPA, 2017d
		Underground injection	U.S. EPA, 2017d
		Municipal landfill	U.S. EPA, 2017d
		Hazardous landfill	U.S. EPA, 2017d
		Other land disposal	U.S. EPA, 2017d
		Municipal waste incinerator	U.S. EPA, 2017d
		Hazardous waste incinerator	U.S. EPA, 2017d
		Off-site waste transfer	U.S. EPA, 2017d

[a] These categories of conditions of use appear in the Life Cycle Diagram, reflect CDR codes and broadly represent conditions of use of carbon tetrachloride in industrial and/or commercial settings.
[b] These subcategories reflect more specific uses of carbon tetrachloride.

2.2.2.3 Overview of Conditions of Use and Lifecycle Diagram

The life cycle diagram provided in Figure 2-1 depicts the conditions of use that are considered within the scope of the risk evaluation during various life cycle stages including manufacturing, processing, use (industrial, commercial), distribution and disposal. Additions or changes to conditions of use based on additional information gathered or analyzed during problem formulation were described in Sections 2.2.2.1 and 2.2.2.2. The activities that EPA determined are out of scope during problem formulation are not included in the life cycle diagram. The information is grouped according to CDR processing codes and use categories (including functional use codes for industrial uses and product categories for industrial, commercial and consumer uses), in combination with other data sources (e.g., published literature and consultation with stakeholders), to provide an overview of conditions of use. EPA notes that some subcategories of use may be grouped under multiple CDR categories.

Use categories include the following: "industrial use" means use at a site at which one or more chemicals or mixtures are manufactured (including imported) or processed. "Commercial use" means the use of a chemical or a mixture containing a chemical (including as part of an article) in a commercial enterprise providing saleable goods or services (U.S. EPA, 2016b). This information has not changed from that provided in the Scope Document.

To understand conditions of use relative to one another and associated potential exposures under those conditions of use, the life cycle diagram includes the production volume associated with each stage of the life cycle, as reported in the 2016 CDR (U.S. EPA, 2017c, 2016b), when the volume was not claimed confidential business information (CBI). The 2016 CDR reporting data for carbon tetrachloride are provided in Table 2-4 for carbon tetrachloride from EPA's CDR database (U.S. EPA, 2017c).

Table 2-4. Production Volume of Carbon Tetrachloride in Chemical Data Reporting (CDR) Reporting Period (2012 to 2015) [a]

Reporting Year	2012	2013	2014	2015
Total Aggregate Production Volume (lbs)	129,145,698	116,658,281	138,951,153	142,582,067

[a] (U.S. EPA, 2017c). Internal communication. The CDR data for the 2016 reporting period is available via ChemView (https://java.epa.gov/chemview) (U.S. EPA, 2016b). Because of an ongoing CBI substantiation process required by amended TSCA, the CDR data available in the problem formulation is more specific than currently in ChemView.

Due to CBI claims in the 2016 CDR, EPA cannot provide the volumes associated with most life cycle stages (U.S. EPA, 2016b). Activities related to distribution (e.g., loading, unloading) will be considered throughout the carbon tetrachloride life cycle, rather than using a single distribution scenario.

Descriptions of the industrial or commercial use categories identified from the 2016 CDR are summarized below and included in the life cycle diagram (Figure 2-1). The descriptions provide a brief overview of the use category and Appendix C contains more detailed descriptions (e.g., process descriptions, worker activities, process flow diagrams, equipment illustrations) for each manufacture, processing, use and disposal category. The descriptions provided below are primarily based on the corresponding industrial function category and/or commercial product category descriptions from the 2016 CDR and can be found in EPA's *Instructions for Reporting 2016 TSCA Chemical Data Reporting* (U.S. EPA, 2016a).

The "**Petrochemicals-derived and Agricultural Products Manufacturing**" category encompasses chemical substances used for a variety of purposes at petrochemicals-derived and agricultural products manufacturing sites. This category includes the use of carbon tetrachloride as a process agent (i.e., processing aid for catalyst regeneration) in uses listed in the MP side agreement, Decision X/14: Process Agents, including manufacture of chlorosulphonated polyolefin, manufacture of styrene butadiene rubber, manufacture of endosulphan (insecticide), production of tralomethrine (insecticide), manufacture of 1-1, Bis (4-chlorophenyl) 2,2,2- trichloroethanol (dicofol insecticide) (see Appendix D).

The "**Other Basic Organic and Inorganic Chemical Manufacturing**" category encompasses chemical substances used to facilitate the manufacturing or production of a particular chemical. Process agents are not feedstocks, and may not be destroyed in a production process. Use of carbon tetrachloride as a process agent is specifically listed under the MP side agreement, Decision X/14: Process Agents. This category includes the use of carbon tetrachloride in the manufacturing of pharmaceuticals (i.e., ibuprofen) and the manufacturing of chlorinated compounds that are subsequently used in the formulation of solvents for cleaning and degreasing, adhesives and sealants and paints and coatings. The process agent applications of carbon tetrachloride as a process agent include manufacturing of chlorinated paraffins (e.g., plasticizer in rubber, paints, adhesives, sealants, plastics) and chlorinated rubber (e.g., additive in paints, adhesives). The category also includes the use of carbon tetrachloride in the manufacturing of inorganic chlorinated compounds, such as the use of carbon tetrachloride in the production of chlorine and caustic.

Figure 2-1 depicts the life cycle diagram of carbon tetrachloride from manufacture to the point of disposal. Activities related to distribution (e.g., loading, unloading) will be considered throughout the life cycle, rather than using a single distribution scenario.

As reflected in the life cycle diagram, intended, known and reasonably foreseen uses of carbon tetrachloride are primarily associated with industrial and commercial activities. As explained above, the Montreal Protocol and Title VI of the Clean Air Act (CAA) Amendments of 1990 led to a phase-out of carbon tetrachloride production in the United States for most non-feedstock domestic uses in 1996 and the CPSC banned the use of carbon tetrachloride in consumer products (excluding unavoidable residues not exceeding 10 ppm atmospheric concentration) in 1970.

EPA has identified use as a feedstock (Processing as Reactant/Intermediate) as the main use for carbon tetrachloride. However, there are other industrial/commercial uses that may still exist including: solvent for laboratory procedures (i.e., extraction solvent), and process agent in the manufacturing of petrochemicals-derived and agricultural products, and in the manufacturing of chlorinated compounds to be used in the formulation of solvents for degreasing and cleaning, in adhesives, sealants, paints, coatings, rubber cement and asphalt formulations [EPA-HQ-OPPT-2016-0733-0003 (U.S. EPA, 2017d)].

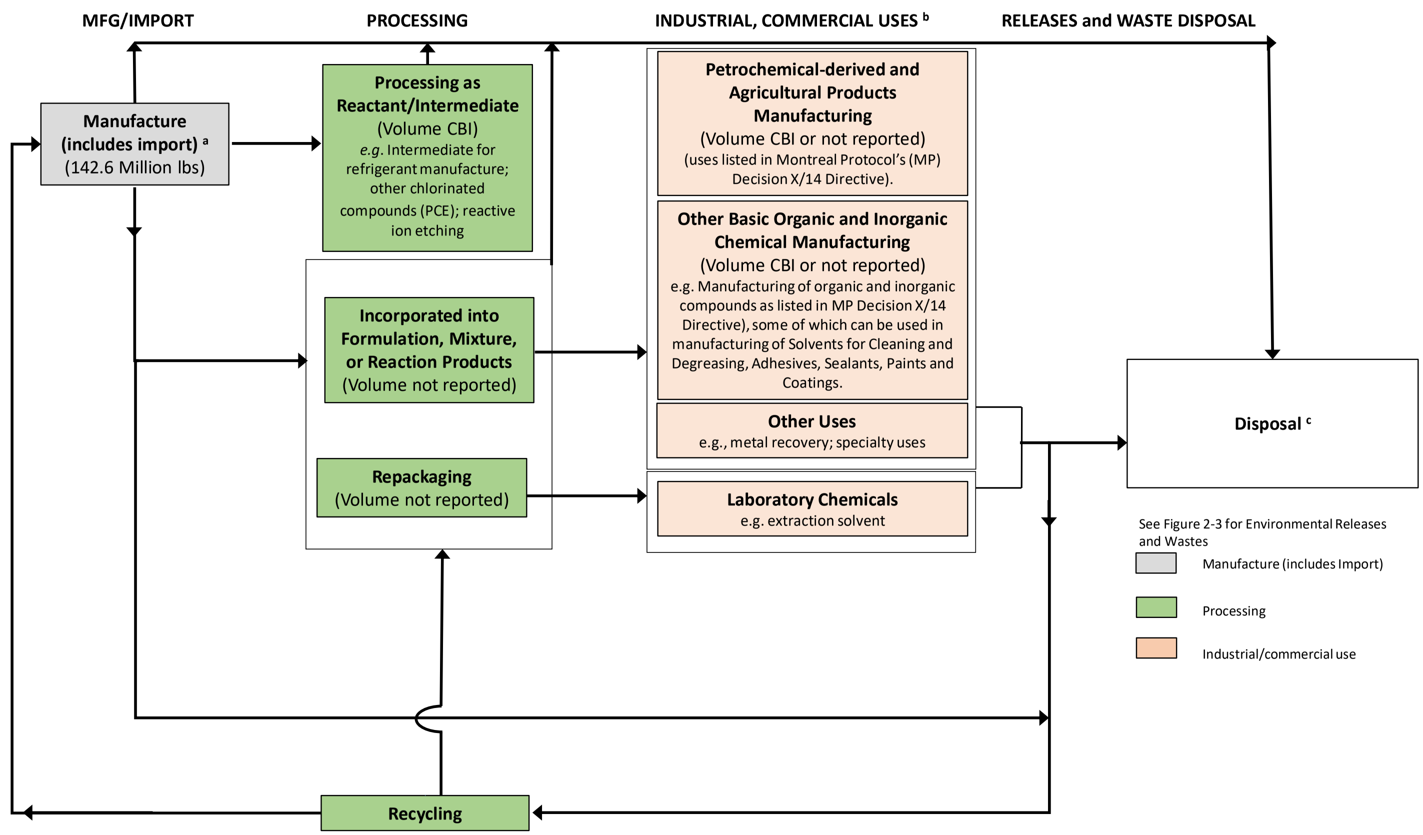

Figure 2-1. Carbon Tetrachloride Life Cycle Diagram

The life cycle diagram depicts the conditions of use that are within the scope of the risk evaluation during various life cycle stages including manufacturing, processing, use (industrial or commercial), distribution and disposal. The production volumes shown are for reporting year 2015 from the 2016 CDR reporting period (U.S. EPA, 2016b). Activities related to distribution (e.g., loading, unloading) will be considered throughout the carbon tetrachloride life cycle, rather than using a single distribution scenario.

[a] Due to CBI claims, EPA cannot differentiate between manufacturing and import sites.

[b] See Table 2-3 for additional uses not mentioned specifically in this diagram.

[c] Disposal refers to all of the following activities - Industrial pre-treatment, Industrial wastewater treatment, Publicly owned treatment works (POTW), Underground injection, Municipal landfill, Hazardous landfill, Other land disposal, Municipal waste incinerator, Hazardous waste incinerator, Off-site waste transfer

2.3 Exposures

For TSCA exposure assessments, EPA expects to evaluate exposures and releases to the environment resulting from the conditions of use applicable to carbon tetrachloride. Post-release pathways and routes will be described to characterize the relationship or connection between the conditions of use for carbon tetrachloride and the exposure to human receptors, including PESS, and ecological receptors. EPA will take into account, where relevant, the duration, intensity (concentration), frequency and number of exposures in characterizing exposures to carbon tetrachloride.

2.3.1 Fate and Transport

Environmental fate includes both transport and transformation processes. Environmental transport is the movement of the chemical within and between environmental media. Transformation occurs through the degradation or reaction of the chemical with other species in the environment. Hence, knowledge of the environmental fate of the chemical informs the determination of the specific exposure pathways and potential human and environmental receptors EPA expects to consider in the risk evaluation. Table 2-5 provides environmental fate data that EPA identified and considered in developing the scope for carbon tetrachloride. This information has not changed from that provided in the scope document.

During problem formulation, EPA considered volatilization during wastewater treatment, volatilization from lakes and rivers followed by upward diffusion in the troposphere, biodegradation rates, and soil organic carbon:water partition coefficient (log K_{OC}) were used when making changes, as described in Section 2.5 to the conceptual models. Systematic literature review is currently underway, so model results and basic principles were used to support the fate data used in problem formulation.

EPI Suite™ (U.S. EPA, 2012a) modules were used to predict volatilization of carbon tetrachloride from wastewater treatment plants, lakes, and rivers. The EPI Suite™ module that estimates chemical removal in sewage treatment plants ("STP" module) was run using default settings to evaluate the potential for carbon tetrachloride to volatilize to air or adsorb to sludge during wastewater treatment. The STP module estimates that about 90% of carbon tetrachloride in wastewater will be removed by volatilization and 2% by adsorption.

The EPI Suite™ module that estimates volatilization from lakes and rivers ("Volatilization" module) was run using default settings to evaluate the volatilization half-life of carbon tetrachloride in surface water. The volatilization module estimates that the half-life of carbon tetrachloride in a model river will be about 1.3 hours and the half-life in a model lake will be about 5 days.

The EPI Suite™ module that predicts biodegradation rates ("BIOWIN" module) was run using default settings to estimate biodegradation rates of carbon tetrachloride under aerobic conditions. Three of the models built into the BIOWIN module (BIOWIN 1, 2 and 6) estimate that carbon tetrachloride will not rapidly biodegrade in aerobic environments. These results support the biodegradation data presented in the scope document for carbon tetrachloride, which demonstrate limited biodegradation under aerobic conditions. However, BIOWIN 5 shows moderate biodegradation under aerobic conditions. On the other hand, the model that estimates anaerobic biodegradation (BIOWIN 7) predicts that carbon tetrachloride will biodegrade moderately under anaerobic conditions. Further, previous assessments of carbon tetrachloride found that aerobic biodegradation was very slow and anaerobic biodegradation was moderate to rapid (ECHA, 2012; OECD, 2011; ATSDR, 2005; CalEPA, 2000).

Conversely, previous assessment of carbon tetrachloride by HSDB found rapid biodegradation in aerobic aquatic conditions (NLM, 2003). This may be largely due to fact that carbon tetrachloride exhibits toxicity to aquatic microorganisms in concentrations higher than 10 mg/L. In water, under aerobic conditions, a negative result has been reported for a ready biodegradability test according to OECD TG 301C MITI (I) (Ministry of International Trade and Industry, Japan) test method, toxicity to aerobic bacteria may have prevented biodegradation due to the high concentration used in this test (ECHA, 2012).

Based on the available environmental fate data, carbon tetrachloride is likely to biodegrade slowly under aerobic conditions with pathways that are environment- and microbial population-dependent. Anaerobic degradation has been observed to be faster than aerobic degradation under some conditions with acclimated microbial populations. Anaerobic biodegradation is expected to be a significant degradation mechanism in soil and ground water.

The log K_{OC} reported in the carbon tetrachloride scoping document were measured values in the range of 1.69 – 2.16, while the estimated value range using EPI Suite™ is 1.6 – 2.5. These values are supported by the basic principles of environmental chemistry which states that the K_{OC} is typically within one order of magnitude (one log unit) of the octanol:water partition coefficient (K_{OW}). Indeed, the log K_{OW} reported for carbon tetrachloride in Table 2-1 is a measured value of 2.83, which is within the expected range. Further, the K_{OC} could be approximately one order of magnitude larger than predicted by EPI Suite™ before sorption would be expected to significantly impact the mobility of carbon tetrachloride in groundwater. The log K_{OC} and log K_{OW} reported in previous assessments of carbon tetrachloride were in the range of 1.69 – 2.16 and 2.64 – 2.83 respectively [(ECHA, 2012; OECD, 2011; ATSDR, 2005)], and these values are associated with low sorption to soil and sediment.

Table 2-5. Environmental Fate Characteristics of Carbon Tetrachloride

Property or Endpoint	Value [a]	References
Direct photodegradation	Minutes (atmospheric-stratospheric)	(OECD, 2011)
Indirect photodegradation	>330 years (atmospheric)	(OECD, 2011)
Hydrolysis half-life	7000 years at 1 ppm	(OECD, 2011)
Biodegradation	6 to 12 months (soil)[b] 7 days to 12 months (aerobic water, based on multiple studies) 3 days to 4 weeks (anaerobic water, based on multiple studies)	(OECD, 2011) (ECHA, 2012) (ATSDR, 2005) (NLM, 2003)
Bioconcentration factor (BCF)	30 bluegill sunfish 40 rainbow trout	(OECD, 2011)
Bioaccumulation factor (BAF)	19 (estimated)	(U.S. EPA, 2012a)
Soil organic carbon:water partition coefficient (log K_{oc})	1.69-2.16	(ECHA, 2012)
	2.06 (weighted mean of two soils-silt loam and sandy loam)	(OECD, 2011)

[a] Measured unless otherwise noted. [b] This figure (6 to 12 months) represents a half-life estimate based on the estimated aqueous aerobic biodegradation half-life of carbon tetrachloride.

Carbon tetrachloride shows minimal susceptibility to indirect photolysis by hydroxyl radicals in the troposphere, where its estimated tropospheric half-life exceeds 330 years. Ultimately, carbon tetrachloride diffuses upward into the stratosphere where it is photodegraded to form the trichloromethyl radical and chlorine atoms (OECD, 2011). Carbon tetrachloride is efficiently degraded by direct photolysis under stratospheric conditions and the DT_{50} (Dissipation Time for 50% of the compound to dissipate) value is in the order of minutes. However, the troposphere to the stratosphere migration of carbon tetrachloride is very long and this migration time limits the dissipation. The rate of photodegradation increases at altitudes >20 km and beyond.

Carbon tetrachloride dissolved in water does not photodegrade or oxidize in any measurable amounts, with a calculated hydrolysis half-life of 7,000 years based on experimental data at a concentration of 1 ppm (OECD, 2011). Removal mechanisms from water could include volatilization due to the Henry's law constant and anaerobic degradation in subsurface environment.

Estimated and measured BCF and BAF values ranging from 19 – 40 indicates that carbon tetrachloride has low bioaccumulation potential in fish (U.S. EPA, 2012a; OECD, 2011).

2.3.2 Releases to the Environment

Releases to the environment from conditions of use (e.g., industrial and commercial processes) are one component of potential exposure and may be derived from reported data that are obtained through direct measurement, calculations based on empirical data and/or assumptions and models.

Under the Emergency Planning and Community Right-to-Know Act (EPCRA) Section 313 rule, carbon tetrachloride is a Toxics Release Inventory (TRI)-reportable substance effective January 1, 1987 (see Appendix A.1). EPA expects to consider data reported under the TRI program for evaluating exposure to carbon tetrachloride.

Table 2-6 provides production-related waste managed data (also referred to as waste managed) for carbon tetrachloride reported by industrial facilities to the TRI program for 2015 (U.S. EPA, 2017f). Table 2-7 provides more detailed information on the quantities released to air or water or disposed of on land.

Table 2-6. Summary of Carbon Tetrachloride TRI Production-Related Waste Managed in 2015 (lbs)

Number of Facilities	Recycling	Energy Recovery	Treatment	Releases [a,b]	Total Production Related Waste
47	5,954,066	5,638,154	15,196,739	151,690	26,940,648

Data source: 2015 TRI Data (updated March 2017) (U.S. EPA, 2017f).
[a] Terminology used in these columns may not match the more detailed data element names used in the TRI public data and analysis access points.
[b] Does not include releases due to one-time event not associated with production such as remedial actions or earthquakes.

Facilities are required to report if they manufacture (including import) or process more than 25,000 pounds of carbon tetrachloride, or if they otherwise use more than 10,000 pounds of carbon tetrachloride. In 2015, 47 facilities reported a total of 27 million pounds of carbon tetrachloride waste managed. Of this total, nearly 6 million pounds were recycled, 5.6 million pounds were recovered for energy, 15 million pounds were treated, and almost 152 thousand pounds were released into the environment.

Of these releases, the largest releases of nearly 105 thousand pounds were to air (fugitive and point source air emissions), a little under 500 pounds were released to water (surface water discharges), 50 thousand pounds were released to land (of which disposal to Resource Conservation and Recovery Act (RCRA) Subtitle C landfills is the primary disposal method), and under 200 pounds were released in other forms such as indefinite storage. Carbon tetrachloride migration to groundwater from RCRA Subtitle C landfills regulated by the state/local jurisdictions will likely be mitigated by landfill design (double liner, leachate capture) and requirements to adsorb liquids onto solid adsorbant and containerize prior to disposal.

Table 2-7. Summary of Carbon Tetrachloride Toxics Release Inventory (TRI) Releases to the Environment in 2015 (lbs)

		Air Releases			Land Releases				
	Number of Facilities	Stack Air Releases	Fugitive Air Releases	Water Releases	Class I Under-ground Injection	RCRA Subtitle C Landfills	All other Land Disposal [a,b]	Other Releases [a]	Total Releases [c]
Subtotal		69,897	34,941		19,608	27,300	401		
Totals	47	104,838		468	47,309			164	152,780

Data source: 2015 TRI Data (updated March 2017) (U.S. EPA, 2017f)
[a] Terminology used in these columns may not match the more detailed data element names used in the TRI public data and analysis access points.

	Number of Facilities	Air Releases		Water Releases	Land Releases			Other Releases [a]	Total Releases [c]
		Stack Air Releases	Fugitive Air Releases		Class I Under-ground Injection	RCRA Subtitle C Landfills	All other Land Disposal [a,b]		

[b] Upon further evaluation of these reports of other land disposal releases, it was found that the reports consist of misreported disposal values. The incorrect code uses or waste identification were used in the reports. Therefore these 401 lbs of released waste do not consist of carbon tetrachloride waste released by other land disposal.
[c] These release quantities do include releases due to one-time events not associated with production such as remedial actions or earthquakes.

While production-related waste managed shown in Table 2-6 excludes any quantities reported as catastrophic or one-time releases (TRI section 8 data), release quantities shown in Table 2-7 include both production-related and non-routine quantities (TRI section 5 and 6 data). As a result, release quantities may differ slightly and may further reflect differences in TRI calculation methods for reported release range estimates (U.S. EPA, 2016a).

During problem formulation, EPA further analyzed the TRI data and examined the definitions of elements in the TRI data to determine the level of confidence that a carbon tetrachloride release would result from other types of land disposal, as reported in Table 2-7, given that carbon tetrachloride waste is regulated as a hazardous waste under RCRA. In 2015, three facilities reported the disposal of a combined total of 401 lbs of carbon tetrachloride through *other land disposal.* Upon further investigation of these reports, EPA has found that these facilities used an incorrect TRI code during reporting or that the disposed waste did not actually consist of carbon tetrachloride waste. These incorrectly reported values cannot be removed from the TRI database until the facilities submit the corresponding revision reports. However, these uncorrected reports are not considered relevant for the purposes of this problem formulation.

2.3.3 Presence in the Environment and Biota

Monitoring studies or a collection of relevant and reliable monitoring studies provide(s) information that can be used in an exposure assessment. Monitoring studies that measure environmental concentrations or concentrations of chemical substances in biota provide evidence of exposure.

Monitoring and biomonitoring data were identified in EPA's data search for carbon tetrachloride. Though carbon tetrachloride's use has significantly decreased from a peak in the 1970's, its long half-life and previous ubiquitous use and disposal has resulted in the continued presence in various environmental media (ATSDR, 2005). Carbon tetrachloride is listed as a Hazardous Air Pollutant (HAP) and is included in several multi-year monitoring programs, with data collected across the nation in both urban and rural locations (U.S. EPA, 2017b, 1996). For example, carbon tetrachloride is included in all three ambient air monitoring programs, collectively known as the National Monitoring Programs: National Air Toxics Trends Stations (NATTS) network, Community-Scale Air Toxics Ambient Monitoring (CSATAM) Program and Urban Air Toxics Monitoring Program (UATMP). NATTS sites are based on preliminary air toxics programs such as the 1996 National Air Toxics Assessment (NATA).

According to the 2015 National Air Toxics Inventory, ambient air monitoring trends from 2003 to 2013 have shown that of the eight HAP monitored, only carbon tetrachloride average concentrations have slightly increased in the atmosphere over the 10-year period. This is likely primarily due to its extremely long half-life in the troposphere (U.S. EPA, 2015a).

Carbon tetrachloride is specifically regulated under the Safe Drinking Water Act (SDWA). Therefore, under the National Primary Drinking Water Regulations, carbon tetrachloride is designated as a volatile organic compound (VOC) contaminant and is monitored in drinking water (U.S. EPA, 2009). Nationally representative drinking water monitoring data are available through EPA's SDWA compliance monitoring. SDWA requires EPA to review each national primary drinking water regulation at least once every six years and revise as necessary. As part of the "Six-Year Review (SYR)," EPA evaluates any newly available data, information and technologies to determine if any regulatory revisions are needed. Internal analysis for SYR3 (2006-2011) data, not yet published, show that 118 systems of 55,735 systems (0.212%) have mean concentrations greater than the Minimum Reporting Level (MRL) of 0.5 µg/L. SYR 2 (1998-2005) data showed 650 systems or 1.289% of 50,446 systems had detects greater than 0.5 µg/L. Of those, over 75% of the detections were in groundwater (versus surface water systems). In addition, only 57 (0.113%) systems had detects of carbon tetrachloride greater than the Maximum Contaminant Level (MCL) of 5 µg/L. During SYR 2, EPA's Office of Water (OW) determined the Estimated Quantitation Level (EQL) to be 0.5 ug/L, which is the threshold for determining if the occurrence data showed a meaningful opportunity to improve health protection. The basis for the SYR 2 EQL for carbon tetrachloride is the modal MRL reported for each sample in the SYR 2 ICR dataset (https://wcms.epa.gov/dwsixyearreview/six-year-review-3-compliance-monitoring-data-2006-2011).

The U.S. Geological Survey (USGS) monitors organic compounds in ground water and has detected carbon tetrachloride in community water systems (USGS, 2007). EPA provides the public with storage and retrieval (STORET) data that maps monitoring sites and allows for download of sampling data of surface water monitoring sites. These data are searchable via the Water Quality Portal (WQP), a cooperative service sponsored by the USGS, the EPA and the National Water Quality Monitoring Council (NWQMC) (NWQMC, 2017). The portal contains data collected by over 400 state, federal, tribal and local agencies.

Biomonitoring data on carbon tetrachloride are collected in the National Health and Nutrition Examination Survey (NHANES) (CDC, 2017).

2.3.4 Environmental Exposures

The manufacturing, processing, use and disposal of carbon tetrachloride can result in releases to the environment. In this section, EPA presents exposures to aquatic and terrestrial organisms.

Aquatic Environmental Exposures

During problem formulation, EPA modeled industrial discharges to surface water to estimate surface water concentration using TRI and EPA NPDES permit Discharge Monitoring Report (DMR) data on the top 10 highest carbon tetrachloride releasing facilities. EPA used the Probabilistic Dilution Model (PDM) within E-FAST to estimate annual discharges for the facilities. In order to estimate a range of conservative surface water concentrations, the 2015 NPDES DMR data reporting carbon tetrachloride discharges were used as a high-end range of possible release days (i.e., 20 and 250 days/year) allowing the estimation of conservative carbon tetrachloride surface water concentrations (i.e., conservative exposure scenarios). Appendix E presents the first-tier estimate of surface water concentrations.

Terrestrial Environmental Exposures

Terrestrial species populations living near industrial and commercial facilities using carbon tetrachloride may be exposed to the chemical through environmental media. Terrestrial species populations living near industrial and commercial facilities using carbon tetrachloride may be exposed via multiple routes such as ingestion of surface waters and inhalation of outdoor air. As described in Section 2.3.3 carbon tetrachloride is present and measurable through monitoring in a variety of environmental media including ambient air, surface water and ground water

2.3.5 Human Exposures

In this section, EPA presents occupational, consumer and general population exposures. Subpopulations, including PESS, within these exposed groups are also presented.

2.3.5.1 Occupational Exposures

Exposure pathways and exposure routes are listed below for worker activities under the various conditions of use described in Section 2.2. In addition, exposures to occupational non-users (ONU), who do not directly handle the chemical but perform work in an area where the chemical is present, are listed. Engineering controls and/or personal protective equipment may impact the occupational exposure levels.

Workers and ONU may be exposed to carbon tetrachloride when performing activities associated with the conditions of use described in Section 2.2, including, but not limited to:

- Unloading and transferring carbon tetrachloride to and from storage containers to process vessels.
- Using carbon tetrachloride in process equipment.
- Cleaning and maintaining equipment.
- Sampling chemical, formulations or products containing carbon tetrachloride for quality control (QC).
- Repackaging chemical, formulations or products containing carbon tetrachloride.
- Handling, transporting and disposing waste containing carbon tetrachloride.
- Use of carbon tetrachloride in laboratories.
- Performing other work activities in or near areas where carbon tetrachloride is used.

Based on these activities, EPA will analyze inhalation exposure to vapor and mists. Dermal exposure, including skin contact with liquids and vapors for workers will also be analyzed. ONU would not intentionally handle liquids containing carbon tetrachloride, therefore, dermal exposure will not be analyzed further in the risk evaluation for ONU. The risk evaluation will not further analyze potential worker exposure through mists that deposit in the upper respiratory tract and are swallowed. Due to the high volatility of carbon tetrachloride which results in a high inhalation absorption of mists, swallowing of carbon tetrachloride mists is not considered a significant route of exposure.

Key Data

Key data that inform occupational exposure assessment and which EPA plans to evaluate include: the OSHA Chemical Exposure Health Data (CEHD) and National Institute of Occupational Safety and Health (NIOSH) Health Hazard Evaluation (HHE) program data. OSHA data are workplace monitoring data from OSHA inspections. The inspections can be random or targeted, or can be the result of a worker complaint. OSHA data can be obtained through the OSHA Integrated Management Information System (IMIS) at https://www.osha.gov/oshstats/index.html. Appendix C.2 provides a summary of carbon tetrachloride personal monitoring air samples obtained from OSHA inspections conducted between 2013 and 2015 and a summary of monitoring data from NIOSH HHEs conducted since 1990. NIOSH HHEs are conducted at the request of employees, union officials, or employers and help inform potential hazards at the workplace. HHEs can be downloaded at https://www.cdc.gov/niosh/hhe/. In public comment, EPA-HQ-OPPT-2016-0733-0064, Halogenated Solvents Industry Alliance characterized potential exposures groups during manufacturing and use of halogenated solvents such as carbon tetrachloride and provided summaries of occupational monitoring data from three different companies. One of the data summaries includes 330 full-shift samples collected over 11 years. In addition, the Department of Defense has provided a compilation of carbon tetrachloride use scenarios with their respective exposure controls and workplace exposure assessment information for some of the use scenarios from the aerospace industry. During risk evaluation, EPA will review these data and evaluate the utility of these datasets in the risk evaluation.

Inhalation

EPA anticipates that inhalation to vapor is the most important exposure pathway of carbon tetrachloride for workers and ONU based on the high volatility of the chemical. ONU are not directly handling carbon tetrachloride; therefore, inhalation exposure to mists are not expected for ONU.

The United States has several regulatory and non-regulatory exposure limits for carbon tetrachloride: including an OSHA Permissible Exposure Limit (PEL) of 10 ppm time-weighted average (TWA) and 25 ppm ceiling and a NIOSH Recommended Exposure Limit (REL) of 2 ppm (12.6 mg/m^3) 60-minute Short-term Exposure Limit (STEL). Also, NIOSH indicates that carbon tetrachloride has an immediately dangerous to life and health (IDLH) value of 200 ppm based on acute inhalation toxicity data in humans, and provides a notation that carbon tetrachloride is considered a potential occupational carcinogen. The influence of these exposure limits on occupation exposures will be considered in the occupational exposure assessment.

During problem formulation, EPA has identified information on the thermal decomposition of carbon tetrachloride into phosgene, a highly toxic gas. However, thermal decomposition of carbon tetrachloride is more likely to occur in open environments and less likely in the type of closed systems used during the manufacturing and processing of carbon tetrachloride. Furthermore, TRI data shows that no single facility ever reported releases of both carbon tetrachloride and phosgene. EPA does not plan to evaluate exposure to phosgene during the manufacturing and processing of carbon tetrachloride.

2.3.5.2 Consumer Exposures

Consumer products and/or commercial products containing chlorinated compounds made with carbon tetrachloride as a process agent are available for public purchase at common retailers [EPA-HQ-OPPT-2016-0733-0003, sections 3 and 4, (U.S. EPA, 2017d)]. However, these products are not expected to contain measurable amounts of carbon tetrachloride because carbon tetrachloride is not used in the manufacturing of the actual products. Trace levels of carbon tetrachloride in the chlorinated substances used to manufacture the products are expected to volatilize during the product manufacturing process. Therefore, EPA does not plan to evaluate consumer exposures to carbon tetrachloride due to the use of products containing chlorinated compounds made with carbon tetrachloride as a process agent (see Section 2.2.2.1).

2.3.5.3 General Population Exposures

Wastewater/liquid wastes, solid wastes or air emissions of carbon tetrachloride could result in potential pathways for inhalation, oral or dermal exposure to the general population.

Inhalation

The volatility of carbon tetrachloride makes inhalation exposures a likely exposure pathway when it is released (via air or as a result of waste disposal) during industrial or commercial uses (see Figure 2-3) Inhalation of carbon tetrachloride, due to its volatilization, during household use of contaminated water (e.g., during bathing/showering, dishwashing) could be a source of exposure to the general population. According to a study from the New Jersey Department of Environmental Protection (NJ DEP), the acceptable shower water criteria for carbon tetrachloride is 0.15 ug/L and the associated shower air concentration of carbon tetrachloride would be acceptable at 1.5 x 10^{-5}ug/m^3 (NJDEP, 2002). Vapor intrusion is an additional source of exposure in indoor environments. VOCs such as carbon tetrachloride can evaporate rapidly and migrate into air. Therefore, there is a potential for carbon tetrachloride from TSCA conditions of use (see Table 2-7) to migrate from groundwater to indoor air via vapor intrusion.

Oral

Oral ingestion pathways may include exposure to contaminated drinking water or breast milk. However, breast milk is not expected to be significantly contaminated with carbon tetrachloride as the chemical does not bioaccumulate in tissues. EPA conducted a screening level estimate of carbon tetrachloride concentrations in drinking water using the PDM and the facility discharges in 2015 as reported in the NPDES Discharge Monitoring Reports. Ninety four percent of the modeled acute exposures were well below the EPA drinking water Minimum Contaminant Level of 5 ug/L.

Oral ingestion may include incidental ingestion of carbon tetrachloride residue on the hand/body. Based on the presence of carbon tetrachloride in water used for bathing or recreation, the oral ingestion of contaminated water could contribute, to a lesser degree, to oral exposures.

Dermal

Dermal exposure via water could occur through contact, such as washing and bathing with household water contaminated with carbon tetrachloride. The source of the contaminated water could either be contaminated surface or ground waters. As explained in Section 2.3.3, a first-tier analysis of the carbon tetrachloride monitored drinking water concentrations (i.e., SYR data) indicates that 94% of the reported facility discharge levels resulted in drinking water estimates below the EPA Minimum Contaminant Level of 5 ug/L.

2.3.5.4 Potentially Exposed or Susceptible Subpopulations

TSCA requires that the determination of whether a chemical substance presents an unreasonable risk to "a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation" by EPA. TSCA § 3(12) states that "the term 'potentially exposed or susceptible subpopulation' 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." General population is "the total of individuals inhabiting an area or making up a whole group" and refers here to the U.S. general population (U.S. EPA, 2011).

As part of the Problem Formulation, EPA identified potentially exposed and susceptible subpopulations (PESS) for further analysis during the development and refinement of the life cycle, conceptual models, exposure scenarios, and analysis plan. In this section, EPA addresses the PESS identified as relevant based on greater exposure. EPA will address the subpopulations identified as relevant based on greater susceptibility in the hazard section.

EPA identifies the following as PESS due to their greater exposure, that EPA expects to consider in the risk evaluation:

- Workers and ONU based on inhalation and dermal routes of exposure (See Figure 2-2).

In developing exposure scenarios, EPA will analyze available data to ascertain whether some human receptor groups may be exposed via exposure pathways that may be distinct to a particular subpopulation or lifestage and whether some human receptor groups may have higher exposure via identified pathways of exposure due to unique characteristics (e.g., activities, duration or location of exposure) (U.S. EPA, 2006).

In summary, in the risk evaluation for carbon tetrachloride, EPA plans to analyze the following potentially exposed groups of human receptors: workers and ONU. EPA may also identify additional PESS that will be considered based on greater exposure.

2.4 Hazards (Effects)

For scoping, EPA conducted comprehensive searches for data on hazards of carbon tetrachloride, as described in the *Strategy for Conducting Literature Searches for Carbon Tetrachloride*: *Supplemental File for the TSCA Scope Document* (EPA-HQ-OPPT-2016-0733). Based on initial screening, EPA plans to analyze the hazards of carbon tetrachloride identified in this problem formulation document. However, when conducting the risk evaluation, the relevance of each hazard within the context of a specific exposure scenario will be judged for appropriateness. For example, hazards that occur only as a result of chronic exposures may not be applicable for acute exposure scenarios. This means that it is unlikely that every identified hazard will be analyzed for every exposure scenario.

Further, as explained in Section 2.3, EPA's focus in the risk evaluation process is on conducting timely, relevant, high-quality, and scientifically credible risk evaluations 82 FR 33726, 33728 (July 20, 2017). Each risk evaluation will be "fit-for-purpose," meaning the Agency may be able to reach some conclusions without extensive or quantitative risk evaluations, and EPA expects to be able to reach conclusions about particular hazards without extensive evaluation.

2.4.1 Environmental Hazards

For the scope document, EPA consulted the following sources of environmental hazard data for carbon tetrachloride: ECHA (ECHA, 2017), OECD SIDS Initial Assessment Profile (SIAP) (OECD, 2011), and Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS). These previous assessments included an evaluation of the environmental hazard data quality. Only the on-topic references listed in the Ecological Hazard Literature Search Results were considered as potentially relevant data/information sources for the risk evaluation. Inclusion criteria were used to screen the results of the ECOTOX literature search (as explained in the *Strategy for Conducting Literature Searches for Carbon Tetrachloride: Supplemental File for the TSCA Scope Document*, EPA-HQ-OPPT-2016-0733. Data from the screened literature are summarized below (Table 2-8) as ranges (min-max). EPA plans to review these data/information sources during risk evaluation using the data quality review evaluation metrics and the rating criteria described in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018).

Toxicity to Sediment and Terrestrial Organisms

During data screening, the limited number of environmental toxicity studies for carbon tetrachloride on sediment and terrestrial organisms were determined to contain data or information not relevant (off-topic) for the risk evaluation. The studies were considered *off-topic* references during the data screening process (see Section 1.3). No relevant (on-topic) toxicity data were available for carbon tetrachloride to birds. Hazard studies for sediment and terrestrial organisms are not likely to be conducted because exposure to carbon tetrachloride by these organisms is not expected due to the fate and transport properties of the chemical.

Toxicity to Aquatic Organisms

During problem formulation, EPA identified aquatic (aqueous-only) data reported in literature to assess the aquatic hazard of carbon tetrachloride. For the aquatic environment, the acute hazard endpoint for fish (96-h LC_{50}) exposed to carbon tetrachloride ranges from 7.6 - 125 mg/L (Japanese Ministry of Environment, 2015; Dawson, 1977). The acute hazard endpoint for aquatic invertebrates (48-h EC_{50}) exposed to carbon tetrachloride ranges from 8.1 - 35 mg/L (Japanese Ministry of Environment, 2015; Leblanc, 1980). The acute hazard endpoint for aquatic plants (72-hr EC_{50}) exposed to carbon tetrachloride ranges from 0.246 – 23.590 mg/L (Tsai, 2007; Brack, 1994). The chronic hazard endpoint for fish (23-day LC_{50}) exposed to carbon tetrachloride is 1.97 mg/L (Black, 1982). The chronic hazard endpoint for aquatic invertebrates (21-day NOEC) exposed to carbon tetrachloride ranges from 0.49 – 3.1 mg/L (Japanese Ministry of Environment, 2015; Thomson et al., 1997). For aquatic plants, the chronic hazard endpoint (72-hr EC_{10}/NOEC) for carbon tetrachloride ranges from 0.0717 - 2.2 mg/L (Gancet, 2011; Brack, 1994). The acute toxicity of amphibian embryo-larval stages ranged from 0.9 to 22.420 mg/L (Black, 1982; Birge, 1980).

Table 2-8. Ecological Hazard Characterization of Carbon Tetrachloride

Duration	Test organism	Endpoint	Hazard value*	Units	Effect Endpoint	References
Acute	Fish	LC_{50}	7.6 - 125	mg/L	Mortality	(Japanese Ministry of Environment, 2015; Dawson, 1977)
	Aquatic invertebrates	EC_{50}	8.1 – 35	mg/L	Immobilization	(Japanese Ministry of Environment, 2015; Leblanc, 1980)
	Algae	EC_{50}	0.246-23.590	mg/L	Biomass/growth rate	(Tsai, 2007; Brack, 1994)
	Amphibians	L/EC_{50}	0.9-22.420	mg/L	Mortality	(Black, 1982; Birge, 1980)
	Acute COC	0.062		mg/L		
Chronic	Fish	ChV	1.97	mg/L	Mortality	(Black, 1982)
	Aquatic invertebrates	NOEC	0.49-3.1	mg/L	Growth and reproduction	(Japanese Ministry of Environment, 2015; Thomson et al., 1997)
	Algae	EC_{10}/NOEC	0.0717 - 2.2	mg/L	Biomass/growth rate	(Gancet, 2011; Brack, 1994).
	Chronic COC	0.007		mg/L		

* Values in the tables are presented as reported by the study authors

Concentrations of Concern

The screening-level acute and chronic COCs for carbon tetrachloride were derived based on the lowest or most toxic ecological toxicity values (e.g., L/EC_{50}). The information below describes how the acute and chronic COC's were calculated for environmental toxicity of carbon tetrachloride using assessment factors. The application of assessment factors is based on established EPA/OPPT methods (U.S. EPA, 2013, 2012b) and were used in this hazard assessment to calculate lower bound effect levels (referred to as the concentration of concern; COC) that would likely encompass more sensitive species not specifically represented by the available experimental data. Also, assessment factors are included in the

COC calculation to account for differences in inter- and intra-species variability, as well as laboratory-to-field variability. It should be noted that these assessment factors are dependent upon the availability of datasets that can be used to characterize relative sensitivities across multiple species within a given taxa or species group, but are often standardized in risk assessments conducted under TSCA, due to limited data availability.

The acute COC is derived by dividing the algal 72-hr EC_{50} of 0.246 mg/L (the lowest acute value in the dataset) by an assessment factor (AF) of 4:

- Lowest value for the 72-hr fish EC_{50} (0.246 mg/L) / AF of 4 = 0.062 mg/L or 62 µg/L.

The acute COC of 62 µg/L, derived from experimental algal endpoint, is used as a conservative hazard level in this problem formulation for carbon tetrachloride.

The chronic COC is derived by dividing the 72-hr algal EC_{10} of 0.0717 mg/L (the lowest chronic value in the dataset) by an assessment factor of 10:

- Lowest value for the 72-hr algal chronic value (0.0717 mg/L) / AF of 10 = 0.007 mg/L or 7 µg/L.

The chronic COC of 7 µg/L, derived from experimental algal endpoint, is used as the lower bound hazard level in this problem formulation for carbon tetrachloride.

2.4.2 Human Health Hazards

Carbon tetrachloride has an existing EPA IRIS Assessment (U.S. EPA, 2010) and an ATSDR Toxicological Profile (ATSDR, 2005); hence, many of the hazards of carbon tetrachloride have been previously compiled. EPA expects to use these previous analyses as a starting point for identifying key and supporting studies to inform the human health hazard assessment, including dose-response analysis. The relevant studies will be evaluated using the data quality criteria in the *Application of Systematic Review in TSCA Risk Evaluations* document. EPA also expects to consider other studies (e.g., more recently published, peer-reviewed alternative test data) that have been published since these reviews, as identified in the literature search conducted by the Agency for carbon tetrachloride (*Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document*, EPA-HQ-OPPT-2016-0733). EPA expects to consider potential human health hazards associated with carbon tetrachloride. Based on reasonably available information, the following sections describe the potential hazards associated with carbon tetrachloride. In addition to these hazards, EPA plans to evaluate hazards (e.g., reproductive toxicity, developmental toxicity) that may be identified during the evaluation of the key studies from the IRIS Toxicological Review of Carbon Tetrachloride.

2.4.2.1 Non-Cancer Hazards

Acute Toxicity

Following acute exposures, human case reports identify liver as a primary target organ of toxicity and the kidney as an additional primary target organ of toxicity (U.S. EPA, 2010). Neurotoxicity indicated as central nervous system (CNS) depression is another primary effect of carbon tetrachloride in humans following acute exposures, with examples of neurotoxic effects including drowsiness, headache, dizziness, weakness, coma and seizures (U.S. EPA, 2010). Gastrointestinal symptoms such as nausea and vomiting, diarrhea and abdominal pain are considered another initial acute effect.

Liver Toxicity

Liver toxicity has consistently been demonstrated following human and animal exposures to carbon tetrachloride (U.S. EPA, 2010). Suggestive evidence of an effect of occupational exposure on serum enzymes indicative of hepatic effects was reported in a cross-sectional epidemiology study. Similar to humans, data from acute, subchronic and chronic animal studies suggest that the liver is the major target organ for carbon tetrachloride toxicity (U.S. EPA, 2010).

Kidney Toxicity

Renal toxicity effects include oliguria, elevated blood urea nitrogen (BUN) and histopathological changes (e.g., nephrosis, degeneration and interstitial inflammation in fatal cases) were observed in humans following acute exposures. In animals, renal toxicity was observed in inhalation (but not oral) studies. In subchronic studies, renal toxicity generally occurred at higher concentrations than those producing liver damage, whereas changes in renal and liver endpoints were reported at the same concentration in chronic inhalation toxicity studies in rats and mice (U.S. EPA, 2010).

Irritation/Sensitization

Following dermal exposures, primary irritation was observed in rabbits and guinea pigs (ATSDR, 2005). Guinea pigs also exhibited degenerative change in epidermal cells and edema (ATSDR, 2005). In the murine local lymph node assay, carbon tetrachloride showed weak dermal sensitization potential (OECD, 2011).

2.4.2.2 Genotoxicity and Cancer Hazards

The IRIS Assessment for carbon tetrachloride evaluated data for genotoxicity and cancer hazard. Carbon tetrachloride has been extensively studied for its genotoxic and mutagenic effects. Overall, results are largely negative. There is little direct evidence that carbon tetrachloride induces intragenic or point mutations in mammalian systems. The mutagenicity studies that have been performed using transgenic mice have yielded negative results, as have the vast majority of the mutagenicity studies that have been conducted in bacterial systems. The weight of evidence suggests that carbon tetrachloride is more likely an indirect mutagenic agent (i.e., lipid peroxidation, protein modifications) rather than a direct mutagen (deoxyribonucleic acid [DNA] modifications) (U.S. EPA, 2010).

In the IRIS carcinogenicity assessment, carbon tetrachloride is considered "likely to be carcinogenic to humans" by all routes of exposure based on inadequate evidence of carcinogenicity in humans, and sufficient evidence in animals by oral and inhalation exposure. The animal evidence shows that carbon tetrachloride is a liver carcinogen in rats, mice and hamsters following oral and inhalation exposure in eight bioassays. Carbon tetrachloride also induced pheochromocytomas in mice exposed by the oral and inhalation routes of exposure.

2.4.2.3 Potentially Exposed or Susceptible Subpopulations

TSCA requires that the determination of whether a chemical substance presents an unreasonable risk include consideration of unreasonable risk to “a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation” by EPA. TSCA § 3(12) states that “the term ‘potentially exposed or susceptible subpopulation’ 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.” In developing the hazard assessment, EPA will analyze available data to ascertain whether some human receptor groups may have greater susceptibility than the general population to the chemical’s hazard(s).

EPA's IRIS assessment identified the following as factors that might influence susceptibility to carbon tetrachloride: age (e.g., childhood, senescence), gender, nutritional status, disease status and exposure to other chemicals (U.S. EPA, 2010, 2006). The IRIS assessment noted that because metabolism of carbon tetrachloride to reactive metabolites by cytochrome P450 (CYP450) enzymes is hypothesized to be a key event in the toxicity of this compound, variability in CYP450 levels due to age-related differences or other factors such as exposure to other chemicals that either induce or inhibit microsomal enzymes may impact an individual's response to carbon tetrachloride. In addition, variability in nutritional status, alcohol consumption and/or underlying diseases (e.g., diabetes) may alter metabolism or antioxidant protection systems and thereby also alter susceptibility to carbon tetrachloride (U.S. EPA, 2010). EPA expects to consider these factors, and others that may be identified from more current literature, in the risk evaluation for carbon tetrachloride.

2.5 Conceptual Models

EPA risk assessment guidance (U.S. EPA, 2014, 1998) defines Problem Formulation as the part of the risk assessment framework that identifies the factors to be considered in the assessment. It draws from the regulatory, decision-making and policy context of the assessment and informs the assessment's technical approach.

A conceptual model describes the actual or predicted relationships between the chemical substance and receptors, either human or environmental. These conceptual models are integrated depictions of the conditions of use, exposures (pathways and routes), hazards and receptors. The initial conceptual models describing the scope of the assessment for carbon tetrachloride, have been refined during problem formulation. The changes to the conceptual models in this problem formulation are described along with the rationales.

In this section EPA outlines those pathways that will be included and further analyzed in the risk evaluation; will be included but will not be further analyzed in risk evaluation; and will not be included in the TSCA risk evaluation; and the underlying rationale for these decisions.

EPA determined as part of problem formulation that it is not necessary to conduct further analysis on certain exposure pathways that were identified in the carbon tetrachloride scope document and that remain in the risk evaluation. Each risk evaluation will be "fit-for-purpose," meaning not all conditions of use will warrant the same level of evaluation and the Agency may be able to reach some conclusions without extensive or quantitative risk evaluations. 82 FR 33726, 33734, 33739 (July 20, 2017).

As part of this problem formulation, EPA also identified exposure pathways under regulatory programs of other environmental statutes, administered by EPA, which adequately assess and effectively manage exposures and for which long-standing regulatory and analytical processes already exist, i.e., the CAA, the SDWA, the Clean Water Act (CWA) and the RCRA. OPPT worked closely with the offices within EPA that administer and implement the regulatory programs under these statutes. In some cases, EPA has determined that chemicals present in various media pathways (i.e., air, water, land) fall under the jurisdiction of existing regulatory programs and associated analytical processes carried out under other EPA-administered statutes and have been assessed and effectively managed under those programs. EPA believes that the TSCA risk evaluation should generally focus on those exposure pathways associated with TSCA conditions of use that are not adequately assessed and effectively managed under the regulatory regimes discussed above because these pathways are likely to represent the greatest areas of risk concern. As a result, EPA does not expect to include in the risk evaluation certain exposure pathways identified in the carbon tetrachloride scope document.

2.5.1 Conceptual Model for Industrial and Commercial Activities and Uses: Potential Exposures and Hazards

The revised conceptual model (Figure 2-2) describes the pathways of exposure from industrial and commercial activities and uses of carbon tetrachloride that EPA expects to include in the risk evaluation. EPA plans to evaluate exposures to workers and/or ONU via inhalation routes and to workers via dermal routes during manufacturing, processing, use and disposal of carbon tetrachloride for all the identified uses. In addition to the pathways illustrated in the figure, EPA will evaluate activities resulting in exposures associated with distribution in commerce (e.g., loading, unloading) throughout the various lifecycle stages and conditions of use (e.g., manufacturing, processing, industrial use, commercial use, disposal) rather than a single distribution scenario.

Inhalation

Based on the physical-chemical properties (e.g., high vapor pressure), inhalation is expected to be the main exposure pathway for carbon tetrachloride. Inhalation exposures for workers are regulated by OSHA's occupational safety and health standards for carbon tetrachloride which include a PEL of 10 ppm TWA, exposure monitoring, control measures and respiratory protection (29 CFR 1910.1000). EPA expects that for workers and ONU, exposure via inhalation will be the most significant route of exposure for most exposure scenarios. EPA plans to further analyze inhalation exposures to vapors for workers and ONU in the risk evaluation.

There are potential worker exposures through mists that deposit in the upper respiratory tract. EPA initially assumed that mists may be swallowed. However, based on physical chemical properties, mists of carbon tetrachloride will likely be rapidly absorbed in the respiratory tract or evaporate and contribute to the amount of carbon tetrachloride vapor in the air. Furthermore, if carbon tetrachloride vapors were ingested orally the available toxicological data do not suggest significantly different toxicity from considering vapors as an inhalation exposure. ONU are not directly handling carbon tetrachloride; therefore, exposure to mists is not expected for ONU. EPA plans no further analysis of this pathway (swallowing of carbon tetrachloride mists) for workers or ONU in the risk evaluation.

Dermal

There is the potential for dermal exposures to carbon tetrachloride in many worker scenarios. These dermal exposures would be concurrent with inhalation exposures and the overall contribution of dermal exposure to the total exposure is expected to be small; however, there may be exceptions for occluded scenarios. ONU are not directly handling carbon tetrachloride; therefore, skin contact with liquid carbon tetrachloride is not expected for ONU. EPA does not plan to further analyze this pathway in the risk evaluation. EPA plans to further analyze dermal exposures for skin contact with liquids and vapors in occluded situations for workers.

Waste Handling, Treatment and Disposal

Figure 2-2 shows that waste handling, treatment and disposal is expected to lead to the same pathways as other industrial and commercial activities and uses. The path leading from the "Waste Handling, Treatment and Disposal" box to the "Hazards Potentially Associated with Acute and/or Chronic Exposures See Section 2.4.2" box was re-routed to accurately reflect the expected exposure pathways, routes, and receptors associated with these conditions of use of carbon tetrachloride.

For each condition of use identified in Table 2-3, a determination was made as to whether or not each unique combination of exposure pathway, route, and receptor will be analyzed further in the risk evaluation. The results of that analysis along with the supporting rationale are presented in Appendix F.

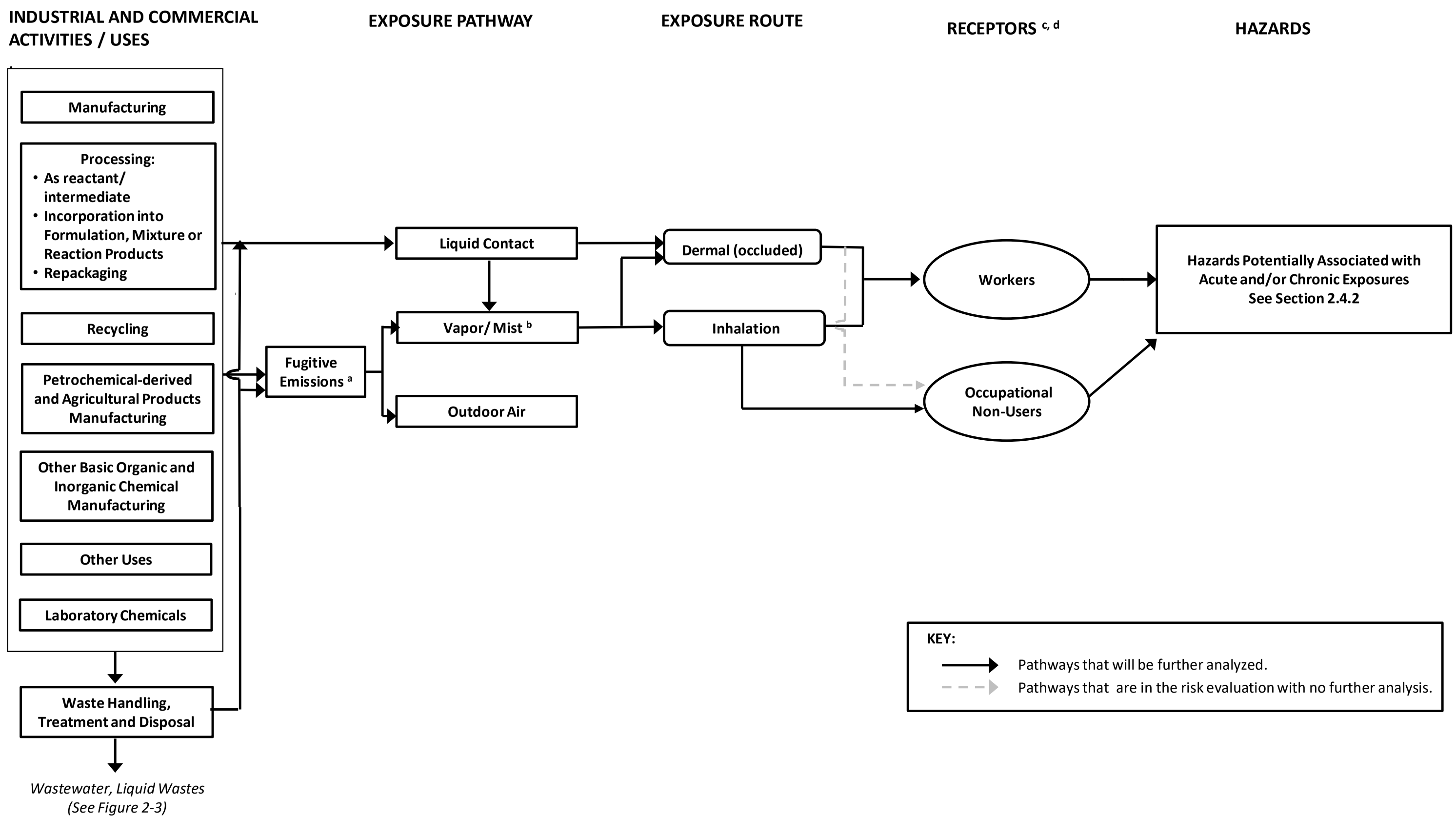

Figure 2-2. Carbon Tetrachloride Conceptual Model for Industrial and Commercial Activities and Uses: Potential Exposures and Hazards

The conceptual model presents the exposure pathways, exposure routes and hazards to human receptors from industrial and commercial activities and uses of carbon tetrachloride.

[a] Fugitive air emissions include fugitive equipment leaks from valves, pump seals, flanges, compressors, sampling connections, open-ended lines; evaporative losses from surface impoundment and spills; and releases from building ventilation systems.

[b] Includes possible vapor intrusion into industrial or commercial facility from carbon tetrachloride ground water; exposure to mists is not expected for ONU.

[c] Receptors include PESS (see Section 2.4.2.3).

[d] When data and information are available to support the analysis, EPA also considers the effect that engineering controls and/or personal protective equipment have on occupational exposure levels.

2.5.2 Conceptual Model for Consumer Activities and Uses: Potential Exposures and Hazards

As explained in Section 2.2.2.1, there are current regulatory actions that prevent the direct use of carbon tetrachloride in the formulation of commercially available products, besides the use of carbon tetrachloride as a laboratory chemical. The domestic and international use of carbon tetrachloride as a process agent is regulated under EPA's stratospheric ozone protection regulations at 40 CFR part 82. This process agent use is also addressed by the MP side agreement, Decision X/14: Process Agents, from the tenth meeting of the parties in November 1998 (UNEP/Ozone Secretariat, 1998). This MP decision lists a limited number of approved uses of carbon tetrachloride as a process agent (i.e., non-feedstock uses) in which carbon tetrachloride is not expected to be destroyed in the production process (see Appendix D). Based on the process agent uses, carbon tetrachloride is used to manufacture other chlorinated compounds (i.e., chlorinated paraffins) that may subsequently be added to commercially available products (i.e., adhesives). Given the high volatility of carbon tetrachloride and the extent of reaction and efficacy of the separation/purification process for purifying final products, EPA does not expect that carbon tetrachloride will be present in the commercially available products. Furthermore, the use of carbon tetrachloride in consumer products has been banned by the CPSC (16 CFR 1500.17) since 1970. EPA does not expect to evaluate consumer activities and uses for carbon tetrachloride, and has excluded these conditions of use from the scope of the risk evaluation (see Section 2.2.2.1). Therefore, there is no conceptual model provided for consumer activities and uses.

2.5.3 Conceptual Model for Environmental Releases and Wastes: Potential Exposures and Hazards

The revised conceptual model (Figure 2-3) illustrates the expected exposure pathways to human and ecological receptors from environmental releases and waste streams associated with industrial and commercial activities for carbon tetrachloride that EPA expects to include in the risk evaluation. The pathways that EPA expects to include but not further analyze in the risk evaluation are described in Section 2.5.3.1 and shown in the conceptual model, Figure 2-3. The pathways that EPA does not expect to include in the risk evaluation are described in Section 2.5.3.2. EPA does not expect to further analyze any exposure pathways to human or ecological receptors from environmental releases and waste streams associated with industrial and commercial activities for carbon tetrachloride.

2.5.3.1 Pathways That EPA Expects to Include But Not Further Analyze

EPA does not expect to further analyze carbon tetrachloride exposures to aquatic species from sediments and suspended solids. Due to its log K_{oc} (1.7 – 2.16) and high solubility of 793 mg/L at 25°C, sorption of carbon tetrachloride to sediments and suspended solids is unlikely.

EPA does not expect to further analyze risk to aquatic species exposed to carbon tetrachloride in surface water. Wastewater from industrial discharges as reported under TRI for 2015 shows only 468.2 pounds of carbon tetrachloride were released to surface water nationally and significant levels of carbon tetrachloride are not expected from disposal of consumer and commercial products.

EPA considered worst-case scenarios to estimate carbon tetrachloride concentrations in surface water resulting from industrial discharges. Using NPDES Discharge Monitoring Reporting data available for 2015, the largest releases of carbon tetrachloride were modeled for releases over 20 days and 250 days per year. In these conservative scenarios, surface water concentrations were below the acute COC for aquatic species (see Appendix E); hence there is not an acute aquatic concern. Although the chronic COC was exceeded by one facility by a factor of 3.5 (i.e., worst-case scenario) based on predicted conservative exposure concentrations in surface water, these carbon tetrachloride releases are not continuously released over time (i.e., chronic exposure); hence there is not a chronic aquatic concern. Furthermore, carbon tetrachloride discharges to surface waters are expected to undergo volatilization and dilution in surface water, processes that were not considered for estimating the predicted conservative exposure concentrations in surface water. Due to its physical-chemical properties, carbon tetrachloride is not anticipated to bioaccumulate in fish (BCF 30-40) thus there is no bioconcentration or bioaccumulation concern. Thus, EPA does not expect to further analyze exposure pathways to ecological aquatic species in the risk evaluation.

2.5.3.2 Pathways that EPA Does Not Expect to Include in the Risk Evaluation

Exposures to receptors (i.e. general population, terrestrial species) may occur from industrial and/or commercial uses; industrial releases to air, water or land; and other conditions of use. As described in Section 2.5, EPA does not expect to include in the risk evaluation pathways under programs of other environmental statutes, administered by EPA, which adequately assess and effectively manage exposures and for which long-standing regulatory and analytical processes already exist. These pathways are described below.

Ambient Air Pathway

The Clean Air Act (CAA) contains a list of HAP and provides EPA with the authority to add to that list pollutants that present, or may present, a threat of adverse human health effects or adverse environmental effects. For stationary source categories emitting HAP, the CAA requires issuance of technology-based standards and, if necessary, additions or revisions to address developments in practices, processes, and control technologies, and to ensure the standards adequately protect public health and the environment. The CAA thereby provides EPA with comprehensive authority to regulate emissions to ambient air of any HAP.

Carbon tetrachloride is a HAP. EPA has issued a number of technology-based standards for source categories that emit carbon tetrachloride to ambient air and, as appropriate, has reviewed or is in the process of reviewing remaining risks. Because stationary source releases of carbon tetrachloride to ambient air are adequately assessed and any risks effectively managed when under the jurisdiction of the CAA, EPA does not expect to include emission pathways to ambient air from commercial and industrial stationary sources or associated inhalation exposure of the general population or terrestrial species in this TSCA evaluation.

Drinking Water Pathway

EPA has regular analytical processes to identify and evaluate drinking water contaminants of potential regulatory concern for public water systems under the SDWA. Under SDWA, EPA must also review and revise “as appropriate” existing drinking water regulations every 6 years.

EPA has promulgated National Primary Drinking Water Regulations (NPDWRs) for carbon tetrachloride under the Safe Drinking Water Act. EPA has set an enforceable MCL as close as feasible to a health based, non-enforceable Maximum Contaminant Level Goal (MCLG). Feasibility refers to both the ability to treat water to meet the MCL and the ability to monitor water quality at the MCL, SDWA Section 1412(b)(4)(D), and public water systems are required to monitor for the regulated chemical based on a standardized monitoring schedule to ensure compliance with the MCL. The MCL and MCLG values for carbon tetrachloride are presented in Appendix A.1.

Hence, because the drinking water exposure pathway for carbon tetrachloride is currently addressed in the SDWA regulatory analytical process for public water systems, EPA does not expect to include this pathway in the risk evaluation for carbon tetrachloride under TSCA. EPA’s OW and OPPT will continue to work together providing understanding and analysis of the SDWA regulatory analytical processes and to exchange information related to toxicity and occurrence data on chemicals undergoing risk evaluation under TSCA.

Ambient Water Pathways

EPA develops recommended water quality criteria under section 304(a) of the CWA for pollutants in surface water that are protective of aquatic life or human health designated uses. EPA develops and publishes water quality criteria based on priorities of states and others that reflect the latest scientific knowledge. When states adopt criteria that EPA approves as part of states' regulatory water quality standards, exposure is considered when state permit writers determine if permit limits are needed and at what level for a specific discharger of a pollutant to ensure protection of the designated uses of the receiving water. This is the process used under the CWA to address risk to human health and aquatic life from exposure to a pollutant in ambient waters.

EPA has identified carbon tetrachloride as a priority pollutant and EPA has developed recommended water quality criteria for protection of human health for carbon tetrachloride which are available for adoption into state water quality standards for the protection of human health and are available for use by NPDES permitting authorities in deriving effluent limits to meet state narrative criteria. As such, EPA does not expect to include this pathway in the risk evaluation under TSCA. EPA's OW and OPPT will continue to work together providing understanding and analysis of the CWA water quality criteria development process and to exchange information related to toxicity of chemicals undergoing risk evaluation under TSCA. EPA may update its CWA section 304(a) water quality criteria for carbon tetrachloride in the future under the CWA.

EPA has not developed CWA section 304(a) recommended water quality criteria for the protection of aquatic life for carbon tetrachloride, so there are no national recommended criteria for this use available for adoption into state water quality standards and available for use in NPDES permits. As a result, this pathway will undergo aquatic life risk evaluation under TSCA but as described in Section 2.5.3.1 (i.e., conservative estimates of surface water concentrations) this pathway will not be further analyzed. EPA may publish CWA section 304(a) aquatic life criteria for carbon tetrachloride in the future if it is identified as a priority under the CWA.

Biosolids Pathways

CWA Section 405(d) requires EPA to 1) promulgate regulations that establish numeric criteria and management practices that are adequate to protect public health and the environment from any reasonably anticipated adverse effects of toxic pollutants during the use or disposal of sewage sludge, and 2) review such regulations at least every two years to identify additional toxic pollutants that occur in biosolids (i.e., "Biennial Reviews") and regulate those pollutants if sufficient scientific evidence shows they may be present in sewage sludge in concentrations which may adversely affect public health or the environment. EPA also periodically conducts surveys to determine what may be present in sewage sludge. EPA has conducted four sewage sludge surveys and identified compounds that occur in biosolids in seven Biennial Reviews. EPA has regulated 10 chemicals in biosolids under CWA 405(d).

EPA has identified carbon tetrachloride in biosolids biennial reviews. The purpose of such reviews is to identify additional toxic pollutants in biosolids. EPA can potentially regulate those pollutants under CWA 405(d), based on a subsequent assessment of risk. EPA's Office of Water is currently developing modeling tools in order to conduct risk assessments for chemicals in biosolids. Because the biosolids pathway for carbon tetrachloride is currently being addressed in the CWA regulatory analytical process, this pathway will not be further analyzed in the risk evaluation for carbon tetrachloride under TSCA.

EPA's OW and OPPT will continue to work together to discuss significant data gaps and exchange information related to exposure and toxicity of this chemical as OW conducts the risk assessment under the CWA.

Disposal Pathways

Carbon tetrachloride is included on the list of hazardous wastes to RCRA 3001 (40 CFR §§ 261.33) as a listed waste on the D, K, F and U lists. The general standard in RCRA section 3004(a) for the technical criteria that govern the management (treatment, storage, and disposal) of hazardous waste are those "necessary to protect human health and the environment," RCRA 3004(a). The regulatory criteria for identifying "characteristic" hazardous wastes and for "listing" a waste as hazardous also relate solely to the potential risks to human health or the environment. 40 C.F.R. §§ 261.11, 261.21-261.24. RCRA statutory criteria for identifying hazardous wastes require EPA to "tak[e] into account toxicity, persistence, and degradability in nature, potential for accumulation in tissue, and other related factors such as flammability, corrosiveness, and other hazardous characteristics." Subtitle C controls cover not only hazardous wastes that are landfilled, but also hazardous wastes that are incinerated (subject to joint control under RCRA Subtitle C and the CAA hazardous waste combustion MACT) or injected into UIC Class I hazardous waste wells (subject to joint control under Subtitle C and the SDWA).

EPA does not expect to include emissions to ambient air from municipal and industrial waste incineration and energy recovery units in the risk evaluation, as they are regulated under section 129 of the Clean Air Act. CAA section 129 also requires EPA to review and, if necessary, add provisions to ensure the standards adequately protect public health and the environment. Thus, combustion by-products from incineration treatment of carbon tetrachloride wastes (over 15 million lbs identified in Table 2-6) would be subject to the aforementioned regulations, as would carbon tetrachloride burned for energy recovery (5.6 million lbs).

EPA does not expect to include on-site releases to land that go to underground injection in its risk evaluation. TRI reporting in 2015 indicated 19,608 pounds released to underground injection to a Class I well and no releases to underground injection wells of Classes II-VI. Environmental disposal of carbon tetrachloride injected into Class I well types is managed and prevented from further environmental release by RCRA and SDWA regulations. Therefore, disposal of carbon tetrachloride via underground injection is not likely to result in environmental and general population exposures.

EPA does not expect to include on-site releases to land that go to RCRA Subtitle C hazardous waste landfills in its risk evaluation. Based on 2015 reporting to TRI, the majority of the chemical is disposed of in Subtitle C landfills (27,300 lbs on-site and 401 lbs other land disposal). Design standards for Subtitle C landfills require double liner, double leachate collection and removal systems, leak detection system, run on, runoff, and wind dispersal controls, and a construction quality assurance program. They are also subject to closure and post-closure care requirements including installing and maintaining a final cover, continuing operation of the leachate collection and removal system until leachate is no longer detected, maintaining and monitoring the leak detection and groundwater monitoring system. Bulk liquids may not be disposed in Subtitle C landfills. Subtitle C landfill operators are required to implement an analysis and testing program to ensure adequate knowledge of waste being managed, and to train personnel on routine and emergency operations at the facility. Hazardous waste being disposed in Subtitle C landfills must also meet RCRA waste treatment standards before disposal. Given these controls, general population and terrestrial organisms exposure to carbon tetrachloride in groundwater from Subtitle C landfill leachate is not expected to be a significant pathway.

EPA does not expect to include on-site releases to land from RCRA Subtitle C hazardous waste landfills or exposures of the general population (including susceptible subpopulations) or terrestrial species from such releases in the TSCA evaluation.

Based on 2015 reporting to TRI, 401 lb of carbon tetrachloride wastes were released as other land disposals (see Table 2-7). Upon evaluation of these reports of other land disposal releases, it was found that the reports consist of misreported disposal values. The incorrect code uses or waste identification were used in the reports. Therefore these 401 lbs of released waste do not consist of carbon tetrachloride waste released by other land disposal. EPA does not expect to include these misreported other land disposals for carbon tetrachloride in the TSCA evaluation.

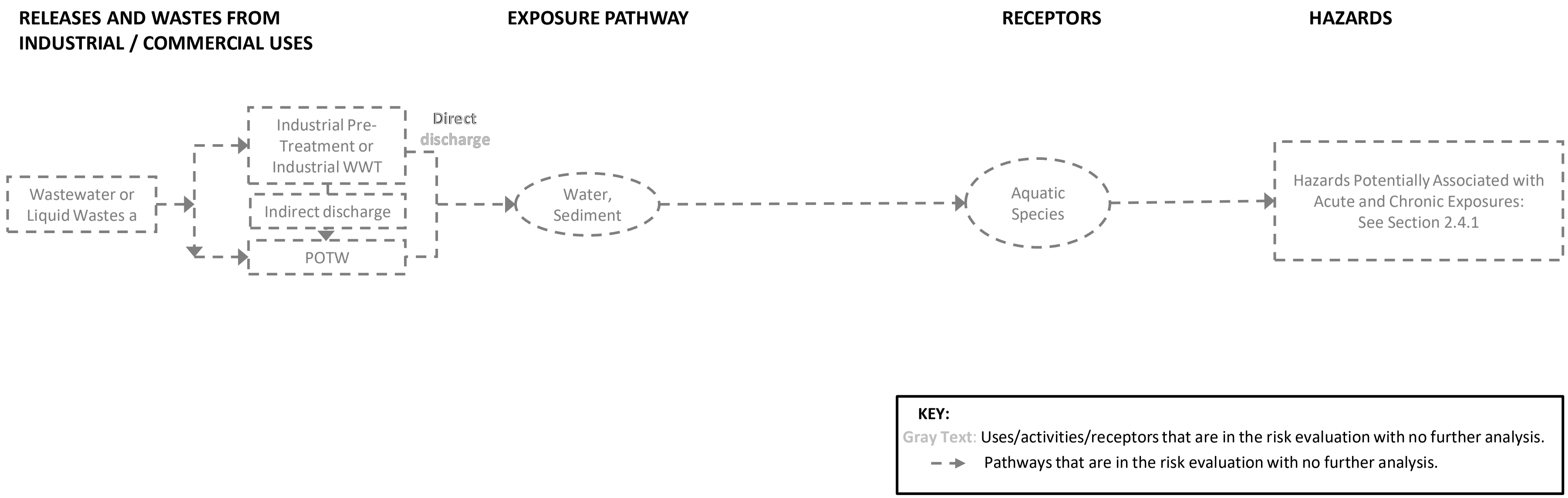

Figure 2-3. Carbon Tetrachloride Conceptual Model for Environmental Releases and Wastes: Potential Exposures and Hazards
The conceptual model presents the exposure pathways, exposure routes and hazards to environmental receptors from environmental water releases of carbon tetrachloride.

2.6 Analysis Plan

The analysis plan in the problem formulation elaborates on the initial analysis plan that was published in the *Scope of the Risk Evaluation for carbon tetrachloride* (U.S. EPA, 2017e).

The analysis plan outlined here is based on the conditions of use of carbon tetrachloride, as described in Section 2.2 of this problem formulation. EPA is implementing systematic review approaches and/or methods to identify, select, assess, integrate and summarize the findings of studies supporting the TSCA risk evaluation. The analytical approaches and considerations in the analysis plan are used to frame the scope of the systematic review activities for this assessment. The supplemental document, *Application of Systematic Review in TSCA Risk Evaluations,* provides additional information about the criteria, approaches and/or methods that have been and will be applied to the first ten chemical risk evaluations.

While EPA has conducted a search for readily available information from public sources as described in the Scope of the Risk Evaluation for Carbon Tetrachloride (U.S. EPA, 2017e), EPA encourages submission of additional existing data, such as full study reports or workplace monitoring from industry sources, that may be relevant for refining conditions of use, exposures, hazards and PESS. EPA will continue to consider new information submitted by the public.

During the risk evaluation, EPA will rely on the comprehensive literature results [*Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document*; (U.S. EPA, 2017a)] or perform supplemental literature searches to address specific questions. Further, EPA may consider any relevant CBI information in the risk evaluation in a manner that protects the confidentiality of the information from public disclosure. The analysis plan is based on EPA's knowledge of carbon tetrachloride to date which includes partial, but not complete review of identified literature. Should additional data or approaches become available, EPA may refine its analysis plan based on this information.

2.6.1 Exposure

Based on physical-chemical properties, expected sources, and transport and transformation within the outdoor and indoor environment chemical substances are more likely to be present in some media and less likely to be present in others. Media-specific concentrations will vary based on the chemical substance of interest. For most chemical substances, level(s) can be characterized through a combination of available monitoring data and modeling approaches.

2.6.1.1 Environmental Releases, Fate and Exposures

EPA does not plan to further analyze environmental releases to environmental media based on information described in Section 2.5. For the purposes of developing estimates of occupational exposure, EPA may use release related data collected under selected data sources such as the Toxics Release Inventory (TRI) and National Emissions Inventory (NEI) programs. Analyses conducted using physical and chemical properties, fate information and TRI/DMR show that TSCA-related environmental releases for carbon tetrachloride do not result in significant exposure to aquatic species through water and sediment exposure pathways (see Section 2.5.3.1). For the pathways of exposures for the general population and terrestrial species, EPA has determined that the existing regulatory programs and associated analytical processes adequately assess and effectively manage the risks of carbon tetrachloride that may be present in other media pathways. EPA believes that the TSCA risk evaluation for carbon tetrachloride should focus not on those exposure pathways, but rather on exposure pathways associated with TSCA conditions of use that are not subject to those regulatory processes, because the latter pathways are likely to represent the greatest areas of risk concern.

2.6.1.2 Occupational Exposures

EPA expects to consider and analyze exposures to workers and ONU as follows:

1) Review reasonably available exposure monitoring data for specific condition(s) of use. Exposure data to be reviewed may include workplace monitoring data collected by government agencies such as OSHA and NIOSH, data submitted by Halogenated Solvents Industry Alliance and Department of Defense and monitoring data found in published literature. These workplace monitoring data include personal exposure monitoring data (direct exposures) and area monitoring data (indirect exposures). During risk evaluation, EPA will review these data and evaluate the utility of these datasets in the risk evaluation. Data, information, and studies will be evaluated using the evaluation strategies laid out in the *Application of Systematic Review in TSCA Risk Evaluations*.

   EPA has reviewed available monitoring collected by OSHA and NIOSH and matched them to applicable conditions of use. EPA has also identified data sources that may contain relevant monitoring data for the various conditions of use. EPA will review these sources. Data gaps will be identified where no data are found for particular conditions of use. EPA will attempt to address data gaps identified as described in steps 2 and 3 below. Where possible, job descriptions may be useful in distinguishing exposures to different subpopulations within a particular condition of use. EPA has also identified additional data sources that may contain relevant monitoring data for the various conditions of use. EPA will review these sources, identified in Table 2-9 and other relevant data sources, and will extract relevant data for consideration and analysis during risk evaluation.

   Table 2-9. Potential Sources of Occupational Exposure Data

ATSDR Toxicological Profile for Carbon Tetrachloride
U.S. OSHA CEHD program data
U.S. NIOSH Health Hazard Evaluation (HHE) Program reports
Industry workplace exposure monitoring summary data submitted to EPA by Halogenated Solvents Industry Alliance
Industry workplace exposure information submitted to EPA by the Department of Defense
U.S. EPA Generic Scenarios
OECD Emission Scenario Documents (ESD)
Sector-specific Worker Exposure Descriptions (SWEDs)

2) Review reasonably available exposure data for surrogate chemicals that have uses and chemical and physical properties similar to carbon tetrachloride. EPA will review literature sources identified and if surrogate data are found, these data will be matched to applicable conditions of use for potentially filling data gaps.

3) For conditions of use where data are limited or not available, review existing exposure models that may be applicable in estimating exposure levels. EPA has identified potentially relevant OECD ESDs and EPA GS corresponding to some conditions of use. EPA will need to critically review these generic scenarios and ESDs to determine their applicability to the conditions of use assessed. EPA is working in the identification of exposure scenarios corresponding to several conditions of use, including manufacture of carbon tetrachloride, use of carbon tetrachloride as an intermediate, and recycling of carbon tetrachloride. EPA will perform additional targeted research to understand those conditions of use, which may inform identification of exposure scenarios. EPA may also need to perform targeted research to identify applicable models that EPA may use to estimate exposures for certain conditions of use.

4) Review reasonably available data that may be used in developing, adapting, or applying exposure models to the particular risk evaluation. This step will be performed after Steps 2 and 3 above. Based on information developed from Step 2 and Step 3, EPA will evaluate relevant data to determine whether the data can be used to develop, adapt, or apply models for specific conditions of use (and corresponding exposure scenarios). EPA will consider the effect of evaporation when evaluating options for dermal exposure assessment. In addition, EPA will consider the impact of occluded exposure or repeated dermal contacts.

5) Consider and incorporate applicable engineering controls and/or personal protective equipment into exposure scenarios. EPA will review potentially relevant data sources on engineering controls and personal protective equipment as identified in Appendix F and to determine their applicability and incorporation into exposure scenarios during risk evaluation.

6) Evaluate the weight of the evidence of occupational exposure data. EPA will rely on the weight of the scientific evidence when evaluating and integrating occupational exposure data. The data integration strategy will be designed to be fit-for-purpose in which EPA will use systematic review methods to assemble the relevant data, evaluate the data for quality and relevance, including strengths and limitations, followed by synthesis and integration of the evidence.

7) Map or group each condition of use to occupational exposure assessment scenario(s). EPA has identified exposure scenarios and mapped them to some conditions of use. EPA grouped similar conditions of use (based on factors including process equipment and handling, usage rates of carbon tetrachloride and formulations containing carbon tetrachloride, exposure/release sources) into scenario groupings but may further refine these groupings as additional information is identified during risk evaluation.

   EPA was not able to identify occupational exposure scenarios corresponding to several conditions of use due generally to a lack of understanding of those conditions of use. EPA will perform targeted research to understand those uses which may inform identification of occupational exposure scenarios.

8) Evaluate the weight of the evidence of occupational exposure data. EPA will rely on the weight of the scientific evidence when evaluating and integrating occupational exposure data. The data integration strategy will be designed to be fit-for-purpose in which EPA will use systematic

review methods to assemble the relevant data, evaluate the data for quality and relevance, including strengths and limitations, followed by synthesis and integration of the evidence.

2.6.1.3 Consumer Exposures

EPA does not expect to consider and analyze consumer exposures in the risk evaluation for carbon tetrachloride. Based on domestic and international regulatory information; Use document, EPA-HQ-OPPT-2016-0733-0003; and submitted public comments; carbon tetrachloride is expected to be present in consumer products at trace levels resulting in de minimis exposures or otherwise insignificant risks.

2.6.1.4 General Population

EPA does not expect to include general population exposures in the risk evaluation for carbon tetrachloride. EPA has determined that the existing regulatory programs and associated analytical processes adequately assess and effectively manage the risks of carbon tetrachloride that may be present in various media pathways (e.g., air, water, land) from TSCA conditions of use and subsequent partitioning and transport processes (i.e., vapor intrusion) for the general population. EPA believes that the TSCA risk evaluation should focus not on those exposure pathways, but rather on exposure pathways associated with TSCA conditions of use that are not subject to those regulatory processes, because the latter pathways are likely to represent the greatest areas of concern to EPA.

2.6.2 Hazards (Effects)

2.6.2.1 Environmental Hazards

Environmental hazards will not be further analyzed because exposure analysis conducted using physical and chemical properties, fate information and TRI/DMR environmental releases for carbon tetrachloride show that aquatic species are not significantly exposed to TSCA-related environmental releases of this chemical. During data screening, the limited number of environmental toxicity studies for carbon tetrachloride on sediment and terrestrial organisms were determined to contain data or information not relevant (off-topic) for the risk evaluation. The studies were considered *off-topic* references during the data screening process (see Section 1.3). No relevant (on-topic) toxicity data were available for carbon tetrachloride to birds. Hazard studies for sediment and terrestrial organisms are not likely to be conducted because exposure to carbon tetrachloride by these organisms is not expected due to the fate and transport properties of the chemical. Furthermore, EPA does not expect to include exposures to sediment and terrestrial organisms in the risk evaluation because these are pathways under programs of other environmental statutes, administered by EPA, which adequately assess and effectively manage exposures and for which long-standing regulatory and analytical processes already exist (see Section 2.5.3.2).

2.6.2.2 Human Health Hazards

EPA expects to consider and analyze human health hazards as follows:

1) Review reasonably available human health hazard data, including data from alternative test methods (e.g., computational toxicology and bioinformatics; high-throughput screening methods; data on categories and read-across; *in vitro* studies; systems biology).

   Human health studies will be evaluated using the evaluation strategies laid out in the *Application of Systematic Review in TSCA Risk Evaluations*. Human, animal, and mechanistic data will be identified and included as described in the inclusion and exclusion criteria in Appendix H. EPA plans to prioritize the evaluation of mechanistic evidence. Specifically, EPA does not plan to evaluate mechanistic studies unless needed to clarify questions about associations between carbon tetrachloride and health effects and its relevance to humans. *Systematic Review Approaches and Methods Applied to TSCA Risk Evaluations* describes how studies will be evaluated using specific data evaluation criteria and a predetermined systematic approach. Study results will be extracted and presented in evidence tables by each hazard endpoint. EPA intends to review studies published after the IRIS assessment (see *Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document*, EPA-HQ-OPPT-2016-0733) using the approaches and/or methods described in the *Application of Systematic Review in TSCA Risk Evaluations* to ensure that EPA is considering information that has been made available since these assessments were conducted. EPA will also evaluate information in the IRIS assessment using OPPT's structured process described in the document, *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018, 2010). For irritation and sensitization (not addressed in the IRIS assessment), EPA will rely on the ATSDR Toxicological Profile and 2011 OECD SIDS Initial Assessment Profile as a starting point to understand data for this chemical (OECD, 2011; ATSDR, 2005). In addition, EPA intends to conduct a full review of the data collected (see *Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document*, EPA-HQ-OPPT-2016-0733) as described in *Application of Systematic Review in TSCA Risk Evaluations* to ensure that EPA is considering information that has been made available since these assessments were conducted.

2) In evaluating reasonably available data, determine whether particular human receptor groups may have greater susceptibility to the chemical's hazard(s) than the general population.

   Reasonably available human health hazard data will be evaluated to ascertain whether some human receptor groups may have greater susceptibility than the general population to carbon tetrachloride hazard(s). Susceptibility of particular human receptor groups to carbon tetrachloride will be determined by evaluating information on factors that influence susceptibility.

3) Conduct hazard identification (the qualitative process of identifying non-cancer and cancer endpoints) and dose-response assessment (the quantitative relationship between hazard and exposure) for identified human health hazard endpoints.

   Human health hazards from acute and chronic exposures will be identified by evaluating the human and animal data that meet the data quality criteria described in the *Application of Systematic Review in TSCA Risk Evaluations* document. Data quality evaluation will be performed on key studies identified from the IRIS assessment (U.S. EPA, 2010) and the ATSDR Toxicological Profile (ATSDR, 2005). Data quality evaluation will also be performed on studies published after 2009 that were identified in the comprehensive literature search and that met the inclusion criteria for full-text screening (see *Systematic Review Approaches and Methods Applied to TSCA Risk Evaluations* for more information). Hazards identified by studies meeting data quality criteria will be grouped by routes of exposure relevant to humans (oral, dermal, inhalation) and by cancer and noncancer endpoints.

   Dose-response assessment will be performed in accordance with methods from EPA technical documents (U.S. EPA, 2011, 2000a, 1994). Dose-response analyses performed for the EPA (2009) IRIS oral and inhalation reference dose determinations may be used if the data meet data quality criteria and if additional information on the identified hazard endpoints are not available or would not alter the analysis.

The cancer mode of action (MOA) determines how cancer risks can be quantitatively evaluated. EPA will evaluate information on genotoxicity and the mode of action for all cancer endpoints to determine the appropriate approach for quantitative cancer assessment in accordance with the U.S. EPA Guidelines for Carcinogen Risk Assessment (ATSDR, 2005).

4) Derive points of departure (PODs) where appropriate; conduct benchmark dose modeling depending on the available data. Adjust the PODs as appropriate to conform (e.g., adjust for duration of exposure) to the specific exposure scenarios evaluated.

   Hazard data will be evaluated to determine the type of dose-response modeling that is applicable. Where modeling is feasible, a set of dose-response models that are consistent with a variety of potentially underlying biological processes will be applied to empirically model the dose-response relationships in the range of the observed data consistent with the EPA *Benchmark Dose Technical Guidance Document*. Where dose-response modeling is not feasible, NOAELs or LOAELs will be identified.

   EPA will evaluate whether the available PBPK and empirical kinetic models are adequate for route-to-route and interspecies extrapolation of the POD, or for extrapolation of the POD to appropriate exposure durations for the risk evaluation.

5) Consider the route(s) of exposure (oral, inhalation, dermal), available route-to-route extrapolation approaches, available biomonitoring data and available approaches to correlate internal and external exposures to integrate exposure and hazard assessment.

   At this stage of review EPA believes there will be sufficient data to conduct dose-response analysis and benchmark dose modeling for both inhalation and oral routes of exposure. If sufficient dermal toxicity studies are not identified in the literature search to assess risks from dermal exposures, then a route-to-route extrapolation from the inhalation and oral toxicity studies would be needed to assess systemic risks from dermal exposures. Without an adequate PBPK model, the approaches described in the EPA guidance document *Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment)* may be applied. These approaches may be able to further inform the relative importance of dermal exposures compared with other routes of exposure.

6) Evaluate the weight of the evidence of human health hazard data.

   EPA will rely on the weight of the scientific evidence when evaluating and integrating human health hazard data. The data integration strategy will be designed to be fit-for-purpose in which EPA will use systematic review methods to assemble the relevant data, evaluate the data for quality and relevance, including strengths and limitations, followed by synthesis and integration of the evidence.

2.6.3 Risk Characterization

Risk characterization is an integral component of the risk assessment process for both ecological and human health risks. EPA will derive the risk characterization in accordance with EPA's *Risk Characterization Handbook* (U.S. EPA, 2000b). As defined in EPA's Risk Characterization Policy, "the risk characterization integrates information from the preceding components of the risk evaluation and synthesizes an overall conclusion about risk that is complete, informative and useful for decision makers." Risk characterization is considered to be a conscious and deliberate process to bring all important considerations about risk, not only the likelihood of the risk but also the strengths and limitations of the assessment, and a description of how others have assessed the risk into an integrated picture.

Risk characterization at EPA assumes different levels of complexity depending on the nature of the risk assessment being characterized. The level of information contained in each risk characterization varies according to the type of assessment for which the characterization is written. Regardless of the level of complexity or information, the risk characterization for TSCA risk evaluations will be prepared in a manner that is transparent, clear, consistent and reasonable (TCCR) (U.S. EPA, 2000b). EPA will also present information in this section consistent with approaches described in the *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726). EPA will also present information in this section consistent with approaches described in the Risk Evaluation Framework Rule. For instance, in the risk characterization summary, EPA will further carry out the obligations under TSCA section 26; for example, by identifying and assessing uncertainty and variability in each step of the risk evaluation, discussing considerations of data quality such as the reliability, relevance and whether the methods utilized were reasonable and consistent, explaining any assumptions used, and discussing information generated from independent peer review. EPA will also be guided by EPA's Information Quality Guidelines (U.S. EPA, 2002) as it provides guidance for presenting risk information. Consistent with those guidelines, in the risk characterization, EPA will also identify: (1) Each population addressed by an estimate of applicable risk effects; (2) the expected risk or central estimate of risk for the PESS affected; (3) each appropriate upper-bound or lower-bound estimate of risk; (4) each significant uncertainty identified in the process of the assessment of risk effects and the studies that would assist in resolving the uncertainty; and (5) peer reviewed studies known to the Agency that support, are directly relevant to, or fail to support any estimate of risk effects and the methodology used to reconcile inconsistencies in the scientific information.

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APPENDICES

Appendix A REGULATORY HISTORY

A.1 Federal Laws and Regulations

Table_Apx A-1. Federal Laws and Regulations

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
EPA Regulations		
TSCA - Section 6(b)	EPA is directed to identify and begin risk evaluations on 10 chemical substances drawn from the 2014 update of the TSCA Work Plan for Chemical Assessments.	Carbon tetrachloride is on the initial list of chemicals to be evaluated for unreasonable risk under TSCA (81 FR 91927, December 19, 2016).
TSCA - Section 8(a)	The TSCA section 8(a) CDR Rule requires manufacturers (including importers) to give EPA basic exposure-related information on the types, quantities and uses of chemical substances produced domestically and imported into the United States.	Carbon tetrachloride manufacturing (including importing), processing and use information is reported under the CDR Rule (76 FR 50816, August 16, 2011).
TSCA - Section 8(b)	EPA must compile, keep current and publish a list (the TSCA Inventory) of each chemical substance manufactured, processed, or imported in the United States.	Carbon tetrachloride was on the initial TSCA Inventory and therefore was not subject to EPA's new chemicals review process under TSCA section 5 (60 FR 16309, March 29, 1995).
TSCA - Section 8(d)	Provides EPA with authority to issue rules requiring producers, importers and (if specified) processors of a chemical substance or mixture to submit lists and/or copies of health and safety studies.	Two submissions received (1947-1994) (U.S. EPA, ChemView. Accessed April 13, 2017).
TSCA - Section 8(e)	Manufacturers (including imports), processors and distributors must immediately notify EPA if they obtain information that supports the conclusion that a chemical substance or mixture presents a substantial risk of injury to health or the environment.	Three submissions received (1992-2010) (U.S. EPA, ChemView. Accessed April 13, 2017).
TSCA - Section 4	Provides EPA with authority to issue rules and orders requiring manufacturers (including importers) and processors to test chemical substances and mixtures.	Seven section 4 notifications received for carbon tetrachloride: two acute aquatic toxicity studies, one bioaccumulation report and four monitoring reports (1978-1980)

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
		(U.S. EPA, ChemView. Accessed April 13, 2017).
EPCRA - Section 313	Requires annual reporting from facilities in specific industry sectors that employ 10 or more full time equivalent employees and that manufacture, process, or otherwise use a TRI-listed chemical in quantities above threshold levels.	Carbon tetrachloride is a listed substance subject to reporting requirements under 40 CFR 372.65 effective as of January 1, 1987.
Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) - Sections 3 and 6	FIFRA governs the sale, distribution and use of pesticides. Section 3 of FIFRA generally requires that pesticide products be registered by EPA prior to distribution or sale. Pesticides may only be registered if, among other things, they do not cause “unreasonable adverse effects on the environment.” Section 6 of FIFRA provides EPA with the authority to cancel pesticide registrations if either (1) the pesticide, labeling, or other material does not comply with FIFRA; or (2) when used in accordance with widespread and commonly recognized practice, the pesticide generally causes unreasonable adverse effects on the environment.	Use of carbon tetrachloride as a grain fumigant was banned under FIFRA in 1986 (51 FR 41004, November 12, 1986).
Federal Food, Drug, and Cosmetic Act (FFDCA) - Section 408	FFDCA governs the allowable residues of pesticides in food. Section 408 of the FFDCA provides EPA with the authority to set tolerances (rules that establish maximum allowable residue limits), or exemptions from the requirement of a tolerance, for all residues of a pesticide (including both active and inert ingredients) that are in or on food. Prior to issuing a tolerance or exemption from tolerance, EPA must determine that the tolerance or exemption is “safe.” Sections 408(b) and (c) of the FFDCA define “safe” to mean the Agency has a reasonable certainty that no harm will result from aggregate exposures to the pesticide residue, including all dietary exposure and all other exposure (e.g., non-occupational exposures) for which	EPA removed carbon tetrachloride from its list of pesticide product inert ingredients used in pesticide products in 1998 (63 FR 34384, June 24, 1998).

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
	there is reliable information. Pesticide tolerances or exemptions from tolerance that do not meet the FFDCA safety standard are subject to revocation. In the absence of a tolerance or an exemption from tolerance, a food containing a pesticide residue is considered adulterated and may not be distributed in interstate commerce.	
CAA - Section 112(b)	This section lists 189 HAPs that must be addressed by EPA and includes authority for EPA to add or delete pollutants. EPA may, by rule, add pollutants that present, or may present, a threat of adverse human health effects or adverse environmental effects.	Lists carbon tetrachloride as a HAP (70 FR 75047, December 19, 2005).
CAA - Section 112(d)	Directs EPA to establish, by rule, National Emission Standards (NESHAPs) for each category or subcategory of major sources and area sources of HAPs. The standards must require the maximum degree of emission reduction that EPA determines is achievable by each particular source category. This is generally referred to as maximum achievable control technology (MACT).	There are a number of source-specific NESHAPs for carbon tetrachloride, including: Rubber tire manufacturing (67 FR 45588, July 9, 2002) Chemical Manufacturing Area Sources (74 FR 56008, October 29, 2009) Organic HAP from the Synthetic Organic Chemical Manufacturing and Other Processes (59 FR 19402, April 22,1994), Halogenated solvent cleaning operations (59 FR 61801, December 2, 1994) Wood Furniture Manufacturing Operations (60 FR 62930, December 7,1995) Group 1 Polymers and Resins (61 FR 46906, September 5, 1996) Plywood and Composite Wood Products (69 FR 45944, July 30, 2004)
CAA – Sections 112(d) and 112(f)	Risk and technology review (RTR) of section 112(d) MACT standards. Section 112(f)(2) requires EPA to conduct risk assessments for each source category subject to section 112(d) MACT standards, and to determine if additional	EPA has promulgated a number of RTR NESHAP (e.g., the RTR NESHAP for Group 1 Polymers and Resins (76 FR 22566; April 21, 2011)) and will do so, as required,

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
	standards are needed to reduce remaining risks. Section 112(d)(6) requires EPA to review and revise the MACT standards, as necessary, taking into account developments in practices, processes and control technologies.	for the remaining source categories with NESHAP.
CAA - Section 604	Establishes a mandatory phase-out of ozone depleting substances.	The production and import of carbon tetrachloride for non-feedstock domestic uses was phased out in 1996 (58 FR 65018, December 10, 1993). However, this restriction does not apply to production and import of amounts that are transformed or destroyed. 40 CFR 82.4. "Transform" is defined as "to use and entirely consume (except for trace quantities) a controlled substance in the manufacture of other chemicals for commercial purposes." 40 CFR 82.3.
CWA - Section 304(a)(1)	Requires EPA to develop and publish ambient water quality criteria (AWQC) reflecting the latest scientific knowledge on the effects on human health that may be expected from the presence of pollutants in any body of water.	In 2015, EPA published updated AWQC for carbon tetrachloride, including recommendations for "water + organism" and "organism only" human health criteria for states and authorized tribes to consider when adopting criteria into their water quality standards.
CWA – Sections 301(b), 304(b), 306, and 307(b)	Requires establishment of Effluent Limitations Guidelines and Standards for conventional, toxic, and non-conventional pollutants. For toxic and non-conventional pollutants, EPA identifies the best available technology that is economically achievable for that industry after considering statutorily prescribed factors and sets regulatory requirements based on the performance of that technology.	
CWA - Section 307(a)	Establishes a list of toxic pollutants or combination of pollutants under the CWA. The statute specifies a list of families of toxic pollutants also listed in the Code of Federal Regulations at 40	Carbon tetrachloride is designated as a toxic pollutant under section 307(a)(1) of the CWA and as such is subject to effluent limitations.

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
	CFR 401.15. The "priority pollutants" specified by those families are listed in 40 CFR part 423, Appendix A. These are pollutants for which best available technology effluent limitations must be established on either a national basis through rules, see section 301(b), 304(b), 307(b), 306, or on a case-by-case best professional judgment basis in NPDES permits. CWA 402(a)(1)(B).	
SDWA - Section 1412	Requires EPA to publish a non-enforceable maximum contaminant level goals (MCLGs) for contaminants which 1. may have an adverse effect on the health of persons; 2. are known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and 3. in the sole judgment of the Administrator, regulation of the contaminant presents a meaningful opportunity for health risk reductions for persons served by public water systems. When EPA publishes an MCLG, EPA must also promulgate a National Primary Drinking Water Regulation (NPDWR) which includes either an enforceable maximum contaminant level (MCL), or a required treatment technique. Public water systems are required to comply with NPDWRs.	Carbon tetrachloride is subject to National Primary Drinking Water Regulations (NPDWR) under SDWA and EPA has set a MCLG of zero and an enforceable MCL of 0.005 mg/L (56 FR 3526 January 30, 1991).
Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) - Sections 102(a) and 103	Authorizes EPA to promulgate regulations designating as hazardous substances those substances which, when released into the environment, may present substantial danger to the public health or welfare or the environment. EPA must also promulgate regulations establishing the quantity of any hazardous substance the release of which must be reported under Section 103. Section 103 requires persons in charge of vessels or facilities to report to the National Response Center if they have	Carbon tetrachloride is a hazardous substance under CERCLA. Releases of carbon tetrachloride in excess of 10 pounds must be reported (40 CFR 302.4).

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
	knowledge of a release of a hazardous substance above the reportable quantity threshold.	
RCRA - Section 3001	Directs EPA to develop and promulgate criteria for identifying the characteristics of hazardous waste, and for listing hazardous waste, taking into account toxicity, persistence, and degradability in nature, potential for accumulation in tissue, and other related factors such as flammability, corrosiveness, and other hazardous characteristics.	Carbon tetrachloride is included on the list of hazardous wastes pursuant to RCRA 3001. Two categories of carbon tetrachloride wastes are considered hazardous: discarded commercial chemicals (U211) (40 CFR 261.31(a)), and spent degreasing solvent (F001) (40 CFR 261.33(f)) (45 FR 33084 May 19, 1980). RCRA solid waste that leaches 0.5 mg/L or more carbon tetrachloride when tested using the TCLP leach test is RCRA hazardous (D019) under 40 CFR 261.24 (55 FR 11798 March 29, 1990). In 2013, EPA modified its hazardous waste management regulations to conditionally exclude solvent-contaminated wipes that have been cleaned and reused from the definition of solid waste under RCRA (40 CFR 261.4(a)(26)) (78 FR 46447, July 31, 2013).
Other Federal Regulations		
Federal Hazardous Substance Act (FHSA)	Requires precautionary labeling on the immediate container of hazardous household products and allows the Consumer Product Safety Commission (CPSC) to ban certain products that are so dangerous or the nature of the hazard is such that required labeling is not adequate to protect consumers.	Use of carbon tetrachloride in consumer products was banned in 1970 by the CPSC (16 CFR 1500.17).
FFDCA	Provides the U.S. Food and Drug Administration (FDA) with authority to oversee the safety of food, drugs and cosmetics.	The FDA regulates carbon tetrachloride in bottled water. The maximum permissible level of carbon tetrachloride in bottled water is 0.005 mg/L (21 CFR 165.110).

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
		All medical devices containing or manufactured with carbon tetrachloride must contain a warning statement that the compound may destroy ozone in the atmosphere (21 CFR 801.433). Carbon tetrachloride is also listed as an “Inactive Ingredient for approved Drug Products” by FDA (FDA Inactive Ingredient Database. Accessed April 13, 2017).
OSHA	Requires employers to provide their workers with a place of employment free from recognized hazards to safety and health, such as exposure to toxic chemicals, excessive noise levels, mechanical dangers, heat or cold stress, or unsanitary conditions. Under the Act, OSHA can issue occupational safety and health standards including such provisions as permissible exposure limits (PELs), exposure monitoring, engineering and administrative control measures, and respiratory protection.	In 1970, OSHA issued occupational safety and health standards for carbon tetrachloride that included a PEL of 10 ppm TWA, exposure monitoring, control measures and respiratory protection (29 CFR 1910.1000). OSHA prohibits all workplaces from using portable fire extinguishers containing carbon tetrachloride (29 CFR 1910.157(c)(3)).
Atomic Energy Act	The Atomic Energy Act authorizes the Department of Energy to regulate the health and safety of its contractor employees.	10 CFR 851.23, Worker Safety and Health Program, requires the use of the 2005 ACGIH TLVs if they are more protective than the OSHA PEL. The 2005 TLV for carbon tetrachloride is 5 ppm (8hr Time Weighted Average) and 10 ppm Short Term Exposure Limit (STEL).

A.2 State Laws and Regulations

Table_Apx A-2. State Laws and Regulations

State Actions	Description of Action
State agencies of interest	
State permissible exposure limits	California PEL: 12.6 mg/L (Cal Code Regs. Title 8, section 5155), Hawaii PEL: 2 ppm (Hawaii Administrative Rules section 12-60-50).

State Actions	Description of Action
State agencies of interest	
State Right-to-Know Acts	Massachusetts (454 Code Mass. Regs. section 21.00), New Jersey (8:59 N.J. Admin. Code section 9.1), Pennsylvania (34 Pa. Code section 323).
State air regulations	Allowable Ambient Levels (AAL): Rhode Island (12 R.I. Code R. 031-022), New Hampshire (RSA 125-I:6, ENV-A Chap. 1400).
State drinking water standards and guidelines	Arizona (14 Ariz. Admin. Register 2978, August 1, 2008), California (Cal Code Regs. Title 26, section 22-64444), Delaware (Del. Admin. Code Title 16, section 4462), Connecticut (Conn. Agencies Regs. section 19-13-B102), Florida (Fla. Admin. Code R. Chap. 62-550), Maine (10 144 Me. Code R. Chap. 231), Massachusetts (310 Code Mass. Regs. section 22.00), Minnesota (Minn R. Chap. 4720), New Jersey (7:10 N.J Admin. Code section 5.2), Pennsylvania (25 Pa. Code section 109.202), Rhode Island (14 R.I. Code R. section 180-003), Texas (30 Tex. Admin. Code section 290.104).
Other	In California, carbon tetrachloride was added to the Proposition 65 list in 1987 (Cal. Code Regs. Title 27, section 27001). Carbon tetrachloride is on the MA Toxic Use Reduction Act (TURA) list of 1989 (301 Code Mass. Regs. section 41.03).

A.3 International Laws and Regulations

Table_Apx A-3. Regulatory Actions by Other Governments and Tribes

Country/Organization	Requirements and Restrictions
Regulatory Actions by other Governments and Tribes	
Montreal Protocol	Carbon tetrachloride is considered an ozone depleting substance (ODS) and its production and use are controlled under the 1987 Montreal Protocol on Substances That Deplete the Ozone Layer and its amendments (Montreal Protocol Annex B – Group II).
Canada	Carbon tetrachloride is on the Canadian List of Toxic Substances (CEPA 1999 Schedule 1). Other regulations include: Federal Halocarbon Regulations, 2003 (SOR/2003-289). ODS Regulations, 1998 (SOR/99-7).
European Union (EU)	Carbon tetrachloride was evaluated under the 2012 Community rolling action plan (CoRAP) under regulation (European Commission [EC]) No

Country/Organization	Requirements and Restrictions
	1907/2006 - REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) ECHA database. Accessed April 18, 2017). Carbon tetrachloride is restricted by regulation (EC) No 2037/2000 on substances that deplete the ozone layer.
Australia	Carbon tetrachloride was assessed under Environment Tier II of the Inventory Multi-Tiered Assessment and Prioritisation (IMAP), and there have been no reported imports of the chemical as a feedstock in the last 10 years (National Industrial Chemicals Notification and Assessment Scheme, NICNAS, 2017, *Environment Tier II Assessment for Methane, Tetrachloro-*. Accessed April, 18 2017).
Japan	Carbon tetrachloride is regulated in Japan under the following legislation: • Industrial Safety and Health Act (ISHA) • Act on the Evaluation of Chemical Substances and Regulation of Their Manufacture, etc. (Chemical Substances Control Law (CSCL)) • Act on Confirmation, etc. of Release Amounts of Specific Chemical Substances in the Environment and Promotion of Improvements to the Management Thereof • Poisonous and Deleterious Substances Control Act • Act on the Protection of the Ozone Layer through the Control of Specified Substances and Other Measures • Air Pollution Control Law • Water Pollution Control Law • Soil Contamination Countermeasures Act (National Institute of Technology and Evaluation (NITE) Chemical Risk Information Platform (CHIRP). Accessed April 13, 2017).
Australia, Austria, Belgium, Canada, Denmark, EU, Finland, France, Germany, Ireland, Israel, Japan, Latvia, New Zealand, People's Republic of China, Poland, Singapore, South Korea, Spain, Sweden, Switzerland, United Kingdom	Occupational exposure limits (OELs) for carbon tetrachloride. (GESTIS International limit values for chemical agents (Occupational exposure limits, OELs) database. Accessed April 18, 2017).
Basel Convention	Halogenated organic solvents (Y41) are listed as a category of waste under the Basel Convention-Annex I. Although the United States is not currently a party to the Basel Convention, this treaty still affects U.S. importers and exporter.

Country/Organization	Requirements and Restrictions
OECD Control of Transboundary Movements of Wastes Destined for Recovery Operations	Halogenated organic solvents (A3150) are listed as a category of waste subject to The Amber Control Procedure under Council Decision C (2001) 107/Final.

Appendix B SECOND SCREENING OF PEER-REVIEWED LITERATURE ON CARBON TETRACHLORIDE

This appendix describes the process used to re-screen the references identified as "on topic" in the first screening round, including prioritizing the literature for screening and the re-categorization criteria applied during the re-screening and tagging.

B.1 Scope of the Literature Re-screening

The aim of the first literature screening phase was to include all potentially relevant references that met the screening criteria. A more detailed review of the "on topic" references revealed a large number of animal studies that were likely to be of limited use for the following reasons:

- The aim of the study was to induce a disease state in an animal (e.g., cirrhosis, fibrosis, organ damage: liver, kidney, testes and others) rather than evaluate the effects of carbon tetrachloride exposure in animals
- Exposure was often via injection

In order to refine the search results for full-text screening, the inclusion/exclusion criteria were revised to remove these studies from the "on topic" pool.

B.1.1 Identifying Studies for Title/Abstract Re-screening

References (a total of 2,244) that were tagged to one or more of the categories below were identified for re-screening. These were studies where carbon tetrachloride-treated animals were used as a model for disease (e.g., cirrhosis, liver fibrosis) and/or in which the therapeutic or ameliorative properties of different compounds were evaluated in carbon tetrachloride-treated animals:

- Animal Hazard ID
- Health Effects (in addition to Animal Hazard ID)
  - Hepatic non-cancer
  - Renal non-cancer
  - Neurological non-cancer
  - Reproductive/Developmental non-cancer
  - Immunological non-cancer
  - Cardiovascular non-cancer
  - Gastrointestinal non-cancer
  - Irritation

  - Respiratory non-cancer
  - Carcinogenicity
  - Other non-cancer health effect
- ADME
- Susceptibility
- MOA
- Unable to Determine

References tagged to "human hazard ID" were not included for re-screening, since they met the screening criteria as "on topic". References tagged to "foreign language" were not considered a priority for re-screening and so were not included for re-screening. Similarly, references included in the IRIS assessment on carbon tetrachloride were not included in the re-screening since those studies conducted on carbon tetrachloride were "on topic", as explained in the Literature Search Strategy documents.

B.2 Prioritizing References for Re-Screening

B.2.1 First Round of Prioritization for Re-screening

A keyword search and topic extraction (i.e., a form of unsupervised machine learning) were used to identify a priority batch of 690 studies from the 2,244 studies eligible for re-screening (see Section B.1.1Identifying Studies for Title/Abstract Re-screening). Topic extraction was conducted in ICF's Document Classification and Topic Extraction Resource or DoCTER which includes functions for supervised and unsupervised machine learning.

B.2.1.1 Keyword Search Method

A set of keywords was derived from the titles and abstracts of the *on-topic* references to be tagged to *off-topic* during the second screening. The following references are examples of the types of studies that EPA identified as *off-topic*:

- HERO ID 3482047; Preethi, KCK, R. (2009). Hepato and reno protective action of *Calendula officinalis* L. flower extract. Indian journal of experimental biology 47: 163-168.

- HERO ID 3481928; Ozturk, FG, M. Ates, B. Ozturk, I. C. Cetin, A. Vardi, N. Otlu, A. Yilmaz, I. (2009). Protective effect of apricot (*Prunus armeniaca* L.) on hepatic steatosis and damage induced by carbon tetrachloride in Wistar rats. The British journal of nutrition 102: 1767-1775.

- HERO ID 3481815; Murugesan, GSS, M. Jayabalan, R. Binupriya, A. R. Swaminathan, K. Yun, S. E. (2009). Hepatoprotective and curative properties of Kombucha tea against carbon tetrachloride-induced toxicity. Journal of microbiology and biotechnology 19: 397-402.

- HERO ID 894818; Quan, JP, L. Wang, X. Li, T. Yin, X. (2009). *Rossicaside B* protects against carbon tetrachloride-induced hepatotoxicity in mice. Basic & Clinical Pharmacology & Toxicology Online Pharmacology Online 105: 380-386.

- HERO ID 1454032; Gao, JS, C. R. Yang, J. H. Shi, J. M. Du, Y. G. Zhang, Y. Y. Li, J. H. Wan, H. T. (2011). Evaluation of the hepatoprotective and antioxidant activities of *Rubus parvifolius* L. Journal of Zhejiang University Science B 12: 135-142.

The keyword search, conducted in EndNote on the 2,244 studies eligible for re-screening (see F-1.1. Identifying Studies for Title/Abstract Re-screening) returned 587 studies using the following search strategy:

(hepatoprotective OR hepato protective OR hepatoprotection OR renoprotective OR reno protective OR renoprotection)

B.2.1.2 DoCTER Method

To identify a priority set of studies for re-screening, we also used DoCTER's topic extraction function. Unsupervised machine learning or topic extraction does not require a training dataset or seed studies. DoCTER clusters or groups a list of titles and abstracts using automated text analysis on titles and abstracts into a user-specified number of clusters. Studies in the same cluster are expected to be more similar to one another based on automated text analysis of the titles and abstracts. DoCTER also produces a set of keywords for each cluster that serves as a *topic signature* and provides insight into the studies contained within.

Topic extraction was used to cluster all 2,749 *on topic* studies into 10 topic clusters using the k-means algorithm and a word grouping length of one word. The terms copyright, publication, and abstract were added as stop words and not included in the DoCTER analysis. Clusters 3 and 5 were prioritized for re-screening and were combined with the results of the keyword search described above (Table_Apx B-1). The 690 studies identified from the keyword search and topic extraction clusters 3 and 5 were re-screened.

Table_Apx B-1. Topic Extraction Results for 2,749 On-topic Studies using 10 Clusters and k-means Algorithm

Cluster	Number of Results	Keywords
1	157	factor	nf	fibrosis	expression	inflammatory	il	tnf	hepatic	anti	rats	levels	ccl	kg	oxidative	effects	treatment	serum	significantly	aminotransferase	injury
2	98	stem	marrow	bone	cells	mscs	transplantation	mesenchymal	derived	fibrosis	human	cell	mice	strong	transplanted	bm	msc	br	injured	differentiation	cirrhosis
3	200	antioxidant	**hepatoprotective**	glutathione	activities	sod	activity	gsh	ast	superoxide	alt	mda	ccl	aminotransferase	oxidative	dismutase	serum	extract	injury	levels	mice
4	96	mir	fibrosis	expression	tgf	hscs	hsc	activation	hepatic	cells	stellate	role	factor	cell	mirnas	proliferation	growth	fibrotic	signaling	microrna	fibrogenesis
5	266	**hepatoprotective**	extract	activity	antioxidant	rats	strong	extracts	br	damage	kg	hepatotoxicity	leaves	effect	mg	silymarin	serum	significant	total	activities	scavenging

Cluster	Number of Results	Keywords
6	370	fibrosis | mice | cells | hepatic | stellate | expression | hscs | activation | strong | injury | cell | br | chronic | hsc | type | activated | role | collagen | inflammation | wild
7	317	kg | rats | ccl | group | mg | oxidative | antioxidant | groups | glutathione | ml | protective | effect | damage | treated | activities | serum | treatment | dose | lipid | control
8	110	cirrhosis | cirrhotic | portal | hypertension | rats | br | strong | pressure | bacterial | intestinal | resistance | arterial | hepatic | vascular | fibrosis | translocation | increased | expression | gut | ascites
9	867	rats | injury | mice | exposure | hepatotoxicity | acute | effect | rat | effects | fibrosis | hepatic | metabolism | toxicity | damage | cell | role | lipid | response | dna | hepatocytes
10	268	strong | br | group | fibrosis | lt | model | rats | groups | expression | control | hepatic | 05 | significantly | weeks | methods | normal | levels | 01 | results | tgf

B.2.1.3 List of Prioritized References for Re-Screening

References identified using both the keyword search and DoCTER's topic extraction were combined and duplicate references removed to identify a priority batch of 690 studies from the 2,244 studies eligible for re-screening (see Section B.1.1). Note the batch of studies eligible for re-screening excludes studies cited in the IRIS assessment or tagged to human hazard identification or foreign-language.

B.2.2 Second Round of Prioritization for Re-screening

B.2.2.1 Keyword Search Method

A second keyword search was conducted in EndNote on the 1,566 remaining studies eligible for re-screening. The 1,566 studies (2,244 studies eligible for screening (see Section B.1.1) minus 678 studies screened in the first round of prioritization; note 12 studies, primarily foreign-language, were screened in the batch of 690 from the first round of screening and were not included in the 2,244 studies eligible for re-screening.) The following search strategy returned 602 studies:

(((carbon tetrachloride-induced OR ccl4-induced) AND (cirrhosis OR fibrosis OR liver damage OR steatosis)) OR (oxidative stress OR oxidative damage OR antioxidant*))

B.2.2.2 DoCTER Method

For the second round of prioritization we used supervised clustering with an ensemble approach. With supervised clustering, DoCTER clusters or groups a list of titles and abstracts plus seed studies using automated text analysis on titles and abstracts into a user-specified number of clusters exactly as described above in Section B.2.1. Seed studies may be positive or negative. Positive seeds or known relevant studies are used to provide a quantitative signal as to which clusters to prioritize. Negative seeds or known *off-topic* studies are optional and are used to predict precision for each cluster.

Supervised clustering using an ensemble approach refers to running topic extraction with seeds using multiple models. A model refers to an algorithm–cluster size combination (e.g., using k-means algorithm to group into 10 clusters or KM-10 as a model). The results from each model run are compiled and each reference is given a score based on how many models predicted it to be relevant. Scores for each reference range from 0 (i.e., study not predicted relevant by any model) to n where n is the number of models used and is the maximum score a study can receive.

We ran the 1,566 eligible studies through six models using the k-means and NMF algorithms and 10, 20, and 30 clusters (i.e., KM-10, KM-20, KM-30, NMF-10, NMF-20, NMF-30) with 50 positive seeds. Seeds (references) were randomly selected from results of the first round of re-screening i.e., references that met the exclusion criteria (see Section B.2). A positive seed is a study used to find similar studies and in this context positive seeds are studies that were excluded or re-tagged as not on topic in the first round of re-screening. Supervised clustering was used here to identify additional studies that may be excluded from the on topic pool of carbon tetrachloride studies.

Recall was set to 0.90 in DoCTER, such that for each model clusters were included until at least 90 percent of seeds were captured. Using all six models 98 percent of seeds were actually captured and 493 studies were identified as a priority for re-screening by one or more models (see Table below).

Table_Apx B-2. Supervised Clustering Results for 1,566 On-topic Studies Using Ensemble Approach (k-means and NMF Algorithms x 10, 20, and 30 clusters), 50 Seeds, and 0.9 Recall

Group	Cluster Score	Number of Studies	Running Total
A	6	7	7
B	5	24	31
C	4	44	75
D	3	80	155
E	2	106	261
F	1	232	493
	Total	**493**	

Notes:
Studies with a cluster score of 6 were predicted relevant by all six models

B.2.2.3 List of Prioritized References for Re-Screening

References identified using both the second keyword search (602) and supervised clustering in DoCTER (493) were combined and duplicate references removed to identify 782 studies from the 1,566 studies eligible for re-screening (see Section B.1.1). These references were screened in two batches; 493 from DoCTER and 289 from the key word search method (duplicates removed). Note the batch of studies eligible for re-screening excludes studies cited in the IRIS assessment or tagged to human hazard identification or foreign-language.

Following the second round of prioritization, 784 studies remained. These were rescreened against the criteria below.

B.3 Re-screening Criteria and Process

This section describes the criteria applied during the second screening of the literature, the new criteria applied and the process used to conduct the screening.

B.3.1 Re-screening Process

All references were re-screened in Distiller. The same screeners involved in the first round of screening were involved in re-screening the literature. The screening process proceeded as follows:

- Batches of prioritized literature were imported into Distiller without the original tags from the first screening round.
- An experienced screener trialed the screening instructions and amended them as needed, prior to conducting the full screening exercise.
- Screeners were briefed on how to conduct the screening and given a set of instructions prior to commencing the screening.
- An experienced screener was available to answer any questions and provide feedback to screeners.
- Each study was screened independently by two reviewers. Two other invididuals not involved in the screening resolved the conflicts.

B.3.2 Re-screening Criteria

Studies were considered *off-topic* if:

Carbon tetrachloride was used to induce a non-cancer effect (e.g., Liver effects: hepatotoxicity, hepatic steatosis, cirrhosis, liver injury, liver fibrosis; renal/kidney effects, repro/developmental effects: testicular injury and others) to evaluate the protective or therapeutic effects of another compound (e.g., plant extracts, drugs, antioxidants, or medicinal herbs).

Carbon tetrachloride was used as a model to induce a particular disease state in an animal. Often includes studies where carbon tetrachloride was given to animals via injection to induce cirrhosis, liver fibrosis or oxidative damage in the testes or brain. Often the study then evaluates either the MOA or ameliorative effects of a therapeutic compound.

Carbon tetrachloride was used to induce toxicity or organ damage by measuring levels of e.g., serum liver enzymes, markers of oxidative stress or damage in a particular organ (liver, kidney, testes, brain), or histological changes, prior to, or after administering another (therapeutic) compound.

Carbon tetrachloride was used to induce fibrosis or cirrhosis and treatment was given after as a way to treat that effect.

Studies that do not meet the exclusion criteria above were also considered *off-topic* if:

- Carbon tetrachloride was not specifically mentioned in the title or abstract
- Incorrectly tagged as *on-topic* during first round screening

Table_Apx B-3. Overview of Complete (Revised) Tagging Structure for Carbon Tetrachloride

Tag Category	Inclusion/Exclusion Criteria	Example Keywords
ON TOPIC, GENERAL HUMAN HEALTH TAGS		
Animal Hazard ID	**INCLUDE:** • Studies evaluating animal health effects resulting from controlled exposure to the chemical in mammals such as primates, rodents, dog, rabbit, and mink. • **Also choose applicable health effect tags in next section "Carbon Tetrachloride Health Effect Tags" **EXCLUDE:** • Studies where carbon tetrachloride was used to induce a particular disease state or noncancer effect in an animal to (e.g., **Liver effects:** hepatotoxicity, hepatic steatosis, cirrhosis, liver injury, liver fibrosis; **renal/kidney effects**; **repro/developmental effects:** testicular injury, and others) to: ○ evaluate the protective or therapeutic effects of another compound (e.g., plant extracts, drugs, antioxidants, or medicinal herbs) or, • Studies where carbon tetrachloride was used in addition to other treatments (e.g., 2-AAf, LPS, or partial hepatectomy) in order to cause a specific effect or response in the liver • Studies that evaluated carbon tetrachloride-induced toxicity or organ damage by measuring levels of e.g., serum liver enzymes, markers of oxidative stress or damage in a particular organ (liver, kidney, testes, brain), or histological changes, prior to, or after administering another (therapeutic) compound.	chronic; developmental; incidence; NOEL/LOEL; NOAEL/LOAEL; dose; response
MOA	**INCLUDE:** • Studies evaluating the mode of action (MOA) of a chemical (i.e., molecular events occurring after exposure that may contribute to the development of adverse health effects) in animals and humans • Studies in knockout mice • Assessment of hormone levels or gland function, immune system parameters **Also choose applicable MOA tags in section below under "Carbon Tetrachloride MOA Tags" **EXCLUDE:** • Studies that evaluated carbon tetrachloride-induced toxicity or organ damage by measuring levels of e.g., serum liver enzymes, markers of oxidative stress or damage in a particular organ (liver, kidney, testes, brain), or histological changes, prior to, or after administering another (therapeutic) compound.	*in vitro* models, genomics, proteomics, genotoxicity, indirect genotoxicity, changes in gene expression or mRNA levels
ON TOPIC, CARBON TETRACHLORIDE (CCL4) HEALTH EFFECT TAGS		
Hepatic non-cancer	**INCLUDE**: • Studies evaluating hepatic effects in the liver, biliary tract, gall bladder	fatty degeneration, cirrhosis, fibrosis, necrosis, hypertrophy, hyperplasia, proliferation, increased/decreased liver enzymes, bile acids, cholesterol and triglycerides in serum/blood, increased/decreased liver weight, jaundice, vacuolization
Renal non-cancer	**INCLUDE:** • Studies evaluating renal effects in the kidney, bladder, ureter and related	nephropathy, oliguria, increased/decreased blood urea nitrogen, nephritis, nephrosis, hyaline droplet formation, necrosis and regeneration of proximal tubules, markers of kidney damage e.g. excretion of proteins/blood in urine, alpha

Tag Category	Inclusion/Exclusion Criteria	Example Keywords
		2U globulin
Neurological non-cancer	**INCLUDE:** • Studies evaluating effects in the central nervous system (CNS) or peripheral nervous system, brain, nerves, behavior, neurochemical alterations, sensory effects, neurodevelopmental effects in exposed infants and children	changes in brain pathology, CNS depression (dizziness, drowsiness, sleepiness, loss of consciousness/ anesthesia, hypo activity, ataxia, lethargy, impaired coordination or balance, narcosis), nerve/neuronal injury and/or degeneration, neuropsychological outcomes (e.g. mood/personality changes), changes in neurobehavioral tests (cognitive, motor function) and neurophysiological effects (visual and auditory function), memory
Reproductive/Developmental non-cancer	**INCLUDE:** • Studies examining reproductive outcomes, offspring and/or studies examining developmental effects **Notes:** Developmental neurotoxicity effects are categorized in the Reproductive/Developmental non-cancer tag and Neurological non-cancer tag	reduced fertility, effects on reproductive organs, sperm, estrous cycle, increased resorption and post implantation loss, viability, fetal death, birth weight, growth, maturation, teratogenicity, birth defects, visceral and/or skeletal malformations, follicle counts
Immunological non-cancer	**INCLUDE**: • Studies examining susceptibility or resistance to infection or disease, function of innate or adaptive immunity	hypersensitization, increased/decreased white blood cells, effects on the spleen
Cardiovascular non-cancer	**INCLUDE:** • Studies examining cardiovascular effects in the heart and vasculature	stroke, hypertension, tachycardia, cardiac arrhythmias
Gastrointestinal non-cancer	**INCLUDE:** • Studies examining gastrointestinal effects on the mouth, on dentition, salivary glands, esophagus, stomach, intestines, rectum	nausea, vomiting, abdominal pain, anorexia
Irritation	**INCLUDE:** • Studies examining irritation (primary or secondary) of the skin, eyes, gastrointestinal tract or respiratory tract	erythema, itching, blisters, swelling, edema (skin); pain swelling, lacrimation, photophobia (eyes); nausea, vomiting, and abdominal pain (gastrointestinal tract), rhinitis, prickling or burning sensation in the nose and throat, dry, scratchy throat (respiratory tract)
Respiratory non-cancer	**INCLUDE:** • Studies examining non-cancer respiratory effects in the lungs	chemical pneumonitis, inflammation, bronchopneumonia, alveolar epithelial proliferation, edema, lung disease, bronchitis, pulmonary function tests, FEF, FEV1, bronchitis, COPD, cough, chest discomfort, PEFR, respiratory symptoms, respiratory infection, dyspnea, wheeze, lung function, effects on the nasal cavity (nasal

Tag Category	Inclusion/Exclusion Criteria	Example Keywords
		respiratory and olfactory epithelium), bronchial or tracheal epithelium
Carcinogenicity	**INCLUDE:** • Studies that evaluate any cancer effect	particular cancers include: breast, liver, kidney, blood, lymph, adrenal gland
Other non-cancer health effect	**INCLUDE:** • Studies in which other non-cancer health effects, not defined by the categories above, were examined	NA
ON TOPIC, CARBON TETRACHLORIDE (CCl4) MOA TAGS		
NOT ON TOPIC		
Not on topic	**INCLUDE:** • Reference is not on topic in the context of any of the outlined categories (or tags)	NA

B.4 Results

Out of the 2,244 studies eligible for re-screening, 678 studies were identified in the first batch of prioritized references and screened independently by two individuals. These references were moved to off-topic since they met the re-screening exclusion criteria. Of the remaining 1,566 studies, the re-screening resulted in 45 references that met the inclusion criteria and were retained as *on-topic* references. The remaining studies, or 1,521, met the criteria for exclusion and were moved to *off-topic*.

Appendix C PROCESS, RELEASE AND OCCUPATIONAL EXPOSURE INFORMATION

This appendix provides information and data found in preliminary data gathering for carbon tetrachloride.

C.1 Process Information

Process-related information potentially relevant to the risk evaluation may include process diagrams, descriptions and equipment. Such information may inform potential release sources and worker exposure activities for consideration.

C.1.1 Manufacture (Including Import)

C.1.1.1 Domestic Manufacture

Carbon tetrachloride was previously produced solely through the chlorination of carbon disulfide (CS_2); however, in the 1950s chlorination of hydrocarbons became popular (Holbrook, 2000). Currently, most Carbon tetrachloride is manufactured using one of three methods: chlorination of hydrocarbons or chlorinated hydrocarbons; oxychlorination of hydrocarbons; or CS_2 chlorination (Holbrook, 2000).

- ***Chlorination of hydrocarbons or chlorinated hydrocarbons*** - The chlorination of hydrocarbons involves a simultaneous breakdown of the organics and chlorination of the molecular fragments at pyrolytic temperatures and is often referred to as chlorinolysis (Holbrook, 2000). A variety of hydrocarbons and chlorinated hydrocarbon waste streams can be used as feedstocks; however, methane is the most common (Holbrook, 2000). PCE is formed as a major byproduct of this process with small volumes of hexachloroethane, hexachlorobutadiene and hexachlorobenzene also produced (Holbrook, 2000).

- ***Oxychlorination of hydrocarbons*** - The oxychlorination of hydrocarbons involves the reaction of either chlorine or hydrochloric acid (HCl) and oxygen with a hydrocarbon feedstock in the presence of a catalyst (Marshall and Pottenger, 2016; Holbrook, 2000). This process can be utilized to convert HCl produced as a byproduct during the manufacture of chlorinated hydrocarbons into useful products (Marshall and Pottenger, 2016).
- ***CS_2 Chlorination*** - The chlorination of CS_2 involves the continuous reaction of CS_2 with chlorine in an annular reaction (Holbrook, 2000). The carbon tetrachloride produced is distilled to have a CS_2 content of 0 to 5 ppm. This process produces disulfur dichloride as a byproduct that is reduced with hydrogen without a catalyst or with a ferric chloride catalyst (Holbrook, 2000).

Based on EPA's knowledge of the chemical industry, worker activities at manufacturing facilities may involve manually adding raw materials or connecting/disconnecting transfer lines used to unload containers into storage or reaction vessels, rinsing/cleaning containers and/or process equipment, collecting and analyzing QC samples, manually loading carbon tetrachloride product or connecting/disconnecting transfer lines used to load carbon tetrachloride product into containers.

C.1.1.2 Import

EPA has identified activities related to the import of carbon tetrachloride through comments submitted in public docket EPA-HQ-OPPT-2016-0733. Based on EPA's knowledge of the chemical industry, imported chemicals are often stored in warehouses prior to distribution for further processing and use. In some cases, the chemicals may be repackaged into differently sized containers, depending on customer demand, and QC samples may be taken for analyses.

C.1.2 Processing and Distribution

C.1.2.1 Reactant or Intermediate

Processing as a reactant or intermediate is the use of carbon tetrachloride as a feedstock in the production of another chemical product via a chemical reaction in which carbon tetrachloride is consumed to form the product. In the past, carbon tetrachloride was mainly used as feedstock for the manufacture chlorofluorocarbons (CFCs) (Marshall and Pottenger, 2016). However, due to the discovery that CFCs contribute to stratospheric ozone depletion, the use of CFCs was phased-out by the year 2000 to comply with the Montreal Protocol (Holbrook, 2000).

Currently, carbon tetrachloride is used as a feedstock to produce a variety of products including HCFCs, HFCs, HFOs, vinyl chloride, ethylene dichloride (EDC), PCE, chloroform, hafnium tetrachloride, thiophosgene and methylene chloride (EPA-HQ-OPPT-2016-0733-0003(U.S. EPA, 2017d; Marshall and Pottenger, 2016; Weil et al., 2006; Holbrook, 2003a, b)) . The specifics of the reaction process (e.g., use and types of catalysts, temperature conditions, etc.) will vary depending on the product being produced; however, a typical reaction process would involve unloading carbon tetrachloride from containers and feeding into the reaction vessel(s), where carbon tetrachloride would either fully or partially react with other raw materials to form the final product. Following the reaction, the product may or may not be purified to remove unreacted carbon tetrachloride (if any exists). Reacted carbon tetrachloride is assumed to be destroyed and thus not expected to be released or cause potential worker exposure.

Carbon tetrachloride is used in reactive ion etching (RIE). RIE involves ion bombardment to achieve directional etching and a reactive gas, such as carbon tetrachloride, to selectively maintain etched layers [EPA-HQ-OPPT-2016-0733-0003 (U.S. EPA, 2017d)].

EPA has not identified specific worker activities related to the processing of carbon tetrachloride as a reactant or intermediate at this time. However, based on EPA's knowledge of the chemical industry, worker activities are expected to be similar to that at manufacturing facilities including unloading and loading activities, rinsing/cleaning activities and collecting and analyzing QC samples.

C.1.2.2 Incorporation into a Formulation, Mixture or Reaction Products

Incorporation into a formulation, mixture or reaction product refers to the process of mixing or blending of several raw materials to obtain a single product or preparation. Process descriptions for use of carbon tetrachloride use as a process agent were not identified at this time. However, the processes are expected to be similar to those described above and typically involve unloading formulation components from transport containers, either directly into the mixing equipment or into an intermediate storage vessel, mixing of components either a batch or continuous system, QC sampling and final packaging of the formulation in to containers. Depending on the product, formulation products may be filtered prior to packaging. Transfer from transport containers into storage or mixing vessels may be manual or automated, through the use of a pumping system. If automated, an automated dispenser may be used to feed the components into the mixing vessel to ensure that precise amounts are added at the proper time during the mixing process. Final packaging occurs either through manual dispensing from transfer lines or through utilization of an automatic system.

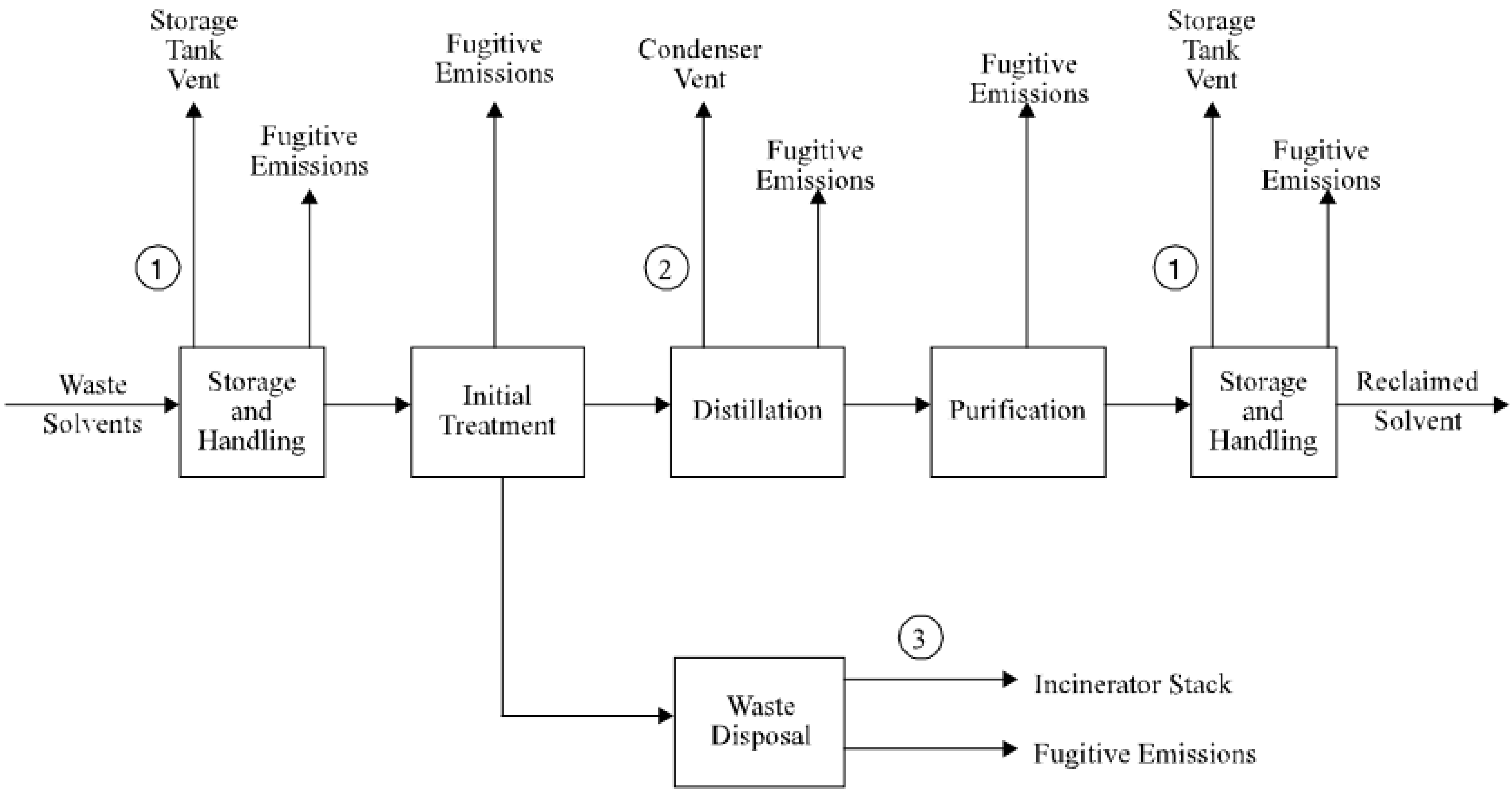
There is significant overlap in worker activities across the various formulation processes. The activities are expected to be similar to manufacturing activities and include unloading and loading activities, rinsing/cleaning activities and collecting and analyzing QC samples (OECD, 2009a, b).

C.1.2.3 Repackaging

Typically, repackaging sites receive the chemical in bulk containers and transfer the chemical from the bulk container into another smaller container in preparation for distribution in commerce. Based on EPA's knowledge of the chemical industry, worker activities at repackaging sites may involve manually unloading carbon tetrachloride from bulk containers into the smaller containers for distribution or connecting/disconnecting transfer lines used to transfer carbon tetrachloride product between containers and analyzing QC samples. EPA will further investigate the potential use of carbon tetrachloride in this type of process during the risk evaluation.

C.1.2.4 Recycling

TRI data from 2015 indicate that some sites ship carbon tetrachloride for off-site recycling. A general description of waste solvent recovery processes was identified. Waste solvents are generated when it becomes contaminated with suspended and dissolved solids, organics, water or other substance (U.S. EPA, 1980). Waste solvents can be restored to a condition that permits reuse via solvent reclamation/recycling (U.S. EPA, 1980). The recovery process involves an initial vapor recovery (e.g., condensation, adsorption and absorption) or mechanical separation (e.g., decanting, filtering, draining, setline and centrifuging) step followed by distillation, purification and final packaging (U.S. EPA, 1980). Worker activities are expected to be unloading of waste solvents and loading of reclaimed solvents. Figure_Apx C-1 illustrates a typical solvent recovery process flow diagram (U.S. EPA, 1980).



Figure_Apx C-1. General Process Flow Diagram for Solvent Recovery Processes

Source: (U.S. EPA, 1980)

C.1.3 Uses

In this document, EPA has grouped uses based on CDR categories and identified examples within these categories as subcategories of use. Note that some subcategories may be grouped under multiple CDR categories. The differences between these uses will be further investigated and defined during risk evaluation.

C.1.3.1 Petrochemicals-derived Products Manufacturing

EPA has identified uses of carbon tetrachloride as a process agent (i.e., processing aid such as catalyst regeneration or as an additive) at manufacturing facilities of petrochemicals-derived products [EPA-HQ-OPPT-2016-0733-0003; (U.S. EPA, 2017d); (UNEP/Ozone Secretariat, 1998)]. EPA has also identified a patent which indicates a potential use of carbon tetrachloride as a fuel additive.

C.1.3.2 Agricultural Products Manufacturing

EPA has identified uses of carbon tetrachloride as a process agent in the manufacturing of fertilizers and other agricultural products [EPA-HQ-OPPT-2016-0733-0003; (U.S. EPA, 2017d); (UNEP/Ozone Secretariat, 1998).

C.1.3.3 Other Basic Organic and Inorganic Chemical Manufacturing

EPA has identified uses of carbon tetrachloride as a process agent in the manufacturing of inorganic compounds (i.e., chlorine), pharmaceuticals (i.e., ibuprofen) and chlorinated compounds that are used in the formulation of solvents for cleaning and degreasing, adhesive and sealants, paints and coatings and asphalt [EPA-HQ-OPPT-2016-0733-0003; (U.S. EPA, 2017d)]. Therefore, EPA expects carbon tetrachloride is only present in cleaning, degreasing, paints, coatings, and asphalt formulations as an impurity rather than serving a specific function. Appendix D presents a list of domestic and internationally approved uses of carbon tetrachloride as a process agent in MP side agreement: Decision X/14: Process Agents (UNEP/Ozone Secretariat, 1998).

C.1.3.4 Laboratory Chemicals

Carbon tetrachloride is used in laboratories as a chemical reagent, extraction solvent and a reference material or solvent in analytical procedures, such as spectroscopic measurements [EPA-HQ-OPPT-2016-0733-0003; (U.S. EPA, 2017d)].

C.1.3.5 Other Uses

Carbon tetrachloride may also be used in metal recovery and other specialty uses identified by the aerospace industry, such as the manufacture, operations and maintenance of aerospace products and for specific cleaning operations (EPA-HQ-OPPT-2016-0733-0063).

C.1.3.6 Disposal

Table 2-6 and Table 2-7 present the production-related waste managed data for carbon tetrachloride reported to the TRI program for 2015. Waste containing carbon tetrachloride is classified as hazardous waste (see Table_Apx A-1). Facilities generating waste containing carbon tetrachloride must comply with EPA regulations for treatment, storage, and disposal.

C.2 Occupational Exposure Data

EPA presents below an example of occupational exposure-related information from the preliminary data gathering. EPA will consider this information and data in combination with other data and methods for use in the risk evaluation. Table_Apx C-1. summarizes OSHA CEHD data by NAICS (North American Industrial Classification System) code (see Section 2.3.5.1) and Table_Apx C-2. summarizes NIOSH HHE data.

Table_Apx C-1. Summary of Carbon Tetrachloride Personal Monitoring Air Samples Obtained from OSHA Inspections Conducted Between 2013 and 2015

Release/Exposure Scenario	NAICS	NAICS Description	8-hr TWA Concentration (ppm)[a]					STEL, Peak, or Ceiling Concentration (ppm)				
			Number of Data Points	Minimum	Maximum	Average	Number of Zero Values[b]	Number of Data Points	Minimum	Maximum	Average	Number of Zero Values[b]
Unknown – job title and company information did not indicate how carbon tetrachloride may be used	322121	Paper (except Newsprint) Mills	4	0	0	0	4	4	0	0	0	4
Vapor degreasing or cold cleaning	331512	Steel Investment Foundries	3	0.026	0.027	0.026	0	No Data Available				
Vapor degreasing or cold cleaning	332439	Other Metal Container Manufacturing	2	0.026	0.026	0.026	0	No Data Available				
Vapor degreasing or cold cleaning	336111	Automobile Manufacturing	2	0	0	0	2	2	0	0	0	2
Unknown – this seems to be for OSHA inspectors which could have been collected during site inspections	926150	Regulation, Licensing, and Inspection of Miscellaneous Commercial Sectors	1	0		1	1	0				1

[a] Assumes all TWA data are 8-hr TWA.
[b] For facilities where all samples are measured as zero, it is unclear if carbon tetrachloride is present at the facility.

Table_Apx C-2. Summary of Monitoring Data from NIOSH Health Hazard Evaluations Conducted since 1990

Data Source	Report Number	Exposure/Release Scenario	Facility Description	Number of Exposure Samples	Minimum of Exposure Values (ppm)	Maximum of Exposure Values (ppm)	Comments
NIOSH 1992a	HETA-1990-223-2211	Vapor degreasing	Cathode ray tube manufacturing	0	No exposure data for carbon tetrachloride provided.		
NIOSH, 1992b	HETA-1991-188-2205	General population exposures	Elementary school	6	ND	0.03	1 to 2-hr area measurements.
NIOSH, 2005	HETA-2004-169-2982	Manufacture of carbon tetrachloride	Magnesium manufacturer	11	PBZ: ND Area: ND	PBZ: 0.03 Area: ND	8-hr TWA values

Appendix D PROCESS AGENT USES FOR CARBON TETRACHLORIDE

Table_Apx D-1. List of Uses of Carbon Tetrachloride as Process Agent in MP side agreement: Decision X/14: Process Agents

1	Elimination of nitrogen trichloride in the production of chlorine and caustic	10	Manufacture of chlorinated paraffin
2	Recovery of chlorine in tail gas from production of chlorine	11	Production of pharmaceuticals - ketotifen, anticol and disulfiram
3	Manufacture of chlorinated rubber	12	Production of tralomethrine (insecticide)
4	Manufacture of endosulphan (insecticide)	13	Bromohexine hydrochloride
5	Manufacture of isobutyl acetophenone (ibuprofen - analgesic)	14	Diclofenac sodium
6	Manufacture of 1-1, Bis (4-chlorophenyl) 2,2,2- trichloroethanol (dicofol insecticide)	15	Cloxacilin
7	Manufacture of chlorosulphonated polyolefin (CSM)	16	Phenyl glycine
8	Manufacture of poly-phenylene-terephtal-amide	17	Isosorbid mononitrate
9	Manufacture of styrene butadiene rubber	18	Omeprazol

Appendix E SURFACE WATER ANALYSIS FOR CARBON TETRACHLORIDE RELEASES

During problem formulation, EPA modeled industrial discharges to surface water to estimate surface water concentration using EPA NPDES permit Discharge Monitoring Report (DMR) data on the top 10 highest carbon tetrachloride releasing facilities. DMR data are submitted by facilities in order to comply with NPDES permit requirements, including limits to pollutants discharged to receiving waters. EPA used the Probabilistic Dilution Model (PDM) within E-FAST to estimate annual discharges for the facilities. In order to estimate a range of conservative surface water concentrations, the 2015 NPDES DMR data reporting carbon tetrachloride discharges were used in a first-tier analysis, which estimates conservative carbon tetrachloride surface water concentrations (i.e., conservative exposure scenarios). The surface water concentrations were estimated using a range of high-end number of release days (i.e., 20 and 250 days/year) instead of the default 365 days/year. Other conservative assumptions in the first-tier analysis include the use of zero percent removal of carbon tetrachloride by the wastewater treatment facility and low hydrological flow.

DMR data confirmed that facility discharges used in this first-tier analysis were discharging at least 20 days per year. EPA did not include a single day release scenario since this was not a likely scenario that would be allowed under current NPDES permit requirements. The other input parameter important for determining surface water concentrations is wastewater removal efficiency since the NPDES permits require industrial wastewater treatment removal. Table_Apx E-1 presents the first-tier estimate of surface water concentrations. Public owned treatment works (POTW with SIC 4952) are municipal facilities that receive industrial discharges containing carbon tetrachloride and reported these concentrations in the facility DMRs. Since these facilities discharge 365 days per year, the 20-day discharge scenario is not considered and the 250 day/year discharge is the only modeled scenario. Using these conservative scenarios, carbon tetrachloride surface water concentrations were mostly below the COCs for aquatic species (62 μg/L and 7 μg/L for acute and chronic, respectively). The PDM calculates the probability of the COC being exceeded using 7Q10 (i.e., 7 consecutive days of 10th percentile low flow) low flow statistics. Thus, surface water concentrations that slightly exceed the chronic COC are not considered statistically significant as to present a concern for aquatic organisms.

Table_Apx E-1. Modeled Carbon Tetrachloride Surface Water Concentrations

SIC Code	Total Pounds (lbs/yr) - 2015 DMR Data	PDM Inputs		Surface Water Concentrations		Acute COC (ug/L)	Chronic COC (ug/L)
		20 days (kg/day)	250 days (kg/day)	20 days (ug/L)	250 days (ug/L)		
4952	134	N/A[a]	0.24	N/A[a]	24.77[b]	62	7
2819	110	2.49	0.20	0.13	0.011	62	7
2819	23.7	0.54	0.04	0.002	0.0002	62	7
2869	325	7.37	0.59	0.030	0.002	62	7
2869	20.9	0.12	0.04	28.37	8.98	62	7
2812	13.9	0.31	0.02	0.037	0.003	62	7
7996	13.8	0.31	0.03	0.74	0.06	62	7
2869	12.9	0.29	0.02	20.14	1.6	62	7

SIC Code	Total Pounds (lbs/yr) - 2015 DMR Data	PDM Inputs		Surface Water Concentrations		Acute COC (ug/L)	Chronic COC (ug/L)
		20 days (kg/day)	250 days (kg/day)	20 days (ug/L)	250 days (ug/L)		
2819	9.85	0.22	0.02	0.0009	0.0001	62	7
4953	8.94	0.20	0.02	13.05	1.04	62	7

[a] Not applicable; the 20-day discharge scenario is not considered because this facility only discharges 365 days per year.
[B] This surface water concentration value above the Chronic COC is based on highly conservative assumptions, including 0% removal of carbon tetrachloride by the waste water treatment facility. As explained in Section 2.3.1, the EPI Suite™ STP module estimates that about 90% of carbon tetrachloride in wastewater will be removed by volatilization and 2% by adsorption.

Appendix F SUPPORTING TABLE FOR INDUSTRIAL AND COMMERCIAL ACTIVITIES AND USES CONCEPTUAL MODEL

During problem formulation, EPA reviewed preliminary data and mapped conditions of use into corresponding exposure scenarios. Table_Apx F-1 summarizes the scenario mapping. The table also provides rationale on whether EPA will further assess each scenario during risk evaluation.

Table_Apx F-1. Industrial and Commercial Activities and Uses Conceptual Model Supporting Table
(Note that rows shaded in gray are not proposed for further analysis)

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Proposed for Further Risk Evaluation	Rationale for Further Evaluation / no Further Evaluation
Manufacture	Domestic Manufacture	Domestic Manufacture	Manufacture of carbon tetrachloride via chlorination of hydrocarbons, oxychlorination of hydrocarbons, chlorination of carbon disulfide, and as a byproduct	Liquid Contact	Dermal	Workers	Yes	Contact time with skin is expected to be <2 min due to rapid volatilization. However, the number of workers exposed may be high per CDR (3 submissions reporting 100-500 workers per submission).
				Vapor	Inhalation	Workers	Yes	Due to high volatility (VP = 115 mmHg) at room temperature, inhalation pathway should be further analyzed.
				Liquid Contact	Dermal	ONU[a]	No	Dermal exposure is expected to be primarily to workers directly involved in working with the chemical.

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Proposed for Further Risk Evaluation	Rationale for Further Evaluation / no Further Evaluation
				Vapor	Inhalation	ONU	Yes	Due to high volatility (VP = 115 mmHg) at room temperature, inhalation pathway should be further analyzed.
				Mist	Dermal/ Inhalation	Workers, ONU	No	Mist generation not expected during manufacturing.
Manufacture	Import	Import	Repackaging of import containers	Liquid Contact	Dermal	Workers	Yes	Contact time with skin is expected to be <2 min due to rapid volatilization. The number of import sites is limited (<6 sites) per CDR. Exposure will only occur in the event the imported material is repackaged.
				Vapor	Inhalation	Workers	Yes	Exposure expected only in the event the imported material is repackaged into different sized containers. Exposure frequency may be low.
				Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in working with the chemical.
				Vapor	Inhalation	ONU	Yes	Exposure expected only in the event the imported material is repackaged into different sized containers. Exposure frequency may be low.

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Proposed for Further Risk Evaluation	Rationale for Further Evaluation / no Further Evaluation
				Mist	Dermal/ Inhalation	Workers, ONU	No	Mist generation not expected during import.
Processing	Processing as a reactant	Intermediate in industrial gas and semiconductor manufacturing;	Manufacture of HCFCs, HFCs, HFOs, and PCE; Reactive ion etching	Liquid Contact	Dermal	Workers	Yes	Contact time with skin is expected to be <2 min due to rapid volatilization. However, the number of workers may be high per CDR (2 submissions reporting <10 workers, 1 submission reporting 10-25 workers, 1 submission reporting 25-50 workers, and 2 submissions reporting 100-500 workers).
				Vapor	Inhalation	Workers	Yes	Due to high volatility (VP = 115 mmHg) at room temperature, inhalation pathway should be further analyzed. However, potential for exposure may be low in scenarios where carbon tetrachloride is consumed as a chemical intermediate.
				Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in working with the chemical

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Proposed for Further Risk Evaluation	Rationale for Further Evaluation / no Further Evaluation
				Vapor	Inhalation	ONU	Yes	Due to high volatility (VP = 115 mmHg) at room temperature, inhalation pathway should be further analyzed. However, potential for exposure may be low in scenarios where carbon tetrachloride is consumed as a chemical intermediate.
				Mist	Dermal/ Inhalation	Workers, ONU	No	Mist generation not expected during processing as an intermediate.

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Proposed for Further Risk Evaluation	Rationale for Further Evaluation / no Further Evaluation
Processing	Incorporated into formulation, mixture or reaction product	Petrochemical-derived and agricultural products manufacturing; Other basic organic and inorganic chemical manufacturing; Other uses	Manufacturing of organic and inorganic chlorinated chemicals, pharmaceutical manufacturing, use in specialty operations by aerospace industry	Liquid Contact	Dermal	Workers	Yes	Contact time with skin is expected to be <2 min due to rapid volatilization.
				Vapor	Inhalation	Workers	Yes	Exposure frequency may be low.
				Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in working with the chemical.
				Vapor	Inhalation	ONU	Yes	Exposure frequency may be low.
				Mist	Dermal/ Inhalation	Workers, ONU	No	Mist generation not expected.
Processing	Repackaging	Laboratory Chemicals	Repackaging into large and small containers	Liquid Contact	Dermal	Workers	Yes	Contact time with skin is expected to be <2 min due to rapid volatilization.
				Vapor	Inhalation	Workers	Yes	Exposure frequency may be low.
				Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in working with the chemical.
				Vapor	Inhalation	ONU	Yes	Exposure frequency may be low.
				Mist	Dermal/ Inhalation	Workers, ONU	No	Mist generation not expected during repackaging.

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Proposed for Further Risk Evaluation	Rationale for Further Evaluation / no Further Evaluation
Processing	Recycling	Recycling	Recycling of process solvents containing carbon tetrachloride	Liquid Contact	Dermal	Workers	Yes	Contact time with skin is expected to be <2 min due to rapid volatilization.
				Vapor	Inhalation	Workers	Yes	Inhalation exposure is expected at recycling sites. Due to high volatility (VP = 115 mmHg) at room temperature, inhalation pathway should be further analyzed.
				Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in working with the chemical.
				Vapor	Inhalation	ONU	Yes	Inhalation exposure is expected at recycling sites. Due to high volatility (VP = 115 mmHg) at room temperature, inhalation pathway should be further analyzed.
				Mist	Dermal/ Inhalation	Workers, ONU	No	Mist generation not expected during recycling.

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Proposed for Further Risk Evaluation	Rationale for Further Evaluation / no Further Evaluation
Distribution in commerce	Distribution	Distribution	Distribution of bulk shipment of carbon tetrachloride; and distribution of formulated products	Liquid Contact, Vapor	Dermal/ Inhalation	Workers, ONU	Yes	EPA will further analyze activities resulting in exposures associated with distribution in commerce (e.g. loading, unloading) throughout the various lifecycle stages and conditions of use (e.g. manufacturing, processing, industrial use) rather than as a single distribution scenario.
Industrial / commercial use	Petrochemical-derived and agricultural products manufacturing	Petrochemical-derived and agricultural products manufacturing	Inert solvent, processing agent, processing aid, and additive	Liquid Contact	Dermal	Workers	Yes	Contact time with skin is expected to be <2 min due to rapid volatilization. However, EPA will need additional information to fully understand the use of carbon tetrachloride in this scenario to determine potential for dermal exposure.
				Vapor	Inhalation	Workers	Yes	Due to high volatility (VP = 115 mmHg) at room temperature, inhalation pathway should be further analyzed. However, EPA will need additional information to fully understand the use of carbon tetrachloride in this scenario to determine potential for inhalation exposure.

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Proposed for Further Risk Evaluation	Rationale for Further Evaluation / no Further Evaluation
				Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in working with the chemical.
				Vapor	Inhalation	ONU	Yes	Due to high volatility (VP = 115 mmHg) at room temperature, inhalation pathway should be further analyzed. However, EPA will need additional information to fully understand the use of carbon tetrachloride in this scenario to determine potential for inhalation exposure.
				Mist	Dermal/ Inhalation	Workers, ONU	No	Mist generation not expected during use of industrial processing agent.
Industrial / commercial use	Other basic organic and inorganic chemical manufacturing	Manufacturing of chlorinated compounds used in solvents for cleaning and degreasing, adhesives and sealants, paints and coatings, and asphalts;	Inert solvent, processing agent, processing aid, and additive	Liquid Contact	Dermal	Workers	Yes	Contact time with skin is expected to be <2 min due to rapid volatilization. However, EPA will need additional information to fully understand the use of carbon tetrachloride in this scenario to determine potential for dermal exposure.

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Proposed for Further Risk Evaluation	Rationale for Further Evaluation / no Further Evaluation
		Manufacturing of inorganic compounds		Vapor	Inhalation	Workers	Yes	Due to high volatility (VP = 115 mmHg) at room temperature, inhalation pathway should be further analyzed. However, EPA will need additional information to fully understand the use of carbon tetrachloride in this scenario to determine potential for inhalation exposure.
				Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in working with the chemical.
				Vapor	Inhalation	ONU	Yes	Due to high volatility (VP = 115 mmHg) at room temperature, inhalation pathway should be further analyzed. However, EPA will need additional information to fully understand the use of carbon tetrachloride in this scenario to determine potential for inhalation exposure.
				Mist	Dermal/ Inhalation	Workers, ONU	No	Mist generation not expected during use of industrial processing agent.

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Proposed for Further Risk Evaluation	Rationale for Further Evaluation / no Further Evaluation
Industrial / commercial	Other uses	Metal recovery; specialty uses by aerospace industry	Metal recovery; and uses in aerospace industry	Liquid Contact	Dermal	Workers	Yes	Contact time with skin is expected to be <2 min due to rapid volatilization.
				Vapor	Inhalation	Workers	Yes	Due to high volatility (VP = 115 mmHg) at room temperature, inhalation pathway should be further analyzed.
				Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in working with the chemical.
				Vapor	Inhalation	ONU	Yes	Due to high volatility (VP = 115 mmHg) at room temperature, inhalation pathway should be further analyzed.
				Mist	Dermal/ Inhalation	Workers, ONU	Yes	EPA will further evaluate to determine if mist generation is applicable to specific conditions of use in this scenario.
Industrial / commercial use	Laboratory chemical	Laboratory chemical	Use as reagent in laboratories	Liquid Contact	Dermal	Workers	Yes	Contact time with skin is expected to be <2 min due to rapid volatilization. Number of exposed workers may be low per CDR (1 submission reports 10-25 workers).

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Proposed for Further Risk Evaluation	Rationale for Further Evaluation / no Further Evaluation
				Vapor	Inhalation	Workers	Yes	Inhalation exposure is expected from laboratory uses. Due to high volatility (VP = 115 mmHg) at room temperature, inhalation pathway should be further analyzed. However, number of exposed workers may be low per CDR (1 submission reports 10-25 workers).
				Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in working with the chemical.
				Vapor	Inhalation	ONU	Yes	Inhalation exposure is expected from laboratory uses. Due to high volatility (VP = 115 mmHg) at room temperature, inhalation pathway should be further analyzed. However, number of exposed workers may be low per CDR (1 submission reports 10-25 workers).
				Mist	Dermal/ Inhalation	Workers, ONU	No	Mist generation not expected during laboratory uses.

Life Cycle Stage	Category	Subcategory	Release / Exposure Scenario	Exposure Pathway	Exposure Route	Receptor / Population	Proposed for Further Risk Evaluation	Rationale for Further Evaluation / no Further Evaluation
Disposal	Waste Handling, Treatment and Disposal	Disposal of carbon tetrachloride wastes	Worker handling of wastes	Liquid Contact	Dermal	Workers	Yes	Contact time with skin is expected to be <2 min due to rapid volatilization. Frequency of exposure and the potential for dermal immersion needs to be further analyzed.
				Vapor	Inhalation	Workers	Yes	Due to high volatility (VP = 115 mmHg) at room temperature, inhalation pathway should be further analyzed.
				Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in working with the chemical.
				Vapor	Inhalation	ONU	Yes	Due to high volatility (VP = 115 mmHg) at room temperature, inhalation pathway should be further analyzed.

[a] ONU = occupational non-users

Appendix G SUPPORTING TABLE FOR ENVIRONMENTAL RELEASES AND WASTES CONCEPTUAL MODEL

As part of the Problem Formulation, EPA considered if each unique combination of exposure pathway, route, and receptor in the lifecycle of carbon tetrachloride would be further evaluated. All possible exposure scenarios for each condition of use were identified according to the conditions of use identified in Table 2-3. EPA used readily available fate, engineering, exposure and/or toxicity information to determine whether to conduct further analysis on each exposure scenario based on available information. EPA identified exposure scenarios and mapped them to relevant conditions of use in Table_Apx G-1.

Table_Apx G-1. Environmental Releases and Wastes Conceptual Model Supporting Table

Life Cycle Stage	Use Category	Category	Release	Exposure Pathway	Receptor	Further Analysis	Rationale for Further Analysis / no Further Analysis
Disposal	Disposal	Wastewater or Liquid Wastes	Industrial WWT operations	Water	Aquatic Species	No	Conservative high-end screening indicates that aquatic species exposures to carbon tetrachloride in water are orders of magnitude below hazardous concentrations.
				Sediment	Aquatic Species	No	Based on the physical and chemical properties of carbon tetrachloride (log Koc of 1.7-2.16, high water solubility and volatility) sorption of carbon tetrachloride to sediments is unlikely.

Life Cycle Stage	Use Category	Category	Release	Exposure Pathway	Receptor	Further Analysis	Rationale for Further Analysis / no Further Analysis
			Industrial wastewater pre treatment operations, then transfer to POTW	Water	Aquatic Species	No	Conservative high-end screening indicates that aquatic species exposures to carbon tetrachloride in water are orders of magnitude below hazardous concentrations.
				Sediment	Aquatic Species	No	Based on the physical and chemical properties of carbon tetrachloride (log Koc of 1.7-2.16, high water solubility and volatility) sorption of carbon tetrachloride to sediments is unlikely.
			Publicly owned treatment works (POTW)	Water	Aquatic Species	No	Conservative high-end screening indicates that aquatic species exposures to carbon tetrachloride in water are orders of magnitude below hazardous concentrations.
				Sediment	Aquatic Species	No	Based on the physical and chemical properties of carbon tetrachloride (log Koc of 1.7-2.16, high water solubility and volatility) sorption of carbon tetrachloride to sediments is unlikely.

Appendix H INCLUSION AND EXCLUSION CRITERIA FOR FULL TEXT SCREENING

This appendix contains the eligibility criteria for various data streams informing the TSCA risk evaluation: environmental fate; engineering and occupational exposure; exposure to the general population and consumers; and human health hazard. The criteria are applied to the *on-topic* references that were identified following title and abstract screening of the comprehensive search results published on June 22, 2017.

Systematic reviews typically describe the study eligibility criteria in the form of PECO statements or a modified framework. PECO stands for Population, Exposure, Comparator and Outcome and the approach is used to formulate explicit and detailed criteria about those characteristics in the publication that should be present in order to be eligible for inclusion in the review. EPA/OPPT adopted the PECO approach to guide the inclusion/exclusion decisions during full text screening.

Inclusion and exclusion criteria were also used during the title and abstract screening, and documentation about the criteria can be found in the *Strategy for Conducting Literature Searches* document published in June 2017 along with each of the TSCA Scope documents. The list of *on-topic* references resulting from the title and abstract screening is undergoing full text screening using the criteria in the PECO statements. The overall objective of the screening process is to select the most relevant evidence for the TSCA risk evaluation. As a general rule, EPA is excluding non-English data/information sources and will translate on a case by case basis.

The inclusion and exclusion criteria for ecotoxicological data have been documented in the ECOTOX SOPs. The criteria can be found at https://cfpub.epa.gov/ecotox/help.cfm?helptabs=tab4) and in the *Strategy for Conducting Literature Searches* document published along with each of the TSCA Scope documents.

Since full text screening commenced right after the publication of the TSCA Scope document, the criteria were set to be broad to capture relevant information that would support the initial scope. Thus, the inclusion and exclusion criteria for full text screening do not reflect the refinements to the conceptual model and analysis plan resulting from problem formulation. As part of the iterative process, EPA is in the process of refining the results of the full text screening to incorporate the changes in information/data needs to support the revised scope.

These refinements will include changes to the inclusion and exclusion criteria discussed in this appendix to better reflect the revised scope of the risk evaluation and will likely reduce the number of data/information sources that will undergo evaluation.

H.1 Inclusion Criteria for Data Sources Reporting Engineering and Occupational Exposure Data

EPA/OPPT developed a generic RESO statement to guide the full text screening of engineering and occupational exposure literature (Table_Apx H-1). RESO stands for Receptors, Exposure, Setting or Scenario, and Outcomes. Subsequent versions of the RESO statement may be produced throughout the process of screening and evaluating data for the chemicals undergoing TSCA risk evaluation. Studies that comply with the inclusion criteria specified in the RESO statement will be eligible for inclusion, considered for evaluation, and possibly included in the environmental release and occupational exposure assessments, while those that do not meet these criteria will be excluded.

The RESO statement should be used along with the engineering and occupational exposure data needs table (Table_Apx H-2) when screening the literature.

Since full text screening commenced right after the publication of the TSCA Scope document, the criteria for engineering and occupational exposure data were set to be broad to capture relevant information that would support the initial scope. Thus, the inclusion and exclusion criteria for full text screening do not reflect the refinements to the conceptual model and analysis plan resulting from problem formulation. As part of the iterative process, EPA is in the process of refining the results of the full text screening to incorporate the changes in information/data needs to support the revised scope.

Table_Apx H-1. Inclusion Criteria for Data Sources Reporting Engineering and Occupational Exposure Data

RESO Element	Evidence
Receptors	• **Humans**: Workers, including occupational non-users (ONU)

Exposure	• Worker exposure to and occupational environmental releases of the chemical substance of interest
	  ○ Any exposure route (list included: dermal, inhalation, oral) as indicated in the conceptual model
	  ○ Any media/pathway [list included: water, land, air, incineration, and other(s)] 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 **S**cenario	• Any occupational setting or scenario resulting in worker exposure and environmental releases (includes all manufacturing, processing, use, disposal indicated in Table A-3 below except (state none excluded or list excluded uses)
Outcomes	• Quantitative estimates* of worker exposures • General information and data related and relevant to the occupational estimates*

* 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 Data Needs (Table_Apx H-2) provides a list of related and relevant general information.

TSCA=Toxic Substances Control Act

Table_Apx H-2. Engineering, Environmental Release and Occupational Data Necessary to Develop the Environmental Release and Occupational Exposure Assessments

Objective Determined during Scoping	Type of Data
General Engineering Assessment (may apply for either or both Occupational Exposures and / or Environmental Releases)	1. 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. [Tags: Life cycle description, Life cycle diagram][a] 2. 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. [Tags: Production volume, Import volume, Use volume, Percent PV] [a] 3. Description of processes, equipment, unit operations, and material flows 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). [Tags: Process description, Process material flow rate, Annual operating days, Annual batches, Weight fractions (for each of above, manufacture, import, processing, use)] [a] 4. Basic chemical properties relevant for assessing exposures and releases, e.g., molecular weight, normal boiling point, melting point, physical forms, and room temperature vapor pressure. [Tags: Molecular weight, Boiling point, Melting point, Physical form, Vapor pressure, Water solubility] [a] 5. Number of sites that manufacture, process, or use the chemical(s) of interest for each industrial/ commercial life cycle step and site locations. [Tags: Numbers of sites (manufacture, import, processing, use), Site locations] [a]
Occupational Exposures	6. 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. [Tags: Worker activities (manufacture, import, processing, use)] [a] 7. Potential routes of exposure (e.g., inhalation, dermal). [Tags: Routes of exposure (manufacture, import, processing, use)] [a] 8. Physical form of the chemical(s) of interest for each exposure route (e.g., liquid, vapor, mist) and activity. [Tags: Physical form during worker activities (manufacture, import, processing, use)] [a] 9. 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). [Tags: PBZ measurements (manufacture, import, processing, use)] [a] 10. 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). [Tags: Area measurements (manufacture, import, processing, use)] [a] 11. For solids, bulk and dust particle size characterization data. [Tags: PSD measurements (manufacture, import, processing, use)] [a] 12. Dermal exposure data. [Tags: Dermal measurements (manufacture, import, processing, use)] 13. Data needs associated with mathematical modeling (will be determined on a case-by-case basis). [Tags: Worker exposure modeling data needs (manufacture, import, processing, use)] [a] 14. Exposure duration (hr/day). [Tags: Worker exposure durations (manufacture, import, processing, use)] [a] 15. Exposure frequency (days/yr). [Tags: Worker exposure frequencies (manufacture, import, processing, use)] [a] 16. Number of workers who potentially handle or have exposure to the chemical(s) of interest in each occupational life cycle stage. [Tags: Numbers of workers exposed (manufacture, import, processing, use)] [a] 17. Personal protective equipment (PPE) types employed by the industries within scope. [Tags: Worker PPE (manufacture, import, processing, use)] [a]

Objective Determined during Scoping	Type of Data
	18. 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. [Tags: Engineering controls (manufacture, import, processing, use), Engineering control effectiveness data] [a]
Environmental Releases	19. 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. [Tags: Release sources (manufacture, import, processing, use)] [a] 20. Estimated mass (lb or kg) of the chemical(s) of interest released from industrial and commercial sites to each environmental medium (air, water, land) and treatment and disposal methods (POTW, incineration, landfill), including releases per site and aggregated over all sites (annual release rates, daily release rates) [Tags: Release rates (manufacture, import, processing, use)] [a] 21. Release or emission factors. [Tags: Emission factors (manufacture, import, processing, use)] [a] 22. Number of release days per year. [Tags: Release frequencies (manufacture, import, processing, use)] [a] 23. Data needs associated with mathematical modeling (will be determined on a case-by-case basis). [Tags: Release modeling data needs (manufacture, import, processing, use)] [a] 24. Waste treatment methods and pollution control devices employed by the industries within scope and associated data on release/emission reductions. [Tags: Treatment/ emission controls (manufacture, import, processing, use), Treatment/ emission controls removal/ effectiveness data] [a]

Notes:

[a] These 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.

Abbreviations:

hr=Hour
kg=Kilogram(s)
lb=Pound(s)
yr=Year
PV=Particle volume
PBZ=
POTW=Publicly owned treatment works
PPE=Personal projection equipment
PSD=Particle size distribution
TWA=Time-weighted average

H.2 Inclusion Criteria for Data Sources Reporting Human Health Hazards

EPA/OPPT developed a carbon tetrachloride-specific PECO statement to guide the full text screening of the human health hazard literature. Subsequent versions of the PECOs may be produced throughout the process of screening and evaluating data for the chemicals undergoing TSCA risk evaluation. Studies that comply with the criteria specified in the PECO statement will be eligible for inclusion, considered for evaluation, and possibly included in the human health hazard assessment, while those that do not meet these criteria will be excluded according to the exclusion criteria.

In general, the PECO statements were based on (1) information accompanying the TSCA Scope document, and (2) preliminary review of the health effects literature from authoritative sources cited in the TSCA Scope documents. When applicable, these authoritative sources (e.g., IRIS assessments, EPA/OPPT's Work Plan Problem Formulations or risk assessments) will serve as starting points to identify PECO-relevant studies.

Table_Apx H-3. Inclusion and Exclusion Criteria for Data Sources Reporting Human Health Hazards Related to Carbon Tetrachloride Exposure [a]

PECO Element	Evidence Stream	Papers/Features Included	Papers/Features Excluded
Population	*Human*	• Any population • All lifestages • Study designs: ○ Controlled exposure, cohort, case-control, cross-sectional, case-crossover, case studies, and case series for all endpoints	
	Animal	• All non-human whole-organism mammalian species • All lifestages	• Non-mammalian species
	Mechanistic	• All data that may inform mechanisms of genotoxicity and carcinogenicity [a]	• Data related to other mechanisms of toxicity [a]
Exposure	*Human*	• Exposure based on administered dose or concentration of carbon tetrachloride, biomonitoring data (e.g., urine, blood or other specimens), environmental or occupational-setting monitoring data (e.g., air, water levels), job title or residence • Primary metabolites of interest as identified in biomonitoring studies • Exposure identified as *or presumed to be* from oral, dermal, inhalation routes • Any number of exposure groups • Quantitative, semi-quantitative or qualitative estimates of exposure • Exposures to multiple chemicals/mixtures only if carbon tetrachloride or related metabolites were independently measured and analyzed	• Route of exposure ***not*** by inhalation, oral or dermal type (e.g., intraperitoneal, injection) • Multiple chemical/mixture exposures with no independent measurement of or exposure to carbon tetrachloride (or related metabolite)
	Animal	• A minimum of 2 quantitative dose or concentration levels of carbon tetrachloride plus a negative control group [a] • Acute, subchronic, chronic exposure from oral, dermal, inhalation routes • Exposure to carbon tetrachloride only (no chemical mixtures)	• Only 1 quantitative dose or concentration level in addition to the control [a] • Route of exposure ***not*** by inhalation, oral or dermal type (e.g., intraperitoneal, injection) • No duration of exposure stated • Exposure to carbon tetrachloride in a chemical mixture
	Mechanistic	• Exposure based on concentrations of the neat material of carbon tetrachloride • A minimum of 2 dose or concentration levels tested plus a control group [a]	• Exposure to carbon tetrachloride in a chemical mixture • Only 1 quantitative dose or concentration level in addition to the control [a]
Comparator	*Human*	• A comparison population [not exposed, exposed to lower levels, exposed below detection] for all endpoints	• No comparison population for all endpoints
	Animal	• Negative controls that are vehicle-only treatment and/or no treatment	• Negative controls ***other than*** vehicle-only treatment or no treatment

PECO Element	Evidence Stream	Papers/Features Included	Papers/Features Excluded
	Mechanistic	• Exposed to vehicle-only treatment and/or no treatment • ***For genotoxicity studies only***, studies using positive controls	• Negative controls ***other than*** vehicle-only treatment or no treatment • ***For genotoxicity studies only***, a lack of positive controls
Outcome	*Human and Animal*	• Endpoints described in the carbon tetrachloride scope document [b]: ○ Cancer ○ Liver toxicity ○ Kidney toxicity ○ Neurotoxicity ○ Gastrointestinal toxicity ○ Irritation ○ Sensitization • Other endpoints (e.g., reproductive toxicity) [b,c]	
	Mechanistic	• All data that may inform the mechanism(s) of cancer and genotoxicity [a]	• Data related to other mechanisms of toxicity [a]
General Considerations		**Papers/Features Included**	**Papers/Features Excluded**
		• Written in English [d] • Reports a primary source or meta-analysis [a] • Full-text available • Reports both carbon tetrachloride exposure ***and*** a health outcome (or mechanism of action)	• Not written in English • Reports a secondary source (e.g., review papers) [a] • No full-text available (e.g., only a study description/abstract, out-of-print text) • Reports a carbon tetrachloride-related exposure ***or*** a health outcome, but not both (e.g. incidence, prevalence report)

[a] Some of the studies that are excluded based on the PECO statement may be considered later during the systematic review process. For carbon tetrachloride, EPA will evaluate studies related to susceptibility and may evaluate toxicokinetics and physiologically based pharmacokinetic models after other data (e.g., human and animal data identifying adverse health outcomes) are reviewed. EPA may need to evaluate mechanistic data in addition to data on mechanisms of genotoxicity and carcinogenicity depending on the review of health effects data. Finally, EPA may also review other data as needed (e.g., animal studies using one concentration, review papers).

[b] EPA will review key and supporting studies in the IRIS assessment that were considered in the dose-response assessment for non-cancer and cancer endpoints as well as studies published after the IRIS assessment.

[c] EPA may screen for hazard effects other than those listed in the scope document if identified in the updated literature search for carbon tetrachloride that accompanied the scope document.

[d] EPA may translate studies as needed.

Appendix I LIST OF RETRACTED PAPERS

The following on-topic articles were retracted by the journal ad are considered off-topic.

Cha, JY; Ahn, HY; Moon, HI; Jeong, YK; Cho, YS. (2012). Effect of fermented Angelicae gigantis Radix on carbon tetrachloride-induced hepatotoxicity and oxidative stress in rats. Immunopharmacol Immunotoxicol 34: 265-274. http://dx.doi.org/10.3109/08923973.2011.600765

El-Sayed, YS; Lebda, MA; Hassinin, M; Neoman, SA. (2015). Chicory (Cichorium intybus L.) root extract regulates the oxidative status and antioxidant gene transcripts in CCl4-induced hepatotoxicity. PLoS ONE 10: e0121549. http://dx.doi.org/10.1371/journal.pone.0121549

Li, C; Jiang, W; Zhu, H; Hou, J. (2012). Antifibrotic effects of protocatechuic aldehyde on experimental liver fibrosis. Pharmaceutical Biology 50: 413-419. http://dx.doi.org/10.3109/13880209.2011.608193

Ping, J; Gao, AM; Qin, HQ; Wei, XN; Bai, J; Liu, L; Li, XH; Li, RW; Ao, Y; Wang, H. (2011). Indole-3-carbinol enhances the resolution of rat liver fibrosis and stimulates hepatic stellate cell apoptosis by blocking the inhibitor of κB kinase α/inhibitor of κB-α/nuclear factor-κB pathway. J Pharmacol Exp Ther 339: 694-703. http://dx.doi.org/10.1124/jpet.111.179820