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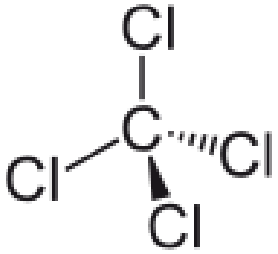
Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-)

CASRN: 56-23-5



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ABBREVIATIONS

°C	Degrees Celsius
AAL	Allowable Ambient Levels
ACGIH	American Conference of Government Industrial Hygienists
ACR	Acute to Chronic Ratio
ADC	Average Daily Concentration
AEC	Acute Exposure Concentration
AIA	Aerospace Industries Association
AIHA	American Industrial Hygiene Association
ALT	Alanine Aminotransferase
APF	Assigned Protection Factor
atm	Atmosphere(s)
ATSDR	Agency for Toxic Substances and Disease Registries
AWQC	Ambient Water Quality Criteria
BCF	Bioconcentration Factor
BLS	Bureau of Labor Statistics
BUN	Blood Urea Nitrogen
CAA	Clean Air Act
CASRN	Chemical Abstract Service Registry Number
CBI	Confidential Business Information
CCl_4	Carbon Tetrachloride
CDR	Chemical Data Reporting
CEHD	Chemical Exposure Health Data
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act
CFC	Chlorofluorocarbon
cm^2	Square Centimeter(s)
cm^3	Cubic Centimeter(s)
CPN	Chronic Progressive Nephropathy
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
CSF	Cancer Slope Factor
CSM	Chlorosulphonated Polyolefin
CYP450	Cytochrome P450
CWA	Clean Water Act
DMR	Discharge Monitoring Report
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DT50	Dissipation Time for 50% of the compound to dissipate
EC	European Commission
ECHA	European Chemicals Agency
EDC	Ethylene Dichloride
ELCR	Excess Lifetime Cancer Risk
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)
GS	Generic scenario
HAP	Hazardous Air Pollutant
HCFC	Hydrochlorofluorocarbons
HCl	Hydrochloric Acid
HFC	Hydrofluorocarbon
HFO	Hydrofluoroolefin
HSIA	Halogenated Solvents Industry Alliance
HVLP	High Volume, Low Pressure
IBC	Intermediate Bulk Containers
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
kg	Kilogram(s)
km	Kilometer(s)
L	Liter(s)
LADC	Lifetime Average Daily Concentration
lb	Pound
LOD	Limit of Detection
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
MEMA	Motor and Equipment Manufacturer Association
mg	Milligram(s)
mmHg	Millimeter(s) of Mercury
MP	Montreal Protocol
mPa·s	Millipascal(s)-Second
NAC/AEGL	National Advisory Committee for Acute Exposure Guideline Levels
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 for Occupational Safety and Health
NPDES	National Pollutant Discharge Elimination System
NPDWR	National Primary Drinking Water Regulations

NTP	National Toxicology Program
NWQMC	National Water Quality Monitoring Council
OARS	Occupational Alliance for Risk Science
OBOD	Open Burn/Open Detection
OCSPP	Office of Chemical Safety and Pollution Prevention
ODS	Ozone Depleting Substance
OECD	Organisation for Economic Co-operation and Development
OELs	Occupational Exposure Limits/Levels
ONU	Occupational Non-Users
OPPT	Office of Pollution Prevention and Toxics
OSHA	Occupational Safety and Health Administration
OW	Office of Water
PCE	Perchloroethylene
PDM	Probabilistic Dilution Model
PEL	Permissible Exposure Limit
PESS	Potentially Exposed or Susceptible Subpopulations
PF	Protection Factor
POD	Point of Departure
POTW	Publicly Owned Treatment Works
ppm	Part(s) per Million
PPE	Personal Protective Equipment
QC	Quality Control
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RCRA	Resource Conservation and Recovery Act
REL	Recommended Exposure Limit
RFI	Reporting Forms and Instructions
RIE	Reactive Ion Etching
SDS	Safety Data Sheet
SDWA	Safe Drinking Water Act
SIAP	Screening Information Dataset Initial Assessment Profile
SIDS	Screening Information Dataset
SOC	Standard Occupational Classification
STEL	Short-term Exposure Limit
SUSB	Statistics of US Businesses
SYR	Six-year Review
TCCR	Transparent, Clear, Consistent and Reasonable
TCLP	Toxicity Characteristic Leaching Procedure
TLV	Threshold Limit Value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TSDF	Treatment, Storage and Disposal Facilities
TURA	Toxic Use Reduction Act
TWA	Time-Weighted Average
UATMP	Urban Air Toxics Monitoring Program
UNEP	United Nations Environment Programme
U.S.	United States
USGS	United States Geological Survey
VOC	Volatile Organic Compounds

WEEL	Workplace Environmental Exposure Limit
WHO	World Health Organization
WQP	Water Quality Portal
Y_{derm}	Weight fraction of the chemical of interest in the liquid phase

EXECUTIVE SUMMARY

This risk evaluation for carbon tetrachloride was performed in accordance with the Frank R. Lautenberg Chemical Safety for the 21st Century Act and is being issued following public comment and peer review. 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, in June 2016. Under the amended statute, EPA is required, under TSCA § 6(b), to conduct risk evaluations to determine whether a chemical substance presents unreasonable risk of injury to health or the environment, under the conditions of use, without consideration of costs or other non-risk factors, including an unreasonable risk to potentially exposed or susceptible subpopulations, identified as relevant to the risk evaluation. Also, as required by TSCA Section (6)(b), EPA established, by rule, a process to conduct these risk evaluations. *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726). (Risk Evaluation Rule).

This risk evaluation is in conformance with TSCA Section 6(b), and the Risk Evaluation Rule, and is to be used to inform risk management decisions. In accordance with TSCA Section 6(b), if EPA finds unreasonable risk from a chemical substance under its conditions of use in any final risk evaluation, the Agency will propose actions to address those risks within the timeframe required by TSCA. However, any proposed or final determination that a chemical substance presents unreasonable risk under TSCA Section 6(b) is not the same as a finding that a chemical substance is "imminently hazardous" under TSCA Section 7. The conclusions, findings, and determinations in this final risk evaluation are for the purpose of identifying whether the chemical substance presents unreasonable risk or no unreasonable risk under the conditions of use, in accordance with TSCA Section 6, and are not intended to represent any findings under TSCA Section 7.

TSCA Sections 26(h) and (i) require EPA, when conducting risk evaluations, to use scientific information, technical procedures, measures, methods, protocols, methodologies and models consistent with the best available science and to base its decisions on the weight of the scientific evidence[1]. To meet these TSCA Section 26 science standards, EPA used the TSCA systematic review process described in *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). The data collection, evaluation, and integration stages of the systematic review process are used to develop the exposure, fate, and hazard assessments for risk evaluations.

Carbon tetrachloride [CASRN: 56-23-5] is a high production volume solvent. Previously, carbon tetrachloride was a high production solvent in consumer and fumigant products, including as a solvent to make refrigerants and propellants for aerosol cans, as a solvent for oils, fats, lacquers, varnishes, rubber waxes, and resins, and as a grain fumigant and dry-cleaning agent. The Montreal Protocol and Title VI of the Clean Air Act (CAA) led to a phase-out of carbon tetrachloride production in the United States for most non-feedstock domestic uses in 1996. The Consumer Product Safety Commission (CPSC) banned the use of carbon tetrachloride in consumer products (with the exception of "unavoidable manufacturing residues of carbon tetrachloride in other chemicals that under reasonably foreseeable conditions of use do not result in an atmospheric concentration of carbon tetrachloride greater than 10 parts per million")

[1] Weight of the scientific evidence means a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance.

in 1970.[2] Currently, carbon tetrachloride is used as a feedstock in the production of hydrochloro-fluorocarbons (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.

Carbon tetrachloride has been reportable to the Toxics Release Inventory (TRI) chemical under Section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA) since 1987. It is designated a Hazardous Air Pollutant (HAP) under the Clean Air Act (CAA), and is a hazardous substance under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). It is subject to National Primary Drinking Water Regulations (NPDWR) under the Safe Drinking Water Act (SDWA) and designated as a toxic pollutant under the Clean Water Act (CWA) and as such is subject to effluent limitations.

Approach

EPA used reasonably available information (defined in 40 CFR 702.33 in part as "*information that EPA possesses or can reasonably generate, obtain, and synthesize for use in risk evaluations, considering the deadlines . . . for completing such evaluation*") in a "fit-for-purpose" approach, to develop a risk evaluation that relies on the best available science and is based on the weight of the scientific evidence. EPA used previous analyses as a starting point for identifying key and supporting studies to inform the exposure, fate, and hazard assessments. EPA also evaluated other studies that were published since these reviews. EPA reviewed the information and evaluated the quality of the methods and reporting of results of the individual studies using the evaluation strategies described in *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). To satisfy requirements in TSCA Section 26(j)(4) and 40 CFR 702.51(e), EPA has provided a list of studies considered in carrying out the risk evaluation and the results of those studies in Appendix C, Appendix F, Appendix G, and several supplemental files.

In the problem formulation document (U.S. EPA, 2018c), EPA identified the carbon tetrachloride conditions of use and presented two conceptual models and an analysis plan for this current risk evaluation. These have been updated in the risk evaluation to remove two activities that are no longer considered conditions of use because they consist of outdated industrial/commercial processes that are not known, intended, or reasonably foreseen to occur, and/or fall outside TSCA's definition of "chemical substance" (see Section 1.4.2).

EPA has quantitatively evaluated the risk to the environment and human health, using both monitoring data and modeling approaches, for the conditions of use identified in Section 1.4.1 of this risk evaluation. EPA used environmental fate parameters, physical-chemical properties, modeling, and monitoring data to assess ambient water exposure to aquatic and sediment-dwelling organisms. While carbon tetrachloride is present in various environmental media, such as groundwater, surface water, and

[2] EPA did not identify any "legacy uses" (*i.e.*, circumstances associated with activities that do not reflect ongoing or prospective manufacturing, processing, or distribution) or "associated disposal" (*i.e.*, future disposal from legacy uses) of carbon tetrachloride, as those terms are described in EPA's Risk Evaluation Rule, 82 FR 33726, 33729 (July 20, 2017). Therefore, no such uses or disposals were added to the scope of the risk evaluation for carbon tetrachloride following the issuance of the opinion in *Safer Chemicals, Healthy Families v. EPA*, 943 F.3d 397 (9th Cir. 2019). EPA did not evaluate "legacy disposal" (*i.e.*, disposals that have already occurred) in the risk evaluation, because legacy disposal is not a "condition of use" under *Safer Chemicals*, 943 F.3d 397.

air, EPA determined during problem formulation that no further analysis beyond what was presented in the problem formulation document would be done for environmental exposure pathways. However, in the final risk evaluation, EPA qualitatively evaluated the soil and land-applied biosolid pathway leading to exposure to terrestrial organisms, and quantitatively and qualitatively evaluated risk to sediment-dwelling organisms considering one low quality ecotoxicity paper on *Chironomus tentans* (Lee et al., 2006) and acceptable aquatic invertebrate data. EPA also quantitatively evaluated the risk to aquatic organisms from surface water further refining the assessment presented in the problem formulation document and draft risk evaluation. Results from these analyses were presented in the final risk evaluation and used to inform the risk determination section. EPA also quantitatively evaluated the risk to workers, from inhalation and dermal exposures, and occupational non-users (ONUs)[3], from inhalation exposures, by comparing the estimated exposures to acute and chronic human health hazards.

Exposures

EPA used environmental monitoring data to assess ambient water exposure to aquatic organisms including sediment organisms. While carbon tetrachloride is present in various environmental media, such as groundwater, surface water, and air, EPA stated in the problem formulation that EPA did not expect to include in the risk evaluation certain exposure pathways that are under the jurisdiction of other EPA-administered statutes, and stated that EPA expected to conduct no further analysis beyond what was presented in the problem formulation document for the environmental exposure pathways that remained in the scope of this risk evaluation. Exposures to terrestrial organisms from air were considered out of scope due to its coverage under the jurisdiction of the Clean Air Act. Exposures to terrestrial organisms from water were not further analyzed because carbon tetrachloride is identified as a priority pollutant under Section 304(a) of the Clean Water Act regulating releases to water and the expectation that any releases to water under the regulation will volatilize into air based on its physical-chemical properties.

Exposures to terrestrial organisms from the suspended soils and biosolids pathway was qualitatively evaluated. However, no further analyses were conducted because the physical-chemical and fate properties of carbon tetrachloride provide evidence indicating that exposures to terrestrial organisms from the soil and biosolids pathways are negligible. These analyses are described in Sections 2.1, 2.3 and 4.1 and Appendix E.

EPA evaluated exposures to carbon tetrachloride in occupational settings for the conditions of use (COUs) included in the scope of the risk evaluation, listed in Section 1.4 (Scope of the Evaluation). In occupational settings, EPA evaluated acute and chronic inhalation exposures to workers and ONUs, and acute and chronic dermal exposures to workers. EPA used inhalation monitoring data where reasonably available and that met data evaluation criteria, as well as modeling approaches where reasonably available to estimate potential inhalation exposures. For some of the COUs (import/repackaging, industrial processing aid, additive, disposal, specialty uses) there is uncertainty in the ONU inhalation risk estimate since the data did not distinguish between worker and ONU inhalation exposure estimates. While the difference between the exposures of ONUs and the exposures of workers directly handling the carbon tetrachloride generally cannot be quantified, ONU inhalation exposures are expected to be lower than inhalation exposures for workers directly handling the chemical. EPA considered the ONU exposures to be equal to the central tendency risk estimates for workers when determining ONU risk attributable to inhalation. While this is likely health protective as it assumes ONU exposure is greater than that of 50% of the workers, this is uncertain, and EPA describes these uncertainties and its

[3] ONUs are workers who do not directly handle carbon tetrachloride but perform work in an area where carbon tetrachloride is present.

confidence in exposure estimates for ONUs in Section 2.4. Dermal exposures are not expected because ONUs do not typically directly handle the carbon tetrachloride. Dermal doses for workers were estimated in these scenarios because dermal monitoring data was not reasonably available. These analyses are described in Section 2.4 of this risk evaluation.

Based on the information identified by EPA, carbon tetrachloride is not a direct reactant or additive in the formulation of any consumer products. However, trace amounts of residual carbon tetrachloride could be present in commercially available solvents for cleaning and degreasing, adhesives and sealants or paints and coatings manufactured with chlorinated compounds derived from carbon tetrachloride. 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 consumer and occupational exposures to those products do not warrant evaluation based on EPA's discretionary authority in TSCA Section 6(b)(4)(D) to exclude from the scope of the risk evaluation conditions of use for which exposures are expected to be de minimis (see Section 1.4.2.3). Furthermore, consumer products with measurable amounts of carbon tetrachloride have not been identified in the Washington State Product Testing Data list, the State of Vermont list of Chemicals in Children's Products or the State of California consumer product database (Safer Consumer Products Information Management System) and no consumer uses are listed in the CDR (Vermont Department of Health, 2020; State of Washington, 2019; State of California, 2013; U.S. EPA, 2016d).

EPA has also exercised its authority in TSCA Section 6(b)(4)(D) to exclude from the scope of this risk evaluation conditions of use associated with carbon tetrachloride generated as a byproduct. Carbon tetrachloride generated as a byproduct during the manufacture of 1,2-dichloroethane will be assessed in the risk evaluation for 1,2-dichloroethane (see Final Scope of the Risk Evaluation for 1,2-Dichloroethane, EPA-HQ-OPPT-2018-0427-0048).

Spills and leaks generally are not included within the scope of TSCA risk evaluations because in general they are not considered to be circumstances under which a chemical substance is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of. To the extent there may be potential exposure from spills and leaks, EPA is also declining to evaluate environmental exposure pathways addressed by other EPA-administered statutes and associated regulatory programs.

First, EPA does not identify carbon tetrachloride spills or leaks as "conditions of use." EPA does not consider carbon tetrachloride spills or leaks to constitute circumstances under which carbon tetrachloride is manufactured, processed, distributed, used, or disposed of, within TSCA's definition of "conditions of use." Congress specifically listed discrete, routine chemical lifecycle stages within the statutory definition of "conditions of use" and EPA does not believe it is reasonable to interpret "circumstances" under which carbon tetrachloride is manufactured, processed, distributed, used, or disposed of to include uncommon and unconfined spills or leaks for purposes of the statutory definition. Further, EPA does not generally consider spills and leaks to constitute "disposal" of a chemical for purposes of identifying a COU in the conduct of a risk evaluation.

In addition, even if spills or leaks of carbon tetrachloride could be considered part of the listed lifecycle stages of carbon tetrachloride, EPA has "determined" that spills and leaks are not circumstances under which carbon tetrachloride is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of, as provided by TSCA's definition of "conditions of use," and EPA is therefore exercising its discretionary authority under TSCA Section 3(4) to exclude carbon tetrachloride

spills and leaks from the scope of the carbon tetrachloride risk evaluation. The exercise of that authority is informed by EPA's experience in developing scoping documents and risk evaluations, and on various TSCA provisions indicating the intent for EPA to have some discretion on how best to address the demands associated with implementation of the full TSCA risk evaluation process. Specifically, since the publication of the Risk Evaluation Rule, EPA has gained experience by conducting ten risk evaluations and designating forty chemical substances as low- and high-priority chemical substances. These processes have required EPA to determine whether the case-specific facts and the reasonably available information justify identifying a particular activity as a "condition of use."

With the experience EPA has gained, it is better situated to discern circumstances that are appropriately considered to be outside the bounds of "circumstances…under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of" and to thereby meaningfully limit circumstances subject to evaluation. Because of the expansive and potentially boundless impacts that could result from including spills and leaks as part of the risk evaluation (*e.g.*, due to the unpredictable and irregular scenarios that would need to be accounted for, including variability in volume, frequency, and geographic location of spills and leaks; potential application across multiple exposure routes and pathways affecting myriad ecological and human receptors; and far-reaching analyses that would be needed to support assessments that account for uncertainties but are based on best available science), which could make the conduct of the risk evaluation untenable within the applicable deadlines, spills and leaks are determined not to be circumstances under which carbon tetrachloride is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of, as provided by TSCA's definition of "conditions of use."

Exercising the discretion to not identify spills and leaks of carbon tetrachloride as a COU is consistent with the discretion Congress provided in a variety of provisions to manage the challenges presented in implementing TSCA risk evaluation. See *e.g.*, TSCA Sections 3(4), 3(12), 6(b)(4)(D), 6(b)(4)(F). In particular, TSCA Section 6(b)(4)(F)(iv) instructs EPA to factor into TSCA risk evaluations "the likely duration, intensity, frequency, and number of exposures under the conditions of use...," suggesting that activities for which duration, intensity, frequency, and number of exposures cannot be accurately predicted or calculated based on reasonably available information, including spills and leaks, were not intended to be the focus of TSCA risk evaluations. And, as noted in the preamble to the Risk Evaluation Rule, EPA believes that Congress intended there to be some reasonable limitation on TSCA risk evaluations, expressly indicated by the direction in TSCA Section 2(c) to "carry out [TSCA] in a reasonable and prudent manner." For these reasons, EPA is exercising this discretion to not consider spills and leaks of carbon tetrachloride to be COUs.

Second, even if carbon tetrachloride spills or leaks could be identified as exposures from a COU in some cases, these are not types of exposure that EPA expects to consider in the carbon tetrachloride risk evaluation. TSCA Section 6(b)(4)(D) requires EPA, in developing the scope of a risk evaluation, to identify the hazards, exposures, conditions of use, and potentially exposed or susceptible subpopulations the Agency "expects to consider" in a risk evaluation. This language suggests that EPA is not required to consider all conditions of use, hazards, or exposure pathways in risk evaluations. EPA has chosen to tailor the scope of the risk evaluation to exclude spills and leaks in order to focus analytical efforts on those exposures that present the greatest potential for risk.

In the problem formulation documents for many of the first 10 chemicals undergoing risk evaluation, EPA applied the same authority and rationale to certain exposure pathways, explaining that "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....” This approach is informed by the legislative history of the amended TSCA, which supports the Agency’s exercise of discretion to focus the risk evaluation on areas that raise the greatest potential for risk. See June 7, 2016 Cong. Rec., S3519-S3520.

In addition to TSCA Section 6(b)(4)(D), the Agency also has discretionary authority under the first sentence of TSCA Section 9(b)(1) to “coordinate actions taken under [TSCA] with actions taken under other Federal laws administered in whole or in part by the Administrator.” TSCA Section 9(b)(1) provides EPA authority to coordinate actions with other EPA offices, including coordination on tailoring the scope of TSCA risk evaluations to focus on areas of greatest concern rather than exposure pathways addressed by other EPA-administered statutes and regulatory programs, which does not involve a risk determination or public interest finding under TSCA Section 9(b)(2). EPA has already tailored the scope of this risk evaluation using such discretionary authorities with respect to exposure pathways covered under the jurisdiction of other EPA-administered statutes and associated regulatory programs (see section 1.4.3).

Following coordination with EPA’s Office of Land and Emergency Management (OLEM), EPA has found that exposures of carbon tetrachloride from spills and leaks fall under the jurisdiction of RCRA. See 40 CFR 261.33(d) (defining in part a hazardous waste as “any residue or contaminated soil, water or other debris resulting from the cleanup of a spill into or on any land or water of any commercial chemical product or manufacturing chemical intermediate having the generic name listed [40 CFR 261.33(e) or (f)], or any residue or contaminated soil, water or other debris resulting from the cleanup of a spill, into or on any land or water, of any off-specification chemical product and manufacturing chemical intermediate which, if it met specifications, would have the generic name listed in [40 CFR 261.33(e) or (f)]”); 40 CFR 261.33(f) (listing carbon tetrachloride as hazardous waste no. U211). As a result, EPA believes it is both reasonable and prudent to tailor the TSCA risk evaluation for carbon tetrachloride by declining to evaluate potential exposures from spills and leaks, rather than attempt to evaluate and regulate potential exposures from spills and leaks under TSCA.

Hazards

EPA reviewed the environmental hazard data 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, 2018a). EPA included a quantitative assessment of carbon tetrachloride exposure from surface water and sediments. EPA concluded that carbon tetrachloride poses a hazard to environmental aquatic receptors with amphibians being the most sensitive taxa for acute and chronic exposures. Algal endpoints are considered separately from the other taxa and not incorporated into acute or chronic concentrations of concern (COCs) because durations normally considered acute for other species (*e.g.*, 48, 72, or 96 hours) can encompass several generations of algae. Distinct COCs were calculated for algal and sediment invertebrate toxicities. The results of the environmental hazard assessment are in Section 3.1.

EPA evaluated reasonably available information for human health hazards and identified hazard endpoints including acute and chronic toxicity for non-cancer effects and cancer. EPA used the *Framework for Human Health Risk Assessment to Inform Decision Making* (U.S. EPA, 2014b) to interpret, extract, and integrate carbon tetrachloride’s human health hazard and dose-response information. EPA reviewed key and supporting information from previous hazard assessments [EPA IRIS Toxicologic Review (U.S. EPA, 2010), an ATSDR Toxicological Profile (ATSDR, 2005) and NAC Acute Exposure Guideline Levels (AEGL) (NRC, 2014) and other international assessments listed

in Table 1-3. EPA also screened and evaluated new studies that were published since these reviews (*i.e.*, from 2010 – 2018).

EPA developed a hazard and dose-response analysis using endpoints observed in inhalation and oral hazard studies, evaluated the weight of the scientific evidence considering EPA and National Research Council (NRC) risk assessment guidance and selected the points of departure (POD) for acute and chronic, non-cancer endpoints, and inhalation unit risk and cancer slope factors for cancer risk estimates. Potential health effects of carbon tetrachloride exposure described in the literature include effects on the central nervous system (CNS), liver, kidney, as well as skin irritation, and cancer. EPA identified acute PODs for inhalation exposures based on acute CNS effects observed in humans (Davis, 1934). The chronic POD for inhalation exposures are based on a study observing increased fatty changes in rodent livers (Nagano et al., 2007a). EPA identified a limited number of toxicity studies by the dermal route that were not adequate for dose-response assessment. Therefore, the dermal candidate values were derived by route-to-route extrapolation from the inhalation PODs mentioned above.

In accordance with U.S. EPA (U.S. EPA, 2005a) *Guidelines for Carcinogen Risk Assessment*, carbon tetrachloride is classified "likely to be carcinogenic to humans" based on sufficient evidence in animals and sufficient evidence in humans. EPA calculated cancer risk with a linear model using cancer slope factors for low dose exposures of carbon tetrachloride, which is EPA's baseline approach to risk assessment when the MOA is unknown (*i.e.*, adrenal gland and brain tumors in animal and human data, respectively). A general correspondence has been observed between hepatocellular cytotoxicity and regenerative hyperplasia and the induction of liver tumors as a potential MOA. As indicated in the EPA IRIS Assessment (U.S. EPA, 2010), this MOA appears to play a significant role at relatively high exposures above the POD, driving the steep increase in liver tumors in this exposure range. Therefore, EPA presents in this final risk evaluation two approaches for assessment of carcinogenic risk from carbon tetrachloride: a threshold approach for assessing risks for liver tumors based on a cytotoxicity and regenerative hyperplasia, in conjunction with the liner extrapolation approach for the adrenal gland and brain tumors. This is based on considerations for the modes of action for the different cancers evaluated. The results of these analyses are described in Section 3.2.

Human Populations Considered in This Risk Evaluation

EPA assumed those who use carbon tetrachloride would be adults (workers) of either sex (>16 years old), including pregnant women, and evaluated risks to individuals who do not use carbon tetrachloride but may be indirectly exposed due to their proximity to the user who is directly handling carbon tetrachloride.

The risk evaluation is based on potential central nervous system depression, which can lead to workplace accidents and which is a precursor to more severe central nervous system effects such as incapacitation, loss of consciousness, and death, as well as liver toxicity and cancer as sensitive endpoints. The risk evaluation also assesses the risk to other potentially exposed or susceptible subpopulations, including people with pre-existing conditions and people with genetic variations that make them more susceptible. Exposures that do not present risks based on sensitive toxicity endpoints are not expected to present risks for other potential health effects of carbon tetrachloride because other health effects occur at levels of exposure higher than the sensitive toxicity endpoints.

Risk Characterization

This risk evaluation characterizes the environmental and human health risks from carbon tetrachloride under the conditions of use, including manufacture, processing, distribution, use and disposal. This risk

characterization identifies potential risks that are used in the identification of unreasonable risks in the risk determination.

Environmental Risk: For environmental risk, EPA utilized a risk quotient (RQ) to compare the environmental concentration to the effect level to characterize the risk to aquatic and sediment-dwelling organisms. EPA included a quantitative assessment describing carbon tetrachloride exposure from ambient water to aquatic and sediment-dwelling organisms. Carbon tetrachloride is not expected to accumulate in sediments, and could be mobile in soil, and migrate to water or volatilize to air. The results of the risk characterization are in Section 4.1, including a table that summarizes the RQs for acute and chronic risks.

EPA identified expected environmental exposures for aquatic species under the conditions of use in the scope of the risk evaluation. While the estimated releases from specific facilities result in modeled surface water concentrations that were equal to or exceed the aquatic benchmark (RQ ≥ 1), other facilities had acute RQs < 1, algae RQ < 1 and < 20 days exceedance, or chronic RQs < 1 indicating that exposures resulting from environmental concentrations were less than the effect concentration, or the concentration of concern. Details of these estimates are in Section 4.1.2.

Human Health Risks: For human health risks to workers, EPA identified potential cancer and non-cancer human health risks from chronic inhalation exposures. EPA did not identify risks from acute exposures for central nervous system depression. For dermal exposures, EPA identified potential risks for non-cancer liver effects and cancer for chronic exposures.

For workers and ONUs, EPA estimated potential cancer risk for tumors other than liver from chronic exposures to carbon tetrachloride using an inhalation unit risk value or dermal cancer slope factor multiplied by the chronic exposure for each COU. The potential cancer risks for liver tumors were estimated by calculating Margins of Exposure (MOEs) for chronic inhalation and dermal exposures based on a threshold approach. For workers and ONUs, EPA also estimated potential non-cancer (liver) risks resulting from acute or chronic inhalation or dermal exposures and used an MOE approach. For workers, EPA estimated risks using several occupational exposure scenarios, which varied assumptions regarding the expected use of personal protective equipment (PPE) for respiratory and dermal exposures for workers directly handling carbon tetrachloride. More information on respiratory and dermal protection, including EPA's approach regarding the occupational exposure scenarios for carbon tetrachloride, is in Section 2.4.1.1.

For workers, chronic non-cancer risks were indicated for high-end inhalation exposures for manufacturing, processing, import, additive, processing aid and disposal COUs and cancer risks were indicated for both high-end and central tendency inhalation exposures for all COUs except central tendency exposures for DOD uses if PPE was not used. With use of PPE during relevant COUs, worker exposures were estimated to be reduced such that MOEs were greater than benchmark MOEs and cancer risks were below the benchmark cancer risk. EPA's estimates for worker risks for each occupational exposure scenario are presented in Section 4.2 and summarized in Table 4-15Table 4-15. Non-cancer risks and cancer risks for workers were identified for high-end and central tendency dermal exposures for all COUs (see Section 4.2.7). Dermal exposures are reduced with the use of gloves resulting in MOEs above the benchmark MOE. Cancer risks for dermal exposures with gloves use (up to PF = 20) remain below the benchmark cancer risk for all COUs with exposures. (see Sections 4.2.4, 4.2.5)

For ONUs, non-cancer risks were indicated for high-end inhalation exposures during manufacturing and processing COUs and cancer risks were indicated for inhalation exposure scenarios for all COUs, except for DOD uses. ONUs are not assumed to be using PPE to reduce exposures to carbon tetrachloride. ONUs are not dermally exposed to carbon tetrachloride and dermal risks to ONUs were not identified. EPA's estimates for ONU risks for each occupational exposure scenario are presented in Section 4.2 and summarized in Table 4-15.

Strengths, Limitations and Uncertainties in the Risk Characterization
Key assumptions and uncertainties in the environmental risk estimation include the uncertainty around modeled releases that have surface water concentrations greater than the highest concentration of concern for aquatic organisms.

For the human health risk estimation, key assumptions and uncertainties are related to the estimates for ONU inhalation exposures, because monitoring data were not reasonably available for many of the conditions of use evaluated. Surrogate monitoring data were used for COUs without monitoring data for ONUs. An additional source of uncertainty in the dermal risk assessment is the inhalation to dermal route-to-route extrapolations. Another source of uncertainty for the human health hazard is the evidence in support of a MOA for carcinogenesis of carbon tetrachloride for the different types of tumors observed in animal and human studies. Based on reasonably available data, regenerative hyperplasia is the cancer MOA identified for the development liver tumors in animals exposed to high doses of carbon tetrachloride. Therefore, a threshold cancer risk model was used to calculate risks for liver tumors. A low dose linear cancer risk model for carbon tetrachloride was used to calculate cancer risk for tumors others than liver. Assumptions and key sources of uncertainty are detailed in Section 4.4.

EPA's assessments, risk estimations, and risk determinations account for uncertainties throughout the risk evaluation. EPA used reasonably available information, in a fit-for-purpose approach, to develop a risk evaluation that relies on the best available science and is based on the weight of the scientific evidence. Systematic review was conducted to identify reasonably available information related to carbon tetrachloride hazards and exposures. The consideration of uncertainties supports the Agency's risk determinations, each of which is supported by substantial evidence, as set forth in detail in later sections of this final risk evaluation.

Potentially Exposed or Susceptible Subpopulations (PESS)
TSCA Section 6(b)(4) requires that EPA conduct risk evaluations to determine whether a chemical substance presents unreasonable risk under the conditions of use, including unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation. TSCA Section 3(12) defines "*potentially exposed or susceptible subpopulation" as 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 risk evaluation, EPA analyzed reasonably available information to ascertain whether some human receptor groups among the worker and ONU may have greater exposure or greater susceptibility than the general population of workers or ONUs to the hazard posed by carbon tetrachloride. For consideration of the most highly exposed groups, EPA considered carbon tetrachloride exposures to be higher among workers using carbon tetrachloride and ONUs in the vicinity of carbon tetrachloride use. Additionally, variability of susceptibility to carbon tetrachloride may be correlated

with genetic polymorphism in its metabolizing enzymes. Factors other than polymorphisms that regulate CYP2E1 induction may have greater influence on the formation of the toxic metabolic product of carbon tetrachloride exposure. The CYP2E1 enzyme is easily induced by many substances, resulting in increased metabolism. For example, moderate to heavy alcohol drinkers may have increased susceptibility to carbon tetrachloride (NRC, 2014). To account for variation in sensitivity within human populations intraspecies uncertainty factors (UFs) were applied for non-cancer effects. The UF values selected are described in Section 3.2.5.2. EPA's decision for unreasonable risk are based on high-end exposure estimates for workers in order to capture individuals who are PESS.

Aggregate and Sentinel Exposures
Section 6(b)(4)(F)(ii) of TSCA requires the EPA, as a part of the risk evaluation, to describe whether aggregate or sentinel exposures under the conditions of use were considered and the basis for their consideration. The EPA has defined aggregate exposure as "*the combined exposures to an individual from a single chemical substance across multiple routes and across multiple pathways"* (40 CFR § 702.33). Exposures to carbon tetrachloride were evaluated by inhalation and dermal routes separately. Inhalation and dermal exposures are assumed to occur simultaneously for workers. EPA chose not to employ simple additivity of exposure pathways at this time within a condition of use, because it would result in an overestimate of risk. In addition, inhalation and dermal exposures are conservative estimates and combining them would generate unrealistic combined estimates. See additional discussions in Section 4.6.

EPA defines sentinel exposure as "*the exposure from a single chemical substance that represents the plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures"* (40 CFR § 702.33). In this risk evaluation, EPA considered sentinel exposure the highest exposure given the details of the conditions of use and the potential exposure scenarios. Sentinel exposures for workers are the high-end no PPE within each OES. In cases where sentinel exposures result in MOEs greater than the benchmark or cancer risk lower than the benchmark, EPA did no further analysis because sentinel exposures represent the worst-case scenario. EPA's decision for unreasonable risk are based on high-end exposure estimates to capture individuals with sentinel exposure. See further information on aggregate and sentinel exposures in Section 4.6.

Unreasonable Risk Determination: In each risk evaluation under TSCA Section 6(b), EPA determines whether a chemical substance presents an unreasonable risk of injury to health or the environment, under the conditions of use. The determination does not consider costs or other non-risk factors. In making this determination, EPA considers relevant risk-related factors, including, but not limited to: the effects of the chemical substance on health and human exposure to such substance under the conditions of use (including cancer and non-cancer risks); the effects of the chemical substance on the environment and environmental exposure under the conditions of use; the population exposed (including any potentially exposed or susceptible subpopulations, as determined by EPA); the severity of hazard (including the nature of the hazard, the irreversibility of the hazard); and uncertainties. EPA also takes into consideration the Agency's confidence in the data used in the risk estimate. This includes an evaluation of the strengths, limitations, and uncertainties associated with the information used to inform the risk estimate and the risk characterization. The rationale for the unreasonable risk determination is discussed in Section 5.2. The Agency's risk determinations are supported by substantial evidence, as set forth in detail in later Sections of this final risk evaluation.

Unreasonable Risk of Injury to the Environment: EPA modeled industrial discharges of carbon tetrachloride to surface water to estimate surface water concentrations. The estimated surface water

concentrations did not exceed the acute COC for any of the sites assessed. None of the sites analyzed had more than 20 days where the chronic and algal COCs were exceeded. EPA considered the biological relevance of the species to determine the concentrations of concern, as well as time and seasonality of the exposures, and uncertainties of the limited number of data points above the RQ. EPA determined that there is no unreasonable risk to aquatic organisms from all conditions of use. With respect to sediment-dwelling aquatic species, carbon tetrachloride is not expected to partition to or be retained in sediment and is expected to remain in aqueous phase due to its water solubility and low partitioning to organic matter. EPA quantitatively assessed risks posed by carbon tetrachloride to sediment-dwelling aquatic organisms and has determined that there is no unreasonable environmental risk to sediment-dwelling species from the conditions of use for carbon tetrachloride. Based on its physical-chemical properties, carbon tetrachloride does not partition to or accumulate in soils. Therefore, EPA determined that there is no unreasonable risk to terrestrial organisms from all conditions of use from exposure to carbon tetrachloride through soil and land-applied biosolids.

Based on the risk estimates, the environmental effects of carbon tetrachloride, the exposures, physical-chemical properties of carbon tetrachloride, and consideration of uncertainties, EPA determined that there is no unreasonable risk of injury to the environment from all conditions of use of carbon tetrachloride.

Unreasonable Risks of Injury to Health: EPA's determination of unreasonable risk for specific conditions of use of carbon tetrachloride listed below are based on health risks to workers and occupational non-users. As described below, EPA did not evaluate unreasonable risk to consumers, bystanders, or to the general population in this risk evaluation. For acute exposures, EPA evaluated unreasonable risks of central nervous system effects that are temporarily disabling, such as dizziness. For chronic exposures, EPA evaluated unreasonable risks of liver toxicity and cancer. Cancer risks were assessed using two approaches: linear extrapolation and threshold. This is based on considerations for the modes of action for the different cancers evaluated. The unreasonable risk determination is based on the risk estimates derived from both approaches.

Unreasonable Risk of Injury to Health of the General Population: General population exposures to carbon tetrachloride may occur from industrial and/or commercial uses; industrial releases to air, water or land; and other conditions of use. During the course of the risk evaluation process for carbon tetrachloride, OPPT worked closely with the offices within EPA that administer and implement regulatory programs under the Clean Air Act (CAA), the Safe Drinking Water Act (SDWA), the Clean Water Act (CWA), the Resource Conservation and Recovery Act (RCRA), and the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Through this intra-agency coordination, EPA determined that carbon tetrachloride exposures to the general population via surface water, drinking water, ambient air and sediment pathways fall under the jurisdiction of other environmental statutes, administered by EPA, *i.e.*, CAA, SDWA, CWA, RCRA, and CERCLA. As explained in more detail in Section 1.4.3, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA believes that coordinated action on exposure pathways and risks addressed by other EPA-administered statutes and regulatory programs is consistent with the statutory text and legislative history, particularly as they pertain to TSCA's function as a "gap-filling" statute, and also furthers EPA aims to efficiently use Agency resources, avoid duplicating efforts taken pursuant to other Agency programs, and meet the statutory deadlines for completing risk evaluations. EPA has therefore tailored the scope of the risk evaluation for carbon tetrachloride using authorities in TSCA

Sections 6(b) and 9(b)(1). EPA did not evaluate hazards or exposures to the general population in this risk evaluation, and as such the unreasonable risk determinations for relevant conditions of use do not account for exposures to the general population.

Unreasonable Risk of Injury to Health of Workers: EPA evaluated cancer and non-cancer effects from acute and chronic inhalation and dermal occupational exposures to determine if there was unreasonable risk of injury to workers' health. The drivers for EPA's determination of unreasonable risk of injury for workers are cancer resulting from chronic dermal exposures.

EPA generally assumes compliance with OSHA requirements for protection of workers including the implementation of the hierarchy of controls. In support of this assumption, EPA used reasonably available information indicating that some employers, particularly in the industrial setting, are providing appropriate engineering, administrative controls, or PPE to their employees consistent with OSHA requirements. While EPA does not have reasonably available information to support this assumption for each condition of use, EPA does not believe that the Agency must presume, in the absence of such information, a lack of compliance with existing regulatory programs and practices. Rather, EPA assumes there is compliance with worker protection standards unless case-specific facts indicate otherwise, and therefore existing OSHA regulations for worker protection and hazard communication will result in use of appropriate PPE in a manner that achieves the stated Assigned Protection Factor (APF) for respirators or Protection Factor (PF) for gloves. EPA's decisions for unreasonable risk to workers are based on high-end exposure estimates in order to account for the uncertainties related to whether or not workers are using PPE. EPA's approach for evaluating risk to workers and ONUs is to use the reasonably available information and professional judgment to construct exposure scenarios that reflect the workplace practices involved in the conditions of use of the chemicals and address uncertainties regarding availability and use of PPE.

An APF is a term used by the OSHA to determine how well a respirator/filter combination will protect an individual from chemical exposure. APFs are used to select the appropriate class of respirators that will provide the necessary level of protection. There are certain levels used for different types of masks. An APF of 10 means that no more than one-tenth of the contaminants to which the worker is exposed will leak into the inside of the mask. An APF of 100 means only one percent leakage. Elastomeric full facepiece respirators have an APF of 50 (see Table 2-4 for additional details). For each occupational condition of use of carbon tetrachloride, EPA assumes worker use of a respirator with an APF of 50. Similarly, EPA assumes worker use of gloves with PF of 20 in commercial and industrial settings.

The unreasonable risk determinations reflect the severity of the effects associated with the occupational exposures to carbon tetrachloride and incorporate EPA assumptions of PPE use. A full description of EPA's unreasonable risk determination for each condition of use is in Section 5.2.

Unreasonable Risk of Injury to Health of Occupational Non-Users (ONUs): ONUs are workers who do not directly handle carbon tetrachloride but perform work in an area where carbon tetrachloride is present. EPA evaluated cancer and non-cancer effects to ONUs from acute and chronic inhalation exposures to determine if there was unreasonable risk of injury to ONU's health. The unreasonable risk determinations reflect the severity of the effects associated with the occupational exposures to carbon tetrachloride and the assumed absence of PPE for ONUs, since ONUs do not directly handle the chemical and are instead doing other tasks in the vicinity of carbon tetrachloride use. Non-cancer effects and cancer from dermal occupational exposures to ONUs were not evaluated because ONUs are not dermally exposed to carbon tetrachloride. For inhalation exposures, EPA, where possible, estimated ONUs'

exposures and described the risks separately from workers directly exposed. When the difference between ONUs' exposures and workers' exposures cannot be quantified, EPA assumed that ONU's inhalation exposures are lower than inhalation exposures for workers directly handling the chemical substance, and EPA considered the central tendency risk estimate when determining ONU risk. A full description of EPA's unreasonable risk determination for each condition of use is in Section 5.2.

Unreasonable Risk of Injury to Health of Consumers and Bystanders: As explained in the problem formulation document for carbon tetrachloride, EPA did not include any consumer conditions of use among the conditions of use within the scope of the risk evaluation for carbon tetrachloride and did not evaluate exposures to consumers and bystanders from contaminant exposure in the risk evaluation. 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. As a result of CPSC's ban, EPA does not consider the use of carbon tetrachloride-containing consumer products produced before 1970 to be known, intended, or reasonably foreseen. While carbon tetrachloride is used in the manufacturing of other chlorinated compounds that may be subsequently added to commercially available products, EPA expects that consumer use of such products would present only negligible exposure to carbon tetrachloride given the high volatility of carbon tetrachloride and the extent of reaction and efficacy of the separation/purification process for purifying final products. As discussed in Section 1.4.2.3, EPA had sufficient basis to conclude during problem formulation that industrial, commercial, and consumer uses of carbon tetrachloride in commercially available aerosol and non-aerosol adhesives and sealants, paints and coatings, and cleaning and degreasing solvent products would present only de minimis exposures or otherwise insignificant risks and did not warrant further evaluation or inclusion in the risk evaluation. Therefore, EPA did not evaluate hazards or exposures to consumers or bystanders in this risk evaluation, and there is no unreasonable risk determination for these populations.

Summary of Unreasonable Risk Determinations: In conducting risk evaluations, "EPA will determine whether the chemical substance presents an unreasonable risk of injury to health or the environment under each condition of use within the scope of the risk evaluation…" 40 CFR 702.47. Pursuant to TSCA Section 6(i)(1), a determination of "no unreasonable risk" shall be issued by order and considered to be final agency action. Under EPA's implementing regulations, "[a] determination by EPA that the chemical substance, under one or more of the conditions of use within the scope of the risk evaluation, does not present an unreasonable risk of injury to health or the environment will be issued by order and considered to be a final Agency action, effective on the date of issuance of the order." 40 CFR 702.49(d).

EPA has determined that the following conditions of use of carbon tetrachloride do not present an unreasonable risk of injury to health or the environment. These determinations are considered final agency action and are being issued by order pursuant to TSCA Section 6(i)(1). The details of these determinations are in Section 5.2, and the TSCA Section 6(i)(1) order is contained in Section 5.4.1 of this final risk evaluation.

Conditions of Use that Do Not Present an Unreasonable Risk
• Processing as a reactant/intermediate in reactive ion etching (*i.e.*, semiconductor manufacturing) • Distribution in commerce

EPA has determined that the following conditions of use of carbon tetrachloride present an unreasonable risk of injury. EPA will initiate TSCA Section 6(a) risk management actions on these conditions of use as required under TSCA Section 6(c)(1). Pursuant to TSCA Section 6(i)(2), the unreasonable risk determinations for these conditions of use are not considered final agency action. The details of these determinations are in Section 5.4.1.

Manufacturing that Presents an Unreasonable Risk
• Domestic manufacture • Import (including loading/unloading and repackaging)

Processing that Presents an Unreasonable Risk
• Processing as a reactant in the production of hydrochlorofluorocarbons, hydrofluorocarbon, hydrofluoroolefin, and perchloroethylene • Processing for incorporation into formulation, mixtures or reaction products (petrochemicals-derived manufacturing; agricultural products manufacturing; other basic organic and inorganic chemical manufacturing) • Repackaging for use in laboratory chemicals • Recycling

Industrial and Commercial Uses[4] that Present an Unreasonable Risk
• Industrial/commercial use as an industrial processing aid in the manufacture of petrochemicals-derived products and agricultural products • Industrial/commercial use as an additive • Industrial/commercial use in the manufacture of other basic chemicals (including chlorinated compounds used in solvents, adhesives, asphalt, and paints and coatings) • Industrial/commercial use in metal recovery • Specialty uses by the Department of Defense • Industrial/commercial use as a laboratory chemical

Disposal
• Disposal

[4] Although EPA has identified both industrial and commercial uses here for purposes of distinguishing scenarios in this analysis, the Agency interprets the authority over "any manner or method of commercial use" under TSCA section 6(a)(5) to reach both.

1 INTRODUCTION

This document presents the final risk evaluation 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, the Nation's primary chemicals management law, in June 2016.

The Environmental Protection Agency (EPA) published the Scope of the Risk Evaluation for Carbon Tetrachloride (U.S. EPA, 2017e) in June 2017, and the problem formulation in June 2018 (U.S. EPA, 2018c), which represented the analytical phase of risk evaluation whereby "the purpose for the assessment is articulated, the problem is defined, and a plan for analyzing and characterizing risk is determined" as described in Section 2.2 of the *Framework for Human Health Risk Assessment to Inform Decision Making*. The problem formulation identified conditions of use and presented three conceptual models and an analysis plan. Based on EPA's analysis of the conditions of use, physical-chemical and fate properties, environmental releases, and exposure pathways, the problem formulation preliminarily concluded that further analysis was necessary for exposure pathways to workers and ONUs. EPA subsequently published a draft risk evaluation for carbon tetrachloride and has taken public and peer review comments. The conclusions, findings, and determinations in this final risk evaluation are for the purpose of identifying whether the chemical substance presents unreasonable risk or no unreasonable risk under the conditions of use, in accordance with TSCA Section 6, and are not intended to represent any findings under TSCA Section 7.

As per EPA's final rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726 (July 20, 2017)), the draft risk evaluation was subject to both public comment and peer review, which are distinct but related processes. EPA provided 60 days for public comment on any and all aspects of the draft risk evaluation, including the submission of any additional information that might be relevant to the science underlying the risk evaluation and the outcome of the systematic review associated with carbon tetrachloride. This satisfies TSCA (15 U.S.C. 2605(b)(4)(H)), which requires EPA to provide public notice and an opportunity for comment on a draft risk evaluation prior to publishing a final risk evaluation.

Peer review was conducted in accordance with EPA's regulatory procedures for chemical risk evaluations, including using the *EPA Peer Review Handbook* and other methods consistent with the science standards laid out in Section 26 of TSCA (See 40 CFR 702.45). As explained in the *Risk Evaluation Rule* (82 FR 33726 (July 20, 2017)), the purpose of peer review is for the independent review of the science underlying the risk assessment. As such, peer review addressed aspects of the underlying science as outlined in the charge to the peer review panel such as hazard assessment, assessment of dose-response, exposure assessment, and risk characterization.

As EPA explained in the *Risk Evaluation Rule* (82 FR 33726 (July 20, 2017)), it is important for peer reviewers to consider how the underlying risk evaluation analyses fit together to produce an integrated risk characterization, which forms the basis of an unreasonable risk determination. EPA believed peer reviewers were most effective in this role if they received the benefit of public comments on the draft risk evaluations prior to peer review. For this reason, and consistent with standard Agency practice, the public comment period preceded peer review. The final risk evaluation changed in response to public comments received on the draft risk evaluation and in response to peer review. EPA responded to public and peer review comments received on the draft risk evaluation and explained changes made in response to those comments in this final risk evaluation and the associated response to comments document.

This document is structured such that the Introduction (Section 0) presents the basic physical-chemical properties of carbon tetrachloride, and background information on its regulatory history, conditions of use and conceptual models, with emphasis on any changes since the publication of the problem formulation. This section also includes a discussion of the systematic review process utilized in this risk evaluation. Exposures (Section 2) provides a discussion and analysis of both human and environmental exposures that can be expected based on the conditions of use for carbon tetrachloride. Hazards (Section 3) discusses environmental and human health hazards of carbon tetrachloride. The Risk characterization (Section 4) integrates and assesses reasonably available information on human health and environmental hazards and exposures, as required by TSCA (15 U.S.C 2605(b)(4)(F)). This section also includes a discussion of any uncertainties and how they impact the risk evaluation. As required under TSCA 15 U.S.C. 2605(b)(4), a determination of whether the risk posed by this chemical substance under its conditions of use is unreasonable is presented in the Risk Determination (see Section 5).

EPA solicited input on the first 10 chemicals as it developed use dossiers, scope documents, problem formulations, and draft risk evaluations. At each step, EPA received information and comments specific to individual chemicals and of a more general nature relating to various aspects of the risk evaluation process, technical issues, and the regulatory and statutory requirements. EPA has considered comments and information received at each step in the process and factored in the information and comments as the Agency deemed appropriate and relevant including comments on the published problem formulation and draft risk evaluation of carbon tetrachloride.

1.1 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 being evaluated. A summary of the physical-chemical properties of carbon tetrachloride are listed in Table 1-1.

Carbon tetrachloride is a colorless liquid at room temperature with a sweet, aromatic and ethereal odor resembling chloroform (Merck, 1996); (U.S. Coast Guard, 1985). It is water miscible, has a melting point of -23 °C, a boiling point of 76.8 °C and its' density is 1.4601 g/cm^3 at 20°C (Lide, 1999). Carbon tetrachloride has a Henry's Law Constant of 0.0276 atm m^3/mole and a log Kow value of 2.83(Leighton and Calo, 1981); (Hansch et al., 1995). Other pertinent physical-chemical properties are listed below in Table 1-1.

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

Property	Value[a]	References
Molecular formula	CCl_4	
Molecular weight	153.82	
Physical form	Colorless liquid with sweet odor	(Merck, 1996); (U.S. Coast Guard, 1985)
Melting point	-23°C	(Lide, 1999)
Boiling point	76.8°C	(Lide, 1999)
Density	1.4601 g/cm^3 at 20°C	(Lide, 1999)

Vapor pressure	115 mm Hg at 25°C	(Boublík et al., 1984)
Vapor density	5.3 (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	(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 flammable	(U.S. Coast Guard, 1999)
Viscosity	2.03 mPa·s at -23°C	(Daubert and Danner, 1989)
Refractive index	1.4607 at 20°C	(Merck, 1996)
Dielectric constant	2.24 at 20°C	(Norbert and Dean, 1967)
[a] Measured unless otherwise noted.		

1.2 Uses and Production Volume

Carbon tetrachloride is a high production volume solvent. Over one hundred forty two million pounds of carbon tetrachloride were produced or imported in the U.S. in 2015 according to the EPA's Chemical Data Reporting (CDR) database. 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). As explained in the problem formulation (U.S. EPA, 2018c), EPA identified additional information on the regulated use of carbon tetrachloride as a process agent (non-feedstock uses) 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.

The 2016 CDR (reporting period 2012 to 2015) provided data for carbon tetrachloride are provided in Table 1-2 for carbon tetrachloride from EPA's CDR database (U.S. EPA, 2016d).

Table 1-2. 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, 2017b). Internal communication. The CDR data for the 2016 reporting period is available via ChemView (https://java.epa.gov/chemview) (U.S. EPA, 2016d).				

Carbon tetrachloride had several uses in the past, primarily as a feedstock for the production of chlorofluorocarbons. Current uses are now confined by the Montreal Protocol to be in contained processes. Sherry *et al*. (2018) reported global industrial production of carbon tetrachloride in 2014 was consumed in: (*i*) incineration (29 gigagram [Gg], while 1Gg = 2.205×10^6 lbs); (*ii*) as a perchloroethylene feedstock (64 Gg); (*iii*) as hydrofluorocarbon feedstock (58 Gg); (*iv*) in methyl chloride production (26Gg); (*v*) in divinyl acid chloride production (23 Gg); and (*vi*) for use as process agent and laboratory purposes (3 Gg). Sherry *et al*. (2018) estimated 13 Gg year^{-1} of global emissions from unreported non-feedstock emissions from chloromethane and perchloroethylene plants as the key carbon tetrachloride source. Additionally, 2 Gg year^{-1} are estimated as fugitive emissions from the usage of carbon tetrachloride as feedstock and possibly up to 10 Gg year^{-1} from legacy emissions and chlor-alkali plants. To resolve the budget discrepancy, Park *et al*. (2018) used a tracer–tracer correlation method based on a top-down interpretation of emissions of carbon tetrachloride by measuring continuous, high frequency, high-precision, atmospheric carbon tetrachloride concentrations at the Gosan station (33° N, 126° E) on Jeju Island, South Korea during 2008–2015. These authors reported that 89% ± 6% of carbon tetrachloride emissions are from the production of methyl chloride, dichloromethane, chloroform, and tetrachloroethylene and its usage as a feedstock and process agent in chemical manufacturing industries. Butler *et al*. (2016) suggested biological sink for carbon tetrachloride in surface or near-surface waters of the ocean is responsible for removing ~18% of the carbon tetrachloride in the atmosphere. Though carbon tetrachloride hydrolyzes in seawater, the hydrolysis rates of gaseous carbon tetrachloride are too slow to support undersaturation based on air–sea gas exchange rates. The undersaturation in intermediate depth waters associated with reduced oxygen levels indicated that carbon tetrachloride could be consumed at ocean mid-depth by microbiota. Butler *et al*. (2016) also recognized the discrepancy remaining between potential emissions based on the data on carbon tetrachloride production and destruction and emissions computed from atmospheric lifetime, and estimated emission discrepancy of the order of 10–20 Gg year^{-1}. Hu *et al.* (2016) performed national-scale emissions of carbon tetrachloride based on inverse modeling of atmospheric observations at multiple sites across the U.S. These authors estimated an annual average U.S. emission of 4.0 (2.0–6.5) Gg year^{-1} during 2008–2012, which was almost two orders of magnitude larger than reported in TRI (mean of 0.06 Gg year^{-1}) but only 8% (3–22%) of global carbon tetrachloride emissions during these years. Hu *et al.* (2016) concluded that the emission distribution derived for carbon tetrachloride throughout the U.S. is more consistent with the distribution of industrial activities included in the TRI than with the distribution of other potential carbon tetrachloride sources such as uncapped landfills or activities that may generate carbon tetrachloride (*e.g.*, result of reactions of chlorine-containing bleach with surfactant, soap, or other organics).

1.3 Regulatory and Assessment History

1.3.1 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 (see Section 2.5.3.2 in (U.S. EPA, 2018c)).

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.

EPA identified numerous previous assessments conducted by Agency Programs and other organizations (see Table 1-3). Since the publication of the problem formulation, an additional assessment by the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been identified. Depending on the source, these assessments may include information on conditions of use, hazards, exposures and potentially exposed or susceptible subpopulations.

Table 1-3. 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 Water	Carbon Tetrachloride Health Advisory, Office of Drinking Water US Environmental Protection Agency (1987)
National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee)	Carbon Tetrachloride – Final AEGL Document (2014)
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[1]	

Authoring Organization	Assessment
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 Organization (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) (2017)
[1]The information on international assessments is based on information presented in Table1-1 in the Problem Formulation document and is not meant to be inclusive for all assessments from other countries	

1.4 Scope of the Evaluation

1.4.1 Conditions of Use Included in the Risk Evaluation

TSCA Section 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." The life cycle diagram is presented below in Figure 1-1. The conditions of use are described below in Table 1-4.

Workplace exposures and water releases have been evaluated in this risk evaluation for the following industrial/commercial uses of carbon tetrachloride:

1. Domestic manufacture
2. Import (including loading/unloading and repackaging)
3. Processing as a reactant in the production of hydrochlorofluorocarbons, hydrofluorocarbon, hydrofluoroolefin, and perchloroethylene
4. Processing as a reactant in reactive ion etching
5. Processing for incorporation into formulation, mixtures or reaction products (petrochemicals-derived manufacturing; agricultural products manufacturing; other basic organic and inorganic chemical manufacturing)
6. Repackaging for use in laboratory chemicals
7. Recycling
8. Distribution in commerce
9. Industrial/commercial use as an industrial processing aid in the manufacture of petrochemicals-derived products and agricultural products
10. Industrial/commercial use in the manufacture of other basic chemicals (including chlorinated compounds used in solvents, adhesives, asphalt, and paints and coatings)
11. Industrial/commercial use in metal recovery
12. Industrial/commercial use as an additive
13. Industrial/commercial use in specialty uses by the Department of Defense
14. Industrial/commercial use as a laboratory chemical
15. Disposal

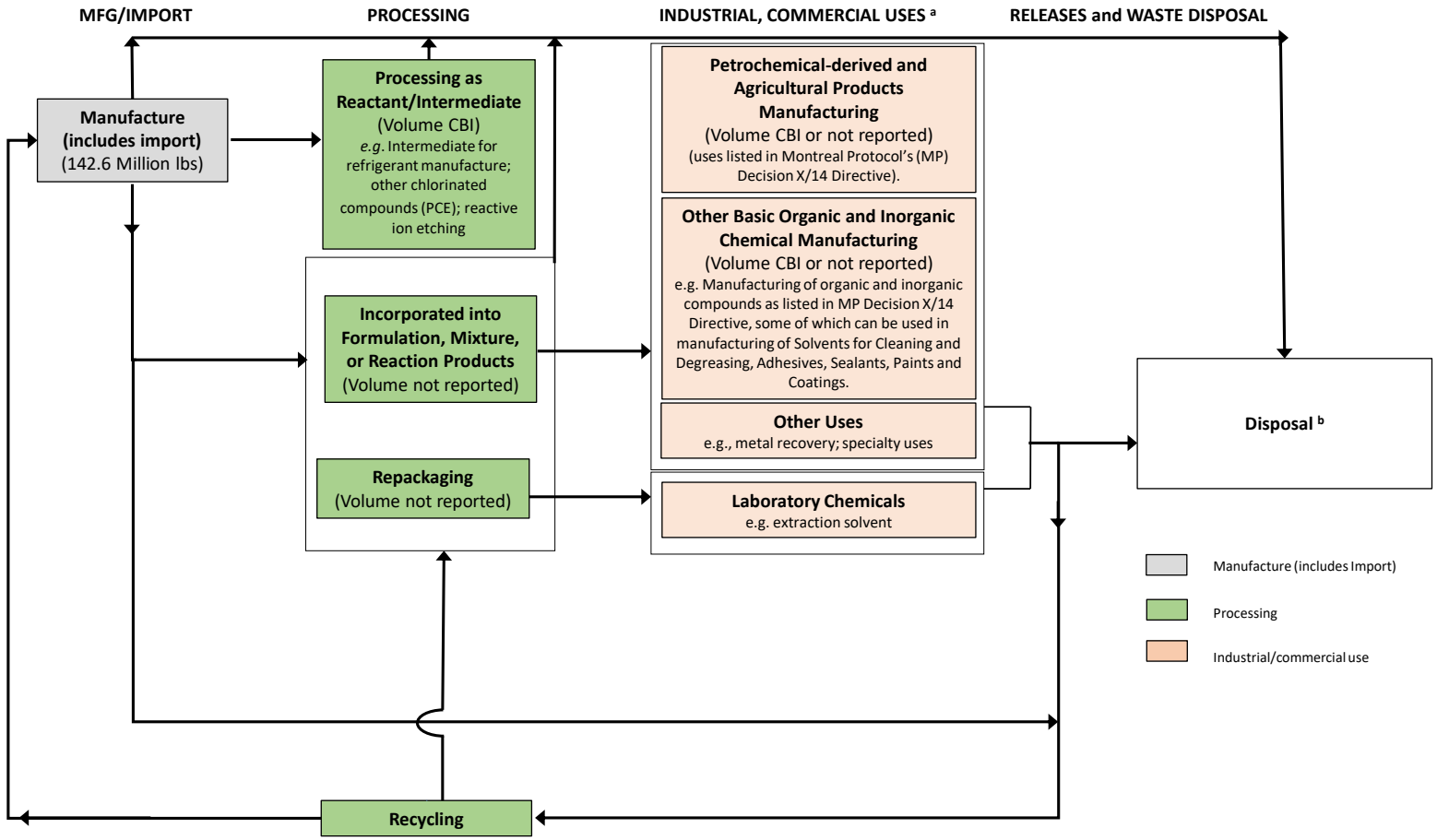

Figure 1-1. Carbon Tetrachloride Life Cycle Diagram

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/commercial), distribution and disposal. The production volumes shown are for reporting year 2015 from the 2016 CDR reporting period (U.S. EPA, 2016d). 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] See Table 1-4 for additional uses not mentioned specifically in this diagram.

[b] Disposal refers to 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

Table 1-4. 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, 2016d)
	Import	Import	(U.S. EPA, 2016d)
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, 2016d)
		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, 2016d)
		Reactive ion etching (*i.e.*, semiconductor manufacturing)	Use document, EPA-HQ-OPPT-2016-0733-0003; Public comment, EPA-HQ-OPPT-2016-0733-0063
	Incorporation into Formulation, Mixture or Reaction Products	Petrochemicals-derived manufacturing; Agricultural products manufacturing; Other basic organic and inorganic chemical manufacturing.	(U.S. EPA, 2016d); Use document, EPA-HQ-OPPT-2016-0733-0003; (U.S. EPA, 2016b); (UNEP/Ozone Secretariat, 1998); Public comment, EPA-HQ-OPPT-2016-0733-0064
	Processing - repackaging	Laboratory Chemicals	(U.S. EPA, 2016b)
	Recycling	Recycling	(U.S. EPA, 2016d), (U.S. EPA, 2016b)
Distribution in commerce	Distribution	Distribution in commerce	(U.S. EPA, 2016b); Use document, EPA-HQ-OPPT-2016-0733-0003.

Life Cycle Stage	Category[a]	Subcategory[b]	References
Industrial/commercial use	Petrochemicals-derived Products Manufacturing	Processing aid	Use document, EPA-HQ-OPPT-2016-0733-0003; (U.S. EPA, 2016d); (UNEP/Ozone Secretariat, 1998)
		Additive	Use document, EPA-HQ-OPPT-2016-0733-0003; Public comment, EPA-HQ-OPPT-2016-0733-0012; (U.S. EPA, 2016b); (UNEP/Ozone Secretariat, 1998)
	Agricultural Products Manufacturing	Processing aid	(U.S. EPA, 2016d), 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)
	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)

Life Cycle Stage	Category[a]	Subcategory[b]	References
		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)
	Other Uses (*i.e.*, Specialty Uses)	Processing aid (*i.e.*, metal recovery, DoD uses).	Use document, EPA-HQ-OPPT-2016-0733-0003
	Laboratory Chemicals	Laboratory chemical	Use document, EPA-HQ-OPPT-2016-0733-0003; (U.S. EPA, 2016d), Public comments, EPA-HQ-OPPT-2016-0733-0007; EPA-HQ-OPPT-2016-0733-0013 and EPA-HQ-OPPT-2016-0733-0063

Life Cycle Stage	Category[a]	Subcategory[b]	References
Disposal	Disposal[c]	Industrial pre-treatment	(U.S. EPA, 2017h)
		Industrial wastewater treatment	(U.S. EPA, 2017h)
		Publicly owned treatment works (POTW)	(U.S. EPA, 2017h)
		Underground injection	(U.S. EPA, 2017h)
		Municipal landfill	(U.S. EPA, 2017h)
		Hazardous landfill	(U.S. EPA, 2017h)
		Other land disposal	(U.S. EPA, 2017h)
		Municipal waste incinerator	(U.S. EPA, 2017h)
		Hazardous waste incinerator	(U.S. EPA, 2017h)
		Off-site waste transfer	(U.S. EPA, 2017h)

[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/commercial settings.
[b]These subcategories reflect more specific uses of carbon tetrachloride.
[c]Disposal subcategories were evaluated for workplace exposures.

1.4.2 Subcategories Determined Not To Be Conditions of Use Or Otherwise Excluded

1.4.2.1 Specialty Uses – Aerospace Industry

EPA conducted public outreach and literature searches to collect information about carbon tetrachloride conditions of use and reviewed reasonably available information obtained or possessed by EPA concerning activities associated with carbon tetrachloride. As a result of that review, EPA has determined certain uses of carbon tetrachloride that were previously thought during problem formulation to be a condition of use are no longer used in current practices and are not reasonably foreseen to be resumed. Consequently, EPA did not evaluate these activities or associated hazards or exposures in the risk evaluation for carbon tetrachloride. Specialty uses of carbon tetrachloride, specifically adhesives and cleaning operations, were identified in the aerospace industry based on information provided by the Aerospace Industries Association (AIA) (Riegle, 2017). However, upon reaching out to AIA for specific use details, AIA replied with the following statement:

After additional investigation, usage identified by AIA companies were based upon products that have been discontinued. There appear to be products that contain trace amounts of carbon tetrachloride (<1%) that might be a reaction by-product, contaminant or imperfect distillation of perchloroethylene. Therefore, carbon tetrachloride is no longer an AIA concern. (AIA, 2019)

EPA did not evaluate the use of carbon tetrachloride in cleaning operations (vapor degreasing, etc.) or use as an adhesive in the aerospace industry as there are no reasonably available data supporting distinct specialty uses of carbon tetrachloride in the aerospace industry. Rather, EPA determined that any use in the aerospace industry would fall within the more generalized category of industrial/commercial uses of commercially available adhesives/sealants and cleaning/degreasing solvent products that may contain trace amounts of carbon tetrachloride. As explained in Section 1.4.2.3, EPA previously excluded those uses from the scope of the risk evaluation during problem formulation because they would present only de minimis exposures or otherwise insignificant risks. Additionally, there are current regulatory actions (under the Montreal Protocol and CAA Title VI) that prohibit the direct use of carbon tetrachloride 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), except as a laboratory chemical (Problem Formulation Section 2.2.2.1) (U.S. EPA, 2018c). Therefore, EPA concluded that there are no known, intended, or reasonably foreseen specialty uses in the aerospace industry, and that any commercially available products used in aerospace or other industries would present only de minimis exposures or otherwise insignificant risks and did not warrant inclusion in the risk evaluation (see further discussion of the exclusion of such products in Section 1.4.2.3).

1.4.2.2 Manufacturing of Pharmaceuticals

While use of carbon tetrachloride as a process solvent in the manufacture of pharmaceuticals was included in the problem formulation, upon further analysis, EPA has determined that this use falls outside TSCA's definition of "chemical substance." Under TSCA Section 3(2)(B)(vi), the definition of "chemical substance" does not include any food, food additive, drug, cosmetic, or device (as such terms are defined in section 201 of the Federal Food, Drug, and Cosmetic Act) when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device. EPA has concluded that carbon tetrachloride use as a process solvent during pharmaceutical manufacturing falls within the afore-mentioned definitional exclusion and is not a "chemical substance" under TSCA.[5]

1.4.2.3 Exclusions During Problem Formulation

TSCA Section 3(2) defines "*chemical substance*" and specifies that the term does not include any mixture; any pesticide when manufactured, processed, or distributed in commerce for use as a pesticide; tobacco or tobacco product, source material, special nuclear material, or byproduct material, any article the sale of which is subject to the tax imposed by the Internal Revenue Code § 4181 of 1986 and any component of such an article, or any food, food additive, drug, cosmetic, or device when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device. Therefore, any conclusions of unreasonable risk do not extend to substances that are not defined as chemical substances under TSCA Section 3(2).

[5] Furthermore, EPA does not have any evidence that carbon tetrachloride is still being used in the manufacture of ibuprofen or any other pharmaceuticals or that such use is reasonably foreseen to resume. The Science History Institute published an article titled, *The Greening of Chemistry*, which explains that ibuprofen was once manufactured with the use of multiple solvents, one of which was carbon tetrachloride. It continues to explain, "…in the early 1990s ibuprofen got a makeover. Using catalysts rather than excess reagents to drive the reactions, chemists halved the number of stages in the ibuprofen manufacturing process and eliminated carbon tetrachloride, a toxic solvent, from the process" (Hoag, 2016). Though advertisements posted in the internet by the distributors of carbon tetrachloride cited pharmaceutical manufacturing as one of the uses of the chemical substance, the information does not by itself indicate that it is being used for this purpose.

EPA has excluded from the scope of this risk evaluation conditions of use associated with carbon tetrachloride generated as a byproduct. In exercising its discretion under TSCA Section 6(b)(4)(D) to identify the conditions of use that EPA expects to consider in a risk evaluation, EPA believes it is important for the Agency to have the discretion to make reasonable, technically sound scoping decisions. EPA anticipates that any risks presented by the presence of carbon tetrachloride as a byproduct formed during the manufacturing, processing or use of the parent compound will be considered in the scope of the risk evaluation of the parent compound. For example, EPA plans to assess risks of carbon tetrachloride generated as a byproduct during the manufacture of 1,2-dichloroethane in the TSCA risk evaluation for 1,2-dichloroethane (see Final Scope of the Risk Evaluation for 1,2-Dichloroethane, EPA-HQ-OPPT-2018-0427-0048).

In the problem formulation, EPA removed from the risk evaluation certain activities and conditions of use that EPA concluded do not warrant inclusion in the risk evaluation. Consequently, EPA did not evaluate these activities and conditions of use or associated hazards or exposures in the risk evaluation for carbon tetrachloride.

First, for one activity that was listed as a "condition of use" in the scope document, incorporation of carbon tetrachloride into an article, EPA had insufficient information following the further investigations during problem formulation to find that it is a circumstance under which the chemical is actually "intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of." (U.S. EPA, 2018c) Accordingly, EPA does not consider incorporation into an article to be a condition of use of carbon tetrachloride.

Second, there are conditions of use for which EPA had sufficient basis to conclude during problem formulation would present only de minimis exposures or otherwise insignificant risks and that did not warrant inclusion in the risk evaluation. These conditions of use consist of industrial/commercial/consumer uses of carbon tetrachloride in commercially available aerosol and non-aerosol adhesives/sealants, paints/coatings, and cleaning/degreasing solvent products.

Based on information obtained by EPA, there are current regulatory actions that prohibit the direct use of carbon tetrachloride as a 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), except 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). As a result of the CPSC ban, carbon tetrachloride is not identified in either the Washington State Product Testing Data list, the State of Vermont list of Chemicals in Children’s Products or the State of California consumer product database (Safer Consumer Products Information Management System) and no consumer uses are listed in the CDR (Vermont Department of Health, 2020; State of Washington, 2019; State of California, 2013).

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. Furthermore, background concentrations to carbon tetrachloride are assessed under the EPA National Air Toxics Assessment (NATA).

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 as a manufacturing residue in the 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. Additional resources are available in *Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: Carbon Tetrachloride* (see Table 1 of Support document for Docket EPA-HQ-OPPT-2016-0733).

Based on the reasonably available 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 to or otherwise insignificant risk from manufacturing residues of carbon tetrachloride in chlorinated compounds, EPA determined during problem formulation that these conditions of use did not warrant evaluation, and excluded these conditions of use from the scope of the risk evaluation in the exercise of EPA's discretionary authority under TSCA Section 6(b)(4)(D). Accordingly, EPA has not evaluated these conditions of use or associated hazards or exposures in the risk evaluation for carbon tetrachloride.

1.4.3 Exposure Pathways and Risks Addressed by Other EPA-Administered Statutes

In its TSCA Section 6(b) risk evaluations, EPA is coordinating action on certain exposure pathways and risks falling under the jurisdiction of other EPA-administered statutes or regulatory programs. More specifically, EPA is exercising its TSCA authorities to tailor the scope of its risk evaluations, rather than focusing on environmental exposure pathways addressed under other EPA-administered statutes or regulatory programs or risks that could be eliminated or reduced to

a sufficient extent by actions taken under other EPA-administered laws. EPA considers this approach to be a reasonable exercise of the Agency's TSCA authorities, which include:

- TSCA Section 6(b)(4)(D): "The Administrator shall, not later than 6 months after the initiation of a risk evaluation, publish the scope of the risk evaluation to be conducted, including the hazards, exposures, conditions of use, and the potentially exposed or susceptible subpopulations the Administrator expects to consider…"
- TSCA Section 9(b)(1): "The Administrator shall coordinate actions taken under this chapter with actions taken under other Federal laws administered in whole or in part by the Administrator. If the Administrator determines that a risk to health or the environment associated with a chemical substance or mixture could be eliminated or reduced to a sufficient extent by actions taken under the authorities contained in such other Federal laws, the Administrator shall use such authorities to protect against such risk unless the Administrator determines, in the Administrator's discretion, that it is in the public interest to protect against such risk by actions taken under this chapter."
- TSCA Section 9(e): "…[I]f the Administrator obtains information related to exposures or releases of a chemical substance or mixture that may be prevented or reduced under another Federal law, including a law not administered by the Administrator, the Administrator shall make such information available to the relevant Federal agency or office of the Environmental Protection Agency."
- TSCA Section 2(c): "It is the intent of Congress that the Administrator shall carry out this chapter in a reasonable and prudent manner, and that the Administrator shall consider the environmental, economic, and social impact of any action the Administrator takes or proposes as provided under this chapter."
- TSCA Section 18(d)(1): "Nothing in this chapter, nor any amendment made by the Frank R. Lautenberg Chemical Safety for the 21st Century Act, nor any rule, standard of performance, risk evaluation, or scientific assessment implemented pursuant to this chapter, shall affect the right of a State or a political subdivision of a State to adopt or enforce any rule, standard of performance, risk evaluation, scientific assessment, or any other protection for public health or the environment that— (i) is adopted or authorized under the authority of any other Federal law or adopted to satisfy or obtain authorization or approval under any other Federal law…"

<u>TSCA authorities supporting tailored risk evaluations and intra-agency referrals</u>

TSCA Section 6(b)(4)(D)

TSCA Section 6(b)(4)(D) requires EPA, in developing the scope of a risk evaluation, to identify the hazards, exposures, conditions of use, and potentially exposed or susceptible subpopulations the Agency "expects to consider" in a risk evaluation. This language suggests that EPA is not required to consider all conditions of use, hazards, or exposure pathways in risk evaluations.

In the problem formulation documents for many of the first 10 chemicals undergoing risk evaluation, EPA applied this authority and rationale to certain exposure pathways, explaining that "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." This approach is informed by the legislative history of the amended TSCA, which supports the Agency's exercise of discretion to focus the risk evaluation on areas that raise the greatest potential for risk. See June 7, 2016 Cong. Rec., S3519-S3520. Consistent with the approach articulated in the problem formulation documents, and as described in more detail below, EPA is exercising its authority under TSCA to tailor the scope of exposures evaluated in TSCA risk evaluations, rather than focusing on environmental exposure pathways addressed under other EPA-administered, media-specific statutes and regulatory programs.

TSCA Section 9(b)(1)

In addition to TSCA Section 6(b)(4)(D), the Agency also has discretionary authority under the first sentence of TSCA Section 9(b)(1) to "coordinate actions taken under [TSCA] with actions taken under other Federal laws administered in whole or in part by the Administrator." This broad, freestanding authority provides for intra-agency coordination and cooperation on a range of "actions." In EPA's view, the phrase "actions taken under [TSCA]" in the first sentence of Section 9(b)(1) is reasonably read to encompass more than just risk management actions, and to include actions taken during risk evaluation as well. More specifically, the authority to coordinate intra-agency actions exists regardless of whether the Administrator has first made a definitive finding of risk, formally determined that such risk could be eliminated or reduced to a sufficient extent by actions taken under authorities in other EPA-administered Federal laws, and/or made any associated finding as to whether it is in the public interest to protect against such risk by actions taken under TSCA. TSCA Section 9(b)(1) therefore provides EPA authority to coordinate actions with other EPA offices without ever making a risk finding or following an identification of risk. This includes coordination on tailoring the scope of TSCA risk evaluations to focus on areas of greatest concern rather than exposure pathways addressed by other EPA-administered statutes and regulatory programs, which does not involve a risk determination or public interest finding under TSCA Section 9(b)(2).

In a narrower application of the broad authority provided by the first sentence of TSCA Section 9(b)(1), the remaining provisions of Section 9(b)(1) provide EPA authority to identify risks and refer certain of those risks for action by other EPA offices. Under the second sentence of Section 9(b)(1), "[i]f the Administrator determines that a risk to health or the environment associated with a chemical substance or mixture could be eliminated or reduced to a sufficient extent by actions taken under the authorities contained in such other Federal laws, the Administrator shall use such authorities to protect against such risk unless the Administrator determines, in the Administrator's discretion, that it is in the public interest to protect against such risk by actions taken under [TSCA]." Coordination of intra-agency action on risks under TSCA Section 9(b)(1) therefore entails both an identification of risk, and a referral of any risk that could be eliminated or reduced to a sufficient extent under other EPA-administered laws to the EPA office(s) responsible for implementing those laws (absent a finding that it is in the public interest to protect against the risk by actions taken under TSCA).

Risk may be identified by OPPT or another EPA office, and the form of the identification may vary. For instance, OPPT may find that one or more conditions of use for a chemical substance present(s) a risk to human or ecological receptors through specific exposure routes and/or

pathways. This could involve a quantitative or qualitative assessment of risk based on reasonably available information (which might include, *e.g.*, findings or statements by other EPA offices or other federal agencies). Alternatively, risk could be identified by another EPA office. For example, another EPA office administering non-TSCA authorities may have sufficient monitoring or modeling data to indicate that a particular condition of use presents risk to certain human or ecological receptors, based on expected hazards and exposures. This risk finding could be informed by information made available to the relevant office under TSCA Section 9(e), which supports cooperative actions through coordinated information-sharing.

Following an identification of risk, EPA would determine if that risk could be eliminated or reduced to a sufficient extent by actions taken under authorities in other EPA-administered laws. If so, TSCA requires EPA to "use such authorities to protect against such risk," unless EPA determines that it is in the public interest to protect against that risk by actions taken under TSCA. In some instances, EPA may find that a risk could be sufficiently reduced or eliminated by future action taken under non-TSCA authority. This might include, *e.g.*, action taken under the authority of the Safe Drinking Water Act to address risk to the general population from a chemical substance in drinking water, particularly if the Office of Water has taken preliminary steps such as listing the subject chemical substance on the Contaminant Candidate List. This sort of risk finding and referral could occur during the risk evaluation process, thereby enabling EPA to use more a relevant and appropriate authority administered by another EPA office to protect against hazards or exposures to affected receptors.

Legislative history on TSCA Section 9(b)(1) supports both broad coordination on current intra-agency actions, and narrower coordination when risk is identified and referred to another EPA office for action. A Conference Report from the time of TSCA's passage explained that Section 9 is intended "to assure that overlapping or duplicative regulation is avoided while attempting to provide for the greatest possible measure of protection to health and the environment." S. Rep. No. 94-1302 at 84. See also H. Rep. No. 114-176 at 28 (stating that the 2016 TSCA amendments "reinforce TSCA's original purpose of filling gaps in Federal law," and citing new language in Section 9(b)(2) intended "to focus the Administrator's exercise of discretion regarding which statute to apply and to encourage decisions that avoid confusion, complication, and duplication"). Exercising TSCA Section 9(b)(1) authority to coordinate on tailoring TSCA risk evaluations is consistent with this expression of Congressional intent.

Legislative history also supports a reading of Section 9(b)(1) under which EPA coordinates intra-agency action, including information-sharing under TSCA Section 9(e), and the appropriately positioned EPA office is responsible for the identification of risk and actions to protect against such risks. See, *e.g.*, Senate Report 114-67, 2016 Cong. Rec. S3522 (under TSCA Section 9, "if the Administrator finds that disposal of a chemical substance may pose risks that could be prevented or reduced under the Solid Waste Disposal Act, the Administrator should ensure that the relevant office of the EPA receives that information"); H. Rep. No. 114-176 at 28, 2016 Cong. Rec. S3522 (under Section 9, "if the Administrator determines that a risk to health or the environment associated with disposal of a chemical substance could be eliminated or reduced to a sufficient extent under the Solid Waste Disposal Act, the Administrator should use those authorities to protect against the risk"). Legislative history on Section 9(b)(1) therefore supports coordination with and referral of action to other EPA offices, especially when statutes and

associated regulatory programs administered by those offices could address exposure pathways or risks associated with conditions of use, hazards, and/or exposure pathways that may otherwise be within the scope of TSCA risk evaluations.

TSCA Sections 2(c) & 18(d)(1)

Finally, TSCA Sections 2(c) and 18(d) support coordinated action on exposure pathways and risks addressed by other EPA-administered statutes and regulatory programs. Section 2(c) directs EPA to carry out TSCA in a "reasonable and prudent manner" and to consider "the environmental, economic, and social impact" of its actions under TSCA. Legislative history from around the time of TSCA's passage indicates that Congress intended EPA to consider the context and take into account the impacts of each action under TSCA. S. Rep. No. 94-698 at 14 ("the intent of Congress as stated in this subsection should guide each action the Administrator takes under other sections of the bill").

Section 18(d)(1) specifies that state actions adopted or authorized under any Federal law are not preempted by an order of no unreasonable risk issued pursuant to TSCA Section 6(i)(1) or a rule to address unreasonable risk issued under TSCA Section 6(a). Thus, even if a risk evaluation were to address exposures or risks that are otherwise addressed by other federal laws and, for example, implemented by states, the state laws implementing those federal requirements would not be preempted. In such a case, both the other federal and state laws, as well as any TSCA Section 6(i)(1) order or TSCA Section 6(a) rule, would apply to the same issue area. See also TSCA Section 18(d)(1)(A)(iii). In legislative history on amended TSCA pertaining to Section 18(d), Congress opined that "[t]his approach is appropriate for the considerable body of law regulating chemical releases to the environment, such as air and water quality, where the states have traditionally had a significant regulatory role and often have a uniquely local concern." Sen. Rep. 114-67 at 26.

EPA's careful consideration of whether other EPA-administered authorities are available and more appropriate for addressing certain exposures and risks is consistent with Congress' intent to maintain existing federal requirements and the state actions adopted to locally and more specifically implement those federal requirements, and to carry out TSCA in a reasonable and prudent manner. EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations in a manner reflective of expertise and experience exercised by other EPA and State offices to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. This approach furthers Congressional direction and EPA aims to efficiently use Agency resources, avoid duplicating efforts taken pursuant to other Agency and State programs, and meet the statutory deadline for completing risk evaluations.

<u>EPA-administered statutes and regulatory programs that address specific exposure pathways and/or risks</u>

During the course of the risk evaluation process for carbon tetrachloride, OPPT worked closely with the offices within EPA that administer and implement regulatory programs under the Clean Air Act (CAA), the Safe Drinking Water Act (SDWA), the Clean Water Act (CWA) and the

Resource Conservation and Recovery Act (RCRA). Through intra-agency coordination, EPA determined that specific exposure pathways are well-regulated by the EPA statutes and regulations described in the following paragraphs.

Ambient Air Pathway

The CAA contains a list of hazardous air pollutants (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 hazardous air pollutant.

Carbon tetrachloride is a HAP. See 42 U.S.C. 7412. 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. See 40 CFR part 63; Appendix A. Because stationary source releases of carbon tetrachloride to ambient air are addressed under the CAA, EPA is not evaluating emissions to ambient air from commercial and industrial stationary sources or associated inhalation exposure of the general population or terrestrial species in this TSCA risk 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 Safe Drinking Water Act (SDWA). Under SDWA, EPA must also review existing national primary drinking water regulations every 6 years, and subsequently revise them as appropriate.

EPA has promulgated National Primary Drinking Water Regulations (NPDWRs) for carbon tetrachloride under SDWA. See 40 CFR part 141; Appendix A. EPA has set an enforceable Maximum Contaminant Level (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. Public water systems are required to monitor for the regulated chemical based on a standardized monitoring schedule to ensure compliance with the maximum contaminant level (MCL).

Hence, because the drinking water exposure pathway for carbon tetrachloride is currently addressed in the NPDWR, EPA is not evaluating exposures to the general population from the drinking water exposure pathway in the risk evaluation for carbon tetrachloride under TSCA.

Ambient Water Pathway

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. A subset of these chemicals is identified as "priority pollutants" (103 human health and 27 aquatic life). The CWA requires states adopt numeric criteria for priority pollutants for which EPA has published recommended criteria under Section 304(a), the discharge or presence of which in the affected waters could reasonably be expected to interfere with designated uses adopted by the state. When states adopt criteria that EPA approves as part of state's 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. Once states adopt criteria as water quality standards, the CWA requires that National Pollutant Discharge Elimination System (NPDES) discharge permits include effluent limits as stringent as necessary to meet standards. CWA Section 301(b)(1)(C). 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 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 criteria.[6] See, *e.g.*, 40 CFR part 423, Appendix A; 40 CFR 131.11(b)(1); 40 CFR 122.44(d)(1)(vi). As such, EPA is not evaluating exposures to the general population from the surface water exposure pathway in the risk evaluation under TSCA.

Land application of biosolids and general population exposure

As wastewater undergoes treatment, some wastewater treatment facilities such as publicly-owned treatment works (POTWs) use the remaining sludge as biosolids for land application. These biosolids could have residual carbon tetrachloride. Carbon tetrachloride in biosolids that are land applied could be transported via runoff from rainwater to surface waters. However, surface waters drawn for drinking water are treated, tested and under the Safe Drinking Water Act, regulated via NPDWRs. EPA promulgates NPDWRs under SDWA when the Agency concludes a contaminant may have adverse health effects, occurs or is substantially likely to occur in public water systems at a level of concern and that regulation, in the sole judgement of the Administrator, presents a meaningful opportunity for health risk reduction. For each contaminant with NPDWRs, EPA sets an enforceable MCL as close as feasible to a health based, non-enforceable MCLG or establishes a treatment technique. The MCL for any residual levels of carbon tetrachloride that could result in exposure to the general population is 0.005mg/L. Residual concentrations of carbon tetrachloride in surface waters not used for drinking water are covered by the CWA Ambient Water Quality Criteria for human health consumption of water and organisms (0.4 µg/L). CWA Section 304(a)(1). States and tribal governments may adopt the EPA Clean Water Act Section 304(a) recommended criteria or may adopt their own criteria that differ from EPA's recommendations, subject to EPA's approval, using scientifically defensible methods. States are required to adopt and implement EPA-approved criteria as part of their regulatory water quality standards, and compliance with these criteria is considered by states in permits and water quality assessment decisions. Thus, general population exposure via the biosolid pathway is not evaluated in the final risk evaluation.

[6] See https://www.regulations.gov/document?D=EPA-HQ-OW-2014-0135-0182.

Onsite Releases to Land Pathway

The Comprehensive Environmental Response, Compensation, and Liability Act – otherwise known as CERCLA or Superfund – provides EPA with broad authority to address uncontrolled or abandoned hazardous-waste sites as well as accidents, spills, and other releases of hazardous substances, pollutants and contaminants into the environment. Through CERCLA, EPA is provided authority to conduct a response action and seek reimbursement of cleanup costs from potentially responsible parties, or in certain circumstances, order a potentially responsible party to conduct a cleanup.

CERCLA Section 101(14) defines “hazardous substance” by referencing other environmental statutes, including toxic pollutants listed under CWA Section 307(a); hazardous substances designated pursuant to CWA Section 311(b)(2)(A); hazardous air pollutants listed under CAA Section 112; imminently hazardous substances with respect to which EPA has taken action pursuant to TSCA Section 7; and hazardous wastes having characteristics identified under or listed pursuant to RCRA Section 3001. See 40 CFR 302.4. CERCLA Section 102(a) also 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 knowledge of a release of a hazardous substance above the reportable quantity threshold.

Carbon tetrachloride is a hazardous substance under CERCLA. Releases of carbon tetrachloride in excess of 10 pounds within a 24-hour period must be reported (40 CFR 302.4, 302.6). The scope of this EPA TSCA risk evaluation does not include on-site releases to the environment of carbon tetrachloride at Superfund sites and subsequent exposure of the general population or non-human species.

Disposal Pathways

Carbon tetrachloride is included on the list of hazardous wastes pursuant to RCRA Section 3001 (40 CFR Sections 261.31, 261.33) as a listed waste on the F and U lists (F001 and U211). 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 SDWA).

EPA is not evaluating on-site releases to land from RCRA Subtitle C hazardous waste landfills or exposures of the general population or terrestrial species from such releases in the TSCA evaluation. 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, including carbon tetrachloride (listed as a hazardous waste in 40 CFR 261.31, 261.33), must also meet RCRA waste treatment standards before disposal. See 40 CFR part 264; Appendix A.

EPA is not evaluating on-site releases to land from RCRA Subtitle D municipal solid waste (MSW) landfills or exposures of the general population or terrestrial species from such releases in the TSCA evaluation. While permitted and managed by the individual states, municipal solid waste landfills are required by federal regulations to implement some of the same requirements as Subtitle C landfills. MSW landfills generally must have a liner system with leachate collection and conduct groundwater monitoring and corrective action when releases are detected. MSW landfills are also subject to closure and post-closure care requirements and must have financial assurance for funding of any needed corrective actions. MSW landfills have also been designed to allow for the small amounts of hazardous waste generated by households and very small quantity waste generators (less than 220 lbs per month). Bulk liquids, such as free solvent, may not be disposed of at MSW landfills. See 40 CFR part 258.

EPA is not evaluating on-site releases to land from industrial non-hazardous waste and construction/demolition waste landfills or associated exposures to the general population or terrestrial species in the carbon tetrachloride risk evaluation. Industrial non-hazardous and construction/demolition waste landfills are primarily regulated under authorized state regulatory programs. States must also implement limited federal regulatory requirements for siting, groundwater monitoring and corrective action and a prohibition on open dumping and disposal of bulk liquids. States may also establish additional requirements such as for liners, post-closure and financial assurance, but are not required to do so. See, *e.g.*, RCRA Section 3004(c), 4007; 40 CFR part 257.

EPA is not evaluating emissions to ambient air from municipal and industrial waste incineration and energy recovery units or associated exposures to the general population or terrestrial species in the risk evaluation, as these emissions are regulated under Section 129 of the Clean Air Act. CAA Section 129 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 would be subject to these regulations, as would carbon tetrachloride burned for energy recovery. See 40 CFR part 60.

EPA is not evaluating on-site releases to land that go to underground injection or associated exposures to the general population or terrestrial species in its risk evaluation. Environmental disposal of carbon tetrachloride injected into Class I hazardous well types are covered under the jurisdiction of RCRA and SDWA and disposal of carbon tetrachloride via underground injection is not likely to result in environmental and general population exposures. See 40 CFR part 144.

1.4.4 Conceptual Models

EPA considered the potential for hazards to human health and the environment resulting from exposure pathways outlined in the preliminary conceptual models of the carbon tetrachloride scope document (U.S. EPA, 2017e). The preliminary conceptual models were refined in the problem formulation document (U.S. EPA, 2018c). Based on review and evaluation of reasonably available data for carbon tetrachloride, EPA determined in the problem formulation that no further analysis of the environmental release pathways outlined in the conceptual models was necessary due to a qualitative assessment of the physical-chemical properties and fate of carbon tetrachloride in the environment, and a quantitative comparison of hazards and exposures for aquatic organisms.

Upon further evaluation of the reasonably available hazard data of carbon tetrachloride after the problem formulation phase, EPA decreased the environmental hazard chronic COC from 7 µg/L to 3 µg/L and conducted further analysis of the aquatic pathway to evaluate risk to aquatic organisms from carbon tetrachloride. EPA found in problem formulation that no further analysis was necessary for the soil and land-applied biosolid pathway leading to exposure to terrestrial and aquatic organisms. However, EPA qualitatively evaluated risk to terrestrial organisms from exposure to soil and biosolids in the final risk evaluation to consider the influence of carbon tetrachloride's physical chemical and fate properties in this exposure pathway.

The conceptual models for this risk evaluation are shown below in Figure 1-2 and Figure 1-3.

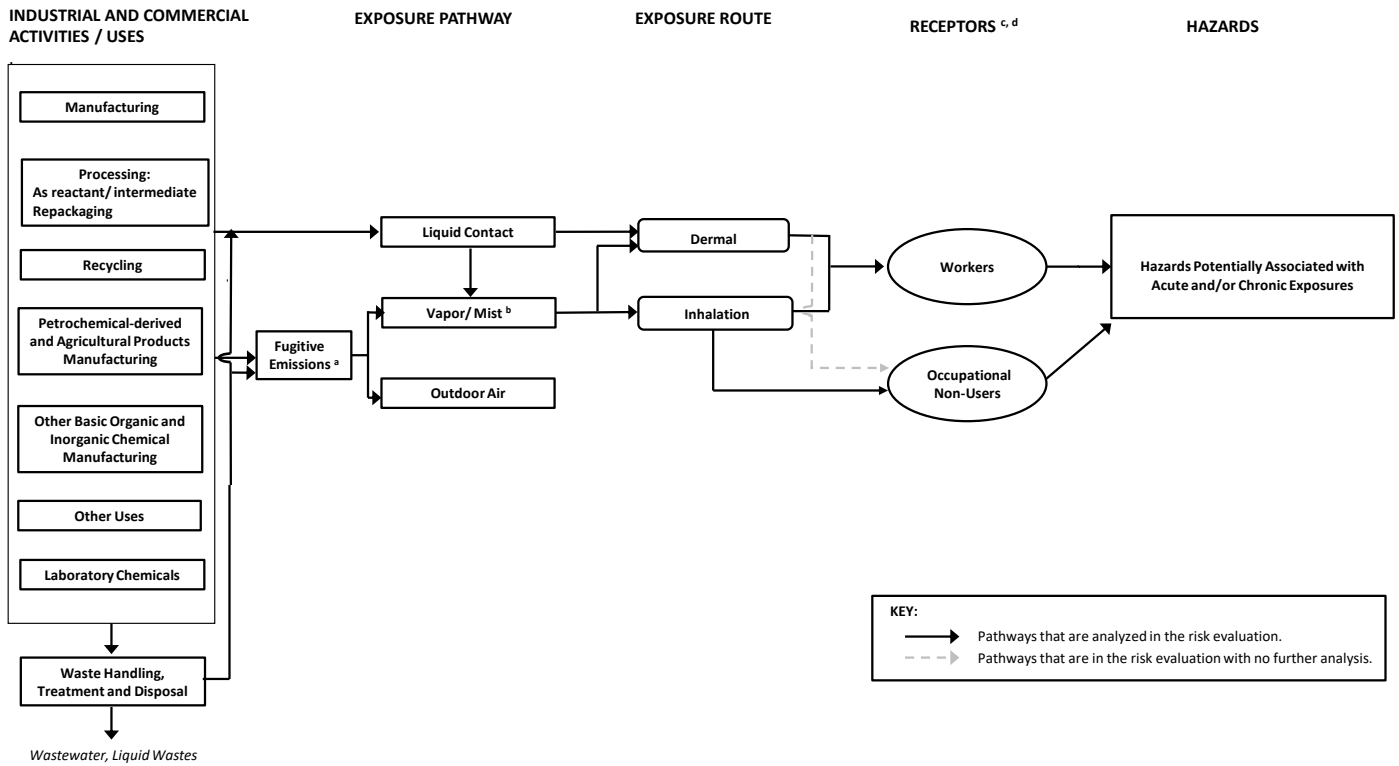

Figure 1-2. Carbon Tetrachloride Conceptual Model for Industrial/Commercial Activities and Uses: Potential Exposures and Hazards

The conceptual model presents the exposure pathways, exposure routes and hazards to human receptors from industrial/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/commercial facility from carbon tetrachloride ground water; exposure to mists is not expected for ONU.

[c]Receptors include PESS.

[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.

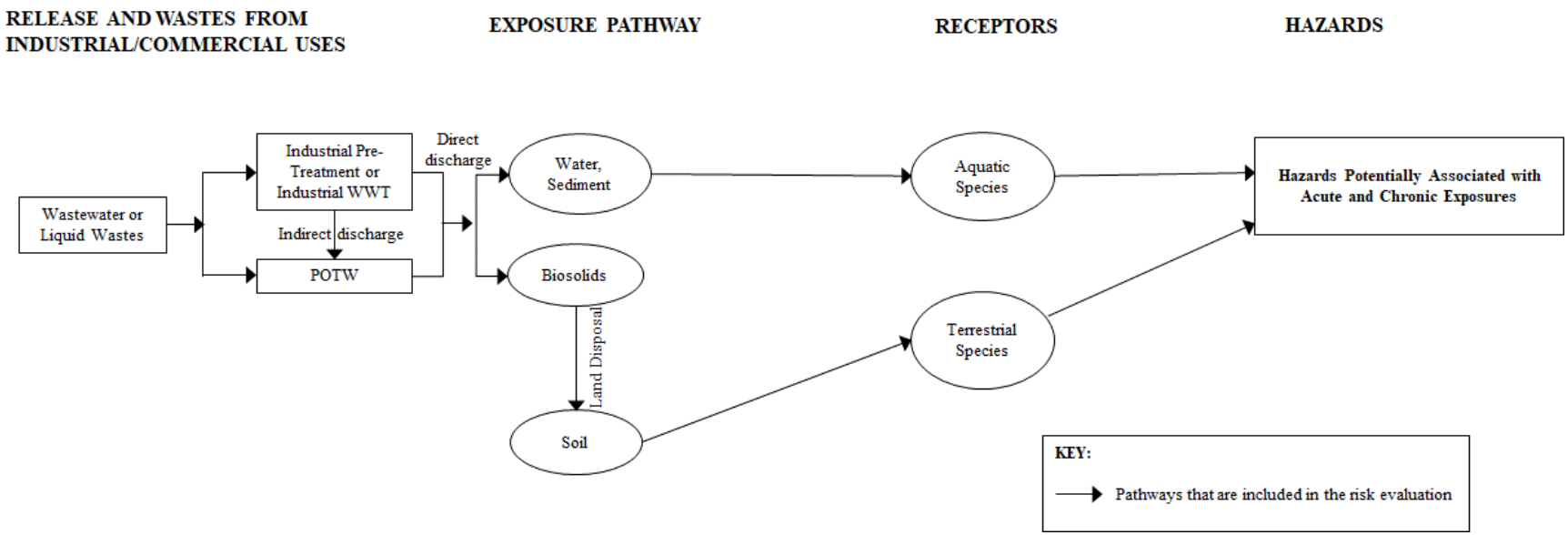

Figure 1-3. Carbon Tetrachloride Conceptual Model for Environmental Releases and Wastes: Potential Exposures and Hazards

The conceptual model presents the exposure pathways, exposure routes and hazards to environmental receptors from environmental water releases of carbon tetrachloride.

1.5 Systematic Review

TSCA requires EPA to use scientific information, technical procedures, measures, methods, protocols, methodologies and models consistent with the best available science and base decisions under TSCA Section 6 on the weight of scientific evidence. Within the TSCA risk evaluation context, the weight of the scientific evidence is defined as "*a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance*" (40 C.F.R. 702.33).

To meet the TSCA science standards, EPA was guided by the systematic review process described in the *Application of Systematic Review in TSCA Risk Evaluations* document (U.S. EPA, 2018a). The process complements the risk evaluation process in that the data collection, data evaluation and data integration stages of the systematic review process are used to develop the exposure and hazard assessments based on reasonably available information. EPA defines "reasonably available information" to mean information that EPA possesses, or can reasonably generate, obtain and synthesize for use in risk evaluations, considering the deadlines for completing the evaluation (40 C.F.R. 702.33).

EPA is implementing systematic review methods and approaches within the regulatory context of the amended TSCA. Although EPA will make an effort to adopt as many best practices as practicable from the systematic review community, EPA expects modifications to the process to ensure that the identification, screening, evaluation and integration of data and information can support timely regulatory decision making under the aggressive timelines of the statute.

1.5.1 Data and Information Collection

EPA planned and conducted a literature search based on key words related to the different discipline-specific evidence supporting the risk evaluation (*e.g.*, environmental fate and transport; engineering releases and occupational exposure; environmental exposure; and environmental and human health hazard). EPA then developed and applied inclusion and exclusion criteria during the title and abstract screening to identify information potentially relevant for the risk evaluation process. The literature and screening strategy as specifically applied to carbon tetrachloride is described in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a) and results of screening were published *in Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document* (U.S. EPA, 2017a).

For studies determined to be on-topic (or relevant) after title and abstract screening, EPA conducted a full text screening to further exclude references that were not relevant to the risk evaluation. Screening decisions were made based on eligibility criteria documented in the form of the populations, exposures, comparators, and outcomes (PECO) framework or a modified

framework.[7] Data sources that met the criteria were carried forward to the data evaluation stage. The inclusion and exclusion criteria for full text screening for carbon tetrachloride are available in Appendix F of the *Problem Formulation of the Risk Evaluation for Carbon Tetrachloride* (U.S. EPA, 2018c).

In addition to the comprehensive literature search and screening process described above, EPA leveraged the information presented in previous assessments,[8] when identifying relevant key and supporting data,[9] and information for developing the carbon tetrachloride risk evaluation. This is discussed in the *Strategy for Conducting Literature Searches for Carbon Tetrachloride: Supplemental Document to the TSCA Scope Document* (EPA-HQ-OPPT-2016-0733-0050). In general, many of the key and supporting data sources were identified in the comprehensive *Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document* (U.S. EPA, 2017a). However, there were instances that EPA missed relevant references that were not captured in the initial categorization of the on-topic references. EPA found additional relevant data and information using backward reference searching, which was a technique that will be included in future search strategies. This issue was discussed in Section 4 of the *Application of Systematic Review for TSCA Risk Evaluations* (U.S. EPA, 2018a). Other key and supporting references were identified through targeted supplemental searches to support the analytical approaches and methods in the carbon tetrachloride risk evaluation (*e.g.*, to locate specific information for exposure modeling) or to identify new data and information published after the date limits of the initial search.

EPA used previous chemical assessments to quickly identify relevant key and supporting information as a pragmatic approach to expedite the quality evaluation of the data sources, but many of those data sources were already captured in the comprehensive literature search as explained above. EPA also considered newer information not taken into account by previous chemical assessments as described in the *Strategy for Conducting Literature Searches for Carbon Tetrachloride: Supplemental Document to the TSCA Scope Document* (EPA-HQ-OPPT-2016-0733-0050). EPA then evaluated the confidence of this information rather than evaluating the confidence of all the underlying evidence ever published on carbon tetrachloride's fate and transport, environmental releases, and environmental and human exposure and hazard potential. Such a comprehensive evaluation of all the data and information ever published for a chemical substance would be extremely labor intensive and could not be achieved under the TSCA statutory deadlines for most chemical substances, especially those that have a data rich database. EPA also considered how this approach to data gathering would change the conclusions presented in the previous assessments.

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[7] A PESO statement was used during the full text screening of environmental fate and transport data sources. PESO stands for Pathways and Processes, Exposure, Setting or Scenario, and Outcomes. A RESO statement was used during the full text screening of the engineering and occupational exposure literature. RESO stands for Receptors, Exposure, Setting or Scenario, and Outcomes.

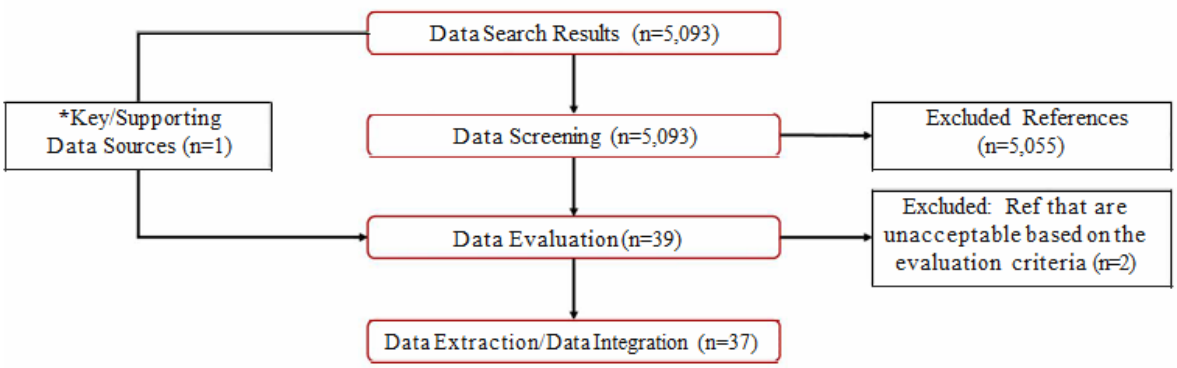
[8] Examples of existing assessments are EPA's chemical assessments (*e.g.*, previous work plan risk assessments, problem formulation documents), ATSDR's Toxicological Profiles, EPA's IRIS assessments and ECHA's dossiers. This is described in more detail in the *Strategy for Conducting Literature Searches for Carbon Tetrachloride: Supplemental File for the TSCA Scope Document* (EPA-HQ-OPPT-2016-0733-0050).

[9] Key and supporting data and information are those that support key analyses, arguments, and/or conclusions in the risk evaluation.

Using this pragmatic approach, EPA maximized the scientific and analytical efforts of other regulatory and non-regulatory agencies by accepting for the most part, the relevant scientific knowledge gathered and analyzed by others, except for influential information sources that may impact the weight of the scientific evidence underlying EPA's findings. This influential information (*i.e.*, key/supporting studies) came from a smaller pool of information sources subjected to the rigor of the TSCA systematic review process to ensure that the best available science is incorporated into the weight of the scientific evidence used to support the carbon tetrachloride risk evaluation.

The literature flow diagrams shown in Figure 1-4 through Figure 1-8 highlight the results obtained for each scientific discipline based on this approach. Each diagram provides the total number of references considered at the start of each systematic review stage (*i.e.*, data search, data screening, data evaluation, data extraction/data integration) and those excluded based on criteria guiding EPA's screening and data quality evaluation decisions.

EPA made the decision to bypass the data screening step for data sources that were highly relevant to the risk evaluation as described above. These data sources are depicted as "key/supporting data sources" in the literature flow diagrams. Note that the number of "key/supporting data sources" were excluded from the total count during the data screening stage and added, for the most part, to the data evaluation stage depending on the discipline-specific evidence. The exception was the engineering releases and occupational exposure data sources that were subject to a combined data extraction and evaluation step (Figure 1-5).



*These are key and supporting studies from existing assessments (e.g., EPA IRIS assessments, ATSDR assessments, ECHA dossiers) that were highly relevant for the TSCA risk evaluation. These studies bypassed the data screening step and moved directly to the data evaluation step. Data sources identified relevant to physical-chemical properties were not included in this literature flow diagram. The data quality evaluation of physical-chemical properties studies can be found in the supplemental document, *Data Quality Evaluation of Physical-Chemical Properties Studies (Docket: EPA-HQ- OPPT-2019-0499)* and the extracted data are presented in Table 1-1.

Figure 1-4. Key/Supporting Data Sources for Environmental Fate and Transport

The number of publications considered in each step of the systematic review of the carbon tetrachloride's fate and transport literature is summarized in Figure 1-4. Literature on the environmental fate and transport of carbon tetrachloride were gathered and screened as described in *Appendix C of the Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). Additional information regarding the literature search and screening strategy for carbon

tetrachloride is provided in EPA's *Strategy for Conducting Literature Searches for Carbon Tetrachloride*: *Supplemental File for the TSCA Scope Document* (EPA-HQ-OPPT-2016-0733-0050). The results of this screening are published in the *Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document* (U.S. EPA, 2017a).

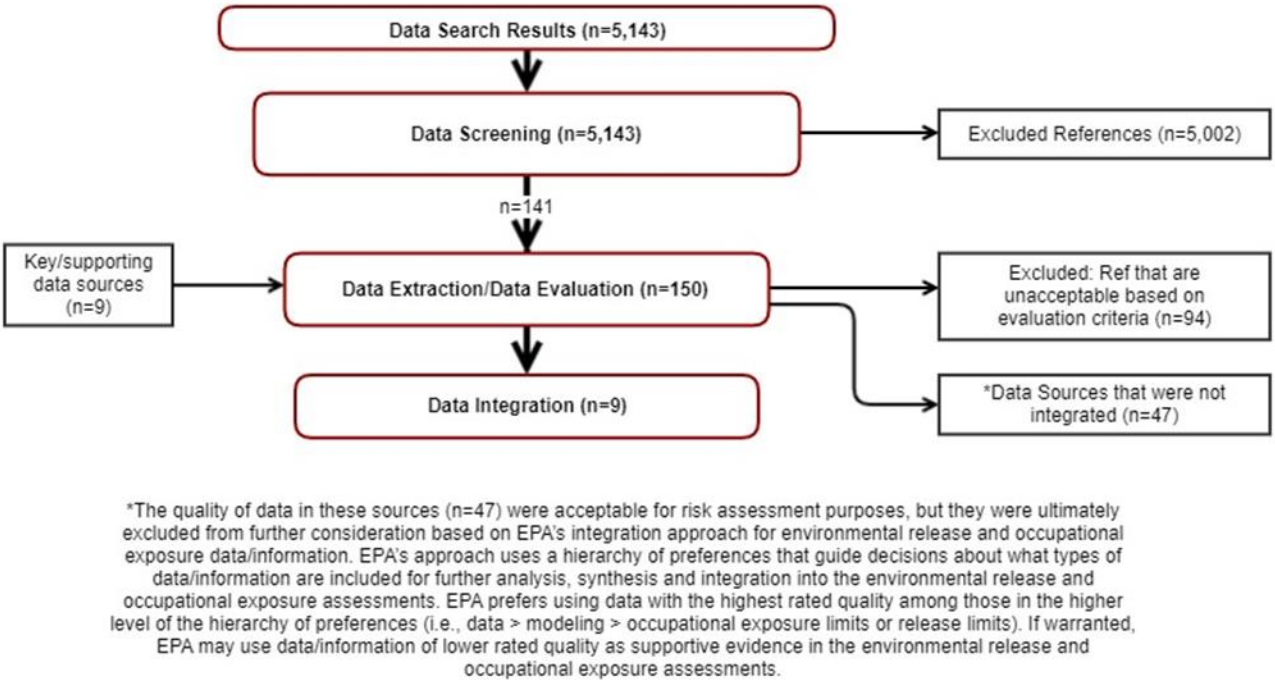


Figure 1-5. Key/Supporting Data Sources for Releases and Occupational Exposures

As shown in Figure 1-5, the literature search strategy for carbon tetrachloride's environmental releases and occupational exposures yielded 5,143 data sources. Of these data sources, 141 were determined to be relevant to the risk evaluation through the data screening process. These relevant data sources were entered to the data extraction/evaluation phase. After data extraction/evaluation, EPA identified several data gaps and performed a supplemental targeted search to address these gaps (*e.g.*, to locate information needed for exposure modeling). The supplemental search yielded nine relevant data sources that bypassed the data screening step and were evaluated and extracted in accordance with Appendix D of Data Quality Criteria for Occupational Exposure and Release Data of the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). Of the 150 sources from which data were extracted and evaluated, 94 sources only contained data that were rated as unacceptable based on flaws detected during the evaluation. Of the 56 sources forwarded for data integration, data from nine sources were integrated, and 47 sources contained data that were not integrated (*e.g.*, lower quality data that were not needed due to the existence of higher quality data, data for release media that were removed from scope after data collection).

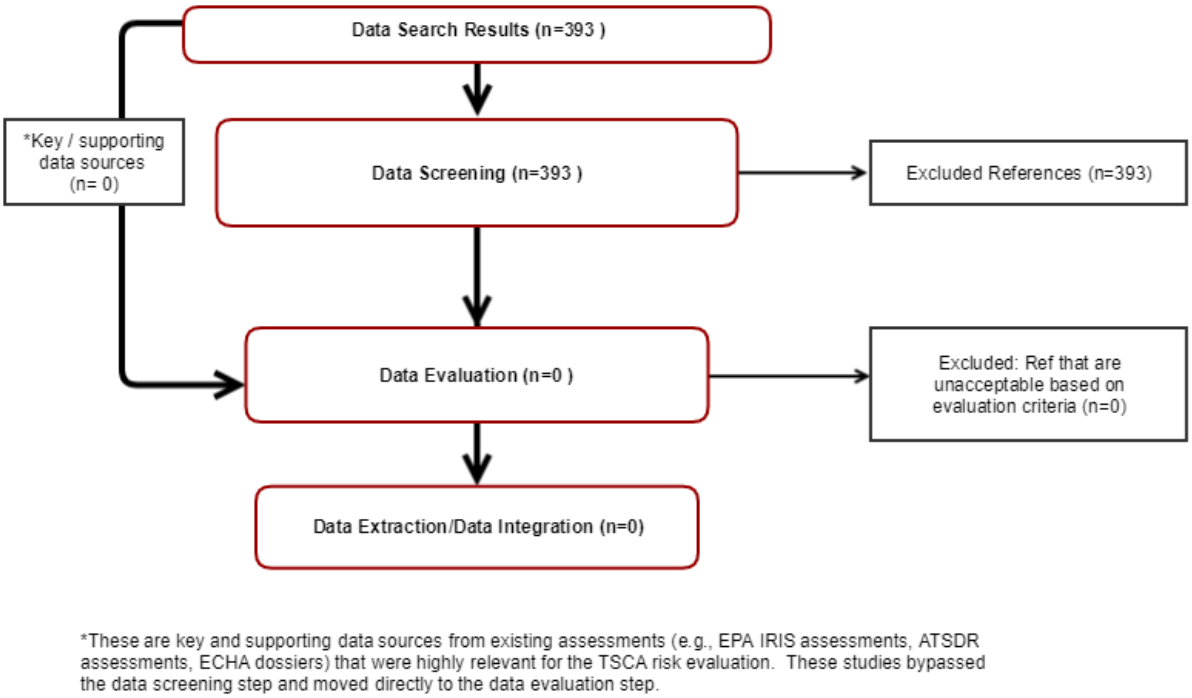


Figure 1-6. Key/Supporting Sources for Environmental Exposures

The number of data and information sources considered in each step of the systematic review of carbon tetrachloride literature on environmental exposure is summarized in Figure 1-6. The literature search results for environmental exposures yielded 393 data sources. Of these data sources, none were determined to be relevant to the risk evaluation through the data screening process.

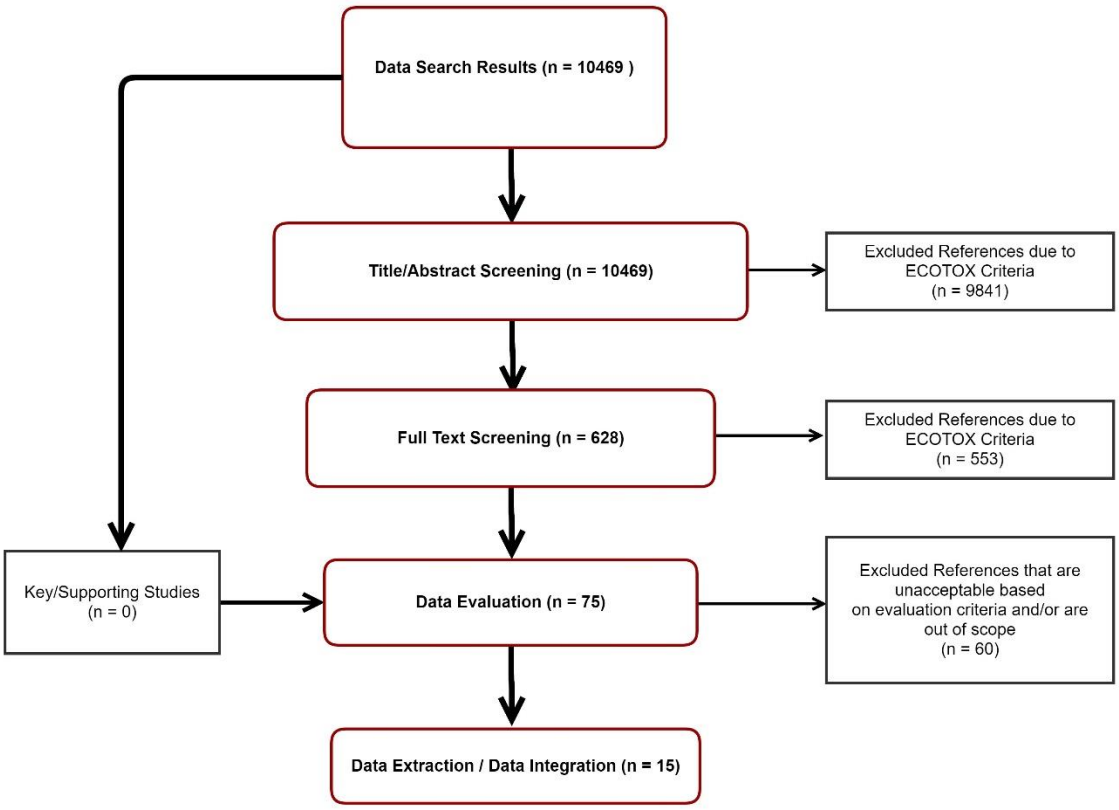


Figure 1-7. Key/Supporting Sources for Environmental Hazards

The environmental hazard data sources were identified through literature searches and screening strategies using the ECOTOX Standing Operating Procedures. For studies determined to be on-topic after title and abstract screening, EPA conducted a full text screening to further exclude references that were not relevant to the risk evaluation. Screening decisions were made based on eligibility criteria as documented in the ECOTOX User Guide (U.S. EPA, 2018b). Additional details can be found in the *Strategy for Conducting Literature Searches for Carbon Tetrachloride:* Supplemental Document to the TSCA Scope Document, EPA-HQ-OPPT-2016-0733-0050. During problem formulation, EPA made refinements to the conceptual models resulting in the exclusion of the terrestrial species exposure pathways and studies that are not biologically relevant from the scope of the risk evaluation. However, in the final risk evaluation, EPA qualitatively considered the soil and land-applied biosolid pathway and one citation on *Chironomus tentans* (Lee et al., 2006) leading to exposure to terrestrial and sediment-dwelling organisms, respectively. Exposures to terrestrial organisms from air were considered out of scope due to its coverage under the jurisdiction of the CAA. *e.g.*, The "Key/Supporting Studies" box represents data sources typically cited in existing assessments and considered highly relevant for the TSCA risk evaluation because they were used as key and supporting information by regulatory and non-regulatory organizations to support their chemical hazard and risk assessments. These citations were found independently from the ECOTOX process. EPA

confirmed these key/supporting studies fulfilled the PECO criteria and were moved directly to the data evaluation step.

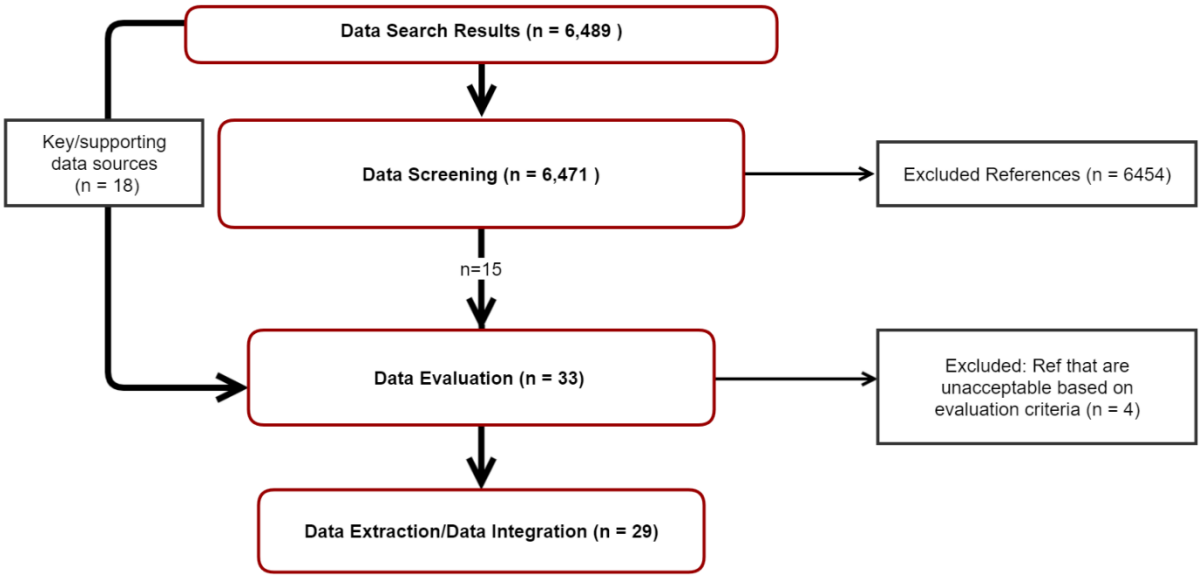


Figure 1-8. Key/Supporting Data Sources for Human Health Hazards

The literature search strategy used to gather human health hazard information for carbon tetrachloride yielded 6,489 studies. This included 18 key and supporting studies (identified from previous regulatory assessments) that skipped the initial screening process and proceeded directly to the data evaluation phase (*i.e.*, data quality review). Of the 6,489 studies identified for carbon tetrachloride 6,454 were excluded as off topic during the title and abstract screening phase. The remaining 15 human health hazard studies advanced to full text screening; a total of 29 studies were determined to be relevant to the risk evaluation. These relevant data sources were evaluated and extracted in accordance with the process described in Appendix G of the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). Additional details can be found in EPA's Strategy for *Strategy for Conducting Literature Searches for Carbon Tetrachloride: Supplemental Document to the TSCA Scope Document* (EPA-HQ-OPPT-2016-0733-0050). The results of this screening process are published in the *Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document* (U.S. EPA, 2017a).

1.5.2 Data Evaluation

During the data evaluation stage, EPA typically assesses the quality of the data sources using the evaluation strategies and criteria described in *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). EPA evaluated the quality of the all data sources that passed full-text screening. Each data source received an overall confidence rating of high, medium, low or unacceptable.

The results of these data quality evaluations are provided in Sections 1.1 (Physical and Chemical Properties), 2.1 (Fate and Transport) and 2.5.2 (Hazards). Supplemental files 1A - 1H (see list of

supplemental files in Appendix B) also provide details of the data evaluations including individual metric scores and the overall study score for each data source.

1.5.3 Data Integration

During data integration and analysis, EPA considers quality, consistency, relevancy, coherence and biological plausibility to make final conclusions regarding the weight of the scientific evidence. As stated in *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a), data integration involves transparently discussing the significant issues, strengths, and limitations as well as the uncertainties of the reasonably available information and the major points of interpretation (U.S. EPA, 2018d).

EPA used previous assessments to identify key and supporting information and then analyzed and synthesized available evidence regarding carbon tetrachloride's physical-chemical properties, environmental fate and transport properties and its potential for exposure and hazard. EPA's analysis also considered recent data sources that were not considered in the previous assessments (Section 1.5.1) as well as reasonably available information on potentially exposed or susceptible subpopulations.

The exposures and hazards sections describe EPA's analysis of the relevant lines of evidence that were found acceptable for the risk evaluation based on the data quality reviews provided in the supplemental files.

2 EXPOSURES

This section describes EPA's approach to assessing environmental and human exposures. First, the fate and transport of carbon tetrachloride in the environment is characterized. Then, carbon tetrachloride's environmental releases are assessed. This information is then integrated into an assessment of environmental exposures. Last, occupational exposures (including potentially exposed or susceptible subpopulations) are assessed. For all exposure-related disciplines, EPA screened, evaluated, extracted and integrated reasonably available empirical data. In addition, EPA used models to estimate exposures. Both empirical data and modeled estimates were considered when selecting values for use in the exposure assessment.

2.1 Fate and Transport

2.1.1 Fate and Transport Approach and Methodology

EPA gathered and evaluated environmental fate information according to the process described in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). Reasonably available environmental fate data were selected for use in the current evaluation. Furthermore, EPA used previous regulatory and non-regulatory chemical assessments to inform the environmental fate and transport information discussed in this section and Appendix C. EPA had confidence in the information used in the previous assessments to describe the environmental fate and transport of carbon tetrachloride and thus used it to make scoping decisions.

EPA conducted a comprehensive search and screening process as described in Section 1.5. Using this pragmatic approach, EPA evaluated the confidence of the key and supporting data sources of previous assessments as well as newer information instead of evaluating the confidence of all the underlying evidence ever published on environmental fate and transport for carbon tetrachloride. This allowed EPA to maximize the scientific and analytical efforts of other regulatory and non-regulatory agencies by accepting for the most part the scientific knowledge gathered and analyzed by others except for influential information sources. Those exceptions would constitute a smaller pool of sources subject to the rigor of the TSCA systematic review process to ensure that the risk evaluation uses the best available science and the weight of the scientific evidence. Other fate estimates were based on modeling results from EPI Suite™ (U.S. EPA, 2012a), a predictive tool for physical-chemical and environmental fate properties. The data evaluation tables describing their review can be found in the supplemental document, *Final Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Fate and Transport Studies (*U.S. EPA, 2019f*)*.

The carbon tetrachloride environmental fate characteristics and physical-chemical properties used in fate assessment are presented in Table 2-1. EPA used EPI Suite™ estimations and reasonably available fate data to characterize the environmental fate and transport of carbon tetrachloride. Please note that this section and Appendix C may also cite other data sources as part of the reasonably available evidence on the fate and transport properties of carbon tetrachloride. EPA did not subject these other data sources to the later phases of the systematic review process (*i.e.*, data evaluation and integration) based on the approach explained above.

2.1.2 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 considered in the risk evaluation. Table 2-1 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 and problem formulation documents (U.S. EPA, 2018c).

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}) when making changes to the conceptual models, as described in Section 2.5.3.1 of the problem formulation document (U.S. EPA, 2018c).

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. This estimation can be confirmed with a wastewater treatment removal study showing that carbon tetrachloride

partitioned to the water column for greater than 99% and the range of <10 to 0.1% was distributed in sludge (Chen et al., 2014).

Based on the results of the STPWIN model, in which removal of carbon tetrachloride from wastewater is dominated by volatilization, concentrations of carbon tetrachloride in land-applied biosolids are expected to be lower than concentrations in wastewater treatment plant effluents. Level III fugacity modeling as implemented in EPI Suite™ using 100% emission to soil as a proxy for land application of biosolids estimates that approximately 87% of carbon tetrachloride volatilizes to air, 12% remains in soil, and 0.5% is transported to water. However, the model assumes constant emissions rather than a pulse as land application of biosolids would occur; thus, those model results likely overstate how much carbon tetrachloride would remain in soil. Although similar dissipation would be expected, pulse applications of biosolids to land would result in varying dissipation rates allowing for greater portioning from soil to air. Overall, based on physical and chemical properties and fate endpoints, along with the estimated results of the models, surface and drinking water exposures from land-applied biosolids are likely negligible.

Overall, carbon tetrachloride is expected to have limited accumulation potential in wastewater biosolids, soil, sediment, and biota. Carbon tetrachloride released to surface water or soil is likely to volatilize to the atmosphere, where it will slowly photooxidize. Carbon tetrachloride may migrate to groundwater, where it may be removed via various anaerobic and abiotic degradation pathways.

EPI Suite™ (U.S. EPA, 2012a) module that estimates volatilization from lakes and rivers ("WVol") was run using inputs to evaluate the volatilization half-lives of carbon tetrachloride in various compartments. Given the measured vapor pressure of 115 mm Hg at 20°C and a calculated Henry's law constant of 2.76×10^{-2} atm-m^3/mol, these physical-chemical property inputs to the WVol model in EPISuite indicates that carbon tetrachloride will volatilize from a model river with a half-life on the order of 1.3 hours and from a model lake on the order of approximately 5 days. Although volatilization is expected to be rapid, a Level III Fugacity model predicted that when carbon tetrachloride is continuously released to water, 80% of the mass will partition to water, 19% to air, < 1% to soil and < 1% to sediment. Level III fugacity modeling results are impacted by which compartments (air, water or soil) receive the chemical releases so a second scenario was run assuming equal releases of carbon tetrachloride to all three compartments. The model predicted that when carbon tetrachloride is continuously released to air, water, and soil, 50% of the mass partitions to water, 47.3% to air, 2.5% to soil and < 1% to sediment. Intermittent or pulse releases of carbon tetrachloride are not expected to result in long-term presence in the aquatic compartment and would allow for greater partitioning from the soil to air compartments.

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. 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.

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. This test method, however, uses high concentrations of the test substance so that toxicity to aerobic bacteria may have occurred, which may have prevented or limited biodegradation (ECHA, 2012). The overwhelming evidence suggests that aerobic biodegradation is very slow and anaerobic biodegradation is moderate to rapid (ECHA, 2012; OECD, 2011; ATSDR, 2005; CalEPA, 2000).

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 could be a significant degradation mechanism in soil and ground water. Studies have shown the formation of degradation products such as chloroform, methylene chloride, methyl chloride, and phosgene under various environmental conditions. Under sulfate reducing conditions, partial complete dechlorination of carbon tetrachloride has been observed (de Best et al., 1997). Carbon tetrachloride has been found to degrade under anaerobic conditions to methane, carbon dioxide and carbon monoxide through various metabolic pathways (Van Eekert et al., 1998). Additionally, abiotic transformation has been observed to play an important role in degradation of carbon tetrachloride to carbon disulfide, however substitutive and oxidative dechlorination processes forming carbon dioxide from degradants may also serve as a potential pathway to producing safe degradation products (Van Eekert et al., 1998).

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 principle 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), while measured values found in studies via the process of systematic review of highly rated literatures are in the range of 1.11 – 2.43 for various surface soil types; 0.79 – 1.93 for aquifer sediments; 1.67 for marine and estuary sediments (Riley et al., 2010; Roose et al., 2001; Zhao et al., 1999; Duffy et al., 1997; Rogers and McFarlane, 1981), and these values are associated with low sorption to soil and sediment.

Table 2-1. 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); (Cox et al., 1976)
Hydrolysis half-life	7000 years at 1 ppm	(OECD, 2011); (Mabey and Mill, 1978)
Abiotic soil degradation	5 days (autoclaved soils)	(Anderson et al., 1991)
Biodegradation	6 to 12 months (soil - estimated)[b] 7 days to 12 months (aerobic water, based on multiple studies) 3 days to 4 weeks (anaerobic water, based on multiple studies) 13 days to 19 months (anaerobic wastewater treatment, based on multiple studies) 7 days (aerobic wastewater treatment)	(OECD, 2011); (ECHA, 2012); (ATSDR, 2005); (HSDB, 2005); (Van Eekert et al., 1998); (Bouwer and McCarty, 1983); (Doong and Wu, 1992); (Tabak et al., 1981); (de Best et al., 1997)
Wastewater Treatment	Mass distribution/partition: Water – >99% Sludge – >10 – 0.1%	(Chen et al., 2014)
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})	1.11 – 2.43 (from various soil types) 0.79 – 1.93 (aquifer sediments) 1.67 (marine and estuary sediments)	(ECHA, 2012); (OECD, 2011); (Duffy et al., 1997); (Rogers and McFarlane, 1981) (Roose et al., 2001); (Zhao et al., 1999); (Riley et al., 2010)

[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 indicate that carbon tetrachloride has low bioaccumulation potential in fish (U.S. EPA, 2012a; OECD, 2011).

2.2 Environmental Releases

Releases to the environment from the conditions of use (*e.g.*, industrial/commercial processes or commercial uses resulting in down-the-drain releases) are a source 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.

2.2.1 Water Release Assessment Approach and Methodology

EPA reviewed reported carbon tetrachloride data from the 2018 Toxics Release Inventory (TRI) (U.S. EPA, 2018e) and multiple years (2014 through 2018) of Discharge Monitoring Report (DMR) data as found in the EPA ECHO database pollutant loading tool to provide a basis for estimating releases (U.S. EPA, 2014a). Facilities are only required to report to TRI if the facility has 10 or more full-time employees, is included in an applicable North American Industry Classification System (NAICS) code, and manufactures, processes, or uses the chemical in quantities greater than a certain threshold (25,000 pounds for manufacturers and processors of carbon tetrachloride and 10,000 pounds for users of carbon tetrachloride). Due to these limitations, some sites that manufacture, process, or use carbon tetrachloride may not report to TRI and are therefore not included in these datasets. 7Appendix D presents a summary of the 2018 TRI reported releases of carbon tetrachloride to various media.

For the DMR data, EPA used the Water Pollutant Loading Tool within EPA's Enforcement and Compliance History Online (ECHO), https://echo.epa.gov/trends/loading-tool/water-pollution-search/, to query all carbon tetrachloride point source water discharges for five years: 2014, 2015, 2016, 2017, and 2018 (U.S. EPA, 2014a).The carbon tetrachloride loadings as reported in DMR were averaged over the five year period for use in estimating carbon tetrachloride surface water concentrations. DMR data are submitted by National Pollutant Discharge Elimination System (NPDES) permit holders to states or directly to the EPA according to the monitoring requirements of the facility's permit. States are only required to load major discharger data into DMR and thus, may or may not load minor discharger data. The definition of major versus minor discharger is set by each state and could be based on discharge volume or facility size. Due to these limitations, some sites that discharge carbon tetrachloride may not be included in the DMR dataset.

2.3 Environmental Exposures

In the problem formulation (U.S. EPA, 2018c), EPA presented an analysis and preliminary conclusions on environmental exposures to aquatic species based on releases to surface water, and from sediments and suspended biosolids. No additional information regarding environmental exposures was received or identified by the EPA following the publication of the problem formulation that would alter the preliminary conclusions about environmental exposures presented in the problem formulation (U.S. EPA, 2018c). As reviewed during problem formulation, carbon tetrachloride is present in environmental media such as groundwater, surface water, and air. EPA conducted analysis of the environmental release pathways to aquatic receptors based on a qualitative assessment of the fate and transport properties of carbon tetrachloride in the environment (described in Section 2.1), and a quantitative comparison of hazards and exposures for aquatic organisms as described in Sections 2.3.1, 2.3.2, 3.1, 4.1.2 and 4.1.3 below.

2.3.1 Environmental Exposures – Aquatic Pathway

As explained in Section 2.5.3.1 of the Problem Formulation document (U.S. EPA, 2018c), EPA conducted a qualitative assessment of carbon tetrachloride exposures to aquatic species from sediments and suspended solids and determined that it was not necessary to further analyze these exposures quantitatively. The qualitative assessment explains that due to the 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.

After publication of the problem formulation, EPA identified additional data on ecological hazards requiring an update of the analysis of carbon tetrachloride releases and surface water concentrations. In order to update this analysis, EPA modeled industrial discharges to surface water to estimate surface water concentration using the five year average (2014 through 2018) of EPA NPDES permit Discharge Monitoring Report (DMR) data for the highest carbon tetrachloride releasing facilities based on the reported annual loadings (lbs/year). The 21 facilities (see Appendix E) represent, on average, 94% of total annual carbon tetrachloride discharges in the United States. EPA used the Probabilistic Dilution Model (PDM) within EPA's Exposure and Fate Assessment Screening Tool, version 2014 (E-FAST 2014) to estimate surface water concentrations resulting from facilities reported annual release/loading amounts. Further information on the releases of carbon tetrachloride to surface water and the estimated surface water carbon tetrachloride concentrations for acute and chronic scenarios based on E-FAST can be found in Table 2-2 and Appendix E.

2.3.1.1 Methodology for Modeling Surface water Concentrations from Facilities releases (E-FAST 2014)

Surface water concentrations resulting from wastewater releases of carbon tetrachloride from facilities that use, manufacture, or process the chemical were modeled using EPA's E-FAST, Version 2014 (U.S. EPA, 2007). As appropriate, two scenarios were modeled per release: release of the annual load over an estimated maximum number of operating days (250 days/year) and over 20 days/year. E-FAST 2014 is a model that estimates chemical concentrations in water to which aquatic life may be exposed using upper percentile and/or mean exposure parametric values, resulting in possible conservative exposure estimates. Advantages to this model are that it requires minimal input parameters and it has undergone extensive peer review by experts outside

of EPA. To obtain more detailed information on the E- FAST 2014 tool from the user guide/background document, visit this web address: https://www.epa.gov/tsca-screening-tools/e-fast-exposure-and-fate-assessment-screening-tool-version-2014.

Overall Confidence in Estimated Water Surface Concentrations

EPA has medium confidence in the estimated water surface concentrations because the modeled estimates are based on conservative assumptions and parameters explained above (*i.e.*, averaging data from top discharging facilities), which could result in overestimation or underestimation of the water concentrations, in addition to the uncertainties associated with the E-FAST model and DMR dataset (see Section 4.4.2).

2.3.1.1.1 E-FAST Calculations

Surface Water Concentrations

EPA used E-FAST 2014 to estimate site-specific surface water concentrations for discharges to both free-flowing water bodies (*i.e.*, rivers and streams) and for still water bodies (*i.e.*, bays, lakes, and estuaries).

For free-flowing water body assessments, E-FAST 2014 calculates surface water concentrations for four streamflow conditions (7Q10, harmonic mean, 30Q5, and 1Q10 flows) using the following equation:

$$\boldsymbol{SWC} = \frac{\boldsymbol{WWR} \times \boldsymbol{CF1} \times \left(1 - \frac{\boldsymbol{WWT}}{100}\right)}{\boldsymbol{SF} \times \boldsymbol{CF2}} \qquad \text{(Eq. 2-1)}$$

where:

SWC	=	Surface water concentration (parts per billion (ppb) or µg/L)
WWR	=	Chemical release to wastewater (kg/day)
WWT	=	Removal from wastewater treatment (%)
SF	=	Estimated flow of the receiving stream (million liters/day (MLD))
CF1	=	Conversion factor (10^9 µg/kg)
CF2	=	Conversion factor (10^6 L/day/MLD)

For still water body assessments, no simple streamflow value represents dilution in these types of water bodies. As such, E-FAST 2014 accounts for dilution by incorporating an acute or chronic dilution factor for the water body of interest instead of stream flows. Dilution factors in E-FAST 2014 are typically 1 (representing no dilution) to 200, based on NPDES permits or regulatory policy. The following equation is used to calculate surface water concentrations in still water bodies:

$$\boldsymbol{SWC} = \frac{\boldsymbol{WWR} \times \left(1 - \frac{\boldsymbol{WWT}}{100}\right) \times \boldsymbol{CF1}}{\boldsymbol{PF} \times \boldsymbol{CF2} \times \boldsymbol{DF}} \qquad \text{(Eq. 2-2)}$$

where:

SWC	=	Surface water concentration (ppb or µg/L)
WWR	=	Chemical release to wastewater (kg/day)
WWT	=	Removal from wastewater treatment (%)
PF	=	Effluent flow of the discharging facility (MLD)
DF	=	Acute or chronic dilution factor (DF) used for the water body

(typically, between 1 and 200)

CF1 = Conversion factor (10^9 µg/kg)

CF2 = Conversion factor (10^6 L/day/MLD)

Outputs

There are two main outputs from E-FAST that EPA used in characterizing environmental exposures: surface water concentration estimates, and the number of days a certain surface water concentration was exceeded. Site-specific surface water concentration estimates for free-flowing water bodies are reported for the 7Q10 stream flows. The 7Q10 stream flow is the lowest consecutive 7-day average flow during any 10-year period. This stream flow represents a conservative scenario as low stream flow would result in higher carbon tetrachloride surface water estimates. Site-specific surface water concentration estimates for still water bodies are reported for calculations using the acute dilution factors. In cases where site-specific flow/dilution data were not available, the releases were modeled using stream flows of a representative industry sector, as calculated from all facilities assigned to the industry sector in the E-FAST database (discussed below). Estimates from this calculation method are reported for the 10th percentile 7Q10 stream flows.

The PDM portion of E-FAST 2014 was also run for free-flowing water bodies. The PDM predicts the number of days/yr a chemical's COC in an ambient water body will be exceeded. COCs are threshold concentrations below which adverse effects on aquatic life are expected to be minimal. The model is based on a simple mass balance approach presented by (Di Toro, 1984) that uses probability distributions as inputs to reflect that streams follow a highly variable seasonal flow pattern and there are numerous variables in a manufacturing process that can affect the chemical concentration and flow rate of the effluent. PDM does not estimate exceedances for chemicals discharged to still waters, such as lakes, bays, or estuaries. For these water bodies, the days of exceedance is assumed to be zero unless the predicted surface water concentration exceeds the COC. In these cases, the days of exceedance is set to the number of release days/yr (see required inputs in Section 2.3.1.1.2).

2.3.1.1.2 Model Inputs

Individual model inputs and accompanying considerations for the surface water modeling are described in this Section.

Chemical Release to Wastewater (WWR)

Annual wastewater loading estimates (kg/site/year or lb/site/year) were obtained from 2014-2018 DMR data and averaged over the 5 year period, as discussed in Section 2.2**.** To model these releases within E-FAST 2014, the annual release is converted to a daily release using an estimated days of release per year. Below is an example calculation:

WWR (kg/day) = Annual loading (kg/site/year) / Days released per year (days/year) (Eq. 2-3)

Release Days (days/yr)

The number of days/yr that the chemical is discharged is used to calculate a daily release amount from annual loading estimates (see above). Current regulations do not require facilities to report the number of days associated with reported releases. Therefore, two release scenarios were modeled for direct discharging facilities to provide upper and lower bounds for the range of surface water concentrations predicted by E-FAST 2014. The two scenarios modeled were a 250 days of release per year scenario

based on estimates specific to the facility's condition of use (see Section 2.2.1 for more details) and a 20 days of release per year scenario. The 250 days of release scenario yields the minimum estimated surface water concentrations for a given facility, and the 20 days of release scenario yields the maximum estimated surface water concentrations for a given facility. For indirect dischargers, only the maximum estimated days of release per year was modeled because it was assumed that the actual release to surface water would mostly occur at receiving treatment facilities, which were assumed to typically operate greater than 20 days/yr.

Removal from Wastewater Treatment (WWT%)
The WWT% is the percentage of the chemical removed from wastewater during treatment before discharge to a body of water. As discussed in Section 2.1, the WWT% for carbon tetrachloride was estimated as 92% using the "STP" module within EPI Suite™, which was run using default settings to evaluate the potential for carbon tetrachloride to volatilize to air or sorb to sludge during wastewater treatment. A WWT% of zero was used for direct releasing facilities because the release reported in DMR already accounts for any wastewater treatment which may have occurred.

Facility or Industry Sector
The required site-specific stream flow or dilution factor information for a given facility is contained in the E-FAST 2014 database and is selected by searching by a facility's NPDES permit number, name, or the known discharging waterbody reach code. For facilities that directly discharge to surface water (*i.e.*, "direct dischargers"), the NPDES code of the direct discharger was selected from the database. For facilities that indirectly discharge to surface water (*i.e.*, "indirect dischargers" because the release is sent to a WWTP prior to discharge to surface water), the NPDES of the receiving WWTP was selected. If a facility NPDES was not available in the E-FAST-2014 database, the release was modeled using water body data for a surrogate NPDES code (preferred) or an industry sector, as described below.

In cases where the site-specific NPDES code was not available in the E-FAST 2014 database, the preferred alternative was to select the NPDES for a nearby facility that discharges to the same waterbody. The surrogate NPDES was chosen to best represent flow conditions in the waterbody that both the carbon tetrachloride releasing facility and surrogate facility discharge to and not actual releases associated with the surrogate facility NPDES.

2.3.2 Environmental Exposure Results

Summary

As discussed in Section 2.2, releases of carbon tetrachloride were estimated for an average over 5 years (2014-2018). For the maximum days of release scenarios (250 days), estimated carbon tetrachloride surface water concentrations under 7Q10 flow conditions ranged from 4.0E-06 to 10 ppb. For the minimum release scenario (20 days), surface water concentrations ranged from 4.9E-05 to 130 ppb. On a per facility basis, the 20-day release scenario yielded higher surface water concentrations than the maximum day of release scenario. Wastewater treatment facilities (POTWs) operate year- round and were modeled using the maximum days of release scenario. The minimum release scenario (20 days) is not applicable to these facilities and is noted in Table 2-2 with N/A. Additional facility data is presented in Appendix E.

Table 2-2. Summary of Estimated Surface Water Concentrations from Facility Carbon Tetrachloride Release

NPDES	Facility Name	Annual Release by Facility (kg/site-yr)	Surface Water Concentration (7Q10 Flow) (µg/L)	
		5yr Mean[a]	(20 day Scenario)	(250 day Scenario)
TX0021458	Fort Bend County WCID2	25	N/A	10
AL0001961	AKZO Chemicals, Inc.	115	3.1E-01	2.5E-02
LA0000329	Honeywell, Baton Rouge	4.0	8.1E-04	6.5E-05
LA0005401	ExxonMobil, Baton Rouge	2.0	4.0E-04	3.2E-05
OH0029149	Gabriel Performance	3.8	45	3.6
WV0004359	Natrium Plant	5.9	3.4E-02	2.9E-03
CA0107336	Sea World, San Diego	1.2	1.5E-01	1.2E-02
OH0007269	Dover Chemical Corp[b]	7.2	25	2.0
LA0006181	Honeywell, Geismar	3.7	7.3E-04	6.1E-05
LA0038245	Clean Harbors, Baton Rouge	6.6	1.3E-03	1.0E-04
TX0119792	Equistar Chemicals LP	13.6	4.4	3.5E-01
WV0001279	Chemours Chemicals LLC	2.1	1.1E-02	8.0E-04
TX0007072	Eco Services Operations	5.3	49	3.9
KY0024082	Barbourville STP	1.8	N/A	3.5E-01
WA0030520	Central Kitsap WWTP	1.2	7.0E+01	5.8E-01
MO0002526	Bayer Cropscience	1.0	5.9E-01	4.7E-02
KY0027979	Eddyville STP	1.3	N/A	1.0
KY0103357	Richmond Silver Creek STP	0.64	N/A	3.1E-01
KY0003603	Arkema Inc.	0.44	9.5E-04	8.7E-05
KY009161	Caveland Environmental Auth	0.59	8.4E-02	5.6E-03
LA0002933	Occidental Chem Corp, Geismar	0.23	4.9E-05	4.0E-06

[a]The five-year mean is the average of discharges reported in EPA ECHO database for the years 2014 through 2018 and if applicable, includes years of reported zero kg of carbon tetrachloride discharges.
[b] The Dover facility's mean discharge was averaged over a four-year period: 2015-2018. 2014 discharges were not included since a spill was reported and is not in scope for the TSCA risk evaluation.

In response to SACC and public comments, releases from five of the facilities with larger average discharges were further investigated to determine when during the year these releases occurred. Depending on permit requirements for each discharger, facilities are required to report releases and sample pollutant loads such as carbon tetrachloride, several times per year. However, monitoring/reporting frequency and data availability varies greatly between the five facilities. The times of year most relevant for amphibians were spring and summer and those monitoring data were used to estimate stream concentrations using E-FAST 2014 for the 20-day release scenario scenarios described in Section 2.2 above.

Table 2-3. Summary of Facility Carbon Tetrachloride Monitoring Data and Estimated Surface Water Concentrations

NPDES	Facility Name	Monitoring Period[a]	Average Daily Release Per Facility (kg/day)	Surface Water Concentration (7Q10 Flow) (µg/L)
TX0021458	Fort Bend County WCID2	5/31/2014	1.2E-01	12
		8/31/2014	1.5E-01	16
		7/31/3015	1.4E-01	14
		4/30/2016	3.0E-02	3.1
		7/31/2016	3.3E-02	3.5
		4/30/2017	2.3E-02	2.4
		7/31/2017	1.7E-02	1.8
		4/30/2018	2.4	2.5
		7/31/2018	3.3	3.5
OH0029149	Gabriel Performance	3/31/2014	4.6E-05	1.1E-02
		6/30/2014	4.2E-02	9.9
		3/31/2015	7.8E-02	18
		6/30/2017	1.2E-02	2.8
		3/31/2018	1.2E-02	2.8
OH0007269	Dover Chemical Corp	4/30/2014	1.4	97
		4/30/2015	8.6E-02	6.0
		7/31/2017	0.70	48
TX0119792	Equistar Chemicals LP	8/31/2016	9.1E-02	5.9E-01
		8/31/2017	1.5E-02	9.8E-02
		8/31/2018	6.0E-02	3.9E-01
TX0007072	Eco Services Operations	7/31/2016	1.8E-02	3.3

		3/31/2017	2.2E-02	4.2
		9/30/2018	2.7E-02	5.0

[a] Spring and summer months are included (3/31 through 9/30) as available. Missing time periods within one permit represent either no discharge of carbon tetrachloride or no sampling data reported.

2.3.3 Terrestrial Environmental Exposure

Terrestrial species populations living near industrial or commercial facilities using carbon tetrachloride may be exposed to the chemical through environmental media, including ambient air, surface water and ground water. During problem formulation EPA determined that carbon tetrachloride 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 (see Section 2.5.3.2 of the problem formulation document) (U.S. EPA, 2018c). However, in the final risk evaluation, exposures to terrestrial organisms from soil and biosolids were qualitatively analyzed. Exposures to terrestrial organisms from air were not evaluated in the final risk evaluation due to existing coverage under the Clean Air Act. EPA has identified carbon tetrachloride as a priority pollutant under Section 304(a) of the CWA and has developed water quality criteria for protection of human health. EPA determined during problem formulation that exposures to terrestrial organisms from water do not need further evaluation due to the current regulation of carbon tetrachloride water releases and the expectation that releases to water will volatilize into air based on its physical-chemical properties.

2.4 Human Exposures

2.4.1 Occupational Exposures

Occupational exposures could be direct or indirect and the magnitude of exposure for an occupational worker could be a function of duration, proximity and intensity of exposures. The duration of exposure, which partially depends on worker mobility, could vary for different employee groups. EPA considers workers at the facility who neither directly perform activities near the carbon tetrachloride source area nor regularly handle carbon tetrachloride to be occupational non-users (ONUs). Workers who are directly handling carbon tetrachloride and/or perform activities near sources of carbon tetrachloride are in the near field and are called workers throughout this risk evaluation. The near-field is reported to be conceptualized as a volume of air within one-meter in any direction of the worker's head and the far-field comprised the remainder of the room (Tielemans et al., 2008). The source area/exposure zone could be judged by several factors such as the chemical inventory, ventilation of the facility, vapor pressure and emission potential of the chemical, process temperature, size of the room, job tasks, and modes of chemical dispersal from activities (Leblanc et al., 2018). Corn and Esmen (1979) indicated that the assignment of zones is a professional judgment and not a scientific exercise.

The job classifications for ONUs could be dependent on the conditions of use. For example, ONUs for manufacturing include supervisors, managers, and tradesmen who may be in the manufacturing area, but do not perform tasks that result in the same level of exposures as production workers. It could be challenging to characterize direct and indirect exposures for some conditions of use since it is not uncommon for employees at a facility to perform multiple types of tasks throughout the workday. Workers could perform activities that bring them into direct contact with carbon tetrachloride and also perform additional tasks as ONUs. The

groupings of employees are not necessarily distinct as workers perform a variety of tasks over the course of the day that could result in direct exposure and indirect exposure. Indirect exposures of employees working near contaminants could be difficult to separate due to overlapping tasks that makes it difficult to delineate exposures of workers and ONUs.

Carbon tetrachloride storage and handling are reported to be performed in closed and secure vessel (OxyChem, 2014). In addition, samples can only be taken (potential release source) from the closed systems that have built-in capabilities to handle vents, provide nitrogen, process unused liquid volume and results in a sample in a closed container (OxyChem, 2014). Oxychem (OxyChem, 2018) reported closed loop unloading systems are designed to minimize solvent vapor emissions during transfer by exchanging the liquid solvent in the trailer with the storage tank vapors. In addition, it was also reported that the closed system cuts the water usage (resource needs) and release of carbon tetrachloride (Cheremisinoff and Rosenfeld, 2009). Carbon tetrachloride has no flash point, it is not flammable. Decomposition of carbon tetrachloride requires ≥ 730°C, a temperature at which phosgene could form from carbon tetrachloride (Noweir et al., 1973). However, phosgene, typically formed otherwise, is not stable at temperatures above 250°C, decomposes to form mixtures of carbon monoxide, chlorine, carbon dioxide, and carbon tetrachloride (ACC, 2018). Carbon tetrachloride should be stored in labelled, airtight containers in a well-ventilated place protected from light and at a temperature below 30°C. It must be stored separated from chemically active metals. Disposal of carbon tetrachloride contaminated wastes via incineration is not recommended due to the non-flammability of carbon tetrachloride and to the formation of phosgene, hydrogen chloride and other toxic gases on heating. Caustic scrubber could reduce phosgene emissions in exhaust gases.

EPA assessed occupational exposures following the analysis plan published in Section 2.6.1.2 of the problem formulation document (U.S. EPA, 2018c). EPA evaluated acute and chronic inhalation exposures to workers and ONUs associated with carbon tetrachloride manufacturing, import and repackaging, its use in industrial applications as a reactant/ intermediate and process agent, laboratory chemicals and disposal. Appendix F of the problem formulation document (U.S. EPA, 2018c) provides additional detail on the mapping of the conditions of use to the Occupational Exposure Scenario (OES) groups used in this risk evaluation. EPA used inhalation monitoring data when available and that met data evaluation criteria (see Section 1.5); and modeling approaches to estimate potential inhalation exposures when inhalation monitoring data were not reasonably available. Specific inhalation assessment methodology is described in further detail below for each type of assessment.

EPA also estimated dermal doses for workers in these scenarios since dermal monitoring data was not reasonably available. EPA modeled dermal doses using the *EPA Dermal Exposure to Volatile Liquids Model* which improves upon the existing *EPA 2-Hand Dermal Exposure* model by accounting for the effect of evaporation on dermal absorption for volatile chemicals and the potential exposure reduction due to glove use. More information about this model and how it was used may be found in Section 2.4.1.4. EPA does not expect dermal exposures for occupational non-users due to no direct contact with the chemical.

Components of the Occupational Exposure Assessment

The occupational exposure assessment of each condition of use comprises the following components:

- **Process Description:** A description of the condition of use, including the role of the chemical in the use; process vessels, equipment, and tools used during the condition of use.
- **Number of Sites:** The sites that use the chemical for the given condition of use.
- **Worker Activities**: Descriptions of the worker activities, including an assessment for potential points of worker exposure and environmental releases.
- **Number of Workers and Occupational Non-Users:** An estimate of the number of sites, number of workers and occupational non-users potentially exposed to the chemical for the given condition of use. Unless mentioned otherwise in this report, the total number of workers and ONUs are number of personnel per site per day. See Appendix A of the supplemental document *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019c) for a discussion of EPA's approach for determining an estimation for the number of affected workers.
- **Inhalation Exposure:** Central tendency and high-end estimates of inhalation exposure to workers and occupational non-users. See Appendix B and Appendix C of the supplemental document *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019c).
- **Dermal Exposure**: It estimates for multiple scenarios, accounting for simultaneous absorption and evaporation, and different protection factors of glove use. A separate dermal exposure Section (2.4.1.8) is included that provides estimates of the dermal exposures for all the assessed conditions of use. EPA assessed dermal exposure to workers using the *Dermal Exposure to Volatile Liquids Model*. The dermal exposure scenarios consider impact of glove use. Dermal exposure assessment is described in more detail Appendix E of the document *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019c).

The OSHA Personal Protective Equipment (PPE) Standard, 29 CFR Section 1910.132, requires that employers conduct a hazard assessment of the workplace to identify all the hazards that exist and determine what methods to use to protect workers from these identified hazards. PPE is one of the options that may be utilized to protect employees from hazardous exposures based on the findings of the hazard assessment. The OSHA determines the technological and economic feasibility of implementing engineering controls on the basis of the best available evidence.

The OSHA respirator protection standard, 29 CFR Section 1910.134, requires employers utilize the hierarchy of controls for reducing or removing chemical hazards. Based on the hierarchy of controls, the most effective controls are elimination, substitution, or engineering controls. These are followed by administrative controls and finally the use of PPE. The respiratory protection standard requires the use of feasible engineering controls as the primary means to control air contaminants. Respirators are required when effective engineering controls are not feasible and are the last means of worker protection in the hierarchy of controls. When effective engineering and administrative controls are not feasible to adequately protect workers and maintain

compliance with other OSHA statutory and regulatory requirements under 29 CFR Section 1910.1000, employers should utilize respirator protective equipment. (29 CFR Section 1910.134(a)(1)).

If information and data indicate that use or handling of a chemical cannot, under worst-case conditions, release concentrations of a respiratory hazard above a level that would trigger the need for a respirator or require use of a more protective respirator, employees would not be assumed to wear them. Employers also use engineering or administrative controls to bring employee exposures below permissible exposure limits for airborne contaminants. Respirators would be used to supplement engineering and administrative controls only when these controls cannot be feasibly implemented to reduce employee exposure to permissible levels.

Occupational Exposures Approach and Methodology

To assess inhalation exposure, EPA reviewed workplace inhalation monitoring data collected by government agencies such as OSHA and NIOSH, monitoring data submitted by industry organizations through public comments, and monitoring data found in published literature (*i.e.*, personal exposure monitoring data and area monitoring data). Studies were evaluated using the evaluation strategies laid out in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a).

For several conditions of use, the EPA modeled exposure in occupational settings. The models were used to either supplement existing exposure monitoring data or to provide exposure estimates where data are insufficient. For example, the EPA developed the *Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model* to estimate worker exposure during container and truck unloading activities that occur at industrial facilities.

- Using the time-weighted average (TWA) exposure concentrations obtained from monitoring data or modeling, EPA calculated the Acute Concentration (AC), Average Daily Concentrations (ADC) and Lifetime Average Daily Concentration (LADC) to assess risk. The AC, ADC, and LADC equations are described in *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019c).

See Appendix E of the supplemental document *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019c) for a discussion of EPA's statistical analysis approach for assessing dermal exposure.

2.4.1.1 Process Description

EPA performed a literature search to find descriptions of processes involved in each condition of use to identify worker activities that could potentially result in occupational exposures. Where process descriptions were unclear or not available, EPA referenced relevant Emission Scenario Documents (ESD's) or Generic Scenarios (GS's). Process descriptions for each condition of use can be found in Section 2.4.1.3.

2.4.1.2 Number of Workers and ONUs

Where available, EPA used CDR data to provide a basis to estimate the number of workers and ONUs. EPA supplemented the available CDR data with U.S. economic data using the following

method:

1. Identify the North American Industry Classification System (NAICS) codes for the industry sectors associated with these uses by reviewing Chemical Data Reporting (CDR) data, Toxics Release Inventory (TRI) data, and EPA Generic Scenarios (GS's) and Organisation for Economic Co-operation and Development (OECD) Emission Scenario Documents (ESDs) for the chemical.
2. Estimate total employment by industry/occupation combination using the Bureau of Labor Statistics' Occupational Employment Statistics data (BLS Data).
3. Refine the Occupational Exposure Scenarios (OES) estimates where they are not sufficiently granular by using the U.S. Census's Statistics of US Businesses (SUSB) data (SUSB Data) on total employment by 6-digit NAICS.
4. Use market penetration data to estimate the percentage of employees likely to be using carbon tetrachloride instead of other chemicals. If no market penetration data were available, estimate of the number of sites using carbon tetrachloride from given NAICS code and multiply by the estimated workers and ONUs/site provided in BLS data.
5. Combine the data generated in Steps 1 through 5 to produce an estimate of the number of employees using carbon tetrachloride in each industry/occupation combination, and sum these to arrive at a total estimate of the number of employees with exposure.

There are a few uncertainties surrounding the estimated number of workers potentially exposed to carbon tetrachloride, as outlined below. Most of these uncertainties regarding worker exposure to carbon tetrachloride are specific to site/facility and may not be uniform depending on the information available, activities performed and industrial process variables across the industry and/or within the same company. There are inherent limitations to the use of CDR data as they are reported by manufacturers and importers of carbon tetrachloride. CDR may not capture all sites and workers associated with any given chemical. There are also uncertainties with BLS data. First, BLS's OES employment data for each industry/occupation combination are only available at the 3-, 4-, or 5-digit NAICS level, rather than the full 6-digit NAICS level. This lack of granularity could result in an overestimate of the number of exposed workers if some 6-digit NAICS are included in the less granular BLS estimates but are not likely to use carbon tetrachloride for the assessed applications. EPA addressed this issue by refining the OES estimates using total employment data from the U.S. Census's SUSB. However, this approach assumes that the distribution of occupation types (SOC codes) in each 6-digit NAICS is equal to the distribution of occupation types at the parent 5-digit NAICS level. If the distribution of workers in occupations with carbon tetrachloride exposure differs from the overall distribution of workers in each NAICS, then this approach could result in inaccuracy. The judgments about which industries (represented by NAICS codes) and occupations (represented by SOC codes) are associated with the uses assessed in this report are based on EPA's understanding of how carbon tetrachloride is used in each industry. Designations of which industries and occupations have potential exposures is nevertheless subjective, and some industries/occupations with few exposures might erroneously be included, or some industries/occupations with exposures might erroneously be excluded. This would result in inaccuracy but would be unlikely to systematically either overestimate or underestimate the count of exposed workers.

2.4.1.3 General Inhalation Exposure Assessment Approach and Methodology

EPA provided occupational exposure results representative of *central tendency* conditions and

high-end conditions. A central tendency could be representative of occupational exposures in the center of the distribution for a given condition of use. For risk evaluation, EPA may use the 50th percentile (median), mean (arithmetic or geometric), mode, or midpoint values of a distribution as representative of the central tendency scenario. EPA's preference is to provide the 50th percentile of the distribution. However, if the full distribution is not known, the mean, mode, or midpoint of the distribution represents the central tendency depending on the statistics available for the distribution.

A high-end could be representative of occupational exposures that occur at probabilities above the 90th percentile but below the exposure of the individual with the highest exposure (U.S. EPA, 1992a). For the risk evaluation, EPA provided high-end results at the 95th percentile. If the 95th percentile is not available, EPA may use a different percentile greater than or equal to the 90th percentile but less than or equal to the 99.9th percentile, depending on the statistics available for the distribution. If the full distribution is not known and the preferred statistics are not available, EPA may estimate a maximum or bounding estimate in lieu of the high-end.

For occupational exposures, EPA may use measured or estimated air concentrations to calculate exposure concentration metrics required for the risk assessment, such as average daily concentration and lifetime average daily concentration. These calculations require additional parameter inputs, such as years of exposure, exposure duration and frequency, and lifetime years. EPA may estimate exposure concentrations from monitoring data, modeling, or occupational exposure limits.

For the final exposure result metrics, each of the input parameters (*e.g.*, air concentrations, working years, exposure frequency, lifetime years) may be a *point estimate* (*i.e.*, a single descriptor or statistic, such as central tendency or high-end) or a *full distribution*. EPA will consider three general approaches for estimating the final exposure result metrics:

- Deterministic calculations: EPA will use combinations of point estimates of each parameter to estimate a central tendency and high-end for each final exposure metric result. EPA will document the method and rationale for selecting parametric combinations to be representative of central tendency and high-end.

- Probabilistic (stochastic) calculations: EPA will pursue Monte Carlo simulations using the full distribution of each parameter to calculate a full distribution of the final exposure metric results and selecting the 50th and 95th percentiles of this resulting distribution as the central tendency and high-end, respectively.

- Combination of deterministic and probabilistic calculations: EPA may have full distributions for some parameters but point estimates of the remaining parameters. For example, EPA may pursue Monte Carlo modeling to estimate exposure concentrations, but only have point estimates of working years of exposure, exposure duration and frequency, and lifetime years. In this case, EPA will document the approach and rationale for combining point estimates with distribution results for estimating central tendency and high-end results.

EPA follows the following hierarchy in selecting data and approaches for assessing inhalation exposures:

1. Monitoring data:
   a. Personal and directly applicable
   b. Area and directly applicable
   c. Personal and potentially applicable or similar
   d. Area and potentially applicable or similar
2. Modeling approaches:
   a. Surrogate monitoring data
   b. Fundamental modeling approaches
   c. Statistical regression modeling approaches
3. Occupational exposure limits:
   a. OSHA Permissible Exposure Limits (PEL)
   b. Company-specific OELs (for site-specific exposure assessments, *e.g.*, there is only one manufacturer who provides to EPA their internal OEL but does not provide monitoring data)
   c. Voluntary limits (ACGIH TLV, NIOSH REL, Occupational Alliance for Risk Science (OARS) workplace environmental exposure level (WEEL) [formerly by AIHA])

Exposures are calculated from the datasets provided in the sources depending on the size of the dataset. For datasets with six or more data points, central tendency and high-end exposures were estimated using the 50th percentile and 95th percentile. For datasets with three to five data points, central tendency exposure was calculated using the 50th percentile and the maximum was presented as the high-end exposure estimate. For datasets with two data points, the midpoint was presented as a midpoint value and the higher of the two values was presented as a higher value. Finally, data sets with only one data point presented the value as a what-if exposure. EPA cannot determine the statistical representativeness of the values for the small sample size. For datasets including exposure data that were reported as below the limit of detection (LOD), EPA estimated the exposure concentrations for these data, following EPA's *Guidelines for Statistical Analysis of Occupational Exposure Data* (U.S. EPA, 1994) which recommends using the $\frac{LOD}{\sqrt{2}}$ if the geometric standard deviation of the data is less than 3.0 and $\frac{LOD}{2}$ if the geometric standard deviation is 3.0 or greater. Specific details related to each condition of use can be found in Section 2.4.1.7. For each condition of use, these values were used to calculate chronic (non-cancer and cancer) exposures. Equations and sample calculations for chronic exposures can be found in the supplemental document *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019c).

EPA used exposure monitoring data and exposure models to estimate inhalation exposures for all conditions of use. When directly applicable exposure monitoring data was not available for a specific condition of use, EPA assessed exposure for that use through potentially applicable or similar monitoring data, also referred to as surrogate monitoring data. Specific details related to the use of monitoring data for each condition of use can be found in Section 2.4.1.7.

A summary of the key occupational acute and chronic inhalation exposure concentration models for carbon tetrachloride are presented below. The supplemental document *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019c) provides detailed discussion on the values of the exposure parameters and air concentrations input into these models.

Acute and Chronic Inhalation Exposure Concentrations Models

A key input to the acute and chronic models for occupational assessment is 8-hr time-weighted average air concentration (TWA). The 8-hr TWA air concentrations are time averaged to calculate acute exposure, average daily concentration (ADC) for chronic, non-cancer risks, and lifetime average daily concentration (LADC) for chronic, cancer risks.

Acute workplace exposures are assumed to be equal to the contaminant concentration in air (8-hr TWA), per Equation 2-1.

Equation 2-1

$$\boldsymbol{AEC} = \frac{\boldsymbol{C} \times \boldsymbol{ED}}{\boldsymbol{AT_{acute}}}$$

Where:

$\boldsymbol{AEC}$ = acute exposure concentration [mg/m^3]
$\boldsymbol{C}$ = contaminant concentration in air (8-hour TWA) [mg/m^3]
$\boldsymbol{ED}$ = exposure duration [hr/day]
$\boldsymbol{AT_{acute}}$ = acute averaging time [hr/day]

ADC and LADC are used to estimate workplace chronic exposures for non-cancer and cancer risks, respectively. These exposures are estimated as follows:

Equation 2-2

$$\boldsymbol{ADC\ or\ LADC} = \frac{\boldsymbol{C} \times \boldsymbol{ED} \times \boldsymbol{EF} \times \boldsymbol{WY}}{\boldsymbol{AT\ or\ AT_C}}$$

Where:

$\boldsymbol{ADC}$ = average daily concentration (8-hr TWA) used for chronic non-cancer risk calculations
$\boldsymbol{LADC}$ = lifetime average daily concentration (8-hr TWA) used for chronic cancer risk calculations
$\boldsymbol{C}$ = contaminant concentration in air (8-hr TWA)
$\boldsymbol{ED}$ = exposure duration (8 hr/day)
$\boldsymbol{EF}$ = exposure frequency (250 days/yr)
$\boldsymbol{WY}$ = exposed working years per lifetime (tenure values used to represent: 50th percentile = 31; 95th percentile = 40)
$\boldsymbol{AT}$ = averaging time, non-cancer risks ($\boldsymbol{WY}$ × 250 days/yr × 8 hr/day)
$\boldsymbol{AT_c}$ = averaging time, cancer risks (lifetime ($\boldsymbol{LT}$) x 365 days/year x 24 hr/day; where $\boldsymbol{LT}$ = 78 years)

2.4.1.4 General Dermal Exposure Assessment Approach and Methodology

Dermal exposure data were not readily available for the conditions of use in the assessment. Because carbon tetrachloride is a volatile liquid, the dermal absorption of carbon tetrachloride depends on the type and duration of exposure. Where exposure is without gloves, only a fraction of carbon tetrachloride that comes into contact with the skin will be absorbed as the chemical readily evaporates from the skin. Specific details used to calculate the dermal exposure to carbon tetrachloride can be found in Section 2.4.1.8.

A summary of the key occupational dermal dose models for carbon tetrachloride are presented below. The supplemental document *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019c) provides detailed discussion on the values of the exposure parameters input into these models.

Key Dermal Exposure Dose Models

Current EPA dermal models do not incorporate the evaporation of material from the dermis. The dermal potential dose rate, D_{exp} (mg/day), is calculated as (U.S. EPA, 2015a):

Equation 2-3

$$\boldsymbol{D_{exp} = S \times Q_u \times Y_{derm} \times FT}$$

Where:

S is the surface area of contact: 535 cm^2 (central tendency) and 1,070 cm^2 (high end), representing the total surface area of one and two hands, respectively (note that EPA has no data on actual surface area of contact for any OES and that the value is assumed to represent an adequate proxy for a high-end surface area of contact with liquid that may sometimes include exposures to much of the hands and other areas of the body (wrists, forearms, and neck) depending scenarios.

$\boldsymbol{Q_u}$ is the quantity remaining on the skin: 1.4 mg/cm^2-event (central tendency) and 2.1 mg/cm^2-event (high end). These are the midpoint value and high end of range default value, respectively, used in the *EPA's dermal contact with liquids models*.

$\boldsymbol{Y_{derm}}$ is the weight fraction of the chemical of interest in the liquid: EPA will assess a unique value of this parameter for each occupational scenario or group of similar occupational scenarios ($0 \leq Y_{derm} \leq 1$).

FT is the frequency of events (integer number per day; 1 event/day).

Here $\boldsymbol{Q_u}$ does not represent the quantity remaining after evaporation, but represents the quantity remaining after the bulk liquid has fallen from the hand that cannot be removed by wiping the skin (*e.g.*, the film that remains on the skin).

One way to account for evaporation of a volatile solvent would be to add a multiplicative factor to the EPA model to represent the proportion of chemical that remains on the skin after evaporation, $\boldsymbol{f_{abs}}$ ($0 \leq \boldsymbol{f_{abs}} \leq 1$):

Equation 2-4

$$\boldsymbol{D_{exp} = S \times (Q_u \times f_{abs}) \times Y_{derm} \times FT}$$

This approach simply removes the evaporated mass from the calculation of dermal uptake. Evaporation is not instantaneous, but the EPA model already has a simplified representation of the kinetics of dermal uptake. More information about this approach is presented in the supplemental document *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019c).

Safety equipment manufacturers recommend Silver Shield®/4H®, Viton (synthetic rubber and fluoropolymer elastomer), Viton/Butyl and Nitrile for gloves and DuPont Tychem® BR and LV, Responder® and TK; ONESuit® TEC; and Kappler Zytron® 300, 400, and 500 as protective materials for clothing. Most nitrile gloves have a breakthrough time of only a few minutes and thus offer little protection when exposed to carbon tetrachloride. For operations involving the use of larger amounts of carbon tetrachloride, when transferring carbon tetrachloride from one container to another or for other potentially extended contact, the only gloves recommended are Viton. The gloves should not be assumed to provide full protection. Regarding glove use, data about the frequency of effective glove use – that is, the proper use of effective gloves – is very limited in industrial settings. The literature review indicated absence of data to estimate a probability distribution for effective glove use for carbon tetrachloride or relevant industrial practices. Instead, the impact of effective glove use was explored by considering different percentages of effectiveness (*e.g.*, 25% vs. 50% effectiveness).

EPA also made assumptions about glove use and associated protection factors. Where workers wear gloves, workers are exposed to carbon tetrachloride-based product that may penetrate the gloves, such as seepage through the cuff from improper donning of the gloves, and if the gloves occlude the evaporation of carbon tetrachloride from the skin. Where workers do not wear gloves, workers are exposed through direct contact with carbon tetrachloride.

Gloves only offer barrier protection until the chemical breaks through the glove material. Using a conceptual model, Cherrie (2004) proposed a glove workplace protection factor – the ratio of estimated uptake through the hands without gloves to the estimated uptake though the hands while wearing gloves: this protection factor is driven by flux, and thus varies with time. The European Centre For Ecotoxicology and Toxicology of Chemicals Targeted Risk Assessment (ECETOC TRA) model represents the protection factor of gloves as a fixed, assigned protection factor equal to 5, 10, or 20 (Marquart et al., 2017), where, similar to the APR for respiratory protection, the inverse of the protection factor is the fraction of the chemical that penetrates the glove. Dermal doses without and with glove use are estimated in the occupational exposure sections below and summarized in Table 2-24.

For most scenarios, EPA did not find enough data to determine statistical distributions of the actual exposure parameters and concentration inputs to the inhalation and dermal models described above. Within the distributions, central tendencies describe 50th percentile or the substitute that most closely represents the 50th percentile. The high-end of a distribution describes the range of the distribution above 90th percentile (U.S. EPA, 1992b). Ideally, EPA would use the 50th and 95th percentiles for each parameter. Where these statistics were unknown, the mean or median (mean is preferable to median) served as substitutes for 50th percentile and the high-end of ranges served as a substitute for 95th percentile. However, these substitutes were

highly uncertain and not ideal substitutes for the percentiles. EPA could not determine whether these substitutes were suitable to represent statistical distributions of various scenarios.

2.4.1.5 Consideration of Engineering Controls and Personal Protective Equipment

OSHA requires and NIOSH recommends employers utilize the hierarchy of controls to address hazardous exposures in the workplace. The hierarchy of controls strategy outlines, in descending order of priority, the use of elimination, substitution, engineering controls, administrative controls, and lastly PPE. The hierarchy of controls prioritizes the most effective measures first which is to eliminate or substitute the harmful chemical (*e.g.*, use a different process, substitute with a less hazardous material), thereby preventing or reducing exposure potential. Following elimination and substitution, the hierarchy recommends engineering controls to isolate employees from the hazard, followed by administrative controls, or changes in work practices to reduce exposure potential (*e.g.*, source enclosure, local exhaust ventilation systems, temperature). Administrative controls are policies and procedures instituted and overseen by the employer to protect worker exposures. The respirators do not replace engineering controls and they are implemented in addition to feasible engineering controls (29 CFR Section 1910.134(a)(1)). As the last means of control, the use of PPE (*e.g.*, respirators, gloves) is recommended, when the other control measures cannot reduce workplace exposure to an acceptable level.

Respiratory Protection

OSHA's Respiratory Protection Standard (29 CFR Section 1910.134) requires employers in certain industries to address workplace hazards by implementing engineering control measures and, if these are not feasible, provide respirators that are applicable and suitable for the purpose intended. Engineering and administrative controls must be implemented whenever employees are exposed to carbon tetrachloride concentrations above the PEL. If engineering and administrative controls do not reduce exposures to below the PEL, respirators must be worn. Respirator selection provisions are provided in Section 1910.134(d) and require that appropriate respirators are selected based on the respiratory hazard(s) to which the worker will be exposed and workplace and user factors that affect respirator performance and reliability. Assigned protection factors (APFs) are provided in Table 1 under § 1910.134(d)(3)(i)(A) (see below in Table 2-4) and refer to the level of respiratory protection that a respirator or class of respirators could be provided to employees when the employer implements a continuing, effective respiratory protection program. Implementation of a full respiratory protection program requires employers to provide training, appropriate selection, fit testing, cleaning, and change-out schedules in order to have confidence in the efficacy of the respiratory protection.

The United States has several regulatory and non-regulatory exposure limits for carbon tetrachloride. The OSHA Permissible Exposure Limit (PEL) is 10 ppm time-weighted average (TWA) and the Ceiling limit is 25 ppm and the 5-minute acceptable maximum peak allowed in any four hours is 200 ppm. The short-term exposure limit (STEL) is 25 ppm for five minutes once every four hours. The NIOSH Recommended Exposure Limit (REL) is 2 ppm (12.6 mg/m^3) for a 60-minute Short-term Exposure Limit (STEL) (OSHA, 2017). NIOSH indicates that carbon tetrachloride has an immediately dangerous to life or health (IDLH) value of 200 ppm (ATSDR, 2017; Barnes and Jones, 1967; AIHA, 1961; Kirk-Othmer, 1964; Doney et al., 2005) based on acute inhalation toxicity data in humans. OSHA's other occupational safety and health standards that would apply to carbon tetrachloride exposures that exceed these levels include hazard

assessment, exposure monitoring, and control measures such as engineering controls and respiratory protection (29 CFR 1910.1000).

OSHA requires the use of PPE including respirators to protect workers if effective engineering controls are not feasible as per OSHA's 29 CFR Section 1910.134. Knowledge of the range of respirator APFs is intended to assist employers in selecting the appropriate type of respirator, based on exposure monitoring data, that could provide a level of protection needed for a specific exposure scenario. Table 2-4 lists the range of APFs for respirators. The APFs are not to be assumed to be interchangeable for any condition of use, workplace, worker or ONU. Employers should first consider elimination, substitution, engineering, and administrative controls to reduce exposure potential and, if exposures remain over a regulatory limit, employers are required to institute a respiratory protection program and provide employees with NIOSH-certified respirators. Where other hazardous agents could exist in addition to carbon tetrachloride, consideration of combination cartridges would be necessary. Table 2-4 can be used as a guide to show the protectiveness of each category of respirator; EPA took this information into consideration as discussed in Section 4.2.1. Based on the APF, inhalation exposures may be reduced by a factor of 5 to 10,000 when employers implement an effective respiratory protection program.

Table 2-4. Assigned Protection Factors for Respirators in OSHA Standard 29 CFR § 1910.134

Type of Respirator	Quarter Mask	Half Mask	Full Facepiece	Helmet/ Hood	Loose-fitting Facepiece
1. Air-Purifying Respirator	5	10	50	-	-
2. Power Air-Purifying Respirator (PAPR)	-	50	1,000	25/1,000	25
3. Supplied-Air Respirator (SAR) or Airline Respirator					
• Demand mode	-	10	50	-	-
• Continuous flow mode	-	50	1,000	25/1,000	**25**
• Pressure-demand or other positive-pressure mode	-	50	1,000	-	-
4. Self-Contained Breathing Apparatus (SCBA)					
• Demand mode	-	10	50	50	-
• Pressure-demand or other positive-pressure mode (*e.g.*, open/closed circuit)	-	-	10,000	10,000	-
Source: 1910.134(d)(3)(i)(A)					

The National Institute for Occupational Safety and Health (NIOSH) and the U.S. Department of Labor's Bureau of Labor Statistics (BLS) conducted a voluntary survey of U.S. employers regarding the use of respiratory protective devices between August 2001 and January 2002. The survey had a 75.5% response rate (NIOSH, 2003). A voluntary survey may not be representative of all private industry respirator use patterns as some establishments with low or no respirator

use could have chosen to not respond to the survey. Therefore, results of the survey could potentially be biased towards higher respirator use. NIOSH and BLS estimated about 619,400 establishments used respirators for voluntary or required purposes (including emergency and non-emergency uses). About 281,800 establishments (45%) were estimated to have had respirator use for required purposes in the 12 months prior to the survey. The 281,800 establishments estimated to have had respirator use for required purposes were estimated to be approximately 4.5% of all private industry establishments in the U.S. at the time (NIOSH, 2003). Various surveys and studies indicated that the performance of respiratory protective equipment programs varied across industry. In a more recent article, Bell *et al*. (2012) reported cross-industry analysis for 20 companies, the majority representing small- or medium-sized enterprises, across various sectors. Four distinct groups emerged from the 20 sites, ranging from learners (low theoretical competence and practical control - 4 sites), developers (acceptable theoretical competence and low practical control - 5 sites), and fortuitous (low theoretical competence and acceptable practical control - two sites), to proficient (acceptable theoretical competence and practical control - nine sites). None of the companies were achieving optimal control using the respiratory protective equipment. Widespread inadequacies were found with program implementation, particularly training, supervision, and maintenance. In a separate study, the University of Pittsburgh, CDC, and RAND Corporation used the OSHA data base to examine all inspections in manufacturing in 47 states from 1999 through 2006 (Mendeloff et al., 2013); the examination starts with 1999 because an expanded OSHA respiratory program standard became effective in late 1998. The article identified inspections and establishments at which respiratory protection violations were cited, and it compares the prevalence of violations by industry with the prevalence reported in the BLS survey of respirator use. The pattern of noncompliance across industries mostly mirrored the survey findings about the prevalence of requirements for respirator use. The probability of citing a respiratory protection violation was similar across establishment size categories, except for a large drop for establishments with over 200 workers. The presence of a worker accompanying the inspector increased the probability that a respiratory program violation could be cited; the presence of a union slightly decreased it.

Additional studies have recognized the needs of appropriate training and maintenance when respirators are used. OSHA's fatality reports from 1990 to 2012 were analyzed by Cowan *et al.* (2017) to characterize historical trends in fatalities associated with respirators. Industry- and time-specific trends were evaluated to determine the effect on respirator-related fatalities. Cowan *et al.* (2017) reported 174 respirator related deaths, and 79% of the fatalities were associated with asphyxia associated with improper employee use or lack of employer compliance.

Dermal Protection

Based on a hazard assessment, employers must also determine whether employees are exposed to skin hazards (29 CFR Section 1910.132(d)). The Hand Protection section of OSHA's Personal Protective Equipment Standard (29 CFR Section 1910.138) indicates employers to select and require workers to wear gloves to prevent exposure to harmful substances identified in the hazard assessment. The gloves of appropriate material of chemical resistance are used to prevent employee exposures to skin hazards. Employers base selection of gloves on the type of hazardous chemical(s) encountered, conditions during use, tasks performed and factors that affect performance and wear ability. Gloves, if proven chemically resistant, and if worn on clean hands and replaced when contaminated or compromised, could provide employees with

protection from hazardous substances. Cherrie *et al.* (2004) used a conceptual model of dermal exposure to analyze how workers' skin could expose while wearing gloves, and proposed a glove workplace protection factor (PF), which is the ratio of the estimated uptake of chemicals through the hands without gloves to the uptake through the hands while wearing protective gloves. Table 2-5 shows these glove PF as suggested by Marquart *et al.* (2017) and the dermal protection strategies. These values could vary depending on the type of gloves used and the presence of employee training program.

Table 2-5. Exposure Control Efficiencies and Protection Factors for Different Dermal Protection Strategies

Dermal Protection Characteristics	Affected User Group	Efficiency	Protection Factor
a. Any glove without permeation data and without employee training	Industrial/Commercial Uses	0	1
b. Gloves with available permeation data indicating that the material of construction offers good protection for the substance		80	5
c. Chemically resistant gloves (*i.e.*, as *b* above) with "basic" employee training		90	10
d. Chemically resistant gloves in combination with specific activity training (*e.g.*, procedure for glove removal and disposal) for tasks where dermal exposure could occur	Industrial Uses	95	20
Source: (Marquart et al., 2017)			

2.4.1.6 Regrouping of Conditions of Use for Engineering Assessment

EPA assessed the conditions of use in Table 1-4. Categories and Subcategories of Conditions of Use Included in the Scope of the Risk Evaluation; however, several of the categories and/or subcategories were regrouped and assessed together due to similarities in their processes and exposures. This regrouping minimized repetitive assessments and this classification could be representative of the potential exposure for the specified process category. Additionally, each condition of use may be assessed at the category or subcategory level depending on the specifics of the processes and the exposure potential for each category/subcategory. For example, import is listed under the manufacture life cycle stage in Table 1-4, however, in the engineering assessment it is analyzed with the processing - repackaging category due to the similar processing steps and worker interactions with carbon tetrachloride that occur during both the importing and repacking of carbon tetrachloride. Similarly, the subcategory reactive ion etching (*i.e.*, semiconductor manufacturing) is listed under the processing as a reactant/ intermediate category, however, it is assessed separately because it is a specialized process that uses small quantities of carbon tetrachloride in a controlled, clean room environment. This category could be different from the use of carbon tetrachloride as a reactant to produce large quantities of another chemical. Exposure from the use of carbon tetrachloride in reactive ion etching would be inaccurately captured if it was included in the assessment for the use of carbon tetrachloride as a reactant.

Similarly, the categories and subcategories originally listed in the problem formulation document (U.S. EPA, 2018c) for incorporation into formulation are regrouped to either the use of carbon

tetrachloride as a reactant to manufacturing a chlorinated compound that is subsequently formulated into a product or as a processing aid/agent used to aid in the manufacture of formulated products (agricultural chemicals, petrochemicals-derived products, and any other basic organic and inorganic chemical manufacturing). The former case (*i.e.*, reactant used upstream in manufacturing of formulated product) is evaluated in the reactant section and the latter (*i.e.*, processing aid/agent in manufacturing of formulated products) in the processing aid section.

A crosswalk of all the conditions of use listed in Table 1-4 to the conditions of use assessed for occupational exposures is provided in Table 2-6 below.

Table 2-6. Crosswalk of Subcategories of Use Listed in Table 1-4 and the Sections Assessed for Occupational Exposure

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4[10]	Category in Current Engineering Assessment
Manufacture	Domestic manufacture	Domestic manufacture	Domestic Manufacturing (Section 2.4.1.7.1)
	Import	Import	Import and Repackaging (Section 2.4.1.7.2)
Processing	Processing as a reactant/ intermediate	Hydrochlorofluorocarbons (HCFCs), Hydrofluorocarbon (HFCs) and Hydrofluoroolefin (HFOs)	Processing as a Reactant or Intermediate (Section 2.4.1.7.3)
		Perchloroethylene (PCE)	
		Reactive ion etching (*i.e.*, semiconductor manufacturing)	Reactive Ion Etching (Section 2.4.1.7.5)
	Incorporation into Formulation, Mixture or Reaction products	Petrochemicals-derived manufacturing; Agricultural products manufacturing; Other basic organic and inorganic chemical manufacturing.	Industrial Processing Agent/Aid (Section 2.4.1.7.6) Additive (Section 2.4.1.7.7) Processing as a Reactant or Intermediate (Section 2.4.1.7.3)

[10] These subcategories reflect more specific uses of carbon tetrachloride.

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4[10]	Category in Current Engineering Assessment
	Processing - repackaging	Laboratory Chemicals	Import and Repackaging (Section 2.4.1.7.2)[11]
	Recycling	Recycling	Disposal/Recycling (Section 2.4.1.7.9)
Distribution in commerce	Distribution	Distribution in commerce	Exposures from distribution are assessed within all conditions of use
Industrial/commercial use	Petrochemicals-derived products manufacturing and Agricultural products manufacturing	Processing aid	Industrial Processing Agent/Aid (Section 2.4.1.7.6)
		Additive	Additive (Section 2.4.1.7.7)
	Other Basic Organic and Inorganic Chemical Manufacturing	Manufacturing of chlorinated compounds used in solvents for cleaning and degreasing	Processing as a Reactant or Intermediate (Section 2.4.1.7.3)
	Other Basic Organic and Inorganic Chemical Manufacturing	Manufacturing of chlorinated compounds used in adhesives and sealants	Processing as a Reactant or Intermediate (Section 2.4.1.7.3)
	Other Basic Organic and Inorganic Chemical Manufacturing	Manufacturing of chlorinated compounds used in paints and coatings	Processing as a Reactant or Intermediate (Section 2.4.1.7.3)
	Other Basic Organic and Inorganic Chemical Manufacturing	Manufacturing of inorganic chlorinated compounds (*i.e.*, elimination of nitrogen trichloride in the production of chlorine and caustic)	Processing as a Reactant or Intermediate (Section 2.4.1.7.3)

[11] Repackaging is assessed, but not specifically for the use of laboratory chemicals. EPA expects exposures from repackaging of carbon tetrachloride to be similar regardless of the end-use function of carbon tetrachloride.

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4[10]	Category in Current Engineering Assessment
	Other Basic Organic and Inorganic Chemical Manufacturing	Manufacturing of chlorinated compounds used in asphalt	Processing as a Reactant or Intermediate (Section 2.4.1.7.3)
	Other uses	Processing aid (*i.e.*, metal recovery).	Industrial Processing Agent/Aid (Section 2.4.1.7.6)
		Specialty uses (*i.e.*, DoD uses)	Specialty Uses – DoD Data (Section 2.4.1.7.4)
	Laboratory chemicals	Laboratory chemical	Laboratory Chemicals (Section 2.4.1.7.8)
Disposal	Disposal	Industrial pre-treatment	Disposal/Recycling (Section 2.4.1.7.9)[12]
		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	

[12] Each of the conditions of use of carbon tetrachloride may generate waste streams of the chemical that are collected and transported to third-party sites for disposal, treatment, or recycling. Industrial sites that treat, dispose, or directly discharge onsite wastes that they themselves generate are assessed in each condition of use assessment. This Section only assesses wastes of carbon tetrachloride that are generated during a condition of use and sent to a third-party site for treatment, disposal, or recycling.

The following Sections contain process descriptions and the specific details (worker activities, analysis for determining number of workers, and exposure assessment approach and results) for the assessment of the regrouped conditions of use, and provide a summary of the engineering assessments focusing on results. Additional details on how EPA arrived at the results can be found in the supplemental *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019c).

2.4.1.7 Inhalation Exposure Assessment

The following sections present inhalation exposure estimates for each condition of use.

2.4.1.7.1 Domestic Manufacturing

Process Description

Currently, most carbon tetrachloride is manufactured using one of three methods:

1. Chlorination of Hydrocarbons or Chlorinated Hydrocarbons
2. Oxychlorination of Hydrocarbons
3. CS_2 Chlorination (Holbrook, 2000)

EPA assessed the import of carbon tetrachloride separate from domestic manufacturing (see 2.4.1.7.2) in order to account for differences in the expected industrial operations and the associated worker activities which would otherwise be inaccurately captured if included in this scenario.

Worker Activities

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 quality control (QC) samples, manually loading carbon tetrachloride product, or connecting/disconnecting transfer lines used to load carbon tetrachloride product into containers.

ONUs for manufacturing include supervisors, managers, and tradesmen that may be in the same area as exposure sources but may not perform tasks that result in the same level of exposures as workers. The presence and activities of the worker or ONUs near/far away from the source or the performance of ventilation units could have a considerable influence on the flow field around the person and thus on the dispersion of the chemical from the source to the breathing zone.

Number of Workers and Occupational Non-Users

The CDR Rule under TSCA (40 CFR Part 711) requires that U.S. manufacturers and importers provide EPA with information on chemicals they manufacture (including imports). For the 2016 CDR cycle, data collected for each chemical include the company name, volume of each chemical manufactured/imported, the number of workers employed at each site, and information on whether the chemical is used in the commercial, industrial, and/or consumer sector. Based on activity information reported in the 2016 CDR and 2016 TRI, EPA identified seven sites that domestically manufacture carbon tetrachloride.

To determine the total number of workers and ONUs, EPA used the reported number of workers range from each CDR entry. Since a range is presented in CDR, EPA determined a low-end and high-end of number of exposed workers and ONUs. Six sites reported 100 to 500 workers and

One site reported 25 to 50 workers (U.S. EPA, 2016c). The CDR data does not differentiate between workers and ONUs; therefore, EPA assumed the ratio of workers to ONUs would be similar to the average worker and ONUs estimates from the BLS analysis (U.S. BLS, 2016). EPA used the average worker and ONUs estimates from the BLS analysis based on the reported NAICS codes (or 325199 when not available) in TRI(U.S. BLS, 2016).

EPA used the seven sites reported as domestic manufacturers in the 2016 CDR and/or 2017 TRI and the average worker and ONUs estimates from the BLS analysis and TRI reported NAICS codes to determine the total number of workers and ONUs. This resulted in 6 sites being classified under 325199 and 1 site under 325180. There is a high-end total of 2,100 exposed workers and 980 exposed ONUs and low-end total of 430 exposed workers and 200 exposed ONUs (see Table 2-7).

Table 2-7. Estimated Number of Workers Potentially Exposed to Carbon Tetrachloride During Manufacturing

Number of Sites	Total Exposed Workers	Total Exposed Occupational Non-Users	Total Exposed
High-End			
7	2,100	980	3,100
Low-End			
7	430	200	630

Inhalation Exposure

EPA assessed inhalation exposures during manufacturing using identified monitoring data. Table 2-8 summarizes 8-hr and 12-hr TWA samples for worker inhalation exposure monitoring data obtained from data submitted by the Halogenated Solvents Industry Alliance (HSIA) via public comment for two companies (HSIA, 2019). For additional details on the methodology and approach for data analysis that produced the following results, refer to *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019c).

HSIA (HSIA, 2019) provided monitoring data for carbon tetrachloride collected by two companies listed as "Company A" and "Company B." The data were collected between 2005 and 2018 with full-shift data collected over 8 to 12 hours during which workers engaged in a variety of activities including collecting catch samples; performing filter changes; line and equipment opening; loading and unloading; process sampling; and transferring of hazardous wastes (HSIA, 2019). EPA assessed two exposure scenarios: 1) 8-hr TWA exposures; and 2) 12-hr TWA exposures. Both sets of manufacturing monitoring data were determined to have a "medium" confidence rating through EPA's systematic review process.

Table 2-8. Summary of Worker Inhalation Exposure Monitoring Data for Manufacture of Carbon Tetrachloride

Exposure Calculation	Number of Samples	Central Tendency (mg/m^3)	High-End (mg/m^3)	Confidence Rating of Associated Air Concentration Data
8-hr TWA Results for Company A and B				
Full-Shift TWA	113	0.76	4.0	Medium
AC		0.76	4.0	
ADC		0.76	4.0	
LADC		0.069	0.47	
12-hr TWA Results for Company A and B				
Full-Shift TWA	243	0.50	4.8	Medium
AC		0.50	4.8	
ADC		0.50	4.8	
LADC		0.069	0.85	

Equations and parameters for calculation of the ADC and LADC are described in supplemental document *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment*.

Additional information was submitted by HSIA to specify that some of the originally submitted HSIA data were for ONU exposure (HSIA, 2019). EPA incorporated the additional information and used it to evaluate ONU exposure during manufacture of carbon tetrachloride. Table 2-9. summarizes 8-hr and 12-hr TWA samples for ONU inhalation exposure monitoring data obtained from data submitted by the Halogenated Solvents Industry Alliance (HSIA) via public comment for two companies (HSIA, 2019).

Table 2-9. Summary of ONU Inhalation Exposure Monitoring Data for Manufacture of Carbon Tetrachloride

Exposure Calculation	Number of Samples	Central Tendency (mg/m^3)	High-End (mg/m^3)	Confidence Rating of Associated Air Concentration Data
8-hr TWA Results				
Full-Shift TWA	14	0.50	1.0	Medium
AC		0.50	1.0	
ADC		0.50	1.0	
LADC		0.046	0.12	
12-hr TWA Results				
Full-Shift TWA	3	0.66	1.3	Medium
AC		0.66	1.3	
ADC		0.66	1.3	
LADC		0.090	0.23	

Equations and parameters for calculation of the ADC and LADC are described in supplemental document *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment*

2.4.1.7.2 Import and Repackaging

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. (40 CFR Part 82, 60 FR 24970, 24971 (May 10, 1995)). Therefore, once imported or manufactured, carbon tetrachloride will be handled again either on-site or by another facility for the identified uses described in detail in the following Sections.

The import and repackaging scenarios cover only those sites that purchase carbon tetrachloride from domestic and/or foreign suppliers and repackage the carbon tetrachloride from bulk containers into smaller containers for resale (*i.e.*, laboratory chemicals). It does not include sites that import carbon tetrachloride and either: (1) store the chemical in a warehouse and resell directly without repackaging; (2) act as the importer of record for carbon tetrachloride but carbon tetrachloride is never present at the site[13]; or (3) import the chemical and process or use the chemical directly at the site. In (1), there is little or negligible opportunity for exposures or releases as the containers are never opened. In (2), the potential for exposure and release is at the site receiving carbon tetrachloride, not the "import" site and exposures/releases at the site receiving carbon tetrachloride are assessed in the relevant scenario based on the condition of use for carbon tetrachloride at the site. Similarly, in (3), the potential for exposure and release at these sites are evaluated in the relevant scenario depending on the condition of use for carbon tetrachloride at the site.

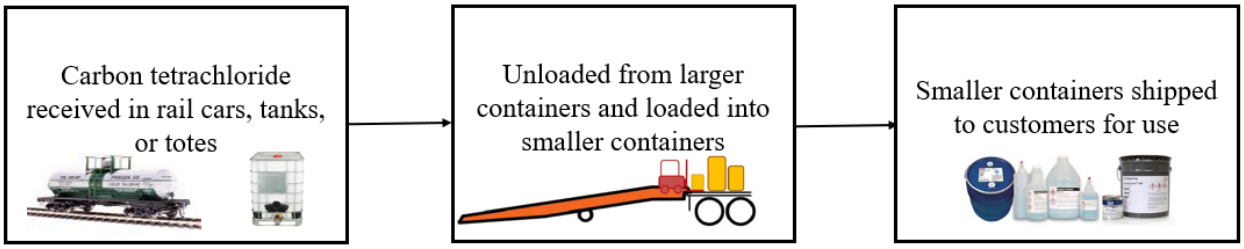
Process Description

EPA assessed the import and repackaging of carbon tetrachloride together because both uses share similar operations and worker activities that are expected to result in similar exposures.

In general, commodity chemicals are imported into the United States in bulk via water, air, land, and intermodal shipments (Tomer and Kane, 2015). These shipments take the form of oceangoing chemical tankers, railcars, tank trucks, and intermodal tank containers. Chemicals shipped in bulk containers may be repackaged into smaller containers for resale, such as drums or bottles. Domestically manufactured commodity chemicals may be shipped within the United States in liquid cargo barges, railcars, tank trucks, tank containers, intermediate bulk containers (IBCs)/totes, and drums. Both import and domestically manufactured commodity chemicals may be repackaged by wholesalers for resale; for example, repackaging bulk packaging into drums or bottles.

For this risk evaluation, EPA assesses the repackaging of carbon tetrachloride from bulk packaging to drums and bottles at wholesale repackaging sites (see Figure 2-1).

[13] In CDR, the reporting site is the importer of record which could be a corporate site or other entity that facilitates the import of the chemical but never actually receives the chemical. The chemical could be shipped directly to the site for processing or handling the chemical.



Not to scale.

Figure 2-1. General Process Flow Diagram for Import and Repackaging

Worker Activities

Based on EPA's knowledge of the chemical industry, worker activities at import and repackaging sites are potentially exposed while connecting and disconnecting hoses and transfer lines to containers and packaging to be unloaded (*e.g.*, railcars, tank trucks, totes), intermediate storage vessels (*e.g.*, storage tanks, pressure vessels), analyzing QC samples, and final packaging containers (*e.g.*, drums, bottles).

ONUs for repackaging include supervisors, managers, and tradesmen that may be in the repackaging area but do not perform tasks that result in the same level of exposures as repackaging workers.

Number of Workers and Occupational Non-Users

Upon review of CDR data, EPA determined one import site. None of the CDR submissions reported a repackaging activity in the industrial processing and use section. The number of potentially exposed workers was estimated based on data from the BLS for NAICS code 424690 (U.S. BLS, 2016; U.S. Census Bureau, 2015).

In the 2017 TRI data (U.S. EPA, 2018e), one submission reported an import activity and one submission reported a repackaging activity. The site reporting import in the 2017 TRI also reported use of carbon tetrachloride as a processing aid and is included in the assessment of use of carbon tetrachloride as a processing aid. The TRI entry marked for repackaging has primary NAICS code 562211, Hazardous Waste Treatment and Disposal, and is most likely a waste disposal facility so it is included in the waste handling/recycling assessment.

Based on the information reported in the 2016 CDR and 2017 TRI, EPA assesses one possible import/repackaging site for carbon tetrachloride (U.S. EPA, 2017f, 2016c). EPA identified the NAICS code 424690, Other Chemical and Allied Products Merchant Wholesalers, as the code could include sites importing and repackaging carbon tetrachloride. EPA assesses the number of potentially exposed workers based on data from the BLS for NAICS code 424690 and related SOC codes. There is a total of one potentially exposed workers and one ONU for sites under this NAICS code (see Table 2-10) (U.S. BLS, 2016; U.S. Census Bureau, 2015).

Table 2-10. Estimated Number of Workers Potentially Exposed to Carbon Tetrachloride During Import and Repackaging

Number of Sites	Total Exposed Workers	Total Exposed Occupational Non-Users	Total Exposed
1	1	1	2

Inhalation Exposure

EPA assessed inhalation exposures during the repackaging of carbon tetrachloride using monitoring data submitted by the HSIA for two companies via public comment (HSIA, 2019). The synopsis and interpretation of HSIA data for the assessment of worker exposure during manufacture of carbon tetrachloride were discussed in Section 2.4.1.7.1. EPA identified 15 of the 356 HSIA submitted data points as worker activities for the unloading and/or loading of carbon tetrachloride into tank trucks or railcars. EPA used these data as surrogate data to estimate exposures at repackaging facilities where the primary exposure activity could involve unloading of carbon tetrachloride from bulk containers to smaller containers. EPA assumed the worker unloading activity would result in exposures similar to unloading/loading activities at manufacturing sites. For this assessment, EPA only considered the 8-hr TWA data as information to substantiate 12-hr shifts at repackaging sites were not identified. Additionally, EPA only used data points if the worker activities were specifically for carbon tetrachloride loading/unloading.

EPA developed a Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model, conservatively assuming carbon tetrachloride is present at 100 percent concentration when imported or repackaged. The model estimates the potential concentration of carbon tetrachloride in air when it is unloaded or loaded at an industrial facility. The model accounts for the displacement of saturated air containing the chemical of interest as the container/truck is filled with liquid, emissions of saturated air containing the chemical of interest that remains in the loading arm, transfer hose and related equipment, and emissions from equipment leaks from processing units such as pumps, seals, and valves. More details included in the model calculations and methodology are discussed in the *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019c).

EPA calculated 8-hr TWA exposures to workers during loading activities that were identified in HSIA data. These HSIA data were also compared with the modeling (Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model) results. Table 2-11 presents a summary of the exposure results for the unloading and loading of carbon tetrachloride.

Table 2-11. Summary of Exposure Results for Import and Repackaging

Exposure Calculation	Number of Samples	Central Tendency (mg/m^3)	High-End (mg/m^3)	Confidence Rating of Associated Air Concentration Data
HSIA Surrogate Data				
Full-Shift TWA	15	0.89	2.9	Medium
AC		0.89	2.9	
ADC		0.89	2.9	
LADC		0.081	0.34	
Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model				
Full-Shift TWA	N/A – Modeled Data	0.057	0.30	N/A – Modeled Data
AC		0.057	0.30	
ADC		0.057	0.30	
LADC		0.0052	0.035	

The model estimated the central tendency exposure of 0.057 mg/m^3 8-hr TWA and a high-end exposure of 0.30 mg/m^3 8-hr TWA. However, exposure results from the monitoring data from unloading and loading resulted in the central tendency exposure of 0.89 mg/m^3 8-hr TWA and a high-end exposure of 2.9 mg/m^3 8-hr TWA. Both the central tendency and high-end exposure calculations are an order of magnitude higher than those calculated from the model. The difference could be that the model only accounted for exposures during a single loading/ unloading event while the monitoring data may have captured exposures from other sources including additional loading/unloading activities and a fugitive emissions from process equipment (*e.g.*, valves, pumps, etc.).

2.4.1.7.3 Processing as a Reactant or Intermediate

Process Description

Through processing as a reactant or intermediate, carbon tetrachloride serves as a feedstock in the production of another chemical product via a chemical reaction in which carbon tetrachloride is consumed. Carbon tetrachloride is a reactant used in the manufacturing of both inorganic and organic chlorinated compounds. In the past, carbon tetrachloride was mainly used as feedstock for the manufacture of 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). One of the primary CFC replacements was the HFCs. Most HFCs, do not require carbon tetrachloride for their manufacture. However, carbon tetrachloride is used as a feedstock to produce HFC-245fa and HFC-365mfc. The production of hydrofluorocarbons HFC-245fa and HFC-365mfc accounted for 71% and 23%, respectively, of total carbon tetrachloride consumption in 2016 (MacRoy, 2017).

Currently, carbon tetrachloride is used as a reactant to manufacture a variety of chlorinated compounds including:

- HCFCs
- HFCs
- Hydrofluoroolefins (HFO)s
- Vinyl Chloride
- Ethylene Dichloride (EDC)
- Perchloroethylene (PCE)
- Chloroform
- Hafnium Tetrachloride
- Thiophosgene
- Methylene Chloride (Krock, 2017; U.S. EPA, 2017d; Marshall and Pottenger, 2016; Weil et al., 2006; Holbrook, 2003).

The listed chlorinated compounds may then be used in solvents for cleaning and degreasing, adhesives and sealants, paints and coatings, and asphalt.

Worker Activities

Similar to when manufacturing carbon tetrachloride, workers are potentially exposed while connecting and disconnecting hoses and transfer lines to containers and packaging to be unloaded (*e.g.*, railcars, tank trucks, totes) and manually adding raw materials into intermediate storage vessels (*e.g.*, storage tanks, pressure vessels) when processing carbon tetrachloride as a reactant.

ONUs for processing as a reactant include supervisors, managers, and tradesmen that may be in the same area as exposure sources but do not perform tasks that result in the same level of exposures as workers.

Number of Workers and Occupational Non-Users

The number of workers and occupational non-users potentially exposed to carbon tetrachloride at sites processing carbon tetrachloride as a reactant were assessed using 2016 CDR data, 2017 TRI data, BLS Data and SUSB Data. From the 2016 CDR data, seven submitters reported eight records of processing carbon tetrachloride as a reactant with each record reporting fewer than 10 sites that process carbon tetrachloride as a reactant. However, five of the eight CDR records are also reported manufacture locations of carbon tetrachloride. EPA assessed these five records among the manufacturing Section (Section 2.4.1.7.1). EPA assesses the remaining three reports from CDR in this Section. Upon review of 2017 TRI, EPA found eight sites reported using carbon tetrachloride as a reactant (U.S. EPA, 2017f), and five of these sites are reported manufacturers of carbon tetrachloride in CDR. This falls within the range reported for number of sites from the 2016 CDR. EPA assessed three of the listed TRI submissions that use carbon tetrachloride as a reactant. Between CDR and TRI, EPA assessed a range of six to thirty sites.

To determine the high-end total number of workers and ONUs, EPA used the high-end of ranges reported for number of sites (nine sites) in the three 2016 CDR reports. The CDR data does not differentiate between workers and ONUs; therefore, EPA considered that the ratio of workers to ONUs could be similar as determined by NAICS code in the BLS data (U.S. BLS, 2016; U.S.

EPA, 2016c). For the other three TRI submissions, the average worker and ONUs estimates from the BLS analysis were used based on their NAICS codes (U.S. BLS, 2016).This resulted in an estimated 3,400 workers and 1,600 ONUs (see Table 2-12).

To determine the low-end total number of workers and ONUs, EPA used the low-end of ranges reported for number of sites in the three CDR reports. Then, EPA assessed using the corresponding number of workers from BLS analysis that are associated with the primary NAICS codes for those entries (U.S. BLS, 2016; U.S. EPA, 2016c). For the remaining three TRI sites, EPA used the average worker and ONUs estimates from the BLS analysis and TRI reported NAICS codes (U.S. EPA, 2017f; U.S. BLS, 2016).This resulted in an estimated 170 workers and 80 ONUs (see Table 2-12).

Table 2-12. Estimated Number of Workers Potentially Exposed to Carbon Tetrachloride During Processing as a Reactant or Intermediate

Number of Sites	Total Exposed Workers	Total Exposed Occupational Non-Users	Total Exposed
High-End			
30	3,400	1,600	4,900
Low-End			
6	170	80	250

Inhalation Exposure

EPA identified one source for inhalation exposure monitoring data related to the use of carbon tetrachloride as a reactant or intermediate; however, the discrete sample values as well as the number of samples taken were not available to estimate exposure concentrations. In a separate study, performed by researchers at Pavia (Italy), collected air samples using personal passive dosimeters; blood and urine samples from 55 workers operating in two chemical plants where carbon tetrachloride was used (Ghittori et al., 1994). The test parameters of the biomonitoring study included age of workers between 20 and 58 years with the average working experience of 10.5 years; the average exposure concentration of carbon tetrachloride was in the range 1.1 to 29.8 mg/m^3. Ghittori *et al.* (1994) reported that the exposure probably came from inhalation of carbon tetrachloride vapor as the involved workers wore poly(viny1 alcohol) gloves during the entire shift to prevent liquid contact. The study does not present individual data points and associated sample durations but provides summarized data from personal-breathing-zone air sampling that took place over four hours, or "half work shifts."

EPA recognizes that the manufacturing setting and associated worker activities are similar for both the manufacture and use as a reactant or intermediate of carbon tetrachloride. Therefore, the exposure sources, exposure routes, and exposure levels for the manufacture of carbon tetrachloride have been used as surrogate data to assess the inhalation exposure during the use of carbon tetrachloride as a reactant or intermediate.

The manufacturing monitoring data were determined to have a "medium" confidence rating through EPA's systematic review process. Although these data are not directly applicable to

processing of carbon tetrachloride as a reactant, EPA expects a high degree of overlap of worker tasks at both manufacturing sites and sites processing carbon tetrachloride as a reactant. Based on this expectation and the strength of the monitoring data, EPA has a medium to high level of confidence in the assessed exposures. See Section 2.4.1.7.2 for the assessment of worker exposure from chemical manufacturing activities.

2.4.1.7.4 Specialty Uses - Department of Defense Data

EPA reached out to the Department of Defense (DoD) for monitoring data for the first 10 chemical substances. The DoD provided monitoring data from its Defense Occupational and Environmental Health Readiness System – Industrial Hygiene (DOEHRS-IH), which collects occupational and environmental health risk data from each service branch. The DoD provided inhalation monitoring data for three branches of the military: The Army, Air Force, and Navy (Defense Occupational and Environmental Health Readiness System - Industrial Hygiene (DOEHRS-IH), 2018). The composite DoD data do not identify whether they are specifically used by the Army, Air Force, and Navy.

The following subsections provide an overview of the DoD data. EPA only used the Open Burn/Open Detonation (OBOD) clean-up data in this assessment as these were the only data EPA could use to assess 8-hr TWA exposures. The sampling results for the remaining six processes were measured over a period less than 50 percent of the duration of the process (or an 8-hr shift if the process duration was not specified). No extrapolation of data was performed to estimate 8-hr TWA exposure using those data that were sampled only a fraction of the process time (or an 8-hr shift).

Data Overview

The data provided by DoD includes 105 data points for carbon tetrachloride from personal breathing zone samples taken during seven processes:

1. OBOD Clean-Up
2. Detonation Chamber
3. Mobile Detonation Test Facility
4. Plastics/Modeling (Thermoforming)
5. Solvent Extraction of Explosive Samples
6. Glue Sound Dampening Material to Torpedo Body
7. Spray Painting – High Volume, Low Pressure (HVLP) Spray Gun

The personal breathing zone samples for the DoD activities are summarized in Table 2-13. All sample results are indicated as less than a value, which is considered to be the limit of detection (LOD). The DoD data stated that all workers monitored worked an 8-hr shift. For some processes, the DoD data do not provide the process duration.

Table 2-13. DoD Inhalation Monitoring Results

Process	Worker Activity Description	Worker Activity Frequency	Process Duration (hours)	Min. Sample Result (mg/m^3)	Max. Sample Result (mg/m^3)	Number of Samples	Sample Duration (min)	Sample Date
OBOD Clean-Up	Cleaning and sampling residual metal and ash	1-2 hours	1-2 hours	< 1.26[1]	-	3	140	Jan. 27, 2015
Detonation Chamber	Destruction of munition and storage of resulting liquid waste	Special Occasions	>10 hours	< 2.9	< 30	95	14-140	2011
Mobile Detonation Test Facility	Destruction of munition and storage of resulting liquid waste	Special Occasions	>10 hours	< 3.8	< 17	3	24-116	June 15, 2011
Plastics/ Modeling (Thermoforming)	None Provided	2-3 Times/ Month	-	< 5000 ppb	-	1	104	Dec. 4, 2015
Solvent Extraction of Explosive Samples	Sampling of energetics with solvent	Weekly	6-8 hours	< 5.52	-	1	60	Sept. 22, 1993
Glue Sound Dampening Material to Torpedo Body	None Provided	Special Occasions	-	< 0.217	-	1	221	June 22, 2011
Spray Painting – High Volume, Low Pressure (HVLP) Spray Gun	None Provided	Weekly	-	< 3.2	-	1	0	June 5, 2016

[1]All three samples provided were listed as < 0.2 ppm (1.26 mg/m^3)

OBOD Clean-Up Process Description

During the OBOD clean-up process, employees clean up residual metal and ash. Small metal pieces and ash are drummed and stored. Once drum(s) are full, personnel perform sampling to determine disposal requirements. Larger pieces of metal can be sold for recycling once deemed inert. Clean-up is performed in steel toe boots, coveralls, and respiratory protection (powered air-purifying respirator [PAPR] with tight-fitting facepiece and organic vapor and HEPA cartridge). A self-contained breathing apparatus (SCBA) is available for emergencies and as needed for clean-up (Defense Occupational and Environmental Health Readiness System - Industrial Hygiene (DOEHRS-IH), 2018).

Inhalation Exposure

As the exposure values are reported to be below the LOD, EPA assessed the data as a range from 0 to 1.26 mg/m^3 using the midpoint (0.68 mg/m^3) to calculate the central tendency 8-hr TWA

and the maximum value (1.26 mg/m^3) to calculate the high end 8-hr TWA. Additionally, the DoD data indicates that OBOD clean-up has a duration of one to two hours. The sampling duration of the January 27, 2015 monitoring was 140 minutes (approximately 2.3 hours). The workers' exposures are zero for the remainder of an 8-hr shift. Therefore, EPA averaged the 140-minute midpoint and maximum sample results over eight hours to calculate the 8-hr TWA exposure.

DoD reported the process frequency for the OBOD cleaning as every 2-3 weeks. EPA incorporated this data and adjusted the exposure frequency to reflect the limited work exposure time when calculating the central tendency and high-end ADC and LADC. The central tendency ADC and LADC are calculated using the midpoint of the process frequency range, 2.5 weeks (125 days/year), and the high-end ADC and LADC are calculated using maximum of the process frequency range, 3 weeks (150 days/year). Results are displayed in Table 2-14.

Table 2-14. Summary of Worker Inhalation Exposure Monitoring Data for Specialty Use of Carbon Tetrachloride

Exposure Calculation	Number of Samples	Central Tendency (mg/m^3)	High-End (mg/m^3)	Confidence Rating of Associated Air Concentration Data
8-hr TWA Results for OBOD Clean-Up				
Full-Shift TWA	3	0.18	0.37	High
AC		0.18	0.37	
ADC		0.092	0.22	
LADC		0.0083	0.026	

Equations and parameters for calculation of the ADC and LADC are described in supplemental document *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment*.

2.4.1.7.5 Reactive Ion Etching

Process Description

Reactive ion etching (RIE) is a microfabrication technique used in miniature electronic component manufacture. Ion bombardment and a reactive gas, such as carbon tetrachloride, are used to selectively etch wafers (U.S. EPA, 2017d).

Typically, a clean environment is essential for manufacturing the miniature electronic components (primarily semiconductors) that require RIE. Flaws in the wafer surface or contamination of the materials used can result in "opens" or "shorts" in the transistor circuits, causing them to be unusable (OECD, 2010). Therefore, current semiconductor fabrication facilities (*i.e.*, 'fabs') are built to Class-1 cleanroom specifications, which means there is no more than one particle larger than 0.5-micron in one cubic foot of air. In addition, cleaning operations precede and follow most of the manufacturing process steps. Wet processing, during which wafers are repeatedly immersed in or sprayed with solutions, is commonly used to minimize the risk of contamination. In addition, many processes operate within a positive pressure environment (OECD, 2010).

EPA assessed the use of carbon tetrachloride in reactive ion etching separately from processing as a reactant or intermediate to account for differences in the work environments, the industrial processes, and the quantities of carbon tetrachloride used which would otherwise be inaccurately captured if reactive ion etching was included in the reactant scenario.

Worker Activities

Specific worker activities for RIE were not identified, but EPA utilized the worker activities listed in the *Emission Scenario Document (ESD) on Photoresist Use in Semiconductor Manufacturing* because worker activities will be similar for RIE as they are for using photoresists. According to the *ESD on Photoresist Use in Semiconductor Manufacturing*, there are two main worker activity groups at a facility that utilizes RIE that include: equipment operators and equipment maintenance/waste management technicians. Equipment operators' main role is to change-out the liquid etching containers containing carbon tetrachloride. Equipment maintenance/waste management technicians clean empty containers, clean/maintain equipment, and change-out the excess solvent collection containers (OECD, 2010).

When workers must enter the cleanroom environment to perform their duties, the worker is required to wear full-body coveralls (*i.e.*, "space suits"), respirators, face shields, and gloves. Additionally, wafers are often manipulated robotically within the closed system, or transferred within "micro" enclosures between process steps to limit worker exposure. However, some sites have separate work areas outside the wafer processing area (*e.g.*, "chemical kitchens") in which the photoresist and other chemical containers and supply lines are connected. If workers handle the photoresist bottles and other chemical containers in a separate area, such as the chemical kitchen, they will likely be wearing solvent-resistant gloves, aprons, goggles, and respirators with organic vapor cartridges to minimize exposure (OECD, 2010)

Number of Workers and Occupational Non-Users

Based on information in the *ESD on Photoresist Use in Semiconductor Manufacturing*, EPA identified the NAICS code 334413, Semiconductor and Related Device Manufacturing, as the NAICS code that could include sites using carbon tetrachloride as a RIE (OECD, 2010). EPA estimated the number of workers and ONUs for this NAICS code using Bureau of Labor Statistics' OES data and the U.S. Census' SUSB (U.S. BLS, 2016; U.S. Census Bureau, 2015). This analysis resulted in an average of 50 workers and 45 ONU per site. EPA does not have data to estimate the number of sites using carbon tetrachloride as a RIE; therefore, only the per site data are presented in Table 2-15.

Table 2-15. Estimated Number of Workers Potentially Exposed to Carbon Tetrachloride During Use as a RIE

Exposed Workers per Site	Exposed Occupational Non-Users per Site	Total Exposed Per Site
50	45	95

Inhalation Exposure
The worker exposures to carbon tetrachloride during RIE are negligible. Due to the performance requirements of products typically produced via RIE, carbon tetrachloride could be applied in small amounts in a highly controlled work area, thus eliminating or significantly reducing the potential for exposures. EPA anticipates that carbon tetrachloride is used in RIE applications in limited quantities and in limited facilities. This is consistent with assumptions for similar industry processes provided in the *ESD on Chemical Vapor Deposition in the Semiconductor Industry* and *ESD on Photoresist Use in Semiconductor Manufacturing* (OECD, 2015, 2010).

2.4.1.7.6 Industrial Processing Agent/Aid

Process Description
According to the TRI *Reporting Forms and Instructions (RFI) Guidance Document*, a processing aid is a "chemical that is added to a reaction mixture to aid in the manufacture or synthesis of another chemical substance but is not intended to remain in or become part of the product or product mixture." Examples of such chemicals include, but are not limited to, process solvents, catalysts, inhibitors, initiators, reaction terminators, and solution buffers (U.S. EPA, 2018f). Additionally, processing agents are intended to improve the processing characteristics or the operation of process equipment, but not intended to affect the function of a substance or article created (U.S. EPA, 2016b).

The domestic and international use of carbon tetrachloride as a process agent is addressed under the 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 reacted or destroyed in the production process. Approved uses of carbon tetrachloride as a process agent is listed below in Table 2-16..

Table 2-16. List of Approved Uses of Carbon Tetrachloride as a Process Agent in the MP Side Agreement, Decision X/14: Process Agents[1]

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

EPA has identified uses of carbon tetrachloride as a process agent in the manufacturing of petrochemical-derived products, agricultural products, inorganic compounds (*i.e.*, chlorine), and chlorinated compounds that are used in the formulation of solvents for cleaning and degreasing, adhesive and sealants, paints and coatings and asphalt (EDF, 2020; U.S. EPA, 2017d). A current example of using carbon tetrachloride as a process agent in petrochemicals-derived product manufacturing is the manufacture of chlorinated rubber resins. The resulting resins are thermoplastic, odorless, and non-toxic. Carbon tetrachloride is preferred in this process as it is the only solvent not attacked by chlorine (U.S. EPA, 2017d).

Worker Activities

During processing, workers are primarily exposed while connecting and disconnecting hoses and transfer lines to containers and packaging to be unloaded (*e.g.*, railcars, tank trucks, totes, drums, bottles) and intermediate storage vessels (*e.g.*, storage tanks, pressure vessels).

ONUs for use of carbon tetrachloride used as a processing agent/aid include supervisors, managers, and tradesmen who may be in the same area as exposure sources but do not perform tasks that result in the same level of exposures as workers.

Number of Workers and Occupational Non-Users

In the 2016 CDR, one submitter reported the use as a processing agent/aid in the pesticide, fertilizer, and other agricultural chemical manufacturing industry and indicated this use occurs at fewer than 10 sites (U.S. EPA, 2016c). EPA identified six sites in TRI that reported using carbon tetrachloride as a processing agent/aid (U.S. EPA, 2017d). However, four of the six TRI reported sites also reported manufacture and/or reactant use of carbon tetrachloride. EPA assesses those four sites among the manufacturing and reactant use sections. EPA assesses the remaining two sites from TRI that reported using carbon tetrachloride as a processing agent/aid in this section. This agrees with the number of sites from the 2016 CDR. Between 2016 CDR and 2017 TRI data, EPA assessed a range of three to twelve sites.

To determine the high-end total number of workers and ONUs, EPA used the high-end of the range reported for number of sites (ten sites) from the 2016 CDR report and two TRI sites. The CDR data does not differentiate between workers and ONUs; therefore, EPA/OPPT assumed the ratio of workers to ONUs would be similar as determined by NAICS code in the BLS data (U.S. BLS, 2016; U.S. EPA, 2016c). For the other two TRI submissions, the average worker and ONUs estimates from the BLS analysis were used based on their NAICS codes (U.S. BLS, 2016). This resulted in an estimated 3,900 workers and 1,200 ONUs (see Table 2-17.).

To determine the low-end total number of workers and ONUs, EPA used the low-end of the range reported for number of sites (one site) from the 2016 CDR report and two TRI sites. The CDR data does not differentiate between workers and ONUs; therefore, EPA/OPPT assumed the ratio of workers to ONUs would be similar as determined by NAICS code in the BLS data (U.S. BLS, 2016; U.S. EPA, 2016c). For the other two TRI submissions, the average worker and ONUs estimates from the BLS analysis were used based on their NAICS codes (U.S. BLS, 2016). This resulted in an estimated 120 workers and 47 ONUs (see Table 2-17.).

Table 2-17. Estimated Number of Workers Potentially Exposed to Carbon Tetrachloride During Use as a Processing Agent/Aid

Number of Sites	Total Exposed Workers	Total Exposed Occupational Non-Users	Total Exposed
High-End			
12	3,900	1,200	5,100
Low-End			
3	120	47	170

Inhalation Exposure
EPA did not find any exposure data for use of carbon tetrachloride as a processing agent/aid; therefore, exposures from incorporation into formulation activities were assessed with surrogate data from HSIA using data that have similar worker activities.

See Section 2.4.1.7.2 for the assessment of worker exposure from chemical unloading activities. The exposure sources, routes, and exposure levels are similar to those at an import/repackaging facility, where unloading and handling are the key worker activities. Inhalation exposure for processing of carbon tetrachloride as a processing agent/aid is estimated using the surrogate data from HSIA as described in the import/repackaging scenario.

2.4.1.7.7 Additive

Process Description
Additives are chemicals combined with a chemical product to enhance the properties of the product. Additives typically stay mixed within the finished product and remain unreacted.

This section includes the assessment of the use of carbon tetrachloride as an additive for petrochemicals-derived products manufacturing and agricultural products manufacturing. Specific uses of carbon tetrachloride as an additive include both an additive used in plastic components used in the automotive industry (HSIA, 2017) and a fuel additive (U.S. EPA, 2017d).

Worker Activities
Similar to manufacturing facilities, worker activities use of carbon tetrachloride as an additive 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 quality control (QC) samples, and packaging formulated products into containers and tank trucks. The exact activities and associated level of exposure will differ depending on the degree of automation, presence of engineering controls, and use of PPE at each facility.

ONUs for use of carbon tetrachloride as an additive include supervisors, managers, and tradesmen that may be in the same area as exposure sources but do not perform tasks that result in the same level of exposures as workers.

Number of Workers and Occupational Non-Users
Upon review of the 2017 TRI data, EPA found that one site reported the use of carbon tetrachloride as a formulation component (U.S. EPA, 2018e). EPA determined the number of workers using the related SOC codes from BLS analysis that are associated with the primary NAICS code, 325211, listed in TRI. This resulted in an estimated 27 workers and 12 ONUs potentially exposed at sites using carbon tetrachloride as an additive (see Table 2-18).

Table 2-18. Estimated Number of Workers Potentially Exposed to Carbon Tetrachloride when used as an Additive

Number of Sites	Total Exposed Workers	Total Exposed Occupational Non-Users	Total Exposed
1	27	12	39

Inhalation Exposure
EPA did not find any exposure monitoring data for use of carbon tetrachloride as an additive; therefore, exposures from incorporation into formulation activities were assessed with surrogate data from HSIA using data that have similar worker activities.

See Section 2.4.1.7.2 for the assessment of worker exposure from chemical unloading activities. The exposure sources, routes, and exposure levels are similar to those at an import/ repackaging facility, where unloading and handling are the key worker activities. Inhalation exposure assessment for processing of carbon tetrachloride as a processing agent/aid is estimated using the surrogate data from HSIA as described in the import/repackaging scenario.

2.4.1.7.8 Laboratory Chemicals

Process Description
Carbon tetrachloride is used in a variety of laboratory applications, which include, but are not limited to, the following:

- Chemical reagent;
- Extraction solvent; and
- Reference material or solvent in analytical procedures, such as spectroscopic measurements (U.S. EPA, 2017d).

Specific process descriptions for how carbon tetrachloride is used in each of these applications is not known. In general, carbon tetrachloride is typically received in small containers and used in small quantities on a lab bench in a fume cupboard or hood. After use, waste carbon tetrachloride is collected and disposed or recycled. Figure 2-2 depicts this general process.

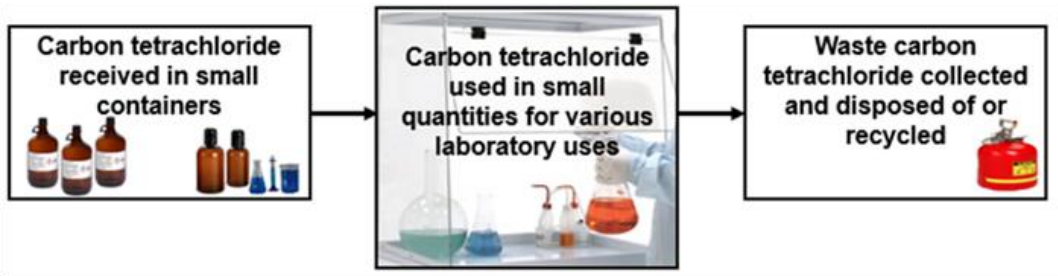


Figure 2-2. General Laboratory Use Process Flow Diagram

EPA assessed the repackaging of carbon tetrachloride separately (see Section 2.4.1.7.2) in order to account for differences in the industrial processing methods, processing quantities, and the associated worker interaction which would otherwise be inaccurately captured if included in this scenario.

Worker Activities

Specific worker activities for using laboratory uses were not identified, but the workers could be potentially exposed to carbon tetrachloride in laboratories during multiple activities, including unloading of carbon tetrachloride from the containers in which they were received, transferring carbon tetrachloride into laboratory equipment (*i.e.*, beakers, flasks, other intermediate storage containers), dissolving substances into carbon tetrachloride or otherwise preparing samples that contain carbon tetrachloride analyzing these samples, and discarding the samples.

ONUs include employees that work at the sites where carbon tetrachloride is used, but they do not directly handle the chemical and are therefore could have lower inhalation exposures and would not have dermal exposures. ONUs for this condition of use include supervisors, managers, and other employees that may be in the laboratory but do not perform tasks that result in the same level of exposures as those workers that engage in tasks related to the use of carbon tetrachloride.

Number of Workers and Occupational Non-Users

Using 2016 CDR data and 2017 TRI data, EPA confirmed one industrial use of carbon tetrachloride as a laboratory chemical for fewer than ten sites (U.S. EPA, 2018e, 2016a). EPA determined the number of workers using the related SOC codes from BLS analysis that are associated with the primary NAICS code, 541380, Testing Laboratories.

To determine the high-end total number of workers and ONUs, EPA used the high-end number of sites from CDR (nine sites) and the BLS OES data to estimate number of workers per site. This resulted in a total of 230 exposed workers and ONUs (see Table 2-19).

To determine the low-end total number of workers and ONUs, EPA used the low-end number of sites from CDR (one site) and the BLS OES data to estimate workers per site listed for these industrial use sites. This resulted in a total of ten exposed workers and ONUs (see Table 2-19).

Table 2-19. Estimated Number of Workers Potentially Exposed to Carbon Tetrachloride During Use as a Laboratory Chemical

Number of Sites	Total Exposed Workers	Total Exposed Occupational Non-Users	Total Exposed
High-End			
9	23	200	230
Low-End			
1	1	9	10

Inhalation Exposure

EPA does not have monitoring data to assess worker exposures to carbon tetrachloride during laboratory use. Following workplace safety protocols for the use of chemicals in laboratories, carbon tetrachloride is generally handled in small amounts as required for reactions or analyses. Carbon tetrachloride is handled under a fume hood as per good laboratory practices, thus reducing the potential for inhalation exposures.

2.4.1.7.9 Disposal/Recycling

This scenario is meant to include sites like hazardous waste treatment sites (TSDFs), including incinerators, landfills, other forms of treatment, and solvent or other material reclamation or recycling. These are sites largely covered under RCRA (*e.g.*, RCRA permitted TSDFs) but also include municipal waste combustors and landfills.

Process Description

Each of the conditions of use of carbon tetrachloride may generate waste streams of the chemical that are collected and transported to third-party sites for disposal, treatment, or recycling. Industrial sites that treat or dispose onsite wastes that they themselves generate are assessed in each condition of use assessment in Sections 2.4.1.7.1 to 2.4.1.7.8. Wastes of carbon tetrachloride that are generated during a condition of use and sent to a third-party site for treatment, disposal, or recycling may include the following:

- Wastewater: Carbon tetrachloride may be contained in wastewater discharged to POTW or other, non-public treatment works for treatment. Industrial wastewater containing carbon tetrachloride discharged to a POTW may be subject to EPA or authorized NPDES state pretreatment programs.
- Solid Wastes: Solid wastes are defined under RCRA as any material that is discarded by being: abandoned; inherently waste-like; a discarded military munition; or recycled in certain ways (certain instances of the generation and legitimate reclamation of secondary materials are exempted as solid wastes under RCRA). Solid wastes may subsequently meet RCRA's definition of hazardous waste by either being listed as a waste at 40 CFR §§ 261.30 to 261.35 or by meeting waste-like characteristics as defined at 40 CFR §§ 261.20 to 261.24. Solid wastes that are hazardous wastes are regulated under the more stringent requirements of Subtitle C of RCRA, whereas non-hazardous solid wastes are regulated under the less stringent requirements of Subtitle D of RCRA.
    - Carbon tetrachloride is both a listed and a characteristic hazardous waste. Carbon tetrachloride is a non-specific-source listed hazardous waste under waste number

F001 (spent halogenated degreasing solvents) [40 CFR Section 261.31] and a source-specific listed hazardous waste under waste number K016 (heavy ends or distillation residues from the production of carbon tetrachloride, which may contain residual carbon tetrachloride) [40 CFR Section 261.32]. Discarded, commercial-grade carbon tetrachloride is a listed hazardous waste under waste number U211 40 CFR § 261.33.

  - Carbon tetrachloride is a toxic contaminant under RCRA with waste number D019. A solid waste can be a hazardous waste due to its toxicity characteristic if its extract following the Toxicity Characteristic Leaching Procedure (TCLP) (or the liquid waste itself if it contains less than 0.5% filterable solids) contains at least 0.5 mg/L of carbon tetrachloride [40 CFR Section 261.24].

- Wastes Exempted as Solid Wastes under RCRA: Certain conditions of use of carbon tetrachloride may generate wastes of carbon tetrachloride that are exempted as solid wastes under 40 CFR Section 261.4(a). For example, the generation and legitimate reclamation of hazardous secondary materials of carbon tetrachloride may be exempt as a solid waste.

2016 TRI data lists off-site transfers of carbon tetrachloride to land disposal, wastewater treatment, incineration, and recycling facilities (U.S. EPA, 2017b, g). See Figure 2-3 for a general depiction of the waste disposal process.

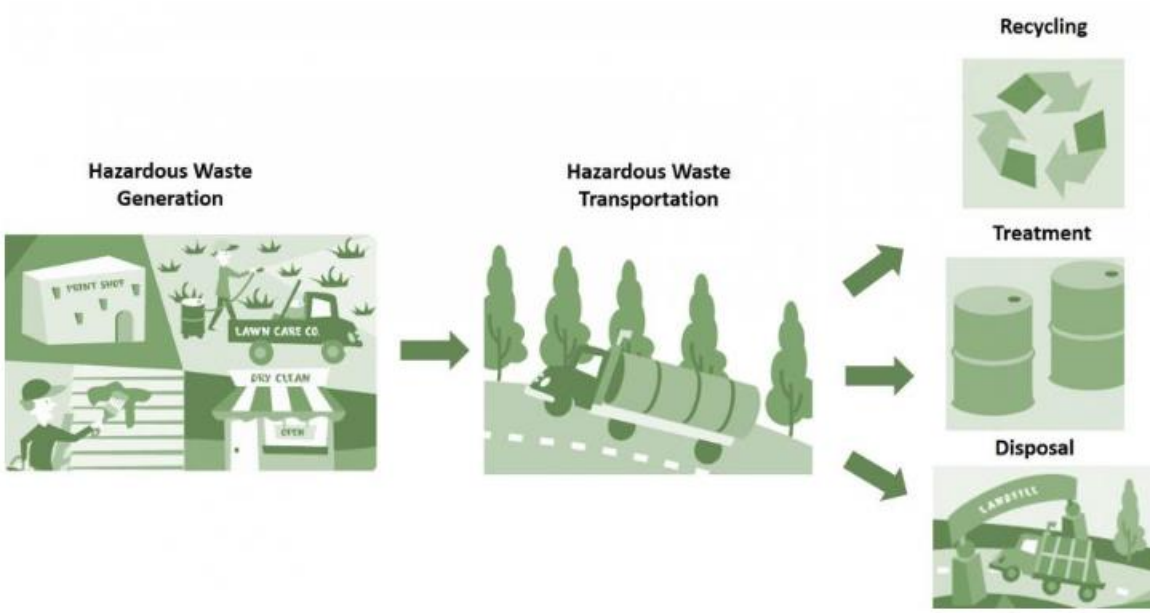


Figure 2-3. Typical Waste Disposal Process
Source: (U.S. EPA, 2017c)

Worker Activities

At waste disposal sites, workers are potentially exposed via dermal contact with waste containing carbon tetrachloride or via inhalation of carbon tetrachloride vapor. Depending on the concentration of carbon tetrachloride in the waste stream, the route and level of exposure may be similar to that associated with container unloading activities. At municipal waste incineration

facilities, there may be one or more technicians present on the tipping floor to oversee operations, direct trucks, inspect incoming waste, or perform other tasks as warranted by individual facility practices. At landfills, typical worker activities may include operating refuse vehicles to weigh and unload the waste materials, operating bulldozers to spread and compact wastes, and monitoring, inspecting, and surveying a landfill site [California Department of Resources Recycling and Recovery (CalRecycle, 2018)].

Number of Workers and Occupational Non-Users
The 2016 CDR uses did not show any submissions for waste handling, so EPA reviewed the 2017 TRI data and found twelve sites reported using carbon tetrachloride during waste handling (U.S. EPA, 2018e, 2017b, 2016d).

EPA determined the number of workers using the related SOC codes from BLS analysis that are associated with the primary NAICS codes listed in TRI (U.S. BLS, 2016). This analysis resulted in 130 workers and 63 ONUs potentially exposed at sites using carbon tetrachloride during waste handling (see Table 2-20).

Table 2-20. Estimated Number of Workers Potentially Exposed to Carbon Tetrachloride During Waste Handling

Number of Sites	Total Exposed Workers	Total Exposed Occupational Non-Users	Total Exposed
12	130	63	188

Inhalation Exposure
EPA did not find any exposure monitoring data for waste handling of carbon tetrachloride; therefore, exposures from waste handling activities were assessed with surrogate data from HSIA using data that have similar worker activities.

The assessments of worker exposure from chemical unloading activities are described in the Section 2.4.1.7.2. The exposure sources, routes, and exposure levels are similar to those at an import/repackaging facility, where unloading and handling are the key worker activities. Inhalation exposure assessment for processing of carbon tetrachloride as a processing agent/aid is estimated using the surrogate data from HSIA as described in the import/repackaging scenario.

2.4.1.7.10 Summary of Occupational Inhalation Exposure Assessment

Table 2-21 presents the occupational exposure assessment summary for the conditions of use described by the previous sections of this risk evaluation.

For additional information on the developmental details, methodology, approach, and results of any part of the occupational exposure determination process, refer to the supplemental document *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019c).

The summary and ranking of occupational exposure of carbon tetrachloride indicating strengths, challenges, whether modelling or monitoring preformed, representativeness and confidence of data assessed, hierarchy of data, and overall rating for various conditions of use are shown in Table 2-22.

Table 2-21. Summary of Occupational Inhalation Exposure Assessment for Workers

Condition of Use	Category	Eight-Hour or Twelve-Hour TWA Exposures		Acute Exposures		Chronic, Non-Cancer Exposures		Chronic, Cancer Exposures		TWA Data Points	Data Type
		$C_{CCl4, 8 \text{ or } 12\text{-hr TWA}}$ (mg/m^3)		$AC_{CCl4\ TWA}$ (mg/m^3)		$ADC_{CCl4\ TWA}$ (mg/m^3)		$LADC_{CCl4\ TWA}$ (mg/m^3)			
		High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency		
Manufacturing - 8-hr TWA	Worker	4.0	0.76	4.0	0.76	4.0	0.76	0.47	0.069	113	Monitoring Data
Manufacturing - 12-hr TWA	Worker	4.8	0.50	4.8	0.50	4.8	0.50	0.85	0.069	243	Monitoring Data
Manufacturing - 8-hr TWA	ONU	1.0	0.50	1.0	0.50	1.0	0.50	0.12	0.046	14	Monitoring Data
Manufacturing - 12-hr TWA	ONU	1.3	0.66	1.3	0.66	1.3	0.66	0.15	0.060	3	Monitoring Data
Import/Repackaging	Worker	2.92	0.89	2.92	0.89	2.92	0.89	0.342	0.081	15	Surrogate Monitoring Data
Import/Repackaging	ONU[a]	2.92	0.89	2.92	0.89	2.92	0.89	0.342	0.081	15	Surrogate Monitoring Data
Processing as Reactant - 8-hr TWA	Worker	4.0	0.76	4.0	0.76	4.0	0.76	0.47	0.069	113	Surrogate Monitoring Data
Processing as Reactant- 12-hr TWA	Worker	4.8	0.50	4.8	0.50	4.8	0.50	0.85	0.069	243	Surrogate Monitoring Data
Processing as Reactant - 8-hr TWA	ONU	1.0	0.50	1.0	0.50	1.0	0.50	0.18	0.069	14	Surrogate Monitoring Data

Condition of Use	Category	Eight-Hour or Twelve-Hour TWA Exposures		Acute Exposures		Chronic, Non-Cancer Exposures		Chronic, Cancer Exposures		TWA Data Points	Data Type
		$C_{CCl4,\ 8\ or\ 12\text{-}hr\ TWA}$ (mg/m^3)		$AC_{CCl4\ TWA}$ (mg/m^3)		$ADC_{CCl4\ TWA}$ (mg/m^3)		$LADC_{CCl4\ TWA}$ (mg/m^3)			
		High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency		
Processing as Reactant- 12-hr TWA	ONU	1.3	0.66	1.3	0.66	1.3	0.66	0.23	0.090	3	Surrogate Monitoring Data
Specialty Uses - DoD	Worker	0.37	0.18	0.37	0.18	0.22	0.092	0.026	0.0083	3	Monitoring Data
Specialty Uses - DoD	ONU[a]	0.37	0.18	0.37	0.18	0.22	0.092	0.026	0.0083	3	Monitoring Data
Processing: Reactive Ion Etching	Negligible - Highly controlled work areas with small quantities applied										
Industrial Processing Aid	Worker	2.92	0.89	2.92	0.89	2.92	0.89	0.342	0.081	15	Surrogate Monitoring Data
Industrial Processing Aid	ONU[a]	2.92	0.89	2.92	0.89	2.92	0.89	0.342	0.081	15	Surrogate Monitoring Data
Additive	Worker	2.92	0.89	2.92	0.89	2.92	0.89	0.342	0.081	15	Surrogate Monitoring Data
Additive	ONU[a]	2.92	0.89	2.92	0.89	2.92	0.89	0.342	0.081	15	Surrogate Monitoring Data
Laboratory Chemical	No data – exposure expected to be low as lab use will likely be in small quantities in a fume hood.										
Waste Handling	Worker	2.92	0.89	2.92	0.89	2.92	0.89	0.342	0.081	15	Surrogate Monitoring Data
Waste Handling	ONU[a]	2.92	0.89	2.92	0.89	2.92	0.89	0.342	0.081	15	Surrogate Monitoring Data

[a]In lieu of ONU-specific exposure data, EPA assessed ONU exposures at the worker central tendency.

Table 2-22. Summary and Ranking of Occupational Exposure of Carbon Tetrachloride for Various Conditions of Use

Occupational Exposure Scenario	Strength	Challenge	Inhalation Exposure						Dermal Exposure		Overall Rating for Workers[b]
			Monitoring			Modeling		Representativeness	Modeling[a]		
			Surrogate	Worker (Data #)	ONU (Data #)	Worker	ONU		Worker	ONU	
Manufacturing	PBZ sampling Medium data quality Source of information available directly from manufacturer CDR provided employee counts for specific manufacturing site Data from multiple facilities	Data is provided from one source Many data points were at or below the limit of detection	✗	✓ (356)	✓ (17)	✗	✗	Routine monitoring data available for worker and ONU environment	✓	–	Higher Lower
Import and Repackaging	PBZ sampling CDR provided employee counts for specific Import and Repackaging sites	Data is provided from one source Surrogate monitoring data are not specific to Import and Repackaging Many data points were at or below the limit of detection	✓	✓ (15)	✗	✗	✗	Assesses exposure based on loading and unloading monitoring data	✓	–	Higher Lower
Processing as a Reactant or Intermediate	PBZ sampling Medium data quality Source of information available directly from manufacturer Data from multiple facilities	Data is provided from one source Data is provided from one source Surrogate monitoring data are not specific to Processing as a Reactant or Intermediate	✓	✓ (356)	✓ (17)	✗	✗	Routine monitoring data available for worker and ONU environment	✓	–	Higher Lower

Occupational Exposure Scenario	Strength	Challenge	Inhalation Exposure						Dermal Exposure		Overall Rating for Workers[b]
			Monitoring			Modeling		Representativeness	Modeling[a]		
			Surrogate	Worker (Data #)	ONU (Data #)	Worker	ONU		Worker	ONU	
Specialty Uses (Department of Defense)	PBZ sampling	Only 3 data points	✗	✓	✗	✗	✗	Routine monitoring data available for work environment	✓	–	Higher
		No Monitoring Data									Lower
Industrial Processing Agent/Aid	PBZ sampling	Data is provided from one source	✓	✓ (15)	✗	✗	✗	Assesses exposure based on loading and unloading monitoring data	✓	–	Higher
		Surrogate monitoring data are not specific to Processing Agent/Aid									
	CDR provided employee counts for specific Processing Agent/Aid sites	Many data points were at or below the limit of detection									Lower
Additive	PBZ sampling	Data is provided from one source	✓	✓ (15)	✗	✗	✗	Assesses exposure based on loading and unloading monitoring data	✓	–	Higher
		Surrogate monitoring data are not specific to Processing Agent/Aid									
	CDR provided employee counts for specific Processing Agent/Aid sites	Many data points were at or below the limit of detection									Lower
Disposal / Recycling	PBZ sampling	Data is provided from one source	✓	✓ (15)	✗	✗	✗	Assesses exposure based on loading and unloading monitoring data	✓	–	Higher
		Surrogate monitoring data are not specific to Processing Agent/Aid									
	CDR provided employee counts for specific Processing Agent/Aid sites	Many data points were at or below the limit of detection									Lower

[a]Dermal exposure estimates, which are based on high-end/central tendency parameters and commercial/industrial settings, have medium level of confidence.
[b]ONU exposure estimates, which are based on central tendency paraments, have low levels of confidence.

2.4.1.8 Dermal Exposure Assessment

Because carbon tetrachloride is a volatile liquid, the dermal absorption of carbon tetrachloride depends on the type and duration of exposure. Where exposure is without gloves, only a fraction of carbon tetrachloride that comes into contact with the skin will be retained as the chemical readily evaporates from the skin. However, dermal exposure may be significant in cases of occluded exposure, repeated contacts, or dermal immersion. For example, work activities with a high degree of splash potential may result in carbon tetrachloride liquids trapped inside the gloves, inhibiting the evaporation of carbon tetrachloride and increasing the exposure duration. Specific methodology for dermal exposure estimation is detailed in the document *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019c).

Dermal exposure is the absorption and transport of carbon tetrachloride from the outer surface of the skin to the inner layers of the skin (Figure 2-4). The relatively thin epidermis lacks vascularization and is generally considered the primary barrier to uptake of carbon tetrachloride encountered in the workplace or general environment. The dermis is vascularized and contains the sweat glands and hair follicles. Dermal interactions of chemical through the skin could occur with or without being noticed by the worker. The rate of dermal absorption depends largely on the outer layer of the skin called the stratum corneum. The stratum corneum serves an important barrier function by keeping molecules from passing into and out of the skin, thus protecting the lower layers of skin. Theoretical equations and models have been developed to describe the transport of a diffusing chemical through the skin. Carbon tetrachloride could permeate the skin's diffusional barriers and enter the systemic circulation via capillaries at the dermo-epidermal junction. The process begins with diffusion through the dead stratum corneum and could involve metabolic processes during traversal of the living epidermis. The released chemical that encounters skin could undergo many processes including:

a) evaporation from the surface of the skin;
b) uptake (absorption) into the stratum corneum, followed by reversible or irreversible binding;
c) penetration into the viable epidermis, followed by metabolism.

There are various factors that influence the dermal absorption of an exposed chemical, and the key factors are shown in Figure 2-4 (Eleftheriadou et al., 2019; WHO, 2006; Semple, 2004). The factors affecting dermal exposure could vary as the working conditions, process operations and work practices, type and conditions of chemical releases, and other site-specific conditions. Various models have been developed to address various factors impacted by risk assessors; pharmaceutical, cosmetics, chemicals, and other industries (Almeida et al., 2019; Eleftheriadou et al., 2019; Kissel et al., 2018; Sugibayashi, 2017; Chittenden and Riviere, 2015; Frasch and Bunge, 2015; Chittenden et al., 2014; Gajjar and Kasting, 2014; Nitsche and Kasting, 2013; Mitragotri et al., 2011). IHSkinPerm©, developed by the American Industrial Hygiene Association (AIHA), is one of the available tools that estimates dermal absorption using the dermal loading, the exposure duration, and physical-chemical properties of chemicals. This model takes into account losses to evaporation and estimates the mass that is absorbed. IH SkinPerm© computes dermal risk assessment for four types of occupational skin exposures found in work environments: a) deposition over time (*e.g.*, from repeated or continuous

emission); b) instantaneous deposition (*e.g.*, from a splash); c) skin absorption from airborne vapors, and d) estimating absorption of carbon tetrachloride in water. The scenario output parameters are shown in Table 2-23.

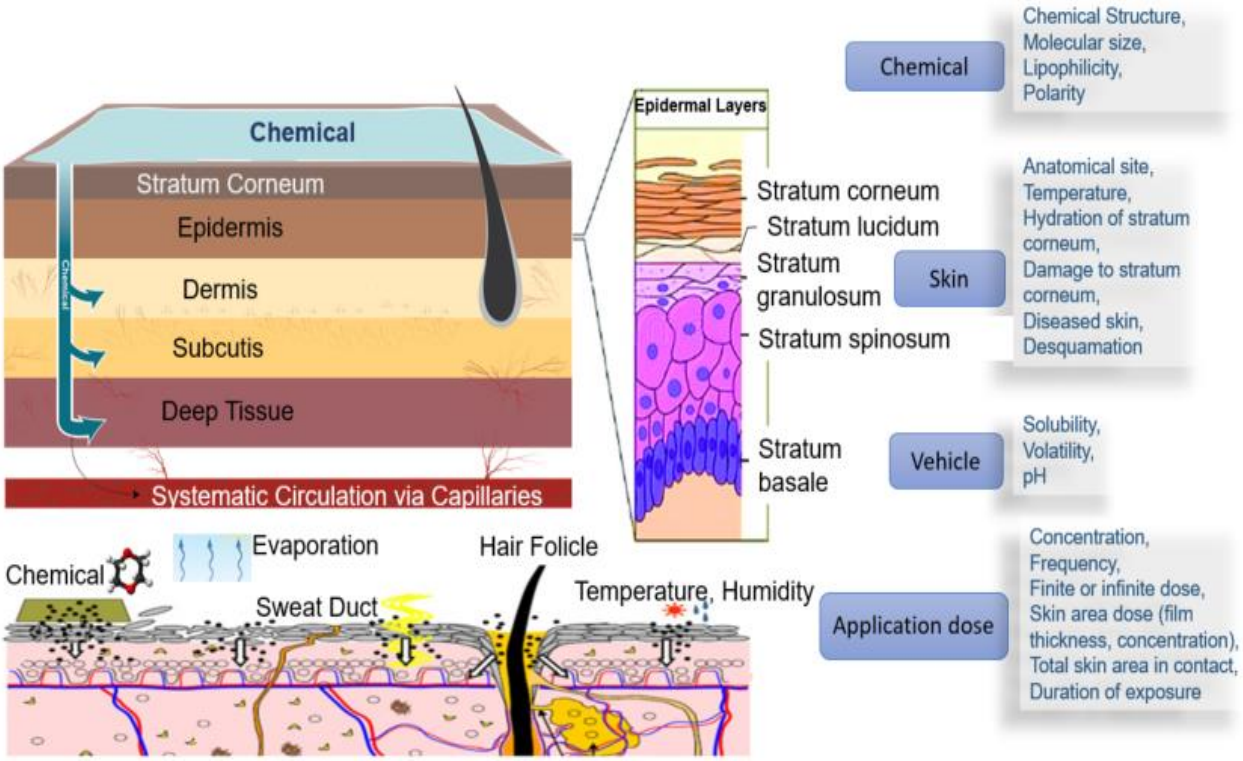


Figure 2-4. Conceptual Diagram Showing Various Key Factors that Influence Dermal Exposures in the Event of Carbon Tetrachloride Releases. (modified after (Chattopadhyay and Taft, 2018)**)**

Table 2-23. IHSkinPerm© Output Data for Carbon Tetrachloride under Various Dermal Exposure Scenarios

Parameter	Unit	Scenario			
		Deposition over time (8hr)	Instantaneous	Vapor to skin	Water solution
Total deposition	Mg	8560	100	1.91E-03	165
Fraction absorbed	%	8.18E-04	4.12E-04	99.9	99.9
Amount absorbed	Mg	7.00E-02	4.12E-04	1.91E-02	165
Kp-lipids (vehicle water)[1]	cm/hr	2.69E-2			
Kp-lipids (vehicle air)[2]	cm/hr	2.22E-2			
Kp-keratins (vehicle water)[3]	cm/hr	4.54E-05			
Kp-keratins (vehicle air)[4]	cm/hr	3.74E-05			
Diffusivity of stratum corneum[5]	cm^2/hr	4.55E-06			
Kp-stagnant air[6]	cm/hr	2.53E+02			
Skin/water partition ratio	Dimensionless	11.9 (12.4 ± 0.6 based on test data reported by Mattie et al. (Mattie et al., 1994))			
Skin/air partition ratio	Dimensionless	9.78			
Permeation coefficient water[7]	cm/hr	2.70E-02			
Permeation coefficient air[8]	cm/hr	2.22E-02			

1: Kp-lipids (vehicle water) = permeability coefficient is a constant that describes the speed at which carbon tetrachloride diffuses through the lipid mortar between skin cells.
2: Kp-lipids (vehicle air) = the estimated permeation coefficient of carbon tetrachloride as vapor in air, valid for the stratum corneum lipid mortar.
3: Kp-keratins (vehicle water) = permeability coefficient is a constant that describes the speed at which carbon tetrachloride diffuses through the dead skin cells. Keratins are a group of tough, fibrous proteins that form the structural framework of epithelial cells that make up tissues such as the hair, skin, and nails.
4: Kp-keratins (vehicle air) = the estimated permeation coefficient of carbon tetrachloride as vapor in air, valid for the dead corneocytes of the stratum corneum.
5: Diffusivity of stratum corneum is a dependent variable describing the effective diffusion of carbon tetrachloride through the stratum corneum.
6: Kp-stagnant air layer = permeability coefficient of carbon tetrachloride at the air boundary layer of the skin.
7: Permeation coefficient water = an estimate of the carbon tetrachloride dermally absorbed into the stratum corneum from water.
8: Permeation coefficient air = an estimate of the carbon tetrachloride dermally absorbed from vapor in air.

Section 2.4.1.4 describes the modeling the dermal absorption of carbon tetrachloride via a liquid vehicle (*e.g.*, liquid carbon tetrachloride on skin or a liquid formulation containing carbon tetrachloride on skin). Table 2-24 presents the estimated dermal retained dose for *workers* in various exposure scenarios, focusing on what-if scenarios for glove use. The dose estimates assume one exposure event (applied dose) per workday and that approximately four percent of the applied dose is absorbed through the skin during industrial settings. The conditions of use for carbon tetrachloride are industrial uses that occur in closed systems where dermal exposure is likely limited to chemical loading/unloading activities (*e.g.*, connecting hoses) and taking quality

control samples. Across all types of uses, the maximum possible exposure concentration (Y_{derm}) exists during industrial uses that generally occur in closed systems. Therefore, all conditions of use for carbon tetrachloride are assessed at the maximum Y_{derm}, or 1. In addition to the what-if scenarios for glove use, EPA considered the potential for occluded dermal exposures; however, based on the worker activities for the condition of use for carbon tetrachloride, EPA determined occluded exposures to be unlikely. Occluded scenarios are generally expected where workers come into contact with bulk liquid carbon tetrachloride during use in open systems (*e.g.*, during solvent changeout in vapor degreasing and dry cleaning). Occluded scenarios are not expected in closed systems (*e.g.*, during connection/disconnection of hoses used in loading of bulk containers in manufacturing). For further description of the applicable scenarios, see Appendix E of *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019c). EPA assesses the following what-if glove use scenarios for all conditions of use of carbon tetrachloride for workers:

- **No gloves used**: Operators in these industrial uses, while working around closed-system equipment, may not wear gloves or may wear gloves for abrasion protection or gripping that are not chemical resistant.
- **Gloves used with a protection factor of 5, 10, and 20**: Operators may wear chemical-resistant gloves when taking quality control samples or when connecting and disconnecting hoses during loading/unloading activities. The gloves could offer a range of protection, depending on the type of glove and employee training provided.
- **Scenarios not assessed**: EPA does not assess occlusion as workers in these industries are not likely to come into contact with bulk liquid carbon tetrachloride that could lead to chemical permeation under the cuff of the glove or excessive liquid contact time leading to chemical permeation through the glove.

The skin is a very complex and dynamic human organ composed of an outer epidermis and inner dermis with functions well beyond that of just a barrier to the external environment. Dermal absorption depends largely on the barrier function of the stratum corneum, the outermost superficial layer of the epidermis, and is modulated by factors such as skin integrity, hydration, density of hair follicles and sebaceous glands, thickness at the site of exposure assessment, physiochemical properties of the substance, chemical exposure concentration, and duration of exposure. The workplace protection factor for gloves is based on the ratio of uptake through the unprotected skin to the corresponding uptake through the hands when protective gloves are worn.

The exposure assessments were conducted considering vapor pressure and other physical-chemical properties of carbon tetrachloride. The key barrier of the skin is located in the outermost layer of the skin, the stratum corneum, which consists of corneocytes surrounded by lipid regions. Due to increased area of contact and reduced skin barrier properties, repeated skin contact with chemicals could have even higher than expected exposure if evaporation of the chemical occurs and the concentration of chemical in contact with the skin increases. In the workplace the wearing of gloves could have important consequences for dermal uptake. If the worker is handling a chemical without any gloves, a splash of the liquid or immersion of the hand in the chemical may overwhelm the skin contamination layer so that the liquid chemical essentially comprises the skin contamination layer. If the material is undiluted, then uptake could

proceed rapidly as there will be a large concentration difference between the skin contamination layer and the peripheral blood supply. Conversely, if the contaminant material is diluted, there will be relatively slow uptake.

If the worker is wearing a pair of gloves the situation will be different. In case the chemical comes into contact with the outer glove surface, there will be no flux into the inner glove contamination layer until the chemical breaks through. The chemical could partition into the glove and then diffuse towards the inner glove surface; then it could partition into the skin contamination layer. Diffusion through the stratum corneum is dependent on the concentration. The glove protection factor is unlikely to be constant for a glove type but could be influenced by the work situation and the duration of the exposure as glove performance and pass/fail criteria are also dependent on cut, puncture and abrasion resistance; chemical permeation and degradation; holes; heat and flame resistance; vibration, and dexterity of operation and operator.

As shown in Table 2-24 the calculated retained dose is low for all dermal exposure scenarios as carbon tetrachloride evaporates quickly after exposure. Dermal exposure to liquid is not expected for occupational non-users, as they do not directly handle carbon tetrachloride.

Table 2-24. Estimated Dermal Acute and Chronic Retained Doses for Workers for All Conditions of Use[14]

Category	Exposure Level	Acute Potential Dose Rate	Acute Retained Dose	Chronic Retained Dose, Non-Cancer	Chronic Retained Dose, Cancer
		$APDR_{exp}$ (mg/day)	ARD (mg/kg-d)	CRD (mg/kg-d)	CRD (mg/kg-d)
Worker, No Gloves	High End	90	1.1	1.1	0.39
	Central Tendency	30	0.37	0.37	0.10
Worker with Gloves; PF = 5	High End	18	0.22	0.22	0.079
	Central Tendency	6.0	0.075	0.075	0.020
Worker with Gloves; PF = 10	High End	9.0	0.11	0.11	0.039
	Central Tendency	3.0	0.037	0.037	0.010
Worker with Gloves; PF = 20	High End	4.5	0.056	0.056	0.020
	Central Tendency	1.5	0.019	0.019	0.0051

2.4.2 Consumer Exposures

As explained in Section 1.4.1, there are no consumer uses of carbon tetrachloride within the scope of the risk evaluation. No additional information was received by EPA following the publication of the problem formulation that would update the conclusion that carbon tetrachloride is expected to be present in consumer products at trace levels resulting in de minimis exposures or otherwise insignificant risks and therefore that consumer uses do not warrant inclusion in the risk evaluation. Accordingly, EPA did not analyze consumer exposures in the risk evaluation for carbon tetrachloride.

[14] Calculation are described in Appendix E of *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment.*

2.4.3 General Population Exposures

As explained above in Section 1.4.3, EPA is not including in this risk evaluation exposure pathways under programs of other environmental statutes administered by EPA. Therefore, based on information obtained by EPA and presented in Section 2.5.3.2 of the problem formulation document (U.S. EPA, 2018c), EPA is not evaluating any exposure pathways to human receptors (*i.e.*, general population) from environmental releases and waste streams associated with industrial/commercial activities for carbon tetrachloride which result in releases to the following pathways: ambient air pathway (carbon tetrachloride is listed as a Hazardous Air Pollutant (HAP) in the Clean Air Act (CAA), drinking water pathway (National Primary Drinking Water Regulations (NPDWRs) are promulgated for carbon tetrachloride under the Safe Drinking Water Act (SDWA)), ambient water pathways (carbon tetrachloride is a priority pollutant with recommended water quality criteria for protection of human health under the Clean Water Act (CWA)), biosolids pathways (carbon tetrachloride in biosolids is currently being addressed in the CWA regulatory analytical process), and disposal pathways (carbon tetrachloride disposal pathways are subject to regulation under the RCRA, CERCLA, SDWA, and CAA). Because there are no other exposure pathways impacting the general population, EPA did not analyze general population exposures in this risk evaluation.

2.5 Other Exposure Considerations

2.5.1 Potentially Exposed or Susceptible Subpopulations

TSCA Section 6(b)(4)(A) requires that a risk evaluation "determine whether at chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of cost 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." TSCA Section 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 risk evaluation, the EPA analyzed the reasonably available information to ascertain whether some human receptor groups may have greater exposure or susceptibility than the general population to the hazard posed by a chemical. During problem formulation, the EPA identified the following potentially exposed or susceptible subpopulations based on their greater exposure to carbon tetrachloride: workers and occupational non-users. Accordingly, EPA has assessed potential risks to these two subpopulations in this risk evaluation. Section 3.2.5.2 describes the hazard information identifying susceptibility to the toxic effects of carbon tetrachloride in individuals with histories of alcohol usage.

2.5.2 Aggregate and Sentinel Exposures

As a part of risk evaluation, Section 6(b)(4)(F)(ii) of TSCA requires EPA to describe whether aggregate or sentinel exposures were considered under the identified conditions of use and the basis for their consideration. EPA has defined aggregate exposure as "the combined exposures to an individual from a single chemical substance across multiple routes and across multiple pathways." (40 C.F.R. 702.33). EPA defines sentinel exposure as "exposure from a single

chemical substance that represents the plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures." (40 C.F.R. 702.33). EPA considered sentinel exposure in the form of high-end estimates for occupational exposure scenarios which incorporate dermal and inhalation exposure, as these routes are expected to present the highest exposure potential based on details provided for the manufacturing, processing and use scenarios discussed in the previous section. The exposure calculation used to estimate dermal exposure to liquid is conservative for high-end occupational scenarios where it assumes full contact of both hands and no glove use. See further information on aggregate and sentinel exposures in Section 4.6.

3 HAZARDS

3.1 Environmental Hazards

EPA conducted comprehensive searches for data on the environmental 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-2016-0733-0050). Based on an initial screening, EPA analyzed the hazards of carbon tetrachloride identified in this risk evaluation document. The relevance of each hazard endpoint within the context of a specific exposure scenario was 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 was analyzed for every exposure scenario.

Further, EPA focused in the risk evaluation process on conducting timely, relevant, high-quality, and scientifically credible risk evaluations. See 82 FR 33726, 33728 (July 20, 2017). Each risk evaluation is "fit-for-purpose," meaning the level of refinement will vary as necessary to determine whether the chemical substance presents an unreasonable risk. Given the nature of the evidence, for the conditions of use of the specific chemical substance, and when information and analysis are sufficient to make a risk determination using assumptions, uncertainty factors, and models or screening methodologies, EPA may decide not to refine its analysis further (40 CFR 702.41(a)(6), (7); see also 82 FR at 33739-40).

3.1.1 Approach and Methodology

As part of the problem formulation, EPA reviewed and characterized the environmental hazards associated with carbon tetrachloride (see Sections 2.4.1 and 2.5.3.1 of the problem formulation document) (U.S. EPA, 2018c). EPA identified the following sources of environmental hazard data for carbon tetrachloride: ECHA (ECHA, 2017b), OECD SIDS Initial Assessment Profile (SIAP) (OECD, 2011), and Australia's 2017 National Industrial Chemicals Notification and Assessment Scheme (NICNAS). In addition, scientific studies were identified in a literature search for carbon tetrachloride (*Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document*, EPA-HQ-OPPT-2016-0733) and were evaluated based on data quality evaluation metrics and rating criteria described in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a) and *Strategy for Assessing Data Quality in TSCA Risk Evaluation* (U.S. EPA, 2018d). Only studies with data quality evaluation ratings of 'high', 'medium', and 'low' were available to characterize the environmental hazards; no studies with 'unacceptable' ratings were used. The Agency attempted

but was not able to obtain the full scientific publications listed in ECHA, SIAP, and NICNAS. As a result, these data could not be systematically reviewed and were not used in the risk evaluation. Even if the Agency had obtained the full studies and considered them acceptable, EPA determined that the ecotoxicity values presented in ECHA, SIAP, and NICNAS would not have resulted in a more conservative environmental hazard assessment. The robust summary endpoints from these sources align with the dataset EPA used to assess the hazards of carbon tetrachloride. Furthermore, the acute and chronic COCs for carbon tetrachloride were based on the lowest toxicity value in the dataset.

Of the 75 on-topic environmental hazard sources identified by the ECOTOX process, 60 citations were considered out of scope and/or unacceptable in data quality based on the data quality evaluation metrics and the rating criteria described in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). The data quality evaluation results for the remaining 15 on-topic studies for carbon tetrachloride environmental hazard are presented in the document *Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Hazard Studies*(U.S. EPA, 2019g). Relevant aquatic toxicity data are summarized in Table 3-1**.** as ranges (min-max).

3.1.2 Hazard Identification-Toxicity to Aquatic Organisms

EPA identified and evaluated carbon tetrachloride environmental hazard data for fish, aquatic invertebrates, amphibians, and algae across acute and chronic exposure durations. During problem formulation, terrestrial species exposure pathways were considered to be covered under programs of other environmental statutes administered by EPA (*e.g.*, RCRA, CERCLA and CAA). For the final risk evaluation, EPA conducted a qualitative assessment of exposure to terrestrial organisms through soil and land application of biosolids by examining physical-chemical and fate properties. EPA did not assess exposure to terrestrial organisms through ambient air because this exposure pathway is covered under the jurisdiction of the CAA. Further analysis was not conducted for exposures to terrestrial organisms from water as carbon tetrachloride is identified as a priority pollutant under Section 304(a) of the CWA regulating releases to water and the expectation that any releases to water under the regulation will volatilize into air based on its physical-chemical properties.

As a result of a screening-level comparison of the reasonably available environmental hazard data with exposure concentrations, it was determined that no further hazard analyses were necessary (see Section 2.5.3.1 of the problem formulation document) (U.S. EPA, 2018c). Upon further evaluation of the reasonably available hazard data of carbon tetrachloride after the problem formulation phase, EPA decreased the environmental hazard chronic COC from 7 µg/L to 3 µg/L. Consequently, EPA assessed the risk to aquatic organisms in this risk evaluation. The derived acute COC (90 µg/L) and chronic COC (3 µg/L) are based on environmental toxicity endpoint values (*e.g.*, EC_{50}) from (Brack and Rottler, 1994) and (Black et al., 1982; Birge et al., 1980), respectively. The data represent the lowest bound of all carbon tetrachloride data available in the public domain and provide the most conservative hazard values.

Previously, algal endpoints were considered together with data from other taxa in the acute and chronic COC calculations. Now, algal endpoints are considered separately from the other taxa and not incorporated into acute or chronic COCs because durations normally considered acute for other species (*e.g.*, 48, 72, or 96 hours) can encompass several generations of algae. A

distinct COC is calculated for algal toxicity. A summary of the environmental studies and hazard ranges considered for carbon tetrachloride are available in Table 3-1..

In the problem formulation phase, EPA eliminated the sediment exposure pathway from further analysis based on physical-chemical and fate properties of carbon tetrachloride. However, in the final risk evaluation, EPA quantitatively estimated toxicity to sediment-dwelling organisms to improve the risk characterization of carbon tetrachloride exposure to sediment-dwelling aquatic organisms. EPA considered one low quality study on *Chironomus tentans* (Lee et al., 2006) and used aquatic invertebrates (*e.g.*, *Gammarus pseudolimnaeus* and *Daphnia magna*) as a surrogate species to provide an additional line of evidence. Daphnia, which feed through the entire water column, were deemed to be an acceptable surrogate species for sediment invertebrates because carbon tetrachloride is not expected to sorb to sediment and will instead remain in pore water.

Table 3-1. Summary of Aquatic Toxicity Studies and Hazard Ranges Evaluated for Carbon Tetrachloride

Exposure Duration	Test organism	Endpoint	Hazard value[a]	Units	Effect Endpoint	References[b]
Acute	Fish	LC_{50}	10.40 – 150.0	mg/L	Mortality	(Brooke, 1987) (high); (Freitag et al., 1994) (high); (Schell, 1987) (high); (Kimball, 1978) (high); (Geiger et al., 1990) (high); (Buccafusco et al., 1981) (low); (Dawson et al., 1977) (medium)
	Aquatic invertebrates	L/EC_{50}	11.10 – 301.0	mg/L	Mortality/ immobilization	(Brooke, 1987) (high); (LeBlanc, 1980) (high); (Freitag et al., 1994) (high); (Khangarot and Das, 2009) (high); (Richie et al., 1984) (high);
	Sediment-dwelling Organism	LOEL[c]	2	mg/L	Biomass	(Lee et al., 2006) (low)
	Amphibians	LC_{50}	**0.900** – 22.42	mg/L	Teratogenesis Leading to Mortality[d]	(Birge et al., 1980) (high); (Black et al., 1982) (high)
	Acute COC	0.09		mg/L		
Chronic	Fish	LC_{50}	1.970	mg/L	Mortality	(Black et al., 1982) (high)
	Aquatic invertebrates	Chronic value	1.100 (ACR10)	mg/L	Growth and reproduction	(Brooke, 1987) (high)
	Sediment-dwelling Organism	Chronic value	0.2 (ACR10)	mg/L	Biomass	(Lee et al., 2006) (low)
	Amphibians	LC_{10}	**0.025-** 0.436	mg/L	Teratogenesis Leading to Mortality	(Birge et al., 1980) (high); (Black et al., 1982) (high)
	Chronic COC	0.003		mg/L		
Algae		EC_{10}	**0.070**	mg/L	Biomass	(Brack and Rottler, 1994) (high)

Exposure Duration	Test organism	Endpoint	Hazard value[a]	Units	Effect Endpoint	References[b]
		EC_{50}	0.250 – 23.59	mg/L	Biomass/growth rate	(Brack and Rottler, 1994) (high); (Freitag et al., 1994) (high); (Tsai and Chen, 2007) (high)
	Algae COC	0.007		mg/L		

[a]Values in **bold** were used to derive the COC.
[b]Data quality evaluation scores for each citation are in the parenthesis.
[c] Lowest Observed Effect Level
[d]The study authors defined embryo-larval teratogenesis as the percent of survivors with gross and debilitating abnormalities likely to result in eventual mortality.

Overall Confidence in COCs

EPA has high confidence in the environmental hazard data for carbon tetrachloride and high confidence that the data incorporates the most conservative (highest toxicity)/environmentally protective acute and chronic concentrations of concern (as described above).

3.2 Human Health Hazards

3.2.1 Approach and Methodology

EPA used the approach described in Section 1.5 to evaluate, extract and integrate carbon tetrachloride's human health hazard and dose-response information. Figure 3-1 presents the steps for the hazard identification and dose response process used by EPA in this risk evaluation. After implementation of this approach and methodology, EPA redesigned the weight of evidence (WOE) narrative for the identified non-cancer hazards for carbon tetrachloride to improve clarity and transparency based on recommendations from the Science Advisory Committee on Chemicals (SACC), a TSCA peer review committee.

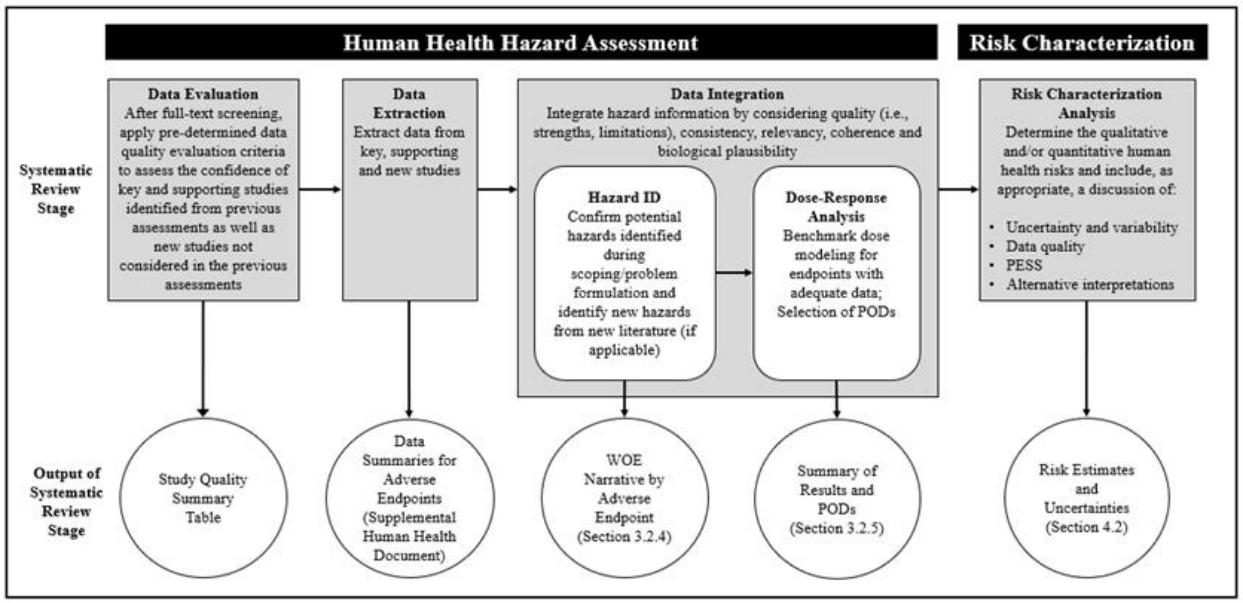


Figure 3-1. Hazard Identification and Dose-Response Process

The new on-topic studies and key and supporting studies from previous hazard assessments were screened against inclusion criteria in the PECO statement. Relevant studies were further evaluated using the data quality criteria in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a).

In the data evaluation step (Step 1), the key and supporting studies from previous hazard assessments and new on-topic studies were evaluated using the data evaluation criteria for human, animal, and *in vitro* studies described in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). Specifically, EPA reviewed key and supporting information from previous EPA hazard assessments, such as U.S. EPA (U.S. EPA, 2010), the ATSDR Toxicological Profile (ATSDR, 2005) and previous assessments listed in Table 1-3 as a starting point. EPA also screened and evaluated new studies that were published since these assessments, 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).

In the data extraction step (Step 2), data is evaluated for consistency and relevance and summarized according to each endpoint in an evidence table, which can be found in the supplemental files for this risk evaluation (see Appendix B). In the data integration step (Step 3), the strengths and limitations of the data are evaluated for each endpoint and a weight of the scientific evidence narrative is developed. In the dose-response analysis (Step 4), data for each selected hazard endpoint is modeled to determine the dose-response relationship. The results are summarized, and the uncertainties are presented in Section 3.2.5.

EPA considered new studies with information on acute, non-cancer and cancer endpoints if the study was found to meet the quality criteria with an overall data quality rating of high, medium, or low. Studies found to be acceptable and rated high, medium or low were used for hazard identification. EPA has not developed data quality criteria for all types of relevant information (*e.g.*, toxicokinetics data). Therefore, EPA is using these data to support the risk evaluation. Information on human health hazard endpoints for all acceptable studies (with high, medium or low scores) evaluated is presented in Appendix G.

Adverse health effects associated with exposure to carbon tetrachloride were identified by considering the quality and weight of the scientific evidence to identify the most sensitive hazards or key endpoints. Based on the systematic review of the reasonably available data, EPA narrowed the focus of the carbon tetrachloride hazard characterization to liver toxicity, neurotoxicity, kidney toxicity, reproductive/ developmental toxicity, and cancer. In addition, a summary of key studies and endpoints carried forward in the risk evaluation can be found in Appendix G, including the no-observed- or lowest-observed-adverse-effect levels (NOAEL and LOAEL) for health endpoints by target organ/system, the corresponding benchmark dose lower confidence limits (BMDLs), when available, and the corresponding human equivalent concentrations (HECs), and uncertainty factors (UFs).

These key studies provided the dose-response information necessary for selection of points of departure (PODs). The EPA defines a POD as the dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on the dose for an estimated

incidence, or a change in response level from a dose-response model (*e.g.*, benchmark dose or BMD), a NOAEL, or a LOAEL for an observed incidence, or a change in the level (*i.e.*, severity) of a given response. PODs were adjusted as appropriate to conform to the specific exposure scenarios evaluated.

The potential mode of action (MOA) for cancer was evaluated according to the framework for MOA analysis described in the EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005b). The evidence for genotoxicity is summarized in Appendix H. The dose-response assessment used for selection of PODs for cancer and non-cancer endpoints and the benchmark dose analysis used in the risk evaluation are found in Section 3.2.5.

Given that inhalation and dermal exposures are the exposures of concern in this risk evaluation, studies conducted via these two routes of exposure were considered for POD derivation. Nevertheless, oral exposure data are presented below for weight of evidence support in the selection of hazard endpoints and PODs. Acceptable toxicological data by the dermal route and physiologically based pharmacokinetic/ pharmacodynamic (PBPK/PD) models that would facilitate route-to-route extrapolation to the dermal route have not been identified for carbon tetrachloride. Therefore, inhalation PODs were extrapolated for use via the dermal route using assumptions about absorption in this risk evaluation.

The EPA consulted *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991) when making the decision to use developmental toxicity studies to evaluate risks that may be associated with acute exposure to carbon tetrachloride during occupational exposure scenarios. This decision is based on the EPA's policy, which is based on the health-protective assumption that a single exposure during a critical window of fetal development may produce adverse developmental effects. The EPA guidelines state that for developmental toxic effects, a primary assumption is that a single exposure at a critical time in development may produce an adverse developmental effect, *i.e.*, repeated exposures is not a necessary prerequisite for developmental toxicity to be manifested (U.S. EPA, 1991). However, limited evidence from gestational exposure studies for carbon tetrachloride in rats suggest that developmental effects are likely associated with the sustained lower maternal weight over gestation days 6-15 rather than the result of exposure to carbon tetrachloride on a single day of the study (NRC, 2014) (see Sections 3.2.4.1 and 3.2.5.1).

A summary table which includes all endpoints considered for this risk evaluation, the NOAEL and LOAEL for health endpoints by target organ/system and the results of the data evaluation is provided in Appendix G. The Sections below present the analysis, synthesis and integration of the hazard information resulting from those data sources that have low, medium or high overall data quality.

3.2.2 Acceptable Studies Reasonably Available for Evaluation

The database for carbon tetrachloride has comprehensive information on non-cancer and cancer effects in experimental animals and humans, through the inhalation and oral routes, but lacks an adequate study for reproductive toxicity. The majority of the animal toxicology studies have been described and evaluated in previous hazard assessments and toxicological profiles for carbon tetrachloride.

The systematic review process evaluated the data quality of the key subchronic and chronic studies in (U.S. EPA, 2010), which identifies the following subchronic oral gavage studies supporting the derivation of the RfD for carbon tetrachloride, (Condie et al., 1986), (Allis et al., 1990) and (Hayes et al., 1986). (Bruckner et al., 1986) was the principal study for the derivation of the RfD and was rated as a high data quality subchronic oral study in rats in the systematic review for this risk evaluation.

The principal study for the derivation of the IRIS RfC is (Nagano et al., 2007a), which consists of a chronic study using two species and preceded by a 13-week subchronic study. This chronic study was rated as a high quality study during the systematic review process. Other key subchronic inhalation studies of acceptable data quality are presented in Table 3-3, below. Similarly, the key study used to derive the acute exposure inhalation guidelines by NAC-AEGL (NRC, 2014) was found to be of acceptable low data quality in the systematic review. Other epidemiological studies with acute exposures were not evaluated for data quality because they were found to lack reliable quantitative exposure data by NAC-AEGL.

Epidemiological studies presented in the EPA IRIS Assessment (U.S. EPA, 2010) were deemed inadequate to show an association between carbon tetrachloride exposure and carcinogenicity by the IRIS program. However, epidemiological studies with acceptable data quality according to the systematic review process and that were published following the cut-off time of the data evaluation period in the IRIS assessment review are considered adequate to show an association between exposures to carbon tetrachloride and carcinogenicity during data evaluation and integration processes for this risk evaluation (see Section 3.2.4.2.2 and Table 3-4). Specifically, three of four epidemiologic studies of brain cancer showed statistically significant increases in risk of brain tumors ((Heineman et al., 1994); (Nelson et al., 2012); (Neta et al., 2012)). The limited number of recent epidemiological studies assessing non-cancer (*i.e.*, Parkinson's disease, autism) endpoints and with acceptable data quality do not show association between exposure and non-cancer hazard effects (see Table 3-2).

Further information on the methodology and findings of the key toxicological studies with acceptable data quality that were taken into consideration for hazard identification are presented in Section 3.2.4 and Appendix G.

Table 3-2. Acceptable Epidemiological Studies on Non-Cancer Effects from Repeated Exposures not Evaluated in Previous EPA Assessments

Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Parkinson's Disease (PD)	99 male twin pairs 35-84 years of age from US National Academy of Sciences/National Research Council World War II Veteran Twins Registry, 1993-1995	Self-reported exposure to carbon tetrachloride	A non-significant association was observed between Parkinson Disease and exposure to carbon tetrachloride	(Goldman et al., 2012)	High

Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Autism Spectrum Disorder	Nurses' Health Study II children 3-18 years (US; 325 cases/22101 controls).	Carbon tetrachloride air concentrations at mother's location at birth	Carbon tetrachloride exposure was not significantly associated with Autism Spectrum Disorder.	(Roberts et al., 2013)	High

Note: Further study details (*i.e.*, p-values, confounders) can be found in *Final Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Human Health Studies-Epidemiological Studies.*

Table 3-3. Acceptable Toxicologic Studies Available for Evaluation

Subjects	Exposure Route	Doses/ Concentrations	Duration	Effect Dose	Effect*	Reference	Data Quality Evaluation
Four subjects (ages 35, 48, 22, and 30; gender not specified)[15]	Inhalation	76 ppm	2.5 hours, 4 hours	NOAEC = 76 ppm	No CNS symptoms or signs of toxicity	(Davis, 1934)	Low; basis for AEGL-2
Rat, Sprague-Dawley, M (n=5/ group)	Oral, gavage (corn oil vehicle)	0, 50, or 2000 mg/kg-bw/day	6, 24, hours (the 72 hours exposure is categorized as subchronic)	LOAEL = 50 mg/kg-bw/day	Weight loss; increased ALP; decreased cholesterol, triglycerides, and glucose; liver histopathology; increased BUN	(Sun et al., 2014)	High
Rat, F344/DuCrj (SPF), M/ F (n=100/ group)	Inhalation, vapor, whole body	0, 31, 157 or 786 mg/m^3 (0, 5, 25 or 125 ppm)	6 hours/ day, 5 days/ week for 104 weeks	NOAEC = 31 mg/m^3, LOAEC = 157 mg/m^3	Increased AST, ALT, LDH, GPT, BUN, CPK; lesions in the liver (fatty changes, fibrosis), cirrhosis, kidney lesions	(Nagano et al., 2007a)	High
Mouse, Crj:BDF1 (SPF), M/F (n= 100/ group)	Inhalation, vapor, whole body	0, 31, 157 or 786 mg/m^3 (0, 5, 25 or 125 ppm)	6 hours/ day, 5 days/ week for 104 weeks	NOAEC = 31 mg/m^3 (M)	Reduced survival; increased ALT, AST, LDH, ALP, protein, total bilirubin, and BUN; decreased urinary pH; increased liver weight; spleen and liver lesions	(Nagano et al., 2007a)	High
Mouse, BDF1, M/ F (n=20/ group)	Inhalation, vapor, whole body	0, 63, 189, 566, 1699, or 5096 mg/m^3 (0, 10, 30, 90, 270, or 810 ppm)	6 hours/ day, 5 days/ week for 13 weeks	LOAEC = 63 mg/m^3	Slight cytological alterations in the liver; cytoplasmic globules	(Nagano et al., 2007b)	High
Rat, F344, M/ F (n=20/ group)	Inhalation, vapor, whole body	0, 63, 189, 566, 1699, 5096 mg/m^3 (0, 10, 30, 90, 270, 810 ppm)	6 hours/ day, 5 days/ week for 13 weeks	NOAEC = 63 mg/m^3 (F), LOAEC = 189 mg/m^3 (F)	Increased liver weight; large droplet fatty change in liver	(Nagano et al., 2007b)	High
Mouse, B6C3F1, M (n=10/ group)	Inhalation, whole body	0, 31, 126, or 629 mg/m^3 (0, 5, 20 or 100 ppm)	6 hours/ day, 5 days/ week for 12 weeks	NOAEC = 31 mg/m^3 (M), LOAEC = 126 mg/m^3 (M)	Increased ALT, SDH; necrosis and cell proliferation in liver	(Benson and Springer, 1999)	Low

[15] Note: information on associated human studies from (Davis, 1934) can be found in text.

Subjects	Exposure Route	Doses/ Concentrations	Duration	Effect Dose	Effect*	Reference	Data Quality Evaluation
Hamster, Syrian, M (n=10/ group)	Inhalation, whole body	0, 31, 127 or 636 mg/m^3 (0, 5, 20 or 100 ppm)	6 hours/ day, 5 days/ week for 12 weeks	NOAEC = 126 mg/m^3 (M), LOAEC = 629 mg/m^3 (M)	Increased ALT, SDH; necrosis and cell proliferation in liver	(Benson and Springer, 1999)	Low
Rat, Wistar-derived, M/ F (n=30-50/ group)	Inhalation, vapor, whole body	0, 31, 63, 157, 315, 629, 1258 or 2516 mg/m^3 (0, 5, 10, 25, 50, 100, 200 or 400 ppm)	7 hours/ day, 5 days/ week for 6 months	NOAEC = 31 mg/m^3, LOAEC = 63 mg/m^3	Increased liver weight; fatty degeneration in liver	(Adams et al., 1952)	Low
Guinea pig, M/ F (n=10-18/ group)	Inhalation, vapor, whole body	0, 31, 63, 157, 315, 629, 1258 or 2516 mg/m^3 (0, 5, 10, 25, 50, 100, 200 or 400 ppm)	7 hours/ day, 5 days/ week for 6 months	NOAEC = 31 mg/m^3, LOAEC = 63 mg/m^3	Increased liver weight; fatty degeneration in liver	(Adams et al., 1952)	Low
Rabbit, albino, M/ F (n=2-4/ group)	Inhalation, vapor, whole body	0, 31, 63, 157, 315, 630, 1260 or 2520 mg/m^3 (0, 5, 10, 25, 50, 100, 200 or 400 ppm)	7 hours/ day, 5 days/ week for 6 months	NOAEC = 63 mg/m^3, LOAEC = 157 mg/m^3	Increased liver weight; fatty degeneration and slight cirrhosis in liver	(Adams et al., 1952)	Low
Monkey, rhesus, M/ F (n=2-4/ group)	Inhalation, vapor, whole body	0, 31, 63, 157, 315 or 630 mg/ m^3 (0, 5, 20, 25, 50 or 100 ppm)	7 hours/ day, 5 days/ week for 6 months	NOAEC = 315 mg/m^3, LOAEC = 629 mg/m^3	Slight fatty degeneration and increased lipid content in liver	(Adams et al., 1952)	Low
Mouse, CD-1, M/ F (n=40/ group)	Oral, gavage (corn oil vehicle)	0, 12, 120, 540 or 1200 mg/kg-bw/day	7 days/ week for 90 days	LOAEL = 12 mg/kg-bw/day	Increased liver weight, ALT, AST, ALP, LDH, 5'-nucleotidase; fatty change, hepato-cytomegaly, necrosis, and hepatitis	(Hayes et al., 1986)	Medium
Rat, Sprague-Dawley, M (n=15-16/ group)	Oral, gavage (corn oil vehicle)	0, 1, 10 or 33 mg/kg-bw/day	5 days/ week for 12 weeks	NOAEL = 1 mg/kg-bw/day (M), LOAEL = 10 mg/kg-bw/day (M)	Two- to three-fold increase in SDH; mild centrilobular vacuolization in liver	(Bruckner et al., 1986)	High

Subjects	Exposure Route	Doses/ Concentrations	Duration	Effect Dose	Effect*	Reference	Data Quality Evaluation
Rat, F344, M (n=48/ group; 6/ group at sacrifice time; sacrificed at intervals from 1 to 15 days post exposure)	Oral, gavage (corn oil vehicle)	0, 20 or 40 mg/kg-bw/day	5 days/ week for 12 weeks	LOAEL = 20 mg/kg-bw/day (M)	Increased liver weight, ALT, AST, LDH; reduced liver CYP450; cirrhosis, necrosis, and degeneration in liver	(Allis et al., 1990)	Medium
Mouse, CD-1, M/ F (n=24/ group)	Oral, gavage (corn oil vehicle)	0, 1.2, 12 or 120 mg/kg-bw/day	5 days/ week for 12 weeks	NOAEL = 1.2 mg/kg-bw/day, LOAEL = 12 mg/kg-bw/day	Increased ALT; mild to moderate hepatic lesions (hepato-cytomegaly, necrosis, inflammation)	(Condie et al., 1986)	High
Mouse, CD-1, M/ F (n=24/ group)	Oral, gavage (1% Tween-60 vehicle)	0, 1.2, 12 or 120 mg/kg-bw/day	5 days/ week for 12 weeks	NOAEL = 12 mg/kg-bw/day, LOAEL = 120 mg/kg-bw/day	Increased liver weight, ALT, AST, LDH; hepato-cytomegaly, vacuolation, inflammation, necrosis, and fibrosis in liver	(Condie et al., 1986)	High
Rat, F344, F (n=12-14/ group)	Oral, gavage (corn oil vehicle or 10% Emulphor vehicle)	0, 25, 50 or 75 mg/kg-bw/day	GDs 6-15	NOAEL = 25 mg/kg-bw/day (F), LOAEL = 50 mg/kg-bw/day (F)	Piloerection; markedly increased full-litter resorption	(Narotsky et al., 1997)	High
Rat, Sprague-Dawley, F (n=24-28/ group)	Inhalation, whole body	0, 300, or 1,000 ppm for 7 hours/day	GDs 6-15	LOAEC = 300 ppm; NOAEC not determined	Decreased fetal body weight and crown-rump length; increased sternebral anomalies	(Schwetz et al., 1974)	High
Guinea pig, gender not specified (n=20)	Dermal	0.5 or 2.0 mL	Single application; contact for 5 days	LOAEL = 260 mg/cm^2 (0.5 mL)	5 of 20 animals died at 0.5 mL; 13 of 20 animals died at 2.0 mL (first animal death on day 1 at 2.0 mL)	(Wahlberg and Boman, 1979)	Medium

* Effect acronyms: ALP = Alkaline Phosphatase, ALT = Alanine Transaminase, AST = Aspartate Transaminase, BUN = Blood Urea Nitrogen, CPK = Creatine Phosphokinase, GPT = Glutamic-Pyruvate Transaminase, LDH = Lactate Dehydrogenase, SDH = Sorbitol Dehydrogenase

3.2.3 Toxicokinetics

The toxicokinetics of carbon tetrachloride have been comprehensively described in previous toxicological assessments (see Table 1-3). In summary, the IRIS assessment describes that carbon tetrachloride is rapidly absorbed by any route of exposure. However, it is noted that the dermally absorbed fraction would be negligible for exposures to carbon tetrachloride vapor (Mccollister et al., 1951).

Once absorbed, carbon tetrachloride is widely distributed among tissues, especially those with high lipid content, reaching peak concentrations in <1–6 hours, depending on exposure concentration or dose. Animal studies show that volatile metabolites are released in exhaled air, whereas nonvolatile metabolites are excreted in feces and to a lesser degree, in urine.

In (Sanzgiri and Bruckner, 1997), the comparison of tissue distribution of inhaled carbon tetrachloride to the equivalent oral dose show that maximal levels in fat were considerably in excess of the maximal levels in other tissues, regardless of route of exposure. Among tissues other than fat, distribution kinetics were generally similar for the tissues, except that maximal levels were higher and attained more quickly in the liver than in other tissues following bolus oral administration.

The metabolism of carbon tetrachloride has been extensively studied in *in vivo* and *in vitro* mammalian systems. Carbon tetrachloride is metabolized in the body, primarily by the liver, but also in the kidney, lung, and other tissues containing CYP450 enzymes. Based on reasonably available information, the initial step in biotransformation of carbon tetrachloride is reductive dehalogenation: reductive cleavage of one carbon-chlorine bond to yield chloride ion and the trichloromethyl radical. Biotransformation of carbon tetrachloride to reactive metabolites, including the trichloromethyl radical, is hypothesized to be a key event in the toxicity of carbon tetrachloride. The fate of the trichloromethyl radical depends on the availability of oxygen and includes several alternative pathways for anaerobic or aerobic conditions. Anaerobic dimerization forms hexachloroethane, while aerobic trapping by oxygen forms a trichloromethyl peroxy radical. The trichloromethyl peroxy radical is the primary initiator of lipid peroxidation that occurs from exposure to carbon tetrachloride (Rao and Recknagel, 1969).

Cytochromes CYP2E1 and CYP2B, the primary enzymes responsible for biotransformation of carbon tetrachloride in rodents, were measured in all exposed and control animals in the metabolic studies by (Benson and Springer, 1999). In all species, microsomal measurement of these enzymes indicated that while enzyme induction increased several fold as dose increased, catalytic activity was not significantly altered. In addition, the rate of carbon tetrachloride metabolism was measured in rat, mouse and hamster species. The metabolic rate of carbon tetrachloride did not vary more than two-fold between the three species (Benson and Springer, 1999).

(Thrall et al., 2000) and (Benson and Springer, 1999) used *in vitro* data on metabolism of carbon tetrachloride by human liver microsomes and *in vitro* and *in vivo* rodent data to estimate the *in vivo* human metabolic rate constants. Estimated rate constants were used by the IRIS Program for interspecies extrapolation (*i.e.*, rat-to-human, mouse-to-human) and route-to-route extrapolation of carbon tetrachloride inhalation dosimetry using a human PBPK model, which

has been described in (Paustenbach et al., 1988), (Thrall et al., 2000) and (Benson and Springer, 1999).

3.2.4 Hazard Identification

3.2.4.1 Non-Cancer Hazards

The high hepatoxicity potential of carbon tetrachloride is well documented in the literature, and carbon tetrachloride is recognized as a model hepatotoxicant in animal and *in vitro* studies. Carbon tetrachoride is used as a reference compound to compare the hepatoxicity of other halogenated solvents and as a positive control for liver damage in the study of potential therapeutic effects of other compounds (Song et al., 2011; Martínez et al., 1995; Sagai and Tappel, 1978). In addition to its high hepatoxicity potential, carbon tetrachloride is also known to affect the CNS and the kidney.

Most of the human case reports of acute inhalation exposure to carbon tetrachloride describe a consistent pattern of carbon tetrachloride toxicity that includes initial dizziness and nausea, followed by abdominal discomfort, liver and kidney effects and subsequent renal failure and death (Manno et al., 1996; Ruprah et al., 1985; New et al., 1962). Despite consistent findings across human acute studies, most case reports lack reliable quantitative data. However, EPA notes that Davis (1934) provides a series of controlled human experiments in which dose regimes were serially adjusted based on previous experimental observations. Because carbon tetrachloride concentrations were determined in those studies on the basis of the room volume and the amount of carbon tetrachloride necessary to achieve the desired concentration, OPPT considers that the identified NOAEC for reversible CNS effect (*i.e.*, dizziness) is a health protective effect and presents an effect level that is applicable for this risk evaluation.

There are no human data on the reproductive toxicity and very limited human data on the developmental toxicity of carbon tetrachloride, which consists of a prospective cohort study with limited power that found no association between occupational exposure to carbon tetrachloride and the risk of infants small for gestational age (Seidler et al., 1999). Limited evidence from gestational exposure studies in animals suggest that developmental toxicity is not an acute effect nor the most sensitive effect for carbon tetrachloride. Developmental toxicity has been observed at oral and inhalation doses accompanied by some degree of maternal toxicity (Narotsky et al., 1997; Narotsky and Kavlock, 1995; Schwetz et al., 1974; Wilson, 1954). Observations from the only high quality developmental toxicity study by the inhalation route (Schwetz et al., 1974) suggests that developmental effects (*i.e.*, decreased fetal body weight and crown-rump length, increase in sternebral anomalies) of carbon tetrachloride occur at concentrations toxic to the mother and at exposure concentrations higher than those associated with liver and kidney toxicity. EPA considers that developmental effects from inhalation exposures to carbon tetrachloride (*i.e.*, decreased fetal body weight and crown-rump length, increase in sternebral anomalies) are not single dose effects and are likely associated with maternal toxicity. Inhalation exposures to carbon tetrachloride during gestation have not been associated with resorptions and mortality, which are effects that can occur following a single exposure during a sensitive developmental stage and are considered a relevant endpoint for acute effects (van Raaij et al., 2003).

Epidemiological data on non-cancer effects from subchronic and chronic inhalation exposures is also limited. The limited dataset includes a medium quality study by Tomenson *et al.* (1995), which was used as supportive evidence in the development of the IRIS RfC on liver effects as was noted in the IRIS Toxicologic Review (U.S. EPA, 2010). This cross-sectional study on hepatic function in workers exposed to carbon tetrachloride provides suggestive evidence of hepatic effects from workplace inhalation exposures.

There are no epidemiological data or human case reports on long term oral exposures to carbon tetrachloride. In contrast, repeated-dose oral and inhalation studies with carbon tetrachloride in rodents (mice, rats and guinea pigs) is quite extensive, but with limited information on reproductive and developmental effects (see discussion of (Schwetz et al., 1974), above). The inhalation database includes a high quality chronic (104 week) inhalation toxicity study in rats and mice by (Nagano et al., 2007a) showing increased incidence and severity of nonneoplastic kidney and liver lesions (*i.e.*, fatty change, fibrosis, cirrhosis) and serum enzyme levels in exposed rats and mice. This chronic study, and its associated 13-week subchronic study, examined an extensive set of non-cancer endpoints showing consistency in hazard levels and effects over time for mice and rats. In agreement with IRIS conclusions, OPPT considers the fatty changes in rat livers as the most sensitive endpoint indicative of adverse effect in the liver and this endpoint was chosen for dose-response analysis for inhalation exposures. As liver toxicity is identified as the most sensitive effect from repeated inhalation exposures to carbon tetrachloride, OPPT assumes, that similarly to developmental toxicity, potential reproductive effects from carbon tetrachloride exposure are, at worst, secondary to liver toxicity. For instance, effects on the reproductive organs (*e.g.*, testes, uterus, etc.) have not been observed in subchronic and chronic animal studies, which suggests that carbon tetrachloride is not likely to be a reproductive toxicant, and that any potential reproductive effects could be only induced at much higher doses than liver toxicity. EPA has also concluded that carbon tetrachloride immunological effects were, at least in part, secondary to hepatotoxicity and the process of hepatic repair, which produces adverse effects on T-cell-dependent immunity at doses that are hepatotoxic.

Moderate primary irritation hazard in rabbits and guinea pigs from acute dermal exposures has been identified for carbon tetrachloride (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). However, there are limited reasonably available studies by the dermal route for carbon tetrachloride, making it difficult to identify adequate quantitative information on effects levels inducing non-local effects. Data on the absorption of carbon tetrachloride demonstrate that compound in liquid form is systematically absorbed via all routes of exposure, including dermal. Therefore, induction of toxic effects by internal doses from dermal exposures is expected. Furthermore, the very limited available dermal exposure data suggest that liver changes can be induced by exposure to carbon tetrachloride through the skin in animals. Among the few dermal studies, (Kronevi et al., 1979) (data quality rating = unacceptable due to lack of negative controls and small number of animals) is the only available animal dermal study that includes histopathological observations of the liver and kidney in addition to skin tissue. There were no reported kidney changes following dermal exposure to carbon tetrachloride in this study, but liver necrosis was observed in guinea pigs after occluded application of 1 mL carbon tetrachloride for 16 hours, but not for 15 minutes, 1 hour, or 4 hours. The results of the dermal study by (Wahlberg and Boman, 1979) (data quality

rating = medium) also suggest that short term (4 hours) application of ≤ 1 mL carbon tetrachloride has low potential for induction of adverse effects. In Wahlberg and Boman, one guinea pig exposed to 0.5 mL died on day 3, and a total of five animals died by the end of the observation period (21 days). Faster and higher rate of mortality was observed for animals in the highest exposure group.

Because quantitative information on the effects of carbon tetrachloride via the dermal route in humans and animals is limited or absent, route-to-route extrapolation is considered in this risk evaluation with the assumption that inhalation is the most relevant route for extrapolation. This assumption is based on the fact that carbon tetrachloride undergoes first-pass metabolism in the liver following oral exposures, which results in lower peak exposure at the target site. Alternatively, there is more opportunity for extrahepatic distribution of carbon tetrachloride following inhalation and dermal exposures, as these exposure routes bypass first-pass metabolism in the liver.

3.2.4.2 Genotoxicity and Cancer Hazards

3.2.4.2.1 Genotoxicity

As documented in the EPA IRIS Toxicological Review of carbon tetrachloride (U.S. EPA, 2010), a substantial body of publications have studied genotoxic effects of carbon tetrachloride. The systematic review for this risk evaluation did not identify additional genetic toxicity studies with carbon tetrachloride rated of medium or high overall quality. The main conclusions and limitations of the *in vitro* and *in vivo* genotoxicity databases for carbon tetrachloride are described below.

OPPT has concluded that there is little direct evidence that carbon tetrachloride induces intragenic or point mutations in mammalian systems. Multiple studies have characterized the formation of endogenously produced DNA adducts, chromosomal aberrations, and micronucleus formation, primarily in the presence of cellular toxicity. Lipid peroxidation, one of the key events in the proposed MOA, products generate compounds (*i.e.*, reactive aldehydes) that may covalently bind to DNA. There is strong evidence of increases in DNA adducts formed from reactive oxygen species *(i.e.*, 8-hydroxy-2'-deoxyguonosine) and lipid peroxidation products such as malondialdehyde and 4-hydroxynonenal in the liver of rodents following administration of carbon tetrachloride. There is limited evidence, however, for the formation of DNA adducts derived directly from carbon tetrachloride. There is no evidence of unscheduled DNA synthesis in the livers of carbon tetrachloride-treated rats or mice even when tested under conditions producing significant hepatotoxicity.

Based on the weight of evidence, EPA has concluded that genotoxic effects have been observed in a consistent and close relationship with cytotoxicity, lipid peroxidation, and/or oxidative DNA damage.[16] Mutagenic effects, if they occur, are likely to be generated through genotoxicity mechanisms resulting from oxidative stress or lipid peroxidation products. Under highly cytotoxic conditions, bioactivated carbon tetrachloride can exert genotoxic effects. These tend to

[16] However, EPA acknowledges that there are important methodologic gaps in the genotoxicity database for carbon tetrachloride, which are described in Appendix H

be modest in magnitude and are manifested primarily as DNA breakage and related sequelae. Chromosome loss leading to aneuploidy may also occur to a limited extent.

In vitro Genotoxicity

The *in vitro* genotoxicity database for carbon tetrachloride, while large in number of studies, is not diverse in the type of assays contained to examine the genotoxicity potential of carbon tetrachloride. The studies identified in Appendix H, while not definitive, provide indications of mutational or chromosomal changes that may be relevant to the MOA of carbon tetrachloride carcinogenesis.

In vivo Genotoxicity

Assessment of potential genotoxic effects of carbon tetrachloride should focus first on effects in the liver, as CYP2E1 activity largely resides in the liver. Data from other tissues (*i.e.*, lung and kidney) may supplement the liver data to a degree, as these tissues have lesser but maybe relevant levels of CYP2E1 activity.[17] It is not apparent that data for other tissues will reflect the CYP2E1 metabolism of carbon tetrachloride.

The carbon tetrachloride database is sparse for *in vivo* studies of mutation and chromosomal changes in liver tissue. Available studies as cited in EPA IRIS Assessment (U.S. EPA, 2010) are presented in Appendix H.

3.2.4.2.2 Carcinogenicity

Epidemiological Data on Carcinogenicity

General Overview of reasonably Available Epidemiological Data

The most recent EPA IRIS assessment (U.S. EPA, 2010) did not indicate that studies in humans showed an association between exposure to carbon tetrachloride and carcinogenicity based on the literature available at that time. The assessment presented some limited evidence for certain types of cancer in occupational populations exposed to carbon tetrachloride, including brain cancer, breast cancer, cervical cancer, esophageal cancer, lymphatic leukemia, lymphosarcoma, non-Hodgkin's lymphoma, and rectal cancer (U.S. EPA, 2010). Table 3-4 presents epidemiological studies of acceptable data quality published after completion of the 2010 EPA IRIS assessment (U.S. EPA, 2010). Among those 11 new studies published since 2010, there was one study of breast cancer, one study of head/neck cancer, one study of kidney cancer, two studies of lung cancer, two studies of lymphohematopoietic cancers, three studies of brain cancers, and one study of neuroblastoma.

Combining these with the several studies noted in the IRIS assessment, there was little evidence of an association between carbon tetrachloride exposure and the lymphohematopoietic cancers (non-Hodgkin lymphoma, lymphosarcoma, lymphatic leukemia, multiple myeloma, and mycosis fungoides – the most common form of cutaneous T-cell lymphoma), breast cancer, head/neck cancer, kidney cancer, or lung cancer.

[17] Yoon (2007) has estimated CYP2E1 activity (Vmax – nmole/min/g) in the lung and kidney as approximately 6% and 5% of that in the liver.

However, three of these newer studies report results for cancers of the brain – as did one study from the 2010 IRIS assessment (Heineman et al., 1994). All four of these brain cancer studies were of brain tumors which include astrocytomas, gliomas, glioblastomas and glioblastoma multiforme and occur in adults. The brain cancer studies were critically and comprehensively reviewed below, as was a single study on neuroblastoma – the most common cancer in infants and most commonly found in the adrenal glands, which is concordant in organ site with the pheochromocytomas findings in mice (see Section 3.2.5.2.5).

Table 3-4. Epidemiologic Studies of Carbon Tetrachloride and Cancer After 2010 EPA IRIS Assessment

Cancer Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Brain (Glioblastoma multiforme)	8,006 men of Japanese descent from the Honolulu Heart Program and Honolulu-Asia Aging Study cohorts, aged 45-68 years at initial examination (1965-1968) and followed through 1998. Nine glioblastoma cases.	Occupational histories reviewed by NIOSH industrial hygienists who assigned levels of exposure.	Crude rate of astrocytic brain cancer among men exposed to carbon tetrachloride (n=2) was 10-fold higher than among unexposed men (n=7; p=0.012). A positive, statistically significant association was found between glioblastoma and high occupational exposure to carbon tetrachloride (n=1) vs. no exposure (HR=26.59; 95% CI: 2.9, 243.5).	(Nelson et al., 2012)	Medium
Brain (Glioma)	Hospitalized patients including 489 glioma cases, 197 meningioma cases, and 799 controls from three hospitals in Boston, Pittsburgh and Phoenix.	Occupational histories reviewed by NCI industrial hygienist who assigned levels of exposure. Proxy interviews were conducted for 16% (n=78) of glioma cases, 8% (n=15) of meningioma cases, and 3% (n=23) of controls.	Carbon tetrachloride was associated with a decreased risks of glioma when the reference group was the unexposed, but a significantly increased in risk when the reference group was the 'low' exposed group for average weekly exposure above the median (OR=7.1; 95% CI: 1.1, 45.2) compared to exposure below the median. Additional adjustment for exposure to lead and magnetic field was also significantly increased (OR=60.2; 95% CI: 2.4, 1533.8) compared to below the	(Neta et al., 2012)	High

Cancer Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
			median. No association with meningioma.		
Brain (Glioma)	Non-farm workers from the Upper Midwest Health Study including 798 cases and 1,141 controls from Iowa, Michigan, Minnesota, and Wisconsin 1995-1997.	Occupational histories reviewed by NCI industrial hygienist who assigned levels of exposure. Of 798 glioma cases, 360 interviews (45%) were conducted with proxies because the cases were deceased. None of the control interviews were conducted with proxies.	Excluding proxy-only interviews: 'Ever' vs. 'never' having carbon tetrachloride exposure was not associated with a risk of glioma per ppm-yr (OR=0.82; 95% CI: 0.64, 1.06) and cumulative exposure was associated with decreased risk of gliomas per ppm-year (OR=0.98; 95% CI: 0.96, 1.00). Including proxy-only interviews: Results were similar to those excluding proxy-only interviews (OR=0.98; 95% CI: 0.96, 0.99).	(Ruder et al., 2013)	High
Breast	Participants in the California Teacher Study, 1995-2011, (n=112,378 women).	National-Scale Air Toxics Assessment modeled air concentrations.	Borderline significant increase in risk of breast cancer incidence associated with 5th quintile carbon tetrachloride exposure compared to 1st quintile exposure (HR=1.08; 95% CI: (1.00, 1.18). Significant trend across quintiles (p=0.03).	(Garcia et al., 2015)	High
Head/Neck	Case-control, women only, 296 cases, 775 controls, diagnosed 2001-2007, general population, aged 18-85 years, subset of ICARE cohort.	Carbon tetrachloride, exposure qualitatively stated as ever (job with likely exposure >1month) or never.	No statistically significant association between carbon tetrachloride and head/neck cancers (OR=0.36; 95% CI: 0.09, 1.55).	(Carton et al., 2017)	Medium
Kidney	General population case-control study of kidney cancer (1,217 cases; 1,235 controls).	Job exposure matrix was used to determine years exposed, average weekly exposure and cumulative	No statistically significant associations observed between exposure to carbon tetrachloride and kidney cancer	(Purdue et al., 2016)	High

Cancer Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
	Detroit (2002 - 2007) and Chicago (2003).	hours exposed. to carbon tetrachloride.	(>90% probability of exposure vs unexposed OR=1.1; 95% CI 0.8, 1.5).		
Lung	Investigation of occupational and environmental causes of respiratory cancers (ICARE) study subjects, population-based case-control study in France 2001-2007 (622 women cases and 760 women controls).	Cumulative Exposure Index based on job histories and probability, intensity, and frequency of exposure to carbon tetrachloride based on jobs.	Carbon tetrachloride was not significantly associated with lung cancer in women (results not presented).	(Mattei et al., 2014)	Medium
Lung	Lung cancer cases and randomly selected population-based controls frequency matched by sex and age in Montreal Canada.	Carbon tetrachloride exposure (any or substantial) was assessed by a team of industrial chemists and hygienists based on job histories.	Reported OR for 'any' exposure to carbon tetrachloride in pooled analysis (OR=1.2; 95% CI: 0.8,2.1); significant increased OR for substantial exposure in pooled analysis (OR=2.5; 95% CI: 1.1,5.7). By histologic type of lung cancer, carbon tetrachloride was significantly associated squamous cell tumors (OR=3.3, 95% CI: 1.4,8.1). Authors noted that this was a unique finding of an association between lung cancer and carbon tetrachloride.	(Vizcaya et al., 2013)	Medium
Lympho-hematopoietic (Multiple myeloma)	180 cases of multiple myeloma (diagnosed between January 1, 2000 and March 21, 2002; 35-74 years old) and 481 controls (35-74 years old).	Exposure to carbon tetrachloride estimated with job exposure matrix. Individual cumulative exposure scores were calculated by multiplying the midpoint of the intensity (in ppm) by the midpoint of the frequency (in	Primary analysis: reported risk of multiple myeloma (OR=1.1; 95% CI: 0.7, 1.8). When individuals with reported exposure rated as "low confidence" were considered unexposed, reported risk of multiple myeloma was observed in individuals ever	(Gold et al., 2010)	High

Cancer Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
		hours/week) by the number of years worked in each exposed job.	exposed to carbon tetrachloride (OR=1.6; 95% CI: 0.8, 3.0). A significant exposure-related trend (p = 0.01) was observed for duration of exposure. The risks of myeloma were not increased with cumulative exposure score (with and without a 10-year lag).		
Lympho-hematopoietic (Mycosis Fungoides)	100 patients with Mycosis Fungoides and 2,846 controls, 35-69 years old, from Denmark, Sweden, France, Germany, Italy, and Spain, 1995-1997.	Occupational exposure to carbon tetrachloride assessed with job exposure matrix.	Reported association between Mycosis Fungoides and subjects with exposure to carbon tetrachloride ≥ median of control exposure vs. unexposed subjects (OR=2.75; 95% CI: 0.27,27.84).	(Morales-Suárez-Varela et al., 2013)	High
Neuroblastoma	Children (75 cases, 14,602 controls), ages <6 years born in 1990-2007 in California within 5 km of exposure monitoring stations, cases from California Cancer Registry.	Carbon tetrachloride (0.105 ppbV) in ambient air, pollution monitoring stations used to estimate maternal exposure during pregnancy from birth certificate address.	Significant positive association between risk of neuroblastomas per interquartile increase in carbon tetrachloride exposure (OR=2.55; 95% CI: 1.07, 6.53) within a 5 km radius and (OR=7.87; 95% CI: 1.37, 45.34) within a 2.5 km radius of monitors. Significant positive association for the highest quartile of carbon tetrachloride exposure compared to the lowest (OR=8.85; 95% CI: 1.19, 66.0).	(Heck et al., 2013)	Medium

Epidemiological Data on Brain Tumors (Astrocytomas, Gliomas and Glioblastomas)

(Heineman et al., 1994)
Heineman *et al.* (1994) is a population-based case-control study designed to evaluate risks of brain tumors, which included astrocytomas, glioblastomas, and mixed glioma with astrocytic cells, associated with specific occupational exposures in the petrochemical industry. The systematic review rated the study as 'Medium' quality. The 741 cases and 741 controls were

selected from U.S. locations with high proportions of workers in these industries in order to increase the likelihood of exposures to chlorinated aliphatic hydrocarbons (including carbon tetrachloride) in the source populations that gave rise to both the cases and the controls. Controls were randomly selected from white male residents who died of causes other than brain tumor, CVD, epilepsy, suicide and homicide and were frequency matched on age, year of death, and location. Next-of-kin were located for 88% of cases (n=654) and 83% of controls (n=612). Among those cases whose proxies completed the interview, 300 were confirmed as astrocytic brain tumor cases with hospital diagnoses and 320 controls whose proxies completed the interview were confirmed not to have other conditions potentially related to chlorinated aliphatic hydrocarbons.

Trained interviewers, who were blinded to the case status of the interviewed family members, administered standardized questionnaires recording all study members' occupations since the age of 15 years including job title, job tasks, name and location of the company, the type of industry/products, employment dates and hours worked per week. These data were coded according to standardized classifications and linked by an industrial hygienist from the U.S. National Cancer Institute (NCI) to specific exposure profiles for each occupation to develop specific exposure profiles for each study participant. Results were presented at varying levels of specificity of exposure from 'ever' exposed (yes/no), by qualitative levels of probability of exposure, by average intensity of exposures, by duration of exposures, and by cumulative exposure score – with results stratified by different exposure metrics.

- OR (*i.e.*, odds ratio) for 'ever' being exposed to carbon tetrachloride was 1.2 (95% CI: 0.9, 1.7).
- No clear pattern of results by 'probability' of exposure
    - Strongest results among the 'Medium probability' group
    - Multi-pollutant model showed similar results
- Increasing OR trend with increasing cumulative exposure scores ($p < 0.05$)
- Increasing OR trend with increasing duration of exposure ($p < 0.05$)
- Increasing OR trend with increased 'average intensity' in high duration workers ($p < 0.05$)
- Higher 'Average intensity' had increased risks; OR = 2.9 (95% CI: 1.2, 7.1)
- Higher 'Average intensity' and duration had increased risk; OR = 3.1 (95% CI: 0.7, 15.3)

<u>Selection bias</u>: No concern that selection was differentially related to exposure or outcome.

<u>Information bias</u>: No specific concern for recall bias about carbon tetrachloride or other exposure misclassification related to outcome (*i.e.*, no differential misclassification) because study participants were asked about individuals' occupational histories which were then coded to specific exposures – respondents are unlikely to know how expert industrial hygienists would code those occupational histories for carbon tetrachloride; some concern that random exposure misclassification caused bias towards the null.

<u>Confounding</u>: Some concern for potential confounding of the association between carbon tetrachloride and astrocytic brain cancer by methylene chloride; however, to be a confounder, methylene chloride must itself be a cause of brain cancer and be more strongly associated with brain cancer then carbon tetrachloride to completely explain the reported carbon tetrachloride association. Comparing the effect sizes for the most specific exposure characterization using

‘High’ average intensity and 20+ years duration, the methylene chloride results (OR = 6.1; 95% CI: 1.5, 28.3) were stronger than the analogous result for carbon tetrachloride (OR = 3.1; 95% CI: 0.7, 15.3). Additional analyses restricted to those workers with 20+ years duration and High average intensity of exposure across all ‘probabilities’, multivariate exposure models showed higher risks for methylene chloride (OR = 6.7; 95% CI: 1.3, 47.4) vs. carbon tetrachloride (OR = 1.8; 0.7, 4.6). However, among only those with ‘High probability’, the OR was higher for carbon tetrachloride (OR= ∞; 2 cases and no controls) compared to methylene chloride (OR = 8.8; 95% CI: 1.0, 200). In other analyses, the effect of methylene chloride was greater than for carbon tetrachloride when adjusting for other chlorinated aliphatic hydrocarbons in addition to age, study area, employment in electronics-related occupations or industries, and the duration and intensity of exposure to three other solvents, but the wide confidence intervals overlapped. In this study, methylene chloride appears to be confounding the association of carbon tetrachloride with risk of astrocytic brain cancer. If methylene chloride were a cause of brain cancer, this would imply that the apparent association between carbon tetrachloride and this cancer was due to the correlation between these two exposures; however, if methylene chloride is not a cause of astrocytic brain cancer, then other explanations for the apparent confounding may involve more complicated issues of correlations among mixture of exposures and their measurement errors.

(Neta et al., 2012)
Neta *et al*. (2012) is a hospital-based case-control study designed to evaluate risks of brain tumors from occupational exposures to six chlorinated solvents. The systematic review rated the study as ‘High’ quality. The 484 glioma cases with 797 controls were enrolled during 1994-1998 from hospitals in three cities (Boston, Pittsburgh, and Phoenix) that were regional referral centers for brain cancer cases. Controls were patients with non-malignant conditions. Participation rates were high with 92% of glioma cases and 86% of controls participating. Proxy interviews were conducted for 16% of gliomas and 3% of controls. Controls were frequency matched by sex, age at interview, race/ethnicity, hospital, and proximity to the hospital. Patients were interviewed by trained research nurses using a computer-based questionnaire about their lifetime occupational histories. An expert industrial hygienist from the U.S. NCI converted the occupational histories into estimated exposures for ‘probability’, ‘frequency’ and ‘intensity’ for six chlorinated solvents.

Results for five of the chlorinated solvents including dichloromethane, chloroform, 1,1,1-trichloroethane, trichloroethylene and perchloroethylene) showed no evidence of increased risks of glioma. There was suggestive evidence of an association between exposure to carbon tetrachloride and increased risk of glioma.

Results for carbon tetrachloride exposures were presented in two ways: with the ‘unexposed’ as the reference group, and with the ‘low’ exposure group as the reference. The authors explained: “*The latter analyses accounted for the possibility that unexposed persons may be substantially different from exposed persons in ways that cannot be adjusted for in our analysis. Thus, comparing highly exposed subjects with those who had lower exposure levels may be a more accurate comparison for evaluating risks, assuming that a dose–response relationship exists.”*

Including the unexposed participants as the reference group:

- OR for ‘possible’ exposure was 0.7 (95% CI: 0.5, 0.9)

- OR for 'probable' exposure was 0.6 (95% CI: 0.3, 1.2)
- For years exposed, Low had OR of 0.5 (0.2, 1.2); High had OR of 0.9 (0.3, 2.2)
- For cumulative exposure, Low had OR of 0.4 (0.1, 1.1); High had OR of 0.9 (0.4, 2.0)
- For average exposure, Low had OR of 0.3 (0.1, 0.9); High had OR of 1.1 (0.5, 2.4)
- For highest exposure, Low had OR of 0.3 (0.1, 1.0); High had OR of 1.0 (0.4, 2.2)

Using the lower exposed participant as the reference group:

- For years exposed, High (8 cases; 7 controls) had OR of 1.6 (0.4, 7.5)
- For cumulative exposure, High (10 cases; 5 controls) had OR of 2.8 (0.6, 14.4)
- For average exposure, High (11 cases; 4 controls) had OR of 7.1 (1.1, 45.2)
- For highest exposure, High (11 cases; 4 controls) had OR of 3.2 (0.6, 17.2)

All four analyses comparing High (above median carbon tetrachloride exposure) to Low (below median exposure) were elevated, but only the above median 'average' exposures were statistically significantly increased. (Neta et al., 2012) noted that earlier studies of occupational exposures to chlorinated solvents "*did not identify specific aetiological agents or disentangle the effects of potentially correlated occupational exposures, such as non-ionising electromagnetic radiation, lead and other chemical agents.*" Thus, (Neta et al., 2012) further adjusted for occupational exposures to lead and magnetic fields. For the other five chlorinated solvents, (Neta et al., 2012) reported no meaningful changes in estimated risk; however, for carbon tetrachloride, further adjustment for exposures to lead and magnetic fields increased the estimated risks for average weekly exposure above median exposures from OR = 7.1 (95% CI: 1.1, 45.2; p-value = 0.04) to OR = 60.2 (95% CI: 2.4 to 1533.8). Similarly, the estimated risks for cumulative exposure above median exposures from OR = 2.8 (95% CI: 0.6, 14.4) to OR = 56.4 (95% CI: 1.9 to 1686.2). Results were not reported for analyses adjusted for insecticide or herbicides.

Selection bias: Some concern that the 'unexposed' people were substantially different from the 'exposed' people. Since exposures were assessed based on occupational histories, only those people who were employed outside the home could have been considered to have been exposed – and people with worse health and shorter occupational histories would have had fewer opportunities for exposure. Workers are known to be healthier than the general population. Thus, both the healthy worker effect and the healthy worker survivor effect may explain why the results using the unexposed as the reference group yielded what appeared to be health protective effects while the comparisons with the low exposed group appeared to show increased risk. Because the participating hospitals were referral centers for brain cancer, it was possible that the brain cancer cases were drawn from a larger catchment area than the controls which could have induced some selection bias; however, the percentages of cases and controls who lived more than 50 miles from the hospital were equivalent (10.5% vs 10.8%), and thus there is little concern for this type of selection bias.

Information bias: No specific concern for recall bias about carbon tetrachloride or other exposure misclassification related to outcome (*i.e.*, no differential misclassification); some concern that random exposure misclassification caused bias towards the null.

Confounding: No concern for potential confounding by other chlorinated solvents, including by methylene chloride in this study; none of the other solvents were significantly associated with

increased risks of brain cancer in any of the analyses including the analyses with 'Low' exposure as the referent or when controlling for lead and magnetic fields. Given the large upward change in effect size of carbon tetrachloride when adjusting for exposures to lead and magnetic fields, there appear to have been either some strong confounding by those covariates, or a chance finding based on small numbers – although those results were statistically significant. If lead and magnetic fields were confounders and were positive risk factors for gliomas, then there must have been a negative correlation between carbon tetrachloride and those exposures. Nevertheless, the observed effect of higher carbon tetrachloride compared to lower exposure was statistically significant both with, and without control of exposure to lead and magnetic fields.

Chance: The main finding was a seven-fold increase in risks of glioma associated with High average carbon tetrachloride exposure. This result was supported by the finding of elevated risks in the three other carbon tetrachloride exposure metrics, but only the High average exposure metric was statistically significantly increased. However, the extremely high risks reported in the *a priori* sub-analyses controlling for exposures to lead and magnetic fields were also highly unstable with wide confidence intervals, that while excluding the null value of 1.00, could be due to chance or an overly stratified model controlling for lead and magnetic fields in addition to five baseline covariates with 14 highly exposed cases and 11 highly exposed controls.

(Ruder et al., 2013)
Ruder (2013) is a case-control study designed to evaluate risks of non-farm related occupational exposures to chlorinated solvents in four states with large farm populations and above-average rates of brain cancer. The systematic review rated the study as 'High' quality. The 798 cases with glioma were ascertained through participating medical facilities and comprised 78% of all cases in those states during the collection period. The 1,175 population controls were residents of those states and were frequency matched on age and sex. Participation rates were high with 91% of cases and 70% of controls participating. All participants lived in non-metropolitan counties. Cases were interviewed when possible with next-of-kin proxies as needed (45%). All of the controls were interviewed without proxies. Interviewers were highly trained, used a standardized protocol, and were blinded to the study hypotheses. An expert industrial hygienist from the U.S. NCI, who was blinded to case-control status, converted the occupational histories into estimated exposures. Results were presented in two ways: with and without the cases with proxy interviews. Including the case-proxies, Ruder (2013) found a decreased risk with 'ever/never' exposure (OR = 0.79; 95% CI: 0.65, 0.97). Excluding the case-proxies, they found similar risks (OR = 0.82; 95% CI: 0.64, 1.06).

Selection bias: Some concern that the controls were significantly older than the cases and thus began their occupational exposures in earlier times and consequently had greater opportunity for increased exposure to carbon tetrachloride. Although age was adjusted for in the analyses, the result of this imbalance in age may have been to exert a downward bias on the effect estimates.

Information bias: No specific concern for recall bias about carbon tetrachloride. Some concern that while the investigators used appropriate methods for interviewing the study participants, 45% of case interviews were with proxies while none of the control interviews were with proxies. The investigators make the point that "*possible poor recall by case respondents could have affected the analysis if work details that might be associated with chlorinated solvent*

exposure were less specific for case than for control responses." The result of this differential measurement error bias may have been to exert a downward bias on the effect estimates by comparing more accurate exposure information from controls with less accurate exposure information from cases.

Confounding: No concern for potential confounding by other chlorinated solvents; none of the other solvents were significantly associated with increased risks of brain cancer in any of the analyses. In fact, all of the solvents were uniformly associated with the same magnitude of decreased risk which raises the possibility of a common methodological issue.

(Nelson et al., 2012)
Nelson *et al*. (2012) is a prospective cohort study of the Honolulu Heart Program that followed the health of 8,009 men for 30 years. The systematic review rated the study as 'Medium' quality. The investigators ascertained exposure to carbon tetrachloride based on review of occupational histories by three industrial hygienists from the National Institute for Occupational Safety and Health (Charles *et al.*, 2006 as cited in (Nelson et al., 2012)). A 'High' score reflected confidence that the occupational exposures were frequent and at least sometimes near the OSHA PEL; a 'medium' score reflected likely exposures that were below the PEL. The OSHA PEL is 10 ppm for an eight hour time-weighted average. Results are presented for 'selected' variables including demographics, biomarkers, diet and occupational exposures. The only occupational exposures reported were for 'solvents' and carbon tetrachloride which appears to have been selectively reported due to the statistical significance of the association – although the investigators reported that they found no effects for metals or pesticides. Such an association should be interpreted with caution as it is unclear how many other exposures were evaluated, but not reported. Nevertheless, the incidence rate of glioblastoma multiforme, a type of brain cancer, among the cohort without occupational exposure to carbon tetrachloride was 7 cases per 191,469 person-years (p-y) or 3.7 per 100,000 p-y. The rate of glioblastoma multiforme among the cohort with occupational exposure to carbon tetrachloride was 2 cases per 5,421 p-y or 36.9 cases per 100,000 p-y. This yields a rate ratio of 10.09 with a p-value of 0.012. The investigators also reported a hazard ratio for carbon tetrachloride of 26.59 (95% CI: 2.90, 243.50) based on a single case with 'high' exposure (*p*-value of 0.004) for this association.

Selection bias: No concern as the cohort was enrolled between 1965-68 with occupational histories taken at the initial enrollment and followed up for mortality through 1998. Only 5 of 8,006 participants were lost to follow-up.

Information bias: No concern that exposure measurement error could have been differential with respect to the outcome as this was a prospective cohort study. Three industrial hygienists from the National Institute for Occupational Safety and Health identified several occupations as being associated with exposure to carbon tetrachloride.

Confounding: No concern as there were no effects reported for metals or pesticides and no other results from other occupational exposures were presented (no results presented for carbon disulfide, the only other specific solvent mentioned) other than 'solvents', this study does not provide evidence to suggest confounding.

Chance: As noted in (Nelson et al., 2012), the known causes of glioblastoma were limited to ionizing radiation and genetic disorders and the objective of this study was to generate hypotheses. Chance is always a potential explanation for any individual finding and the apparent selective reporting of results needs to be considered in the evidence integration across all the available epidemiologic studies.

Evidence Integration for Studies on Brain Tumors (Astrocytomas, Gliomas and Glioblastomas)
While all four studies on brain tumors were evaluated during systematic review as either 'high' or 'medium' quality, there were distinctive differences in some study quality elements that were not reflected in the overall scores. The case-control study by Ruder *et al*. (2013) found no evidence of increased risk of brain cancer − but there were two methodological issues that could have resulted in downward biases: first, while the methods appeared to be sound, the controls happened to be significantly older than the cases making them potentially more likely to have had occupational exposures to carbon tetrachloride and to greater extent; second, with 45% of case interviews conducted with proxies compared to none of the controls, there is a strong potential for exposure measurement error to be differentially associated with the outcome.

The prospective cohort study (Nelson et al., 2012) was well designed, but the results appear to have been selectively presented as carbon tetrachloride exposure was the only specific occupational exposure presented – possibly because the results were highly statistically significant. This does not change those results, but suggests that the statistical significance should be evaluated in context. Nevertheless, the finding that those subjects exposed to carbon tetrachloride were 10 times more likely to die of brain cancer and that the one highly exposed case generated a more than 26-fold increase in risks cannot be completely set aside.

Heineman *et al*. (1994) provided the most thorough evaluation across a variety of exposure measures with different levels of specificity including results by 'ever' exposed, probability of exposure, average intensity of exposure, cumulative exposure, and exposure duration, with results provided for combinations of these exposures. The study was the only one that targeted populations with higher likelihoods of being exposed to carbon tetrachloride associated with occupations in the petrochemical industry. Results for the cruder metrics of exposure ('ever' and probability of exposure) did not show increased risks, while the more specific metrics of average intensity of exposure showed increased risk at the highest level (OR = 2.9; 95% CI: 1.2, 7.1) as well as statistically significant trends with increasing cumulative exposure and duration of exposure. The strongest results were for the highest average intensity for the longer duration of exposure (OR = 3.1; 95% CI: 0.7 – 15.3). However, while methylene chloride appears to have been a potential confounder, methylene chloride is not a known cause of astrocytic brain cancer and therefore cannot be a confounder.

Neta *et al*. (2012) reported an unexpectedly health protective effect when analyses used the unexposed as the reference group but reported increased risks for carbon tetrachloride when using the 'low' exposed group as the reference group. Such results can arise when the unexposed people are different from the exposed people in other ways that may be related to the outcome, thus a comparison between participants with industrial occupational exposures to non-industrial occupations may attenuate risks due to difference in underlying health status. The set of results that the investigators considered to be more accurate showed a statistically significant increased

risk for average weekly exposure greater than the median (OR = 7.1; 95% CI: 1.1, 45.2) compared to below the median. Further, additional analyses controlling for exposure to lead and magnetic fields (selected as additional variables *a priori*) show an even stronger association for high average weekly exposure (OR = 60.2; 95% CI: 2.4 to 1533.8). Similarly, the estimated risks for cumulative exposure above median exposures from OR = 2.8 (95% CI: 0.6, 14.4; *p*-value = 0.04) to OR = 56.4 (95% CI: 1.9 to 1686.2).

There are only four epidemiological studies in the literature that evaluate the associations between carbon tetrachloride exposure and risks of brain cancer; one prospective cohort study and three case-control studies. All four studies were of adequate quality and all have evaluated occupational exposures based on job histories according to standard practices of industrial hygienists at the U.S. National Cancer Institute or the U.S. National Institute for Occupational Safety and Health. Three studies reported increased risks of brain tumors associated with exposures to carbon tetrachloride while one did not. Within a small database, three of four show consistency; and all three showed some evidence of strong associations with carbon tetrachloride exposures preceding brain cancer, and two showed exposure-response trends. It is plausible that carbon tetrachloride can cause brain cancer because carbon tetrachloride has been shown to be a liver carcinogen in rats, mice, and hamsters by oral and inhalation exposure (U.S. EPA, 2010) as well as causing pheochromocytomas in mice by oral and inhalation exposure and neuroblastomas by inhalation exposure in humans (Heck et al., 2013). Considerable research in animals further supports the biological plausibility for these demonstrated associations from epidemiological studies. Carbon tetrachloride can pass through the blood-brain barrier (Thrall et al., 2000), is rapidly absorbed by the brain and liver (Szymonik-Lesiuk et al., 2003), causes oxidative stress in the brain (Ritesh et al., 2015), and is metabolized in the brain (Navarro-Mabarak et al., 2018).

Selection bias cannot explain these positive results, nor can information bias − although these two potential biases might explain the one study that did not report a positive association. There was evidence that methylene chloride appeared to have been a potential confounder in Heineman *et al*. (1994), but there does not appear to be any evidence of systematic confounding across the studies that would provide an alternative explanation for the observed associations of carbon tetrachloride exposure with increased risk of astrocytic brain cancer consistently observed in these studies. Chance may explain an association in a single study, but is highly unlikely to explain how three of four studies, including two with exposure-response relationships – albeit limited, all reported increased risks of brain cancer with exposure to carbon tetrachloride with two reporting large magnitude ORs for a rare cancer in two different study designs and among three different populations from Japanese-American men in Honolulu to hospitalized people in Boston, Pittsburg, and Phoenix to men working in areas with large petrochemical industries in northern New Jersey, Philadelphia, and southern Louisiana.

Causal Evaluation

The causal evaluation for carbon tetrachloride exposure and the risk of brain cancer placed the greatest weight on five particular considerations: 1) the generally consistent increases in risk observed across a set of High and Medium confidence results with varied study designs and populations; 2) the strength of the association showing increases in risk; 3) the reported exposure-response relationships showing that increased exposure to carbon tetrachloride were associated with increased risk of brain cancer; 4) a biologically coherent temporal relationship

consistent with a pattern of exposure to carbon tetrachloride and subsequent brain cancer; and 5) reasonable confidence that alternative explanations are ruled out, including chance, bias and confounding within individual studies or across studies.

Overall Conclusions on Cancer Hazard Based on Epidemiological Data for Brain Tumors (Astrocytomas, Gliomas, and Glioblastomas)

The available epidemiologic studies provide evidence of an association between carbon tetrachloride exposure and increased risk of brain cancer that demonstrates suggestive carcinogenic potential to humans. This epidemiologic evidence did not reach the level of convincing evidence (*i.e*., "Carcinogenic to humans") of a causal association between human exposure and cancer due to the limited number of available epidemiological studies which did have some individual limitations even if their overall study quality rating were above an acceptable threshold.

Epidemiological Data on Neuroblastoma

There is only one study of neuroblastoma in the epidemiological literature which evaluated risks associated with maternal or in utero exposure to carbon tetrachloride. Neuroblastoma is the most common cancer in infants and is most commonly found in the adrenal glands. Heck *et al*. (2013) is a 'Medium' quality case-control study designed to evaluate risks of neuroblastoma in infants associated with a variety of air toxics, including carbon tetrachloride, based on in utero exposures. The 75 cases and 14,602 controls were selected from locations in California within 5 km of an air toxics monitoring station. Controls were frequency matched on birth year. The birth date and birth address were used to estimate OR for living within different radii of the nearest monitor. Monitors are "primarily positioned either near heavily trafficked highways, in industrial areas, or in agriculturally intense rural regions."(Heck et al., 2013). Results were presented for interquartile change (IQR) in entire pregnancy average exposure (IQR = 75th% minus 25th% = 0.034 ppbV carbon tetrachloride) within different radii from the monitoring station.

- OR for the 4th quartile of exposure vs. the lowest quartile was 8.85 (95% CI: 1.19, 66.0)
- OR per IQR for living within 5 km of the nearest monitor was 2.65 (95% CI: 1.07, 6.53)
- OR per IQR for living within 4 km of the nearest monitor was 3.72 (95% CI: 1.20, 11.6)
- OR per IQR for living within 3 km of the nearest monitor was 6.52 (95% CI: 1.54, 27.6)
- OR per IQR for living within 2.5 km of the nearest monitor was 7.87 (95% CI: 1.37, 45.3)

Selection bias: No concern that selection was differentially related to exposure or outcome as all cases and controls had to have been born within 5 km of the nearest air toxics station.

Information bias: No concern for recall bias since residential address was the basis of the exposure assessment or other exposure misclassification related to outcome (*i.e.*, no differential misclassification); some concern that exposure misclassification due to changes of address during pregnancy – although the investigators noted that most moves were local thereby somewhat limiting any bias or measurement error. The observation that the magnitude of the adverse effect of one IQR change in exposure increased with proximity to the air toxics monitors may reflect increased precision in the exposure estimate – or it may reflect closer proximity to the sources of the air toxics.

Confounding: No concern for potential confounding by other air toxics as none of the other toxics were as strongly associated with increased risks of neuroblastoma in any of the analyses.

Chance: This was an exploratory study which evaluated risks for 27 air toxics and thus there were many comparisons which Heck stated (2013) "increased the likelihood of spurious associations," but cited (Goldberg and Silbergeld, 2011) who argue along with others like Rothman (1990) that "it is not appropriate to adjust for multiple comparisons" and they restate from (Hill, 1965) that "we do not want to obscure our ability to detect associations that should be confirmed or strengthened by further study, as this philosophy is one that encourages inaction in the face of important risks to health."

Overall Conclusions on Cancer Hazard Based on Neuroblastoma Epidemiological Data
There is only this one study of maternal or in utero exposure to carbon tetrachloride and the risk of neuroblastoma. However, with the knowledge that carbon tetrachloride has been shown to cause pheochromocytomas in mice by oral and inhalation exposure (pheochromocytomas are benign tumors of the adrenal glands), a strong association between neuroblastoma and carbon tetrachloride in a single well-conducted epidemiological study in the same organ provides suggestive evidence of an association between carbon tetrachloride exposure and increased risk of neuroblastoma that raises concern for potential carcinogenic effects in humans.

General Overview of Database of Animal Studies - Bioassays

As discussed in (U.S. EPA, 2010), several chronic toxicity and carcinogenicity studies for carbon tetrachloride conducted in experimental strains of rats, mice, and hamsters by the oral route identified the liver as a primary target organ of carbon tetrachloride toxicity and carcinogenicity (Della Porta et al., 1961; Edwards and Dalton, 1942; Edwards et al., 1942; Edwards, 1941). These early studies used only single dose levels of oral administration, and so did not provide information on the relationship of dose and liver tumors. If there were enough single dose studies, those could all be plotted on the same graph and a dose-response function could have been derived.

Studies conducted by the National Cancer Institute (NCI, 1977, 1976a, b) did employ two dose levels of carbon tetrachloride by oral gavage to rats and mice, but high early mortality observed in these studies, particularly at the high dose, limited interpretation of the results. In the rat study, incidence of liver tumors was low in all groups (hepatocellular carcinoma in 1/99 pooled control, 2/49 low-dose, and 2/50 high-dose males and in 0/98 pooled control, 4/49 low-dose, and 2/49 high-dose females). In the mouse study, hepatocellular carcinomas were observed at almost 100% incidence (49/49 low-dose males, 47/48 high-dose males, 40/41 low-dose females, and 43/45 high-dose females). In pooled controls, incidence was only 5/77 (6%) in males and 1/80 (1%) in females. The incidence of adrenal adenoma and pheochromocytoma was also increased in male mice (concurrent control: 0/18, low-dose: 28/49, high-dose: 27/48) and female mice (concurrent control: 0/18, low-dose: 15/41, high-dose: 10/45).

EPA has identified the (Nagano et al., 2007a) bioassays in mice and rats with carbon tetrachloride by the inhalation route as the most detailed study of both chronic toxicity and

carcinogenicity of carbon tetrachloride available by the most relevant route of exposure. In this inhalation study, groups of F344/DuCrj rats (50/sex/group) were exposed (whole-body) to 0, 5, 25, or 125 ppm (0, 31.5, 157, or 786 mg/m^3) of carbon tetrachloride (99.8% pure) vapor for 6 hours/day, 5 days/week for 104 weeks. These same researchers also conducted a 2-year study using Crj:BDF1 mice. Groups of Crj:BDF1 mice (50/sex/group) were exposed to 0, 5, 25, or 125 ppm (0, 31.5, 157, or 786 mg/m^3) of carbon tetrachloride (99% pure) vapor for 6 hours/day, 5 days/week for 104 weeks. Endpoints monitored were the same as for the 2-year rat study. In these bioassays, carbon tetrachloride produced a statistically significant increase in hepatocellular adenomas and carcinomas in rats and mice of both sexes, and adrenal pheochromocytomas in mice of both sexes.

3.2.4.3 MOA for Carcinogenicity

This section summarizes available information on MOA for carbon tetrachloride carcinogenicity based on the MOA analysis performed in the 2010 EPA IRIS assessment (U.S. EPA, 2010) and additional information made available since 2010. The Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a) identifies steps for determining whether a hypothesized MOA is operative. The steps include an outline of the sequence of events leading to cancer, identification of the key events, and determination of whether there is a causal relationship between events and cancer.

3.2.4.3.1 Mode of Action for Liver Tumors

In the case of carbon tetrachloride, experimental data are available to describe the MOA for production of liver tumors observed from exposure to carbon tetrachloride in experimental animal studies. Thus, the purpose of this section is to present the postulated MOA for carbon tetrachloride induced liver carcinogenesis in laboratory animals and the evidence that supports it. When relying on laboratory animal data, two critical assumptions govern cancer risk assessment. In the absence of information to the contrary, it is generally assumed that (1) experimental data on animal tumors are predictive of human cancer, and (2) that the animal tumor effects found at high experimental doses can be used to predict human risk at lower exposures.

A postulated MOA is a biologically plausible hypothesis for describing the sequence of events leading to an observed adverse outcome (in this case, liver tumors). It identifies "key" cellular and biochemical events—*i.e.*, those that are both measurable (quantifiable) and critical to the observed adverse response. Mode of action contrasts with mechanism of action which generally implies a more detailed description of the molecular and biochemical basis for an effect. The key events analysis presented below and Appendix I for carbon tetrachloride follows a mode of action framework developed by the International Programme on Chemical Safety (IPCS) and the U.S. EPA in the Guidelines for Carcinogen Risk Assessment (*i.e.*, EPA cancer risk guidelines) (U.S. EPA, 2005b) which is used by other regulatory agencies and international organizations (*e.g.*, the World Health Organization, Expert Panel of the Joint Meeting on Pesticide Residues). The analysis presented below and in Appendix I is based on the Bradford Hill criteria for causality, originally developed for application in epidemiological investigations (Hill, 1965). Both EPA and IPCS have emphasized that this framework "is not a checklist of criteria, but rather presents an analytical approach to considering the weight-of-evidence of a MOA and whether a precursor event is shown to be causally linked to the tumor response."

EPA has qualitatively evaluated the weight of evidence for several proposed MOAs for liver carcinogenicity using the framework outlined in EPA cancer risk guidelines (U.S. EPA, 2005a). This analysis considers the MOA analysis previously conducted by the IRIS program (U.S. EPA, 2010), more recent evidence identified through the systematic review process for this risk evaluation, and information submitted to EPA through public comments EPA-HQ-OPPT-2016-0733-0066 and EPA-HQ-OPPT-2016-0733-0088 (see 0) to evaluate supporting and counterfactual evidence for proposed MOAs.

A general correspondence has been observed between hepatocellular cytotoxicity and regenerative hyperplasia and the induction of liver tumors. At lower exposure levels, this correspondence is less consistent (U.S. EPA, 2010). A hypothesized carcinogenic MOA for carbon tetrachloride-induced liver tumors has been proposed and includes the following key events (U.S. EPA, 2010):

(1) metabolism to the trichloromethyl radical by CYP2E1 and subsequent formation of the trichloromethyl peroxy radical,
(2) radical-induced mechanisms leading to hepatocellular cytotoxicity, and
(3) sustained regenerative and proliferative changes in the liver in response to hepatotoxicity,
(4) resulting cellular proliferation increases the probability of tumor formation through replicative processes that increase the probability of mutations becoming fixed or increase the rate of clonal expansion of cells carrying somatic mutations - in both cases without hypothesizing a direct mutagenic effect from carbon tetrachloride or its metabolites.

In this MOA, biotransformation of carbon tetrachloride to the trichloromethyl radical and trichloromethyl peroxy radical have been identified in *in vitro* studies. The formation of these radicals has been shown to be a required step in the MOA. However, due the high reactivity of the radicals, the concentration-response relationship between the amount of radical formation associated with cytotoxicity is not known. Similarly, available *in vitro* studies only used high concentrations of carbon tetrachloride to evidence lipid peroxidation caused by trichloromethyl and trichloromethyl peroxy radicals, making quantitative dose-response concordance challenging (U.S. EPA, 2010).

A MOA analysis for liver tumors, including the qualitative and quantitative evidence on the identified key events, formation of radicals, lipid peroxidation, cytotoxicity and regenerative proliferation are described in Appendix I.

Conclusions on the MOA for Liver Tumors

Based on the MOA analysis presented in Appendix I, there is robust evidence supporting the inference that metabolism of carbon tetrachloride to reactive compounds is responsible for its primary biological activities including hepatocellular toxicity. This metabolic activation would be consistent with other possible MOAs as well as the hypothesized MOA based on sustained regenerative proliferation. Examining the most relevant evidence for the present cancer risks assessment (the subchronic and chronic bioassays of (Nagano et al., 2007a; 2007b) robust evidence is not available to support the occurrence of continued cell killing and regeneration over the lifetime of carbon tetrachloride exposure. Studies in another mouse strain from another

laboratory (Benson and Springer, 1999) provide direct evidence of cytotoxic processes and enhanced cell replication in carbon tetrachloride treated mice in a relevant air concentration range (20-100 ppm), however findings of this study with regard to serum levels of liver enzymes and necrosis appear inconsistent with the findings of (Nagano et al., 2007b). Considerations of temporal concordance are consistent with the proposed cancer MOA in that they draw on findings from subchronic studies (the cause proceeds proposed effect), but that does not contribute much additional weight to the hypothesis. Due to the limited toxic effects reported, dose-response evaluation provides little information when limited to the results of the Nagano studies. However, results of the Benson and Springer studies, in the different mouse strain, do indicate a sharp increase in toxicity and cell proliferation at a dose of 20 ppm and above, as consistent with the Nagano tumor findings. However, in (Nagano et al., 2007a) liver adenomas were significantly elevated at the 5 ppm dose level, a finding that was supported by comparison with historical controls in the same laboratory. Available data do not indicate occurrence of cytotoxic or regenerative processes in mice at dose levels of 5 ppm (or 10 ppm). While the proposed role of metabolism in causing carbon tetrachloride toxicity has been effectively challenged and supported in a range of studies, no studies to challenge the proposal of carbon tetrachloride cytotoxicity as a cause of liver cancer are available. Finally, while data are complex and not conclusive, other MOAs resulting from the interaction of reactive carbon tetrachloride metabolites with biomolecules may be relevant. Despite the presence of a numerically large database of studies on genotoxicity, the potential for carbon tetrachloride metabolites or oxidative radicals resulting from subsequent lipid peroxidation to induce genotoxicity cannot be fully evaluated.

In summary there is biological support for the involvement of the hypothesized MOA of sustained cytotoxicity and regenerative cell proliferation as key events in the hepatocellular mode of action for carbon tetrachloride exposure in the mouse. However, important uncertainties and inconsistencies exist. The hypothesized MOA by itself is not consistent with observations of increased hepatocellular adenomas in the mouse at 5 ppm. This evaluation suggests that while cytotoxicity and regenerative proliferation may strongly influence dose response at higher doses, these processes may not reflect the potential for carcinogenic action of this compound at lower doses. Despite a massive database of historical studies on the toxicity of carbon tetrachloride, it should be noted that there has been relatively little study of this compound using more modern methods (*e.g.*, for the study of dose response for specific adducts to DNA or other macromolecules or through use of genomic endpoints) thus limiting important lines of evidence that could further define the carcinogenic MOA for carbon tetrachloride.

3.2.4.3.2 Mode of Action for Adrenal Gland and Brain Tumors

Key Events and Reasonably Available Information on MOAs for Other Tumor Types

Adrenal Gland Tumors: Pheochromocytomas and Neuroblastomas

In addition to liver tumors observed from exposure to carbon tetrachloride, an increased incidence of pheochromocytomas (a neuroendocrine tumor of adrenal chromaffin cells-derived from neural crest stem cells) associated with carbon tetrachloride administration has been observed in male and female mice by oral (NTP, 2007; NCI, 1977, 1976a, b) and inhalation exposure (Nagano et al., 2007a), but not in rats by either route of exposure.

Some data suggests that carbon tetrachloride metabolism plays a role in the induction of toxicity in the adrenal gland as it does in the liver (Colby et al., 1994). Metabolism of carbon tetrachloride leads to the production of free peroxy radicals which induce oxidative stress which can damage proteins, DNA and lipids. *In vitro* studies in (Colby et al., 1994) showed that preincubation of adrenal microsomes with 1-aminobenzotriazole, a CYP450 suicide inhibitor, prevented the effects of carbon tetrachloride on lipid peroxidation and covalent binding. Nevertheless, there is not sufficient information to elucidate the other key events for cancer induction in the adrenal gland. Similarly, there are no reasonably available information demonstrating cytotoxic regenerative hyperplasia responses in the induction of adrenal gland tumors at doses that do not cause hepatotoxic effects in animals or humans.

Conclusions on Cancer MOA and Biological Relevance of Adrenal Tumors (Pheochromocytomas) in Mice

In the review of the draft carbon tetrachloride risk evaluation, the SACC suggested consideration of the extent that MOA hypotheses for liver tumors may also be relevant to the adrenal pheochromocytomas that were also observed in mice in Nagano (2007a). Based on the MOA analysis presented in Appendix I for adrenal gland tumors, biological support exists to infer that the metabolism of carbon tetrachloride to reactive compounds is responsible for toxicity in the adrenal gland. However, this hypothesis cannot be confirmed due to the lack of mechanistic data for adrenal tumors. However, the process of metabolic activation would be consistent with other possible MOAs as well as the hypothesized MOA based on sustained regenerative proliferation. The Nagano studies (Nagano et al., 2007a; 2007b) are the most relevant studies for evaluating the hypothesized MOA because the adrenal gland was examined after subchronic and chronic exposures of mice (and rats) to carbon tetrachloride. However, these studies did not report noncancer pathological effects in the adrenal gland. High dose exposures to carbon tetrachloride cause necrosis in guinea pigs, but rats appear more resistant. Historical reports indicate that high dose carbon tetrachloride can cause adrenal toxicity in humans.

In summary, while carbon tetrachloride can cause cytotoxicity under certain conditions, mice under the cancer bioassay dose conditions did not have reported adrenal toxicity and thus there is little support for the proposed MOA. The available bioassay data can be seen to provide substantial data against a hypothesized MOA based on cytotoxicity and regenerative proliferation. There are few data upon which to develop alternate MOA proposals specific to the adrenal gland, however, processes resulting from the interaction of reactive carbon tetrachloride metabolites with biomolecules are relevant. Despite the presence of a numerically large database of studies on genotoxicity, the potential for carbon tetrachloride metabolites or oxidative radicals resulting from subsequent lipid peroxidation to induce genotoxicity cannot be fully evaluated.

EPA has determined that the pheochromocytomas incidence data in mice from the Nagano (2007a) have biological relevance and are adequate for extrapolating cancer hazard to humans. This determination is based on the following:

- While the survival rates of rats are associated with non-cancer effect (*i.e.*, severe chronic progressive nephropathy), the reduction in survival rate of mice was clearly linked to cancer effects (*i.e.*, hepatocellular neoplasia) only.

- In NTP studies, mice have a low spontaneous incidence of pheochromocytomas and are known to have a lower susceptibility to chemical induction of pheochromocytomas compared to rats (Greaves, 2012).
- The designation of the adrenal gland lesions by Nagano (2007a) as benign cannot be considered evidence of lack of relevance towards predicting human risk due in part to variability in the diagnoses of non-neoplastic changes accompanying neoplastic incidences in rodent cancer bioassays.
- The incidence data on pheochromocytomas in mice provide information on the carbon tetrachloride-induced carcinogenic process.

Brain Tumors (Astrocytomas, Gliomas, and Glioblastomas)

Among the human epidemiological studies showing an association between carbon tetrachloride exposure and brain tumors (astrocytoma, glioma, and glioblastoma), there are no specific data supporting a MOA for the induction of these tumors. Although it is known that the brain contains cytochrome P450, including CYP2E1 [*i.e.*, (Ferguson and Tyndale, 2011)], total levels are in the range of 0.5-2.0% of those in the liver. However, there is high heterogenicity of P450 enzymes content and metabolic capacity in the different brain regions, suggesting that CYP2E1 is highly localized within the brain. This suggests that carbon tetrachloride metabolism plays a role in the induction of toxicity in the brain. Nevertheless, there is not sufficient information to elucidate the other key events for cancer induction in the glial-derived brain tissues. There is also lack of evidence demonstrating cellular injury cytotoxicity in nervous system and regenerative response leading to cancer.

3.2.4.3.3 Overall Cancer MOA Conclusions

Based on information presented in Section 3.2.4.3.1, EPA has concluded that there is evidence for a cytotoxic regenerative hyperplasia mode of action for liver cancers in animal models. In the absence of a cytotoxic regenerative hyperplasia MOA for carbon tetrachloride to explain other tumor responses at doses that do not cause hepatotoxic effects in animal or humans, and in the absence of other MOAs to explain carbon tetrachloride-induced tumors of adrenal gland (*i.e.*, pheochromocytoma tumors in mice and neuroblastoma in humans) and brain tumors (*i.e.*, astrocytomas, gliomas, and glioblastomas) in humans at all doses, a linear extrapolation approach for assessment of carcinogenic risk is presented in this risk evaluation in conjunction with a threshold approach for assessing risks for liver tumors.

This conclusion is based on general considerations for MOA analysis in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005b) for addressing data limitations informing the cancer MOA in different tumor types. These general considerations are relevant for carbon tetrachloride given the data limitations in adrenal glands and brain acknowledged by both EPA and SACC for carbon tetrachloride. MOA analysis considerations in (U.S. EPA, 2005b) recognize the possibility of an agent working by more than one MOA at different tumor sites and at the same tumor site to indicate that the cancer MOA cannot be generalized to other tissues or cell types without additional analyses.

3.2.4.3.4 Classification of Carcinogenicity

Based on the previously evaluated animal data and new epidemiological information and under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005b), EPA classifies carbon tetrachloride as "likely to be carcinogenic to humans" based on: (1) suggestive evidence of carcinogenicity in humans and (2) sufficient evidence in animals.

The available epidemiologic studies provide evidence of an association between carbon tetrachloride exposure and increased risk of brain cancer and neuroblastoma that demonstrates carcinogenic potential to humans. This evidence did not reach the level of convincing evidence (*i.e.*, "*Carcinogenic to humans"*) of a causal association between human exposure and cancer due to the limited number of available epidemiological studies which did have some individual limitations even if their overall study quality rating were above an acceptable threshold.

With the knowledge that carbon tetrachloride has been shown to cause pheochromocytomas in male and female mice by oral and inhalation exposure (pheochromocytomas are tumors of the adrenal glands), and a strong association between neuroblastoma and carbon tetrachloride in a single well-conducted epidemiological study in the same organ raises concern for potential carcinogenic effects in humans and is "likely to be carcinogenic to humans."

Evidence of cancers from multiple species (humans, rats, mice) and multiple tumors types (*e.g.*, liver tumors, pheochromocytomas and brain cancers) in both sexes and by multiple routes of exposures (*e.g.*, oral and inhalation) contribute to the weight of the scientific evidence for overall cancer classification of carcinogenic effects which is "likely to be carcinogenic to humans."

3.2.5 Dose-Response Assessment

3.2.5.1 Selection of Studies for Dose-Response Assessment

EPA evaluated data from studies described in Sections 3.2.2 and 3.2.4 to characterize the dose-response relationships of carbon tetrachloride and selected studies and endpoints to quantify risks for specific exposure scenarios. The selected studies had adequate information to select PODs.

3.2.5.1.1 Toxicity After Acute Inhalation Exposures in Humans

For the characterization of the dose-response of acute inhalation exposures to carbon tetrachloride, EPA considered human reports, controlled human studies, animal acute and developmental toxicity studies described in the 2014 NAC Acute Exposure Guideline Levels (AEGL) (NRC, 2014). The key study (Davis, 1934) used for the development of the AEGL-2 value was rated of acceptable low data quality in the systematic review for this risk evaluation. The systematic review did not identify additional reasonably available acute or developmental toxicity data for carbon tetrachloride based on the criteria in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a).

Acute inhalation exposures to carbon tetrachloride above the AEGL-2 values are expected to induce immediate and temporary CNS effects, which consist of escape-impairing symptoms in occupational settings (*i.e.*, dizziness). Acute inhalation human data were used by the AEGL program for the identification of a NOAEL for transient CNS effects of 76 ppm in humans exposed carbon tetrachloride for 4 hours (Davis, 1934). EPA considers that the acute NOAEL

identified by the AEGL program is adequate for assessing acute effects in inhalation occupational exposure scenarios for TSCA conditions of use of carbon tetrachloride. EPA reviewed the acute dose-response information in the AEGL report (NRC, 2014), including the identification of the PODs and uncertainty factors identified for CNS effects, but did not conduct further dose-response analysis.

The endpoint and effect level identified by NAC/AEGL for the AEGL-2 values are considered to provide both a relevant effect and robust POD because the values represent the concentration above which it is predicted that irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape can be experienced by workers. On the other hand, the AEGL-2 values protect from life-threatening health effects or death, which are appropriate for emergency or accidental releases of the chemical.

Developmental toxicity studies were also considered in the derivation of acute toxicity values as adverse effects in the fetus may be related to the unique susceptibility of the fetus at discrete times during gestation (U.S. EPA, 1991). Therefore, EPA conservatively assumes that the adverse fetal effects observed in a developmental toxicity study that includes exposures across multiple days of embryonic or fetal development, or even throughout gestation, could have occurred as the result of exposure on a single day of the study (U.S. EPA, 1991). EPA has concluded that the observed developmental effects (*i.e.*, decreased fetal body weight and crown-rump length) are likely associated with the sustained lower maternal weight over gestation days 6-15 rather than the result of exposure to carbon tetrachloride on a single day of the study.

Oral studies are considered less relevant for route-to-route extrapolation for this risk evaluation because oral exposures to carbon tetrachloride undergo first-pass metabolism in the liver, the organ with the highest concentration of CYP2E1 enzymes involved in the generation of carbon tetrachloride's toxic metabolites.[18] This major difference in the metabolism of carbon tetrachloride between oral and inhalation routes of exposure limits the usefulness of extrapolating a developmental inhalation POD from the oral developmental study, given that different developmental toxicity processes may be involved between the two routes of exposure.

For instance, while the oral developmental studies by Narotsky *et al*., (1997), which were rated of high quality in the systematic review, identified a developmental NOAEL of 25 mg/kg-d based on observed full-litter resorption at 50 mg/kg-d, a developmental toxicity study in rats by Schwetz *et al*. (Schwetz et al., 1974) (data quality rating = high) identified less severe effects that correlate with maternal toxicity (*i.e.*, decreased fetal body weight (7%) and decreased crown-rump length (3.5%) at 300 ppm).

[18] The EPA IRIS assessment (U.S. EPA, 2010) indicates that among the PBPK models developed for carbon tetrachloride, the model by (Yoon et al., 2007) is the only one that addressed extrahepatic metabolism of carbon tetrachloride. (Yoon et al., 2007) reported that no metabolic activity was detected in the fat, brain, or skin. The proportion of liver metabolism estimated for the lung and kidney was quite small, 0.79 and 0.93%, respectively, based on the microsomal studies. The EPA IRIS assessment also indicates that the human kidney has been reported by multiple laboratories to not express any detectable CYP2E1 protein. Considerations taken for determining the subchronic to chronic UF in the EPA IRIS assessment included the observation of early onset of toxicity following oral exposure. For instance, assessment reviewers commented that oral exposure leads to first-pass metabolism in the liver resulting in peak exposure at the target site after oral exposures while more opportunity for extrahepatic targeting is expected from inhalation exposures.

EPA's POD for acute inhalation exposures in this risk evaluation is 360 mg/m^3 – 8 hours for disabling effects (*i.e.*, CNS effects such as dizziness) from elevated, but short inhalation exposures. For 12-hours of exposure, the acute inhalation POD is 310 mg/m^3 (49 ppm) based on temporal scaling using the equation $C^n \times t = k$, where an empirical value of n was determined to be 2.5 on the basis of rat lethality data (NRC, 2014). A benchmark MOE of 10 is used for intraspecies variability to account for susceptible individuals, such as moderate to heavy alcohol users, in agreement with the AEGL program conclusions. (NRC, 2014) explains that the intraspecies uncertainty factor of 10 was retained for protection of susceptible individuals due to the known variability in the metabolic disposition of carbon tetrachloride that may result in an altered toxic response.

The dose response assessment for the acute inhalation exposures to carbon tetrachloride is based on the conclusions and key studies presented in (NRC, 2014). NAC/AEGL's key study for the development of the AEGL-2 values, (Davis, 1934) (data quality = low), consist of a series of human controlled experiments that provide a reasonable characterization of the exposure concentrations and hazard effects. The main data quality limitation on these studies is based on the fact that the studies were conducted prior to the development of the current guidelines for inhalation toxicity studies and/or exposure characterization. Even though, the database for carbon tetrachloride contains a large number of human reports on acute exposures, the systematic review did not identify additional acute human toxicity information with better data quality and/or characterization of exposure concentrations according to the criteria in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). Other considerations for characterizing dose response for acute inhalation exposures (*i.e.*, developmental toxicity) are in agreement with the NAC/AEGL program conclusions.

3.2.5.1.2 Toxicity from Chronic Inhalation Exposures

The 13-week and 104-week inhalation studies by Nagano *et al*., (Nagano et al., 2007a; Nagano et al., 2007b) were rated as high data quality in the systematic review for this risk evaluation. The basis for the chronic inhalation PODs is the 104-week inhalation study with F344/DuCrj rats (Nagano et al., 2007b), in which the lowest exposure concentration (*i.e.*, 5 ppm) was considered a NOAEC based on liver and kidney toxicity at ≥25 ppm.

Reliance on Nagano bioassays (Nagano et al., 2007a) for dose-response characterization of chronic exposures is supported by the high data quality rantings of the 2 year bioassays and associated 13-week subchronic studies. Furthermore, information collected in these studies is considered comprehensive because both mice and rats of both sexes were used, and an extensive set of endpoints was examined.

Fatty change in the liver of rats was selected as the endpoint for dose-response analysis because this histopathologic lesion, which is indicative of cellular damage, was a more sensitive endpoint than other histopathologic changes that were also observed in rats exposed to 25 ppm from the (Nagano et al., 2007a) study.

The only histopathological change observed in the 5 ppm group in the chronic rat study is an increase in eosinophilic granules in the nasal cavity of the female rats. This histopathological change is not considered an adverse effect by itself because it is not

accompanied by any other evidence of adversity in the nasal cavity. Furthermore, while severe renal and hepatic effects are observed in the high-exposure group, the nasal lesion is only of moderate severity in the high-exposure group.

The dose response analysis included the use of the PBPK model and BMD modeling methodology used in the IRIS Toxicological Review (U.S. EPA, 2010) to estimate internal doses and analyze the relationship between the estimated internal doses and fatty change (*i.e.*, response). The resulting BMDL values were converted to estimates of equivalent human exposure concentrations (HECs) by applying a human PBPK model.

Estimated values for HECs corresponding to $BMDL_{10}$ values for fatty changes of the liver for alternative values of VmaxC in the rat and human are presented in in Tables 5-6 and 5-7 of the IRIS Toxicological Review (U.S. EPA, 2010). A human VmaxC estimated from *in vitro* human data can reasonably be presumed to be more relevant than a human VmaxC based entirely on rodent data. Because the MOA for carbon tetrachloride-induced hepatotoxicity involves metabolism to reactive metabolites in the liver, HECs based on the mean rate of metabolism in the liver (MRAMKL) dose metric is the most proximate to the critical effect. The resulting $BMCL_{10[HEC]}$ based on data for the male rat is 14.3 mg/m^3 for continuous exposures.

3.2.5.1.3 Toxicity from Dermal Exposures

Due to the lack of repeated-dose dermal toxicity data and the irritating properties of carbon tetrachloride (*i.e.*, irritation is associated with increased dermal absorption for repeated dermal exposures), the limited acute dermal data with histopathology observations and information on dermal absorption rate were considered in the derivation of PODs for acute and chronic dermal exposures.

The limited information on non-cancer effects after acute dermal toxicity from carbon tetrachloride includes an acute toxicity study with histopathological information on liver and kidney tissues (Kronevi et al., 1979). The study was found to be unacceptable in the systematic review due to the lack of negative controls and small number of animals per dose group. Therefore, EPA extrapolated a POD for acute dermal exposures by multiplying the derived POD for chronic dermal exposures by a factor of 10 to account for the chronic-to-acute extrapolation. Extrapolation of the acute dermal POD from the acute inhalation POD was not performed because the critical acute inhalation effects of neurotoxicity are influenced by the accessibility to brain tissue by inhaled carbon tetrachloride.

PODs for chronic dermal exposures were derived using reasonably available inhalation data. Extrapolation from oral exposure data is not recommended due to differences in the biotransformation process between the oral, dermal and inhalation routes of exposure for carbon tetrachloride. First-pass metabolism and activation of carbon tetrachloride in the liver is only a metabolic step for oral exposures to the chemical.

The chronic inhalation HEC was first converted to a dermal human equivalent dose (HED), then the dermal HED was used to derive a dermal POD for retained doses by accounting for 63% absorption of the inhalation HEC or 63% of the retained inhalation dose. This derivation is necessary because dermal exposures are presented in this risk evaluation as dermal retained doses.

The equation for extrapolating the dermal HED from the inhalation POD is shown below. Equation 3-1 takes into account the human inhalation rate and body weight, and assumes average exposure factors from the Exposure Factors Handbook (U.S. EPA, 2011). Information in (U.S. EPA, 2010) indicates that 63% is the estimated inhalation absorption for carbon tetrachloride.

Equation 3-1. HED_{Dermal} = inhalation POD [mg/m^3] × inhaled volume (m^3) ÷ body weight (kg)

where the inhaled volume is based on the default worker ventilation rate of 1.25 m^3 per hour for light activities and 8 hours per day of exposure, and a body weight of 80 kg.

3.2.5.2 Derivation of PODs and UFs for Benchmark Margins of Exposure (MOEs)

3.2.5.2.1 PODs for Acute Inhalation Exposure

The AEGL Program identified a NOAEL of 76 ppm (480 mg/m^3) for CNS effects (*i.e.*, dizziness) in humans exposed to carbon tetrachloride for 4 hours.[19] The resulting AEGL-2 value is 7.6 ppm (48 mg/m^3) for 4 hours and 5.8 ppm (36 mg/m^3) for 8 hours based on a UF_H of 10 to account for individuals who may be more susceptible to the toxic effects of carbon tetrachloride (*e.g.*, variability in metabolism and disposition from alcohol usage).

Based on AEGL program recommendations for carbon tetrachloride, the POD for acute inhalation exposures in this risk evaluation is 360 mg/m^3 – 8 hours for disabling effects (CNS effects such as dizziness) from elevated, but short inhalation exposures. For 12-hours of exposure, the acute inhalation POD is 310 mg/m^3 (49 ppm) based on temporal scaling using the equation $C^n \times t = k$, where an empirical value of n was determined to be 2.5 on the basis of rat lethality data (NRC, 2014). A benchmark MOE of 10 is used for intraspecies variability to account for susceptible individuals, such as moderate to heavy alcohol users, in agreement with the AEGL program conclusions. NRC (NRC, 2014) explains that the intraspecies uncertainty factor of 10 was retained for protection of susceptible individuals due to the known variability in the metabolic disposition of carbon tetrachloride that may result in an altered toxic response.

Table 3-5. PODs for Acute Inhalation Exposures based on Human Data

Study	Study Details	Endpoint	POD	UFs/Dose Metric	Benchmark MOE
Acute: CNS (temporarily disabling effects) protective of heavy alcohol users					
(Davis, 1934)	Human Data	CNS	360 mg/m^3- 8 hours[a]	UF_H 10	10
			310 mg/m^3- 12 hours		

[a] Temporal scaling was performed using the equation $C^n \times t = k$ (Ten Berge et al., 1986), where an empirical value of n was determined to be 2.5 on the basis of rat lethality data (NRC, 2014).

[19] Transient kidney effects were also reported for acute exposures, but at higher exposure concentrations (see Section 3.2.4.1).

EPA applied a composite UF of 10 for the acute inhalation benchmark MOE, based on the following considerations:

1) **Interspecies uncertainty/variability factor (UF_A) of 1.** Accounting for differences between animals and humans is not needed because the POD is based on data from humans.

2) **Intraspecies uncertainty/variability factor (UF_H) of 10** to account for variation in sensitivity within human populations due to limited information regarding the degree to which human variability may impact the disposition of or response to carbon tetrachloride, including reasonably available quantitative information on human variability in CYP2E1 enzyme in adults.

3.2.5.2.2 PODs for Chronic Inhalation Exposure

The basis for the chronic inhalation PODs is the 104-week inhalation study with F344/DuCrj rats (Nagano et al., 2007a), in which the lowest exposure concentration (*i.e.*, 5 ppm) was considered a NOAEC based on liver and kidney toxicity at ≥25 ppm. The dose response analysis included the use of the PBPK model and BMD modeling methodology used in the IRIS Toxicological Review (U.S. EPA, 2010) to estimate internal doses and analyze the relationship between the estimated internal doses and fatty changes in the liver. Using this approach, the $BMDL_{10[HEC]}$ for fatty changes of the liver is 14.3 mg/m^3 for continuous exposures.

Because the relationship between the PBPK-estimated internal dose metric and the external concentration is linear, a periodic time adjustment of the 24-hour chronic HEC would produce a nearly equivalent result as running the PBPK model assuming periodic exposures. While additional nonlinearities in the model can be introduced when simulating periodic (as opposed to continuous) exposures, the difference is small for chemicals that are rapidly absorbed and cleared from the body. Such is the case with carbon tetrachloride. The linearity of the PBPK model was determined by analysis of Tables C-6 and C-10 of the IRIS assessment (see Appendix K). These tables presented the external:internal dose ratios for the human PBPK model over a span of concentrations, using the model assumptions adopted by the IRIS assessment (*i.e.*, model parameter VmaxC = 1.49 mg/hr/kg BW$^{0.70}$, continuous 24 hour/day, 7 days/week exposure). Table C-6 presented PBPK model results for the mean arterial concentration (MCA) internal dose metric, while Table C-10 presented results for the MRAMKL (mean rate of metabolism in the liver) internal dose metric. An adaptation of these tables is presented in Appendix K. The MRAMKL dose metric was used for RfC derivation in the IRIS assessment. For the inhalation unit risk derivation, the MCA dose metric was used. For the MRAMKL internal dose metric, the external:internal dose ratio remains relatively constant (within 10% of the value estimated at the lowest simulated concentration) at external concentrations below 95 mg/m^3. The value of the 24-hour continuous $BMDL_{10[HEC]}$ used for RfC derivation was 14.3 mg/m^3, and thus is within the linear range. Therefore, in this lower dose exposure regimen (*i.e.*, below 95 mg/m^3), where the pharmacokinetic metrics are essentially proportional to inhaled concentration, a direct proportioning of risk between continuous exposures and periodic occupational exposures is appropriate. However, in this risk evaluation, periodic time adjustments of the 24-hour chronic HEC are based on the Haber's law equation, $C^n \times t = k$. This alternative approach for estimation

of HEC values for non-continuous exposures was reviewed by SACC and no modifications to this approach were presented by the committee.

U.S. EPA (U.S. EPA, 2002) notes that extrapolation from longer to shorter time durations will result in a higher extrapolated exposure concentration value when using downward slope equations such as $C^n \times t = k$, especially when n = 1 or 0.8. When n = 3 in the equation, the downward slope is less appreciable than for n = 1 or 0.8. For instance, the slope for the equation with n = 2.5 (equation for carbon tetrachloride) is -0.1, while the slopes for the equations with n = 3 and n = 1 are -0.07 and -2, respectively, based on a k value of 343. The slope of -0.1 for n = 2.5 suggests that the extrapolated concentrations of carbon tetrachloride for shorter times of exposure are less shifted to higher values because they are influenced by a much lower downward slope.

Conservatively, the $BMDL_{10}$ value for continuous exposures was extrapolated to shorter occupational exposure durations (8 hours/day and 12 hours/day) using the equation $C^n \times t = k$, where an empirical value of n was determined to be 2.5 on the basis of rat lethality data. Further information on this temporal scaling equation can be found in (NRC, 2014).

Table 3-6. PODs for Chronic Inhalation Exposures based on Animal Data

Study	Study Details	Endpoint	POD	UFs/Dose Metric	Benchmark MOE
(Nagano et al., 2007a)	Chronic inhalation rat	Fatty changes in the liver	$BMCL_{10[HEC]}$: 14.3 mg/m^3 for continuous exposures, which is equivalent to **31.1 mg/m^3 for 8 hours/day and 5 days per week of exposure and 26.4 mg/m^3 for 12 hours/day and 5 days per week***	UF_H 10 UF_A 3	30

* Time adjustments based on $C^n \times t = k$, where n = 2.5 and adjustment for 5 days/week exposures.

EPA applied a composite UF of 30 for the chronic inhalation benchmark MOE, based on the following considerations:

1) **Interspecies uncertainty/variability factor (UF_A) of 3.** To account for species differences in animal to human extrapolation, an interspecies uncertainty/variability factor (UF_A) of 3 was applied for toxicodynamic differences between species. This UF is comprised of two separate areas of uncertainty to account for differences in the toxicokinetics and toxicodynamics of animals and humans. In this assessment, the toxicokinetic uncertainty was accounted for by the PBPK modeling. As the toxicokinetic differences are accounted for, only the toxicodynamic uncertainties in extrapolating from animals to humans remain, and an UF_A of 3 is retained to account for this uncertainty.

2) **Intraspecies uncertainty/variability factor (UF_H) of 10** to account for variation in sensitivity within human populations due to limited information regarding the degree to

which human variability may impact the disposition of or response to carbon tetrachloride, including reasonably available quantitative information on human variability in CYP2E1 enzyme in adults.

3.2.5.2.3 PODs for Acute Dermal Exposures

Due to the lack of information with acceptable data quality on the non-cancer (besides non-local or non-lethal) effects after acute dermal toxicity from carbon tetrachloride, EPA extrapolated a POD for acute dermal exposures by multiplying the derived POD for chronic dermal exposures presented in Section 0 by a factor of 10 to account for the chronic to acute extrapolation. The resulting POD for acute dermal exposures is 250 mg/kg-d.

Table 3-7. PODs for Acute Dermal Exposures (non-occluded)

Study	Study Details	Endpoint	POD	UFs/Dose Metric	Benchmark MOE
(Nagano et al., 2007a)	Chronic inhalation rat	Fatty changes in the liver	250 mg/kg-d (estimated retained/absorbed dose per day)	UF_H 10 UF_A 3	30

EPA applied a composite UF of 30 for the acute dermal benchmark MOE, based on the following considerations:

1) **Interspecies uncertainty/variability factor (UF_A) of 3.** To account for species differences in animal to human extrapolation, an interspecies uncertainty/variability factor (UF_A) of 3 was applied for toxicodynamic differences between species. This UF is comprised of two separate areas of uncertainty to account for differences in the toxicokinetics and toxicodynamics of animals and humans. In this assessment, the toxicokinetic uncertainty was accounted for by the PBPK modeling. As the toxicokinetic differences are accounted for, only the toxicodynamic uncertainties in extrapolating from animals to humans remain, and an UF_A of 3 is retained to account for this uncertainty.

2) **Intraspecies uncertainty/variability factor (UF_H) of 10** to account for variation in sensitivity within human populations due to limited information regarding the degree to which human variability may impact the disposition of or response to carbon tetrachloride, including reasonably available quantitative information on human variability in CYP2E1 enzyme in adults.

3.2.5.2.4 PODs for Chronic Dermal Exposure

PODs for chronic dermal exposures were derived by converting the chronic inhalation HEC into a dermal HED using **Equation 3-1**.. The resulting dermal HED was then converted into a POD for retained doses for repeated dermal exposures by accounting for the 63% absorption of the inhalation HEC or 63% of the retained inhalation dose.

Using **Equation 3-1**., the POD for chronic dermal exposures is calculated as follows:
[(31 mg/m^3 for 8 hours/day and 5 days/week) x (1.25 m^3/hour) x (8 hours/day) x (0.63)] ÷ 80 kg

where 31 mg/m^3 for 8 hours/day and 5 days/week is the chronic inhalation POD (*i.e.*, $BMCL_{10[HEC]}$), 1.25 m^3 per hour is the default worker ventilation rate for light activities and 8 hours per day of exposure, and 80 kg is the average worker body weight.

The resulting POD for chronic dermal exposures is 2.50 mg/kg-d. Similar to the evaluation of chronic inhalation exposures, a benchmark MOE of 30 (based on UF_H 10 and UF_A 3) is used to evaluate risk from chronic dermal exposures for workers and ONUs.

Table 3-8. PODs for Chronic Dermal Exposures

Study	Study Details	Endpoint	POD	UFs/Dose Metric	Benchmark MOE
(Nagano et al., 2007a)	Chronic inhalation rat	Fatty changes in the liver	$BMCL_{10[HEC]}$: 14.3 mg/m^3 for continuous exposures, which is equivalent to **HED_{Dermal} = 2.50 mg/kg-d**	UF_H 10 UF_A 3	30

3.2.5.2.5 Cancer Inhalation Unit Risk and Dermal Slope Factor

Cancer Inhalation Unit Risk (IUR)

EPA has identified (Nagano et al., 2007a) bioassays in mice and rats as study that provides the most appropriate data for cancer dose-response evaluation. As shown below in Table 3-9 incidence of hepatocellular adenoma and carcinoma was statistically significantly increased in male and female rats at 125 ppm. The incidence of hepatocellular carcinoma in female 25-ppm rats (6%) was not statistically elevated compared with the concurrent control but did exceed the historical control range for female rats (0–2%). The increase in liver carcinoma over historical control (2/1,797) was statistically significant (based on Fisher's exact test; two-tailed p-value = 0.0002). No other tumors occurred with an increased incidence in treated rats. Incidences of foci of cellular alteration (preneoplastic lesions of the liver), including clear, acidophilic, basophilic, and mixed cell foci, were significantly increased in the 25-ppm female rats; in males, only the incidence of basophilic cell foci was increased at 125 ppm.

Tumor incidence data in mice are presented in Table 3-10. The incidence of benign adrenal pheochromocytomas was significantly increased in males at 25 or 125 ppm and females at 125 ppm. The incidences of hepatocellular adenomas and carcinomas were significantly elevated in both sexes at ≥25 ppm. At 5 ppm, the incidence of liver adenomas in female mice (8/49 or 16%) was statistically significantly elevated compared to the concurrent control group and exceeded the historical control range (2–10%).

The possibility that the increased incidence of liver adenomas in the 5 ppm female mice is an experimental artifact from an unusually low incidence of liver adenomas in the control mice was explored by comparing the incidence of liver adenomas in the study controls to the laboratory historical control data. The incidence of liver adenomas in control female mice (4%) were similar to historical control data for liver adenomas in Crj:BDF1 female mice (overall incidence

4.4%) in 10 bioassays conducted at the Japan Bioassay Research Center (JBRC) (Katagiri et al., 1998). Thus, the historical control data from the laboratory seems to strengthen the conclusion that the low dose female adenoma result is likely compound related.

Survival rates were decreased in the 125-ppm-exposed rats and mice of both sexes and in the female mice from the 25-ppm group, in association with decreased body weights. Terminal body weight was significantly decreased by 32% and 22% in the 25-ppm-exposed male and female mice, and by 39% and 31% in the 125-ppm-exposed male and female mice, respectively (Nagano et al., 2007a). The decreased survival rates are considered to be causally related to both various tumors including hepatocellular carcinomas and severe chronic progressive nephropathy in rats and to hepatocellular carcinomas in mice. At the end of the exposure period, the survival rates of the mice in the 0, 5, 25, and 125-ppm exposure groups were 70, 72, 50, and 2% in males and 52, 48, 20, and 2% in females, respectively. Macroscopic and microscopic examinations of the mice that died before the end of the exposure period showed that 44 males and 39 females died of hepatocellular tumors in the 125-ppm exposure group and 18 males and 14 females died of hepatocellular tumors in the 25-ppm-exposure group. Incidences of palpable liver masses first appeared at week 43 in a male and week 41 in a female (Nagano et al., 2007a).

Although body weights and survival rates are influenced by substantial morbidity and mortality occurring as direct consequence of liver tumors, EPA considers that these experimental observations do not impair the suitability of the male mice pheochromocytoma data for IUR derivation. EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005b) specifies that adequate high doses in studies should not affect mortality from effects other than cancer, a study design condition that has been met in (Nagano et al., 2007a). EPA also concludes that the male pheochromocytoma data provide suitable information to characterize the dose-response curve as much as possible. But because the liver tumors were the primary cause of early deaths in treated mice, the impact of failing to apply a time to tumor analysis on the IUR derived from pheochromocytoma data is unknown.

Table 3-9. Incidence of liver tumors in F344 rats exposed to carbon tetrachloride vapor for 104 weeks (6 hours/day, 5 days/week)[a]

Tumor	Male				Female			
	0 ppm	5 ppm	25 ppm	125 ppm	0 ppm	5 ppm	25 ppm	125 ppm
Hepatocellular adenoma	0/50[b]	1/50	1/50	21/50[c]	0/50[b]	0/50	0/50	40/50[c]
Hepatocellular carcinoma	1/50[b]	0/50	0/50	32/50[c]	0/50[b]	0/50	3/50[d]	15/50[c]
Hepatocellular adenoma or carcinoma	1/50[b]	1/50	1/50	40/50[c]	0/50[b]	0/50	3/50[d]	44/50[c]

[a]The exposure concentrations adjusted to continuous exposure (*i.e.*, multiplied by 5/7 × 6/24) = 0.9, 4.5, and 22.3 ppm.
[b]Statistically significant trend for increased tumor incidence by Peto's test ($p \leq 0.01$).
[c]Tumor incidence significantly elevated compared with that in controls by Fisher's exact test ($p \leq 0.01$).
[d]Statistically significant ($p \leq 0.001$ by Fisher's exact test) in comparison to the historical control incidence (2/1,797). Sources: (Nagano et al., 2007a)

Table 3-10. Incidence of liver and adrenal tumors in BDF_1 mice exposed to carbon tetrachloride vapor for 104 weeks (6 hours/day, 5 days/week)[a]

Tumor	Male				Female			
	0 ppm	5 ppm	25 ppm	125 ppm	0 ppm	5 ppm	25 ppm	125 ppm
Hepatocellular adenoma	9/50[b]	10/50	27/50[c]	16/50	2/50[b]	8/49[d]	17/50[c]	5/49
Hepatocellular carcinoma	17/50[b]	12/50	44/50[c]	47/50[c]	2/50[b]	1/49	33/50[c]	48/49[c]
Hepatocellular adenoma or carcinoma	24/50[b]	20/50	49/50[c]	49/50[c]	4/50[b]	9/49	44/50[c]	48/49[c]
Adrenal pheochromocytoma[e]	0/50[b]	0/50	16/50[c]	31/50[c]	0/50[b]	0/49	0/50	22/49[c]

[a]The exposure concentrations adjusted to continuous exposure (*i.e.*, multiplied by 5/7 × 6/24) = 0.9, 4.5, and 22.3 ppm.
[b]Statistically significant trend for increased tumor incidence by Peto's test ($p \leq 0.01$).
[c]Tumor incidence was significantly elevated compared with controls by Fisher's exact test ($p \leq 0.01$).
[d]Tumor incidence was significantly elevated compared with controls by Fisher's exact test ($p \leq 0.05$).
[e]All pheochromocytomas in the mouse were benign with the exception of one malignant pheochromocytoma in the 125-ppm male mouse group. Sources: (Nagano et al., 2007a)

IUR estimates based on the tumor data sets in (Nagano et al., 2007a) were calculated by the EPA IRIS Program (U.S. EPA, 2005b) using the following equation: IUR = BMR ÷ HEC , where BMR = benchmark response, HEC = human equivalent concentration.
The highest estimated IUR for carbon tetrachloride via the inhalation pathway is 6×10^{-6} $(\mu g/m^3)^-1$, which is associated with pheochromocytomas in the male mouse (see Table 3-11). The data set on pheochromocytomas in the male mouse was judged by the EPA IRIS Program to be applicable, scientifically sound, and yielded the highest estimate of risk. The slope of the linear extrapolation from the central estimate based on pheochromocytomas in the male mouse is calculated as $0.1 \div (3.13 \times 10^4\ \mu g/m^3) = 3.2 \times 10^{-6}\ (\mu g/m^3)^{-1}$, or rounded to one significant figure, $3 \times 10^{-6}\ (\mu g/m^3)^{-1}$.

Table 3-11. IUR Estimate for Male Mouse Pheochromocytoma Data Using Linear Low-Dose Extrapolation Approach

Exposure Groups Modeled	Model Parameters	HEC (mg/m^3)	Average HEC (mg/m^3)[a]	IUR estimate $(\mu g/m^3)^{-1}$
0, 5, 25, 125 ppm	MCA; Fisher model BMR= 10%	12.00	17.78	5.6×10^{-6}
	MCA; Thrall model BMR = 10%	23.56		

The question of combining risks from the liver and adrenal tumors was considered in the IRIS Assessment. As noted in the IRIS Assessment, it is not possible to combine the tumor risks directly because each tumor risk was based on a different internal dose metric from the PBPK model. The risks in the male mice could not be combined because the liver cancer IUR was too uncertain and the upper bound combination of the risks in female mice was still lower than just the pheochromocytomas in male mice and thus would not have affected the bottom-line results.

The BMDS MS-Combo model provides BMD and BMDL estimates for the risk of getting one or more tumors for any combination of tumors observed in a single bioassay. However, the MS-

combo model could not be applied in this case because the dose metric is different for the two different tumor types, and even if they could be combined, the risk estimates would not change.

Cancer Slope Factor for Dermal Exposures
To avoid uncertainties related to the first-pass metabolism of carbon tetrachloride from oral exposures, a cancer slope factor for dermal exposures was derived using the IUR of 6×10^{-6} per μg/m^3 and similar approach presented in Section 0.

Starting with time adjusted IUR of 6×10^{-6} per μg/m^3

- Adjusting for a default worker ventilation rate of 1.25 m^3 per hour for light activities for 8 hrs/day (10 m^3/day).
  - 6×10^{-6} per μg/m^3 × 1 day/10 m^3 = 6×10^{-7} per μg/d
- Adjusting for average worker bodyweight of 80 kg
  - 6×10^{-7} per μg/d × 80 kg = 5×10^{-5} per μg/kg-d or 5×10^{-2} per mg/kg-d
- Adjusting for absorption: 63% inhalation absorption.
  - Dermal Cancer Slope Factor = (5×10^{-2} per mg/kg-d) (1/0.63) = 8×10^{-2} per mg/kg-d

3.2.5.2.6 Cancer Inhalation and Dermal PODs and Benchmark MOEs

Cancer Inhalation POD for Liver Tumors
EPA has identified the (Nagano et al., 2007a) bioassay in mice as the study that provides the most appropriate data for identification of a POD for liver tumors. The liver tumor data in Table 3-10 **s**how that female mice show higher sensitivity to the induction of liver tumors by carbon tetrachloride than male mice. The LOAEC for liver adenomas in female mice is the lowest treatment exposure concentration of 5 ppm. This LOAEC level is equivalent to 31 mg/m^3 based on Equation 3-2.

Equation 3-2. LOAEC in *mg/m^3 = [(LOAEC in ppm)(MW)] ÷ 24.3*
where MW = molecular weight for carbon tetrachloride of 153.8 g/mol,
24.3 =ideal gas constant for 23 degrees Celsius based on the reported experimental of 23 +/- 2 degrees Celsius in (Nagano et al., 2007a)

The cancer POD is the identified LOAEC of 31 mg/m^3 for 6 hrs/day and 5 days/week of exposure is equivalent to **6 mg/m^3** for continuous (24 hrs/days and 7 days/week) exposures. The POD is further adjusted by applying a dosimetric adjustment per the Agency's guidance on the use of the regional gas dose ratio for systemic effects (U.S. EPA, 2012c), resulting in a dosimetric adjustment factor (DAF) of 1. The resulting cancer POD is **6 mg/m^3** for continuous exposures.

Cancer Dermal POD for Liver Tumors
A cancer POD for chronic dermal exposures was calculated using route-to-route extrapolation from the cancer inhalation POD using the following parameter values: [(Inhalation POD of 6 mg/m^3 for continuous exposures)(1.25 m^3 per hour for light activities)(24 hrs /day of exposure)(0.63 inhalation absorption of inhalation POD] ÷ 80 kg. The cancer dermal POD is **1.4 mg/kg-d** for chronic dermal retained doses.

Cancer Inhalation and Dermal Benchmark MOE for Liver Tumors
A cancer benchmark MOE of 300 for inhalation and dermal exposures has been identified based on:

- A default 10-fold UF for intraspecies differences to account for variability among members of the human population.
- A non-default three-fold UF for interspecies extrapolation to account for potential differences between mice and humans. The non-default value of 3 accounts for the toxicodynamic component of the interspecies UF. The toxicokinetic component was reduced to 1 because a dosimetric adjustment was applied, per the Agency's guidance on the use of the regional gas dose ratio for systemic effects.
- A default 10-fold UF for extrapolation from a LOAEC to a NOAEC.
- A UF of 1 for extrapolation from a subchronic to a chronic exposure duration based on identification of a cancer POD from a study using a chronic exposure protocol.

3.2.5.3 PODs for Human Health Hazard Endpoints and Confidence Levels

Section 3.2.5.2 summarizes the PODs derived for evaluating human health hazards from acute and chronic inhalation scenarios, acute dermal scenarios and PODs extrapolated from inhalation studies to evaluate human health hazards from chronic dermal scenarios. EPA has also determined confidence levels for the acute, non-cancer chronic and cancer chronic values used in the risk evaluation. These confidence levels consider the data quality ratings of the study chosen as the basis of dose-response modeling and also consider the strengths and limitations of the body of evidence including the strengths and limitations of the human, animal and MOA information to support the endpoint both qualitatively and quantitatively.

Confidence Levels
NAS/AEGL considered several reports providing data on nonlethal effects of acute exposure of humans to carbon tetrachloride to establish an AEGL-2 value. Some of the reports include Davis (Davis, 1934), which includes a series of controlled exposure experiments that allowed the determination of a no-effect level for non-lasting CNS effects (*i.e.*, dizziness). The data set was determined to provide suitable data to derive AEGL-2 values by NAS/AEGL. Overall, there is high confidence in this endpoint because the quantitative dataset consists of a series of controlled exposure experiments that identify a no-effect level for CNS effects in humans. EPA found that this study is an acceptable study with low data quality based upon our review using the systematic review protocol. Further information on the data quality evaluation of this study can be found in the *Final Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Human Health Studies - Epidemiological Studies* (U.S. EPA, 2019j).

For the chronic non-cancer endpoint, confidence in the principal study (Nagano et al., 2007a) is high. According to EPA (U.S. EPA, 2010) and systematic review for this risk evaluation, this chronic study was well conducted, using two species and 50 animals/sex/group. The chronic study was preceded by a 13-week subchronic study, and an extensive set of endpoints was examined in both studies. Thus, EPA has high confidence in the chronic non-cancer endpoint based on liver effects.

For the chronic cancer endpoint, the same high-quality chronic cancer bioassay in rats and mice provided data adequate for dose-response modeling for the linear extrapolation (*i.e.*, IUR) and threshold (*i.e.*, cancer POD) approaches for cancer assessment. The calculated IUR is based on pheochromocytomas observed in only one of the rodent species, mice. The calculated cancer POD is based on liver tumors observed in the female mouse, which is the most sensitive sex and species. Furthermore, the cancer MOA for carbon tetrachloride is not fully elucidated, especially at low doses. Thus, EPA has medium confidence in the chronic cancer endpoint and dose-response model used in this risk evaluation.

Table 3-12. Summary of PODs for Evaluating Human Health Hazards from Acute and Chronic Inhalation and Dermal Exposure Scenarios

Exposure Route	Hazard Endpoint	Value	Hazard POD/HEC	Units	Benchmark MOE	Basis for Selection	Key Study
Inhalation	Temporary CNS effects	Single 4 hour exposure	360	mg/m^3 - 8 hours	10 (UF_H 10)	Study exposure duration and endpoint are relevant for worker acute exposures; PODs are in agreement with AEGL acute exposure guidelines	(Davis, 1934)
	Non-cancer	Extrapolated $BMCL_{10[HEC]}$	31.1	mg/m^3 - 8 hours	30 (UF_H 10; UF_A 3)	POD is relevant for most sensitive liver effects; Effect and effect level are in agreement with IRIS non-cancer conclusions	(Nagano et al., 2007a)
	Cancer (liver)	Inhalation Unit Risk (IUR)	6×10^{-6}	$(\mu g/m^3)^{-1}$	1 in 10^4 for occupational risk	Male mouse pheochromocytoma data set with adequate resolution for dose-response analysis yielding the highest estimate of the IUR. In agreement with IRIS cancer conclusions for carbon tetrachloride	(Nagano et al., 2007a)
	Cancer (adrenal)	Point of Departure (POD)	6	mg/m^3 for continuous exposures	300 (UF_H 10; UF_A 3; $UF_{LOAEC\ to\ NOAEC}$ 10)	Female mice liver tumor data showing higher sensitivity to the induction of liver tumors by carbon tetrachloride. In agreement with SACC recommendations for identification of threshold POD	

Exposure Route	Hazard Endpoint	Value	Hazard POD/HEC	Units	Benchmark MOE	Basis for Selection	Key Study
Dermal	Short term-Liver effects	Single exposure	250	mg/kg-d	30 (UF_H 10; UF_A 3)	POD is relevant for most sensitive liver effect for acute dermal exposures. CNS effects are less relevant for acute dermal exposures.	(Nagano et al., 2007a)
	Non-cancer	Extrapolated Human Equivalent Dose (HED)	2.50	mg/kg-d	30 (UF_H 10; UF_A 3)	POD is relevant for most sensitive liver effects; Effect and effect level are in agreement with IRIS non-cancer conclusions	(Nagano et al., 2007a)
	Cancer (liver)	Cancer Slope Factor (CSF)	8×10^{-2} (derived from IUR)	$(mg/kg\text{-}d)^{-1}$	1 in 10^4 for occupational risk	Male mouse pheochromocytoma data set with adequate resolution for dose-response analysis yielding the highest estimate of the IUR In agreement with IRIS cancer conclusions for carbon tetrachloride	(Nagano et al., 2007a)
	Cancer (adrenal)	Extrapolated Point of Departure (POD)	1.4	mg/kg-d	300 (UF_H 10; UF_A 3; $UF_{LOAEC\ to\ NOAEC}$ 10)	Female mice liver tumor data showing higher sensitivity to the induction of liver tumors by carbon tetrachloride. In agreement with SACC recommendations for identification of threshold POD	

Uncertainty Factors: UF_A = interspecies UF; UF_H = intraspecies UF; $UF_{LOAEC\ to\ NOAEC}$ = LOAEC to NOAEC extrapolation

3.2.5.4 Potentially Exposed or Susceptible Subpopulations

EPA evaluated reasonably available information to identify human subpopulations that may have greater susceptibility to carbon tetrachloride than the general population. Because the scope of this human health assessment is limited to workers and ONUs, this section focuses on identifying subpopulations within workers and ONUs who may be have greater susceptibility to carbon tetrachloride. This hazard assessment does not address factors that may make non-workers/ONUs more susceptible to carbon tetrachloride. Based on reasonably available information, some individuals in the workplace may be more biologically susceptible to the effects of carbon tetrachloride due to age, alcohol consumption, nutritional status, pre-existing disease (*e.g.*, diabetes or liver disease), exposure to other chemicals, and genetic variation.

Metabolism of carbon tetrachloride to reactive metabolites by cytochrome P450 enzymes (particularly CYP2E1 and CYP3A) is hypothesized to be a key event in the toxicity of this compound. Therefore, heterogeneity in the human population distribution of microsomal enzymes metabolizing carbon tetrachloride has influence in the susceptibility to carbon tetrachloride toxicity. Reasonably available quantitative information on the variation in human hepatic levels of the main metabolic enzyme, CYP2E1, demonstrates considerable intrahuman variability. For example, (Lipscomb et al., 1997) reported a seven-fold range in activity of CYP2E1 among hepatic microsomal samples from 23 subjects. Snawder and Lipscomb (2000) demonstrated 12-fold differences in CYP2E1 protein content between the highest and lowest samples from 40 samples of microsomes from adult human liver organ donors. Consideration of this PESS quantitative information is incorporated in the uncertainty factors used for risk characterization.

In addition to differences in the metabolism due to alcohol consumption (see below and Section 3.2.5.2 for quantitative information on effect and associated alcohol usage), exposure to other chemicals, age, nutritional status, genetic variability in CYP expression, or impaired liver function due to liver disease can increase susceptibility to carbon tetrachloride (U.S. EPA, 2010). For example, alcohol is known to induce CYP2E1 expression. Cases of acute toxicity from occupational exposures indicate that heavy drinkers are more susceptible to carbon tetrachloride and this observation has been verified in numerous animal studies. Exposure to other chemicals that induce P450 enzymes, including isopropanol, methanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, 2-butanone, phenobarbital, methamphetamine, nicotine, trichloroethylene, polychlorinated and polybrominated biphenyls, DDT, mirex, and chlordecone have also been shown to potentiate carbon tetrachloride liver toxicity (U.S. EPA, 2010; ATSDR, 2005).

The AEGL-2 values (see Section 3.2.4.1), which are the basis for the PODs for acute inhalation exposures in this risk evaluation, were derived using an intraspecies uncertainty factor of 10 to account for individuals who may be more susceptible to the toxic effects of carbon tetrachloride, including greater potential of carbon tetrachloride-induced toxicity in individuals with histories of alcohol usage. Susceptibility to carbon tetrachloride due to elevated (*i.e.*, moderate to high) alcohol use is in agreement with the known dispositional potentiation of carbon tetrachloride toxicity by inducers of cytochrome CYP2E1 enzymes. The AEGL document states that the variability in response to carbon tetrachloride is emphasized by the fact that an estimated exposure at 63 ppm-h was fatal in a heavy drinker whereas controlled exposures at 190 ppm-h were without effect for individuals not categorized as heavy drinkers. This exposure information indicates that a three-fold exposure reduction to the NOEC value produces an extreme toxic response in heavy drinkers, suggesting that a UF of 10 for intraspecies variability is protective of heavy drinkers.

Age can influence susceptibility to carbon tetrachloride due to differences in metabolism, antioxidant responses, and reduced kidney function in older adults. While lower CYP expression may reduce susceptibility of older adults to carbon tetrachloride in some tissues, reduced kidney function and increased CYP3A activity in the liver (indicated by animal studies) suggest that older populations could be at greater risk of carbon tetrachloride-associated kidney damage (U.S. EPA, 2010).

Nutrition has also been shown to influence susceptibility to carbon tetrachloride in animals. Food restriction has been shown to increase liver toxicity of carbon tetrachloride. Diets low in antioxidants increase lipid peroxidation and liver damage in following carbon tetrachloride exposure (reversed with antioxidant supplementation) and zinc deficient diets increase carbon tetrachloride-induced liver toxicity (U.S. EPA, 2010).

4 RISK CHARACTERIZATION

4.1 Environmental Risk

EPA integrated fate, exposure, and environmental hazard information when characterizing the environmental risk of carbon tetrachloride. As stated in Section 2.1, carbon tetrachloride is not expected to bioconcentrate in biota or accumulate in wastewater biosolids, soil, sediment, or biota. Releases of carbon tetrachloride to the environment are likely to volatilize into the atmosphere, where it will photodegrade under stratospheric conditions. It may migrate to groundwater, where it will slowly hydrolyze. Section 2.1 also explains that the bioconcentration potential of carbon tetrachloride is low. EPA modeled environmental exposure with surface water concentrations of carbon tetrachloride ranging from 4.9E-05 µg/L to 1.3E+02 µg/L for acute exposures and 4.1E-06 µg/L to 1.0E+01 µg/L for chronic exposures from facilities releasing the chemical to surface water. The modeled data represent estimated concentrations near facilities that are actively monitoring and reporting carbon tetrachloride releases to surface receiving water via EPA's Discharge Monitoring Reports as required under the National Pollutant Discharge Elimination System (NPDES) permitting rules.

EPA concluded that carbon tetrachloride poses a hazard to environmental aquatic receptors (Section 3.1). Amphibians were the most sensitive taxa for acute and chronic exposures. For acute exposures, a hazard (toxicity) value of 0.9 mg/L was established for amphibians using data on teratogenesis leading to lethality in frog embryos and larvae. Additionally, acute exposures of carbon tetrachloride to fish, freshwater aquatic invertebrates, and sediment invertebrates resulted in hazard values as low as 10.4 mg/L, 11.1 mg/L, and 2 mg/L, respectively. For chronic exposures, carbon tetrachloride has a hazard value for amphibians of 0.03 mg/L based on teratogenesis and lethality in frog embryos and larvae. Furthermore, chronic exposures of carbon tetrachloride to fish, freshwater aquatic invertebrates, and sediment invertebrates resulted in hazard values as low as 1.97 mg/L, 1.1 mg/L (acute to chronic ratio of 10), and 0.2 mg/L (acute to chronic ratio of 10), respectively. In algal studies, carbon tetrachloride has hazard values ranging from 0.07 to 23.59 mg/L.

EPA considered the biological relevance of the species that the COCs were based on when integrating the COCs with surface water concentration data to produce risk quotients (RQs). For example, life-history and the habitat-use influence the likelihood of exposure above the hazard benchmark in an aquatic environment. In general, amphibian distribution is typically limited to freshwater environments. Larvae of the amphibian species (*Lithobates* sp. and *Rana* sp.) evaluated for hazards from sub-chronic exposure (Appendix 7F.2) can occupy a wide range of freshwater habitats including wetlands, lakes, springs, and streams throughout development and metamorphosis. However, as adults, these species are semi-aquatic and may interact with surface

water for fewer days per year. In contrast, fish occupy a wide range of freshwater habitats throughout their entire life cycle. If hazard benchmarks are exceeded by both larval amphibians and fish from a modeled and estimated chronic exposure, it provides additional evidence that the site-specific releases could affect that specific aquatic environment.

A total of 15 aquatic environmental hazard studies were reviewed and determined to have acceptable data quality for carbon tetrachloride. EPA's data quality evaluation of these studies resulted in either high, medium, or low data quality rating for each of the studies (Appendix 7F.1). The document *Final Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Hazard Studies* (U.S. EPA, 2019g) presents details of the data evaluations for each study, including scores for each metric and the overall study score.

For this risk evaluation, EPA conducted a multi-year analysis of 21 facilities that released the highest concentration of carbon tetrachloride from 2014-2018 as reported in the EPA Discharge Monitoring Reports (see Table 2-2 in Section 2.3.2 above). These facility releases represent, on average, 94% of total annual carbon tetrachloride releases. Environmental releases of carbon tetrachloride occur through disposal from industrial/commercial facilities as well as from POTWs. Sources of carbon tetrachloride from POTWs releases may not be tied to a specific condition of use given that POTWs may have multiple release sources. However, EPA is confident that the risks from releases of carbon tetrachloride include all conditions of use considered within the scope of the risk evaluation because EPA used the worst-case, high end exposures and modeled surface water concentrations.

Exposure pathways to terrestrial species through ambient air were determined to fall under the jurisdiction of the CAA. This pathway was excluded from the scope of this risk evaluation. Exposures to terrestrial organisms from the suspended soils and biosolids pathway were qualitatively evaluated by examining physical-chemical and fate properties.

4.1.1 Aquatic and Sediment Pathways

To assess environmental risk, EPA evaluates environmental hazard and exposure data. Although EPA did not calculate risks to the aquatic environment at problem formulation, EPA conducted further analysis of the environmental release pathway in this risk evaluation during data quality evaluation. The results of the analyses are presented below and in Appendix E.

The environmental risk of carbon tetrachloride is characterized by calculating risk quotients or RQs (U.S. EPA, 1998). The RQ is defined as:

$$RQ = \text{Environmental Concentration} / \text{Effect Level}$$

An RQ equal to 1 indicates that the exposures are the same as the concentration that causes effects. If the RQ is above 1, the exposure is greater than the effect concentration. If the RQ is below 1, the exposure is less than the effect concentration. The Concentrations of Concern (COCs) for aquatic organisms shown in Table 4-1 were used to calculate RQs.

Table 4-1. Concentrations of Concern (COCs) for Environmental Toxicity

Environmental Toxicity	Most Sensitive Test	Assessment Factor **/ Acute to Chronic Ratio (ACR)	Concentration of Concern (COC)*
Acute Toxicity, aquatic organisms	9-day amphibian LC_{50}	10	90 µg/L
Chronic Toxicity, aquatic organisms	9-day amphibians LC_{10}	10	3 µg/L
Algae	72-hour algal EC_{10}	10	7 µg/L
Acute Toxicity, sediment-dwelling organisms	48-hour LOEL	5	400 µg/L
Chronic Toxicity, sediment-dwelling organisms	48-hour LOEL	10 (ACR)	40 µg/L

*The Concentration of Concern is derived from the most sensitive acute, chronic, and algal toxicity values (hazard values) divided by an assessment factor of 10.
**Assessment factors are applied to account for variation within and across taxa.

As described in Appendix E and Appendix F, EPA used model exposure data that was calculated from E-FAST, monitored data from Discharge Monitoring Reports (DMR), and aquatic and sediment-dwelling organisms COCs from the available hazard data to determine the risk of carbon tetrachloride to aquatic and sediment-dwelling organisms using the RQ method.

EPA quantitatively evaluated risk to aquatic organisms from exposure to surface water and assessed the available monitoring data for carbon tetrachloride to adequately evaluate any potential environmental risk to aquatic organisms posed by carbon tetrachloride. The results of the review are summarized in Appendix E. All facilities were modeled in E-FAST. Facilities with an RQ ≥ 1 for the acute COC, RQ ≥ 1 and 20 days or more of exceedance for the algae COCs, or a RQ ≥ 1 for the chronic COC (based on a developmental endpoint) suggest the potential for environmental risks posed by carbon tetrachloride. The 20-day exceedance time frame was derived from partial life cycle tests (*e.g.*, daphnid chronic and fish early life stage tests) that typically range from 21 to 28 days in duration.

EPA derived the acute COC (90 µg/L), chronic COC (3 µg/L), and algal COC (7 µg/L) based on LC_{50} data from (Brack and Rottler, 1994), LC_{10} data from (Black et al., 1982; Birge et al., 1980), and EC_{10} data from (Brack and Rottler, 1994), respectively. These three studies were rated high quality and represented the lowest bound of carbon tetrachloride data available in the public domain.

EPA estimated carbon tetrachloride concentrations in surface water resulting from individual industrial direct discharges as well as from indirect discharges that receive and treat wastewater from multiple facilities and sources such as the municipal POTWs. EPA compiled five years of carbon tetrachloride NPDES permit Discharge Monitoring Report (DMR) release data (2014 through 2018). The total annual facility releases of carbon tetrachloride per DMR data indicated that 2019 and 2017 data were similar (7Appendix E); and analyzing DMR data from 2015 to 2019 would not change EPA's findings. This expanded data set provides a range of facilities and

a range of discharge amounts for this time period within the United States. EPA used E-FAST to estimate site-specific receiving water concentrations of carbon tetrachloride at the point of discharge. Based on physical-chemical properties, EPA anticipates that in surface waters, carbon tetrachloride will dissipate and volatilize. The E-FAST model, however, did not include these processes in surface water estimates, thereby providing conservative estimates. Two release scenarios were modeled for direct discharging facilities to provide upper and lower bounds for the range of surface water concentrations estimated by E-FAST 2014. The two scenarios modeled were a 250 days of release scenario (which yields the minimum estimated surface water concentrations for a given facility) and a 20 days of release scenario (which yields the maximum estimated surface water concentrations for a given facility). Days of exceedance, the number of days per year that the surface water concentrations were estimated to exceed the COCs, were also calculated using the Probabilistic Dilution Model (PDM) in E-FAST. Surface water concentrations and days of exceedance are summarized in Table 4-2 below.

Table 4-2. Modeled Facilities Showing Risk to Aquatic and Sediment-dwelling Organisms from the Release of Carbon Tetrachloride; RQs Greater Than One are Shown in Bold

NPDES	Facility Name	Days of Release Scenario (PDM) [a]	Amount Discharged (kg/day)	Stream Conc. (µg/L)	Concentration of Concern (COC) Type	COC (µg/L)	Days Exceedance (days/year, PDM)	RQ
TX0021458	**Fort Bend County WCID2[a]**	20	N/A	N/A	Acute Amphibian	90	N/A	N/A
					Chronic Amphibian	3	N/A	N/A
					Acute Sediment	400	N/A	N/A
					Chronic Sediment	40	N/A	N/A
					Algae	7	N/A	N/A
		250	1.0E-01	10	Chronic Amphibian	3	0	**3.4E+00**
					Chronic Sediment	40	0	2.6E-01
					Algae	7	0	**1.5E+00**
AL0001961	AKZO Chemicals, Inc.	20	5.7	3.1E-01	Acute Amphibian	90	0	3.4E-03
					Chronic Amphibian	3	0	1.0E-01
					Acute Sediment	400	0	7.8E-04
					Chronic Sediment	40	0	7.8E-03
					Algae	7	0	4.4E-02
		250	4.6E-01	2.5E-02	Chronic Amphibian	3	0	8.3E-03
					Chronic Sediment	40	0	6.2E-04
					Algae	7	0	3.5E-03
LA0000329	Honeywell, Baton Rouge	20	2.0E-01	8.1E-04	Acute Amphibian	90	0	9.0E-06
					Chronic Amphibian	3	0	2.7E-04
					Acute Sediment	400	0	2.0E-06

NPDES	Facility Name	Days of Release Scenario (PDM) [a]	Amount Discharged (kg/day)	Stream Conc. (µg/L)	Concentration of Concern (COC) Type	COC (µg/L)	Days Exceedance (days/year, PDM)	RQ
					Chronic Sediment	40	0	2.0E-05
					Algae	7	0	1.2E-04
		250	2.0E-02	8.1E-04	Chronic Amphibian	3	0	2.2E-05
					Chronic Sediment	40	0	1.6E-06
					Algae	7	0	9.3E-06
LA0005401	ExxonMobil, Baton Rouge	20	1.0E-02	4.0E-04	Acute Amphibian	90	0	4.5E-06
					Chronic Amphibian	3	0	1.3E-04
					Acute Sediment	400	0	1.0E-06
					Chronic Sediment	40	0	1.0E-05
					Algae	7	0	5.7E-05
		250	1.0E-02	3.2E-05	Chronic Amphibian	3	0	1.1E-05
					Chronic Sediment	40	0	8.1E-07
					Algae	7	0	4.6E-06
OH0029149	**Gabriel Performance**	20	1.9E-01	45	Acute Amphibian	90	0	5.0E-01
					Chronic Amphibian	3	4	**1.5E+01**
					Acute Sediment	400	0	1.1E-01
					Chronic Sediment	40	0	**1.1E+00**
					Algae	7	2	**6.4E+00**
		250	2.0E-02	3.6	Chronic Amphibian	3	2	**1.2E+00**
					Chronic Sediment	40	0	8.9E-02
					Algae	7	0	5.1E-01
WV0004359	Natrium Plant	20	2.9E-01	3.4E-02	Acute Amphibian	90	0	3.8E-04

NPDES	Facility Name	Days of Release Scenario (PDM) [a]	Amount Discharged (kg/day)	Stream Conc. (µg/L)	Concentration of Concern (COC) Type	COC (µg/L)	Days Exceedance (days/year, PDM)	RQ
					Chronic Amphibian	3	0	1.2E-02
					Acute Sediment	400	0	8.6E-05
					Chronic Sediment	40	0	8.6E-04
					Algae	7	0	4.9E-03
		250	2.0E-02	2.9E-03	Chronic Amphibian	3	0	9.5E-04
					Chronic Sediment	40	0	7.2E-05
					Algae	7	0	4.1E-04
CA0107336	Sea World, San Diego[c,d]	20	6.3E-02	1.5E-01	Acute Amphibian	3	N/A	5.0E-02
					Chronic Amphibian	400	N/A	0.0E+00
					Acute Sediment	40	N/A	3.8E-04
					Chronic Sediment	7	N/A	2.0E-02
					Algae	3	N/A	5.0E-02
		250	5.0E-03	1.2E-02	Chronic Amphibian	40	N/A	4.0E-03
					Chronic Sediment	7	N/A	3.0E-04
					Algae	3	N/A	1.7E-03
OH0007269	**Dover Chemical Corp**	20	0.36	25	Acute Amphibian	90	13	2.8E-01
					Chronic Amphibian	3	8	**8.3E+00**
					Acute Sediment	400	0	6.0E-02
					Chronic Sediment	40	0	6.3E-01
					Algae	7	0	**3.6E+00**
		250	2.9E-02	2E+00	Chronic Amphibian	3	15	6.7E-01
					Chronic Sediment	40	0	0.0E+00

NPDES	Facility Name	Days of Release Scenario (PDM) [a]	Amount Discharged (kg/day)	Stream Conc. (µg/L)	Concentration of Concern (COC) Type	COC (µg/L)	Days Exceedance (days/year, PDM)	RQ
					Algae	7	3	0.0E+00
LA0006181	Honeywell, Geismar	20	1.8E-01	7E-04	Acute Amphibian	90	0	8.1E-06
					Chronic Amphibian	3	0	2.4E-04
					Acute Sediment	400	0	1.8E-06
					Chronic Sediment	40	0	1.8E-05
					Algae	7	0	1.0E-04
		250	2.0E-02	6E-05	Chronic Amphibian	3	0	2.0E-05
					Chronic Sediment	40	0	1.5E-06
					Algae	7	0	8.7E-06
LA0038245	Clean Harbors, Baton Rouge	20	3.3E-01	1E-03	Acute Amphibian	90	0	1.5E-05
					Chronic Amphibian	3	0	4.5E-04
					Acute Sediment	400	0	3.4E-06
					Chronic Sediment	40	0	3.4E-05
					Algae	7	0	1.9E-04
		250	3.0E-02	1E-04	Chronic Amphibian	3	0	3.5E-05
					Chronic Sediment	40	0	2.6E-06
					Algae	7	0	1.5E-05
TX0119792	**Equistar Chemicals LP**	20	6.8E-01	4.4	Acute Amphibian	90	0	4.9E-02
					Chronic Amphibian	3	3	**1.5E+00**
					Acute Sediment	400	0	1.1E-02
					Chronic Sediment	40	0	1.1E-01
					Algae	7	1	6.3E-01

NPDES	Facility Name	Days of Release Scenario (PDM) [a]	Amount Discharged (kg/day)	Stream Conc. (µg/L)	Concentration of Concern (COC) Type	COC (µg/L)	Days Exceedance (days/year, PDM)	RQ
		250	5.0E-02	3.5E-01	Chronic Amphibian	3	0	1.2E-01
					Chronic Sediment	40	0	8.8E-03
					Algae	7	0	5.0E-02
WV0001279	Chemours Chemicals LLC	20	1.1E-01	1.0E-02	Acute Amphibian	90	0	1.2E-04
					Chronic Amphibian	3	0	3.7E-03
					Acute Sediment	400	0	2.8E-05
					Chronic Sediment	40	0	2.8E-04
					Algae	7	0	1.6E-03
		250	1.0E-02	8.0E-04	Chronic Amphibian	3	0	2.7E-04
					Chronic Sediment	40	0	2.0E-05
					Algae	7	0	1.2E-04
TX0007072	**Eco Services Operations**	20	2.6E-01	49	Acute Amphibian	90	0	5.4E-01
					Chronic Amphibian	3	3	**1.6E+01**
					Acute Sediment	400	0	1.2E-01
					Chronic Sediment	40	0	**1.2E+00**
					Algae	7	2	**7.0E+00**
		250	2.0E-02	3.9	Chronic Amphibian	3	2	**1.3E+00**
					Chronic Sediment	40	0	9.7E-02
					Algae	7	0	5.6E-01
KY0024082	Barbourville STP[b]	20	N/A	N/A	Acute Amphibian	90	N/A	N/A
					Chronic Amphibian	3	N/A	N/A
					Acute Sediment	400	N/A	N/A

NPDES	Facility Name	Days of Release Scenario (PDM) [a]	Amount Discharged (kg/day)	Stream Conc. (µg/L)	Concentration of Concern (COC) Type	COC (µg/L)	Days Exceedance (days/year, PDM)	RQ
					Chronic Sediment	40	N/A	N/A
					Algae	7	N/A	N/A
		250	1.0E-02	3.5E-01	Chronic Amphibian	3	0	1.2E-01
					Chronic Sediment	40	0	8.8E-03
					Algae	7	0	5.0E-02
WA0030520	Central Kitsap WWTP[a,b,d]	N/A	N/A	N/A	Acute Amphibian	90	N/A	N/A
					Chronic Amphibian	3	N/A	N/A
					Acute Sediment	400	N/A	N/A
					Chronic Sediment	40	N/A	N/A
					Algae	7	N/A	N/A
		250	1.0E-02	5.8E-01	Chronic Amphibian	3	N/A	1.9E-01
					Chronic Sediment	40	N/A	1.5E-02
					Algae	7	N/A	8.3E-02
MO0002526	Bayer Crop Science	20	5.0E-02	5.9E-01	Acute Amphibian	90	0	6.6E-03
					Chronic Amphibian	3	0	2.0E-01
					Acute Sediment	400	0	1.5E-03
					Chronic Sediment	40	0	1.5E-02
					Algae	7	0	8.4E-02
		250	0.0E+00	4.7E-02	Chronic Amphibian	3	0	1.6E-02
					Chronic Sediment	40	0	1.2E-03
					Algae	7	0	6.7E-03
KY0027979	Eddyville STP[b]	20	N/A	N/A	Acute Amphibian	90	N/A	N/A

NPDES	Facility Name	Days of Release Scenario (PDM) [a]	Amount Discharged (kg/day)	Stream Conc. (µg/L)	Concentration of Concern (COC) Type	COC (µg/L)	Days Exceedance (days/year, PDM)	RQ
					Chronic Amphibian	3	N/A	N/A
					Acute Sediment	400	N/A	N/A
					Chronic Sediment	40	N/A	N/A
					Algae	7	N/A	N/A
		250	1.0E-02	1.0E+00	Chronic Amphibian	3	1	3.4E-01
					Chronic Sediment	40	0	2.6E-02
					Algae	7	0	1.5E-01
KY0103357	Richmond Silver Creek STP[b]	20	N/A	N/A	Acute Amphibian	90	N/A	N/A
					Chronic Amphibian	3	N/A	N/A
					Acute Sediment	400	N/A	N/A
					Chronic Sediment	40	N/A	N/A
					Algae	7	N/A	N/A
		250	0.0E+00	3.1E-01	Chronic Amphibian	3	0	1.0E-01
					Chronic Sediment	40	0	7.8E-03
					Algae	7	0	4.4E-02
KY0003603	Arkema Inc.	20	2.0E-02	9.5E-04	Acute Amphibian	90	0	1.1E-05
					Chronic Amphibian	3	0	3.2E-04
					Acute Sediment	400	0	2.4E-06
					Chronic Sediment	40	0	2.4E-05
					Algae	7	0	1.4E-04
		250	0.0E+00	8.7E-05	Chronic Amphibian	3	0	2.9E-05
					Chronic Sediment	40	0	2.2E-06
					Algae	7	0	1.2E-05

NPDES	Facility Name	Days of Release Scenario (PDM) [a]	Amount Discharged (kg/day)	Stream Conc. (µg/L)	Concentration of Concern (COC) Type	COC (µg/L)	Days Exceedance (days/year, PDM)	RQ
KY009161	Caveland Environmental Auth	20	3.0E-02	8.4E-02	Acute Amphibian	90	0	9.3E-04
					Chronic Amphibian	3	0	2.8E-02
					Acute Sediment	400	0	2.1E-04
					Chronic Sediment	40	0	2.1E-03
					Algae	7	0	1.2E-02
		250	0.0E+00	5.6E-03	Chronic Amphibian	3	0	1.9E-03
					Chronic Sediment	40	0	1.4E-04
					Algae	7	0	8.0E-04
LA0002933	Occidental Chem Corp, Geismar	20	1.0E-02	4.9E-05	Acute Amphibian	90	0	5.4E-07
					Chronic Amphibian	3	0	1.6E-05
					Acute Sediment	400	0	1.2E-07
					Chronic Sediment	40	0	1.2E-06
					Algae	7	0	6.9E-06
		250	0.0E+00	4.0E-06	Chronic Amphibian	3	0	1.4E-06
					Chronic Sediment	40	0	1.0E-07
					Algae	7	0	5.8E-07

[a]Because acute RQs were all < 1 under the 20 days of release scenario (corresponding to the maximum estimated surface water concentrations), acute RQs for the 250day release (minimum estimated surface water concentrations, RQs all < 1) were not included in the table.
[b]Days of release were assumed to be over 20 days for POTW facilities, because these facilities operate continuously. Thus, 20-day release probabilistic dilution models (PDM) were not run for POTW facilities, and RQs are N/A under the 20-day release scenario.
[c]San Diego Sea World facility (CA0107336) was not available in the NPDES in database in EFAST so CA0107409 San Diego WWT was used as proxy to model surface water
[d]Probabilistic dilution models (PDM) were not well suited to the release data provided for these facilities (and not run) because the locations released to saltwater. E-FAST treats ocean/bays differently and specifies a dilution of 1 (*i.e.*, no dilution). Days of exceedance are N/A for these facilities.

4.1.2 Risk Estimation for Aquatic Environment

To characterize potential risk from exposures to carbon tetrachloride, EPA calculated RQs based on modeled data from E-FAST for sites that had surface water discharges according to carbon tetrachloride DMR data (Appendix E). The predicted exposure concentrations in surface water of carbon tetrachloride (from 4.9E-05 µg/L to 1.3E+02 µg/L for acute exposures and 4.1E-06 µg/L to 1.0E+1 µg/L for chronic exposures; see Appendix E) were based on conservative assumptions, including 0% removal of carbon tetrachloride by the waste water treatment facility. As explained in Section 2.1, the EPI Suite™ STP module estimates that about 90% of carbon tetrachloride in wastewater will be removed by volatilization and 2% by adsorption. Also 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.

All facilities assessed in this risk evaluation were modeled in E-FAST, and the RQs are presented in Table 4-2. There were five facilities that indicated risk for aquatic organisms (RQ ≥ 1 for the acute COC, RQ ≥ 1 and 20 days or more of exceedance for the algae COCs, or a RQ ≥ 1 for the chronic COC based on a developmental endpoint). Other facilities had acute RQs < 1, algae RQ < 1 and < 20 days exceedance, or chronic RQs < 1, indicating they do not present risk to aquatic organisms from acute and chronic exposure. At one facility, Dover Chemical in Ohio (OH0007269), EPA identified an elevated environmental release of carbon tetrachloride in 2014 due to an unexpected chemical spill. Because spills and leaks are not included within the scope of TSCA risk evaluations, the 2014 release was not included in the analysis. Other releases from the facility, not due to the chemical spill, were evaluated.

EPA's analysis did not identify risk from acute exposure to aquatic organisms (acute RQ ≥ 1) for any facilities (summarized in Table 4-2). EPA's initial analysis did not indicate risk from chronic exposure to aquatic organisms (chronic RQ ≥ 1 and 20 days or more of exceedance of the chronic COC). However, because the chronic COC is based on mortality observed during amphibian development, and exposures during development have the potential to cause long-term adverse effects (*e.g.*, malformations) from short exposure periods (*i.e.*, < 20 days), EPA calculated a lower bracket of chronic risk (where RQs were ≥ 1). This scenario was compared to the traditional EPA assessment methodology for chronic endpoints (where chronic RQ ≥ 1 and 20 days or more exceedance). Under this conservative scenario, which accounted for the possibility that short exposures during developmental could produce adverse chronic effects (chronic RQ ≥ 1), EPA identified risk to development of aquatic organisms from chronic exposure to carbon tetrachloride near five facilities: Fort Bend in Texas (TX0021458), Gabriel Performance in Ohio (OH0029149), Dover Chemical in Ohio (OH0007269), Equistar Chemicals in Texas (TX0119792), and Eco Services Operations in Texas (TX000707072). Risk quotients and days of exceedance are summarized in Table 4-2.

To determine if amphibian development could realistically be affected at each of the five facilities where risk from chronic exposure was identified, EPA further refined the assessment by examining the time of year when exposure was predicted to occur. Timing of exposure is important to consider because amphibian development is constrained seasonally throughout the U.S., and typically spans only 2-4 months out of any given year. Thus, EPA examined whether releases occurred during the months relevant to amphibian development (April – September at the Ohio facilities or March – September in Texas facilities). Where releases occurred and data

were available, EPA calculated surface water concentrations using E-FAST and associated, site-specific RQs to determine whether risk was or was not indicated at the facilities during these key time periods. Risk was not indicated during time periods relevant to amphibian development at Eco Services Operations Facility (RQs < 1 for the three years where monitoring information was available). At the other four facilities, risk was indicated (RQs > 1) during the time periods relevant to amphibian development for at least 2 separate reporting periods. At the OH 0028149 and the TX0007072 facilities, the 20-day stream concentrations also exceed the unadjusted amphibian endpoint (*e.g.*, 30 µg/L the amphibian LC_{10}). However, because risk was not consistent or predictable across years or facilities (*e.g.*, some years, no releases of carbon tetrachloride occurred, or RQs < 1), it is important to acknowledge that the timing of future exposures is an uncertainty in the risk evaluation. Facilities may not release carbon tetrachloride consistently throughout the year, which makes it difficult to predict whether risk will/will not occur during months key to amphibian development in future years. Seasonal release information and associated RQs for each of the five sites that indicated risk for development from chronic exposures to carbon tetrachloride are available in 7F.10.

EPA's analysis did not indicate risk from exposure to carbon tetrachloride for algae (RQ ≥ 1 and 20 days or more of exceedance of the chronic COC). EPA considered algal endpoints separately from the other taxa and used a sensitive hazard endpoint (EC_{10}) instead of an acute endpoint (EC_{50}) to generate a concentration of concern relevant to algae (see Section 3.1). EPA's approach considered point effects beyond mortality (*e.g.*, reductions in growth, yield, etc.) that are observed to effect at most 10% of an algae population and, as such, was protective of acute exposures to algae. In addition, the PDM model estimates the total number of days out of 1 year that the COC is exceeded in surface water, and the days are not necessarily consecutive. Thus, the 20-day exceedance criterion was considered protective of algae.

4.1.3 Risk Estimation for Sediment

EPA quantitatively analyzed exposure to sediment-dwelling aquatic organisms. Only one low quality study on *Chironomus tentans* (Lee et al., 2006) was available for sediment-dwelling organisms. Lee *et al.*, examined body weight and expression of two genes that are general biomarkers for stress (*i.e.*, heat shock protein and hemoglobin) after an acute exposure to carbon tetrachloride. The lowest effect level (LOEL) for mRNA expression of the heat shock protein and hemoglobin genes in larvae was 0.02 mg/L carbon tetrachloride; the LOEL for dry body weight was 2 mg/L carbon tetrachloride. Since the heat shock protein and hemoglobin genes are general biomarkers that cannot be attributed to an adverse outcome pathway, the sediment-dwelling organism COC were calculated based on body dry weight and an AF of 5 for acute COC and an ACR of 10 for chronic COC.

Acute COC
The acute COC = (2.0 mg/L) / (AF of 5) = 0.4 mg/L x 1,000 = 400 µg/L or 400 ppb

Chronic COC
400 µg/L / (ACR of 10) = 40 µg/L or 40 ppb

The acute COC of 400 µg/L and chronic COC of 40 µg/L, derived from an experimental sediment-dwelling endpoint, are used as the conservative (screening-level) hazard levels for the sedimental pathway in this risk evaluation for carbon tetrachloride. Because only one low quality

study was available for sediment-dwelling organisms, EPA also generated acute and chronic COCs using aquatic invertebrates (*e.g.*, *Gammarus pseudolimnaeus* and *Daphnia magna*) as a surrogate species to provide an additional line of evidence to estimate toxicity to sediment-dwelling organisms in the final TSCA risk evaluation. Daphnia, which feed through the entire water column, were deemed to be an acceptable surrogate species for sediment invertebrates because carbon tetrachloride is not expected to sorb to sediment and will instead remain in pore water. EPA calculated an acute aquatic invertebrate COC of 2,220 ppb, and a chronic aquatic invertebrate COC of 110 ppb. These COCs were greater than the COCs based on (Lee et al., 2006) and indicate that carbon tetrachloride may be more toxic to sediment-dwelling species.

Carbon tetrachloride concentrations in sediment and pore water were expected to be similar to or less than the concentrations in the overlying water, and concentrations of carbon tetrachloride in the deeper part of sediment, where anaerobic conditions prevail, are expected to be lower due to its water solubility (793 mg/L), low partitioning to organic matter (log K_{OC} = 0.79 – 1.93 (aquifer sediments) and marine and estuary sediments (log K_{OC} = 1.67), and biodegradability in anaerobic environments (see Section 2.1).

Given that the COCs for acute and chronic exposure of carbon tetrachloride to *Chironomus tentans* were less toxic than the COCs for amphibian acute and chronic toxicity and algal toxicity, EPA did not calculate exposure numbers specific for sedimental dwelling organisms. EPA used modeled surface water concentrations to estimate the concentration of carbon tetrachloride in pore water near facilities. Based on the COCs generated from both (Lee et al., 2006) and from the use of aquatic invertebrates as a surrogate, risks to sediment-dwelling organisms were not indicated for acute or chronic exposures to carbon tetrachloride (RQs derived from (Lee et al., 2006) are listed in Table 4-2).

4.1.4 Risk Estimation for Terrestrial Organisms

During Problem Formulation, EPA conducted a screening level analysis to consider whether pathways of exposure for terrestrial organisms should be further analyzed and determined that terrestrial organism exposures to carbon tetrachloride was not of concern partially based on estimates of soil concentrations several orders of magnitude below concentrations observed to cause effects in terrestrial organisms. For the final risk evaluation, EPA conducted a qualitative assessment of exposure to terrestrial organisms from soil and land application of biosolids by examining physical-chemical and fate properties. EPA identified carbon tetrachloride as a priority pollutant under Section 304(a) of the CWA and has developed water quality criteria for protection of human health. EPA determined during problem formulation that exposures to terrestrial organisms from water do not need further evaluation due to the current regulation of carbon tetrachloride water releases and the expectation of releases to water will volatilize into air based on its physical-chemical properties. EPA did not assess exposure to terrestrial organisms from ambient air because this exposure pathway is covered under jurisdiction of the CAA.

Carbon tetrachloride is not expected to partition to or accumulate in soil; rather, it is expected to volatilize to air or migrate through soil into groundwater based on its physical-chemical properties (log K_{OC} = 2.83, Henry's Law constant = 0.0276 atm-m^3 /mole, vapor pressure = 115 mmHg at 25°C). Carbon tetrachloride is not anticipated to be retained in biosolids (processed sludge) obtained through wastewater treatment. Furthermore, carbon tetrachloride is not anticipated to remain in soil, as it is expected to either volatilize into air or migrate through soil

into groundwater. Because the physical-chemical properties and fate endpoints do not support an exposure pathway through soil and biosolids to terrestrial organisms, no further analysis from this pathway was conducted.

Last, carbon tetrachloride is not expected to bioaccumulate in tissues, and concentrations will not increase from prey to predator in either aquatic or terrestrial food webs. Based on the Guidance for Ecological Soil Screening Levels (U.S. EPA, 2003a, b) document, for wildlife relative exposures associated with inhalation and dermal exposure pathways are insignificant, even for volatile substances, compared to direct ingestion and ingestion of food (by approximately 1,000-fold).

4.2 Human Health Risk

4.2.1 Risk Estimation Approach

Development of the carbon tetrachloride hazard and dose-response assessment used for the selection of PODs for non-cancer and cancer endpoints and the benchmark dose analyses used in the risk characterization are found in Section 3.2.5.2.

The use scenarios, populations of interest and toxicological endpoints that were selected for determining potential risks from acute and chronic exposures are presented in Table 4-3, Table 4-4, Table 4-5 and Table 4-6.

Table 4-3. Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing Occupational Risks Following Acute Inhalation Exposures to Carbon Tetrachloride

Populations and Toxicological Approach	Occupational Use Scenarios of Carbon Tetrachloride
Population of Interest and Exposure Scenario:	***Occupational Users:*** Adult worker (>16 years old) exposed to carbon tetrachloride for a single 8-hr exposure. ***Occupational Non-users:*** Adult (>16 years old) exposed to carbon tetrachloride indirectly by being in the same work area of building.
Health Effects of Concern, Concentration and Time Duration	Non-Cancer Health Effects: CNS **1.** *Non-Cancer Point of Departure (POD)*: 58 ppm-8 hr (or 360 mg/m^3 – 8 hr) for temporary disabling CNS effects Cancer Health Effects: Cancer risks following acute exposures were not estimated. Relationship is not known between a single short-term exposure to carbon tetrachloride and the induction of cancer in humans.
Uncertainty Factors (UF) used in Non-Cancer Margin of Exposure (MOE) calculations	UF_H = 10 (based on human data and susceptibility from alcohol consumption) Total UF = Benchmark MOE = 10
Adult workers (>16 years old) include both healthy female and male workers. UF_H = intraspecies UF	

Table 4-4. Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing Occupational Risks Following Chronic Inhalation Exposures to Carbon Tetrachloride

Populations and Toxicological Approach	Occupational Use Scenarios of Carbon Tetrachloride
Population of Interest and Exposure Scenario:	***Occupational Users:*** Adult worker (>16 years old) exposed to carbon tetrachloride for the entire 8-hr workday for 250 days per year for 40 working years. ***Occupational Non-users:*** Adult worker (>16 years old) repeatedly exposed to indirect carbon tetrachloride exposures by being in the same work area of building.
Health Effects of Concern, Concentration and Time Duration	Non-Cancer Health Effects: Fatty changes in the liver **1.** *Non-Cancer Point of Departure (POD)*: $BMCL_{10[HEC]}$: 14.3 mg/m^3 for continuous exposures, which is equivalent to 31.1 mg/m^3 for 8 hrs (U.S. EPA, 2010) Cancer Health Effects: Carbon tetrachloride is classified as "likely to be carcinogenic to humans" **1.** *Cancer Inhalation Unit Risk (IUR)*: 6×10^{-6} per µg/m^3 for lifetime continuous exposure POD for liver tumors: 6 mg/m^3 for continuous exposures based on female mice data in (Nagano et al., 2007a)
Uncertainty Factors (UF) Used in Non-Cancer Margin of Exposure (MOE) calculations	$(UF_H = 10) \times (UF_A = 3) = 30$ Total UF = Benchmark MOE = 30
Cancer Benchmark	1 in 10^4 cancer risk for worker populations Benchmark MOE of 300 for liver tumors based on $(UF_H = 10) \times (UF_A = 3) \times (UF_{LOAEC\ to\ NOAEC} = 10) = 300$
Adult workers (>16 years old) include both healthy female and male workers. UF_H = intraspecies UF; UF_A = interspecies UF; $UF_{LOAEC\ to\ NOAEC}$ = LOAEC to NOAEC extrapolation UF	

Table 4-5. Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing Occupational Risks Following Acute Dermal Exposures to Carbon Tetrachloride

Populations and Toxicological Approach	Occupational Use Scenarios of Carbon Tetrachloride
Population of Interest and Exposure Scenario:	***Occupational Users:*** Adult worker (>16 years old) exposed to carbon tetrachloride for a single 8-hr exposure.
Health Effects of Concern, Concentration and Time Duration	Non-Cancer Health Effects: Liver effects **1.** *Non-Cancer Point of Departure (POD)*: 250 mg/kg-d for liver effects Cancer Health Effects: Cancer risks following acute exposures were not estimated. Relationship is not known between a single short-term exposure to carbon tetrachloride and the induction of cancer in humans.
Uncertainty Factors (UF) used in Non-Cancer Margin of Exposure (MOE) calculations	$(UF_H = 10) \times (UF_A = 3) = 30$ Total UF = Benchmark MOE = 30
Adult workers (>16 years old) include both healthy female and male workers. UF_H = intraspecies UF; UF_A = interspecies UF	

Table 4-6. Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing Occupational Risks Following Chronic Dermal Exposures to Carbon Tetrachloride

Populations and Toxicological Approach	Occupational Use Scenarios of Carbon Tetrachloride
Population of Interest and Exposure Scenario:	***Occupational Users:*** Adult worker (>16 years old) exposed to carbon tetrachloride for the entire 8-hr workday for 250 days per year for 40 working years.
Health Effects of Concern, Concentration and Time Duration	Non-cancer Health Effects: Fatty changes in the liver **1.** *Non-Cancer Point of Departure (POD)*: 2.50 mg/kg-d based on route-to-route extrapolation from $BMCL_{10[HEC]}$: 14.3 mg/m^3 for continuous exposures. Cancer Health Effects: Carbon tetrachloride is classified as "likely to be carcinogenic to humans" **1.** Cancer Slope factor derived from Inhalation Unit Risk (IUR) of 6×10^{-6} per µg/m^3 for lifetime continuous exposure POD for liver tumors: 6 mg/m^3 for continuous exposures based on female mice data in (Nagano et al., 2007a)
Uncertainty Factors (UF) Used in Non-Cancer Margin of Exposure (MOE) calculations	$(UF_H = 10) \times (UF_A = 3) = 30$ Total UF = Benchmark MOE = 30
Cancer Benchmark	1 in 10^4 cancer risk for worker populations Benchmark MOE of 300 for liver tumors based on $(UF_H = 10) \times (UF_A = 3) \times (UF_{LOAEC\ to\ NOAEC} = 10) = 300$
Adult workers (>16 years old) include both healthy female and male drinking workers. The risk evaluation for repeated exposures focused on the most sensitive life stage in humans, which is alcohol drinkers (see Section 3.2.4.1) UF_H = intraspecies UF; UF_A = interspecies UF; $UF_{LOAEC\ to\ NOAEC}$ = LOAEC to NOAEC extrapolation UF	

EPA used a Margin of Exposure (MOE) approach to identify potential non-cancer risks. The MOE is the ratio of the non-cancer POD divided by a human exposure, which is then compared to a benchmark MOE. If the calculated MOE is less than the benchmark MOE, this indicates potential risk to human health, whereas if the calculated MOE is equal to or greater than the benchmark MOE, it suggests that the risks are negligible.

Acute or chronic MOEs (MOE_{acute} or $MOE_{chronic}$) were used in this assessment to estimate non-cancer risks using Equation 4-1..

Equation 4-1. Equation to Calculate Non-Cancer Risks Following Acute or Chronic Exposures Using Margin of Exposures

$$MOE_{acute\ or\ chronic} = \frac{Non\text{–}cancer\ Hazard\ Value\ (POD)}{Human\ Exposure}$$

Where:

MOE	**= Margin of exposure (unitless)**
Hazard value (POD)	= NOAEC or HEC (mg/m^3)
Human Exposure	= Exposure estimate (in mg/m^3) from occupational exposure assessment

The Acute Exposure Concentration (AEC) was used to estimate acute/short-term inhalation risks, whereas the Average Daily Concentration/Dose (ADC)/D) was used to estimate chronic non-cancer inhalation/dermal.

EPA used MOEs[20] to estimate acute and chronic risks for non-cancer based on the following:

1. the HECs/HEDs identified for the highest quality studies within each health effects domain;
2. the endpoint/study-specific UFs applied to the HECs/HEDs per the review of the EPA Reference Dose and Reference Concentration Processes (U.S. EPA, 2002); and
3. the exposure estimates calculated for carbon tetrachloride conditions under the conditions of use (see Section 2.4).

MOEs allow for the presentation of a range of risk estimates. The occupational exposure scenarios considered both acute and chronic exposures. Different adverse endpoints were used based on the expected exposure durations. For occupational exposure calculations, the 8-hour and 12-hour TWAs were used to calculate MOEs for risk estimates for acute and chronic exposures. The occupational inhalation exposure scenarios considered both acute and chronic exposures. For non-cancer effects, risks for transient CNS effects were evaluated for acute (short-term) exposures, whereas risks for toxicity to the liver was evaluated for repeated (chronic) exposures to carbon tetrachloride because of their human relevance and relevance to occupational exposures as discussed in Section 3.2.4.

The total UF for each non-cancer POD was the benchmark MOE used to interpret the MOE risk estimates for each use scenario. The MOE estimate was interpreted as human health risk if the MOE estimate was less than the benchmark MOE (*i.e.*, the total UF). On the other hand, the MOE estimate indicated negligible concerns for adverse human health effects if the MOE estimate exceeded the benchmark MOE. Typically, the larger the MOE, the more unlikely it is that a non-cancer adverse effect would occur.

To determine the level of personal protection needed by workers to reduce the high-end exposures to below the level of concern for non-cancer risks, EPA evaluated the impact of respirator use. Typical APF values of 10, 25 and 50 were compared to the calculated MOE and the benchmark MOE to determine the level of APF required to reduce exposure so that risk is below the level of concern for non-cancer risks (*i.e.*, calculated MOE ≥ benchmark MOE).

EPA estimated potential cancer risks from chronic exposures to carbon tetrachloride using probabilistic approaches, which consisted of calculating the added cancer risk. Each of these approaches is discussed below.

Added cancer risks for repeated exposures to carbon tetrachloride were estimated using Equation 4-2. Equation to Calculate Cancer Risks. Estimates of added cancer risks should be interpreted as the incremental probability of an individual developing cancer over a lifetime as a result of exposure to the potential carcinogen (*i.e.*, incremental or added individual lifetime cancer risk).

[20] Margin of Exposure (MOE) = (Non-cancer hazard value, POD) ÷ (Human Exposure) Equation 4-1.. The benchmark MOE is used to interpret the MOEs and consists of the total UF.

Equation 4-2. Equation to Calculate Cancer Risks

$$\textit{Inhalation Cancer Risk} = \textit{Human Exposure} \times \textit{IUR}$$
$$\textit{or}$$
$$\textit{Dermal Cancer Risk} = \textit{Human Exposure} \times \textit{CSF}$$

Where:

Risk	**= Added cancer risk (unitless)**
Human exposure	= Occupational exposure estimate (LADC in ppm)
IUR	= Inhalation unit risk (6×10^{-6} per µg/m^3 for continuous exposures)
CSF	= Inhalation unit risk adjusted for dermal absorption

For carbon tetrachloride, EPA, consistent with 2017 NIOSH guidance *NIOSH [2017] Current intelligence bulletin 68: NIOSH chemical carcinogen policy*, available at https://www.cdc.gov/niosh/docs/2017-100/pdf/2017-100.pdf, used 1×10^{-4} as the benchmark for the purposes of this risk determination for individuals in industrial/commercial work environments subject to Occupational Safety and Health Act (OSHA) requirements. It is important to note that 1×10^{-4} is not a bright line and EPA has discretion to find unreasonable risks based on other benchmarks as appropriate based on analysis. Additionally, it is also important to note that exposure related considerations (duration, magnitude, population exposed) can affect EPA's estimates of the added cancer risk.

4.2.2 Risk Estimation for Non-Cancer Effects Following Acute Inhalation Exposures

Non-cancer risk estimates for acute inhalation exposures to carbon tetrachloride were derived for occupational scenarios for the TSCA conditions of use. The risk estimates for acute inhalation exposures are based on CNS effects that are temporarily disabling (NRC, 2014) and focus on the high-end (95th percentile) and central tendency (50th percentile). Non-cancer risk estimates for acute occupational exposure scenarios are presented in Table 4-7, below. Risk estimates were calculated for the occupational inhalation exposure scenarios described in Section 2.4.1.7. The calculated MOEs without respirators are greater than the benchmark MOE of 10 for the high-end and central tendency exposures for all the conditions of use.

Table 4-7. Risk Estimates for Acute Inhalation Exposures based on a POD of 360 mg/m^3 – 8hrs (= 310 mg/m^3-12 hrs) and Benchmark MOE of 10

Condition of Use	EXPOSURE		Calculated MOE without Respirator		Calculated MOE with Respirator (Worker)*					
	ADC (mg/m^3)				APF =10		APF =25		APF =50	
	High-End	Central Tendency	MOE High-End	MOE Central Tendency	MOE High-End	MOE Central Tendency	MOE High-End	MOE Central Tendency	MOE High-End	MOE Central Tendency
Manufacturing - 8-hr TWA (Workers)	4.0	0.76	90	474	900	4,740	2,250	11,850	4,500	23,700
Manufacturing - 8-hr TWA (ONUs)	1.0	0.50	360	720	3,600	7,200	9,000	18,000	18,000	36,000
Manufacturing - 12-hr TWA (Workers)	4.8	0.50	65	620	650	6,200	1,625	15,500	3,250	31,000
Manufacturing - 12-hr TWA (ONUs)	1.3	0.66	238	470	2,380	4,700	5,950	11,750	11,900	23,500
Import/ Repackaging (Workers)	2.92	0.89	123	404	1,230	4,040	3,075	10,100	6,150	20,200
Import/ Repackaging (ONUs) [a]	2.92	0.89	123	404	1,230	4,040	3,075	10,100	6,150	20,200
Processing as Reactant/Intermediate – 8-hr TWA (Workers)	4.0	0.76	90	474	900	4,740	2,250	11,850	4,500	23,700
Processing as Reactant/Intermediate – 8-hr TWA (ONUs)	1.0	0.50	360	720	3,600	7,200	9,000	18,000	18,000	36,000
Processing as Reactant/Intermediate – 12-hr TWA (Workers)	4.8	0.50	65	620	650	6,200	1,625	15,500	3,250	31,000

Processing as Reactant/Intermediate – 12-hr TWA (ONUs)	1.3	0.66	238	470	2,380	4,700	5,950	11,750	11,900	23,500
Industrial Processing Aid (Workers)	2.92	0.89	123	404	1,230	4,040	3,075	10,100	6,150	20,200
Industrial Processing Aid (ONUs) [a]	2.92	0.89	123	404	1,230	4,040	3,075	10,100	6,150	20,200
Additive (Workers)	2.92	0.89	123	404	1,230	4,040	3,075	10,100	6,150	20,200
Additive (ONUs) [a]	2.92	0.89	123	404	1,230	4,040	3,075	10,100	6,150	20,200
Disposal: Waste Handling (Workers)	2.92	0.89	123	404	1,230	4,040	3,075	10,100	6,150	20,200
Disposal: Waste Handling (ONUs) [a]	2.92	0.89	123	404	1,230	4,040	3,075	10,100	6,150	20,200
Specialty Uses-DoD (Workers)	0.37	0.18	973	2,000	9,730	20,000	24,325	50,000	48,650	100,000
Specialty Uses-DoD (ONUs) [a]	0.37	0.18	973	2,000	9,730	20,000	24,325	50,000	48,650	100,000
Reactive Ion Etching	Negligible – highly controlled work areas with small quantities applied.									
Laboratory Chemicals	No data – exposure is low as laboratory typically uses small quantities inside a fume hood.									

* MOEs with respirator use were calculated by multiplying the MOE without a respirator by the respirator APF.
[a] In lieu of ONU-specific exposure data, EPA assessed ONU exposures at the worker central tendency.

4.2.3 Risk Estimation for Non-Cancer Effects Following Chronic Inhalation Exposures

Chronic non-cancer risk estimates for inhalation exposures to carbon tetrachloride were derived for occupational scenarios using estimated inhalation average daily concentrations (ADCs). The risk estimates for chronic non-cancer health effects are based on the $BMCL_{10[HEC]}$ for liver effects: 14.3 mg/m^3 for continuous exposures, which is equivalent to 31.1 mg/m^3 for 8 hrs of exposure and 26.4 mg/m^3 for 12 hrs.[21] Non-cancer risk estimates for chronic exposures for each occupational use scenario are presented in Table 4-8 below.

The calculated MOEs are below the benchmark MOE of 30 for the high-end exposures without respirator use for manufacturing and processing as reactant/intermediate, industrial processing aid, additive, import/repackaging and disposal COUs for workers, and for manufacturing and processing COUs for ONUs. The high-end exposures with MOEs below the benchmark MOE have exposure reductions during use of respirator with APF 10 that result in MOEs greater than the benchmark MOE.

[21] Time adjustment from continuous exposure to 5 days per week and to 8 or 12 hrs/day

Table 4-8. Risk Estimates for Chronic Inhalation Exposures based on a POD of 31.1 mg/m^3 - 8 hrs (= 26.4 mg/m^3 - 12 hrs) and Benchmark MOE of 30

Condition of Use	EXPOSURE		Calculated MOE without Respirator		Calculated MOE with Respirator (Worker)*					
	ADC (mg/m^3)				APF = 10		APF = 25		APF = 50	
	High-End	Central Tendency	MOE High-End	MOE Central Tendency	MOE High-End	MOE Central Tendency	MOE High-End	MOE Central Tendency	MOE High-End	MOE Central Tendency
Manufacturing - 8-hr TWA (Workers)	4.0	0.76	**8**	41	80	410	200	1,025	400	2,050
Manufacturing - 8-hr TWA (ONUs)	1.0	0.50	31	62	310	620	775	1,550	1,550	3,100
Manufacturing - 12-hr TWA (Workers)	4.8	0.50	**6**	53	60	530	150	1,325	300	2,650
Manufacturing - 12-hr TWA (ONUs)	1.3	0.66	**20**	40	200	400	500	1,000	1,000	2,000
Import/ Repackaging (Workers)	2.92	0.89	**11**	35	110	350	275	875	550	1,750
Import/ Repackaging (ONUs) [a]	2.92	0.89	**11**	35	110	350	275	875	550	1,750
Processing as Reactant/Intermediate – 8-hr TWA (Worker)	4.0	0.76	**8**	41	80	410	200	1,025	400	2,050
Processing as Reactant/Intermediate – 8-hr TWA (ONUs)	1.0	0.50	31	62	310	620	775	1,550	1,550	3,100
Processing as Reactant/Intermediate – 12-hr TWA (Workers)	4.8	0.50	**6**	53	60	530	150	1,325	300	2,650
Processing as Reactant/Intermediate – 12-hr TWA (ONUs)	1.3	0.66	**20**	40	200	400	500	1,000	1,000	2,000
Industrial Processing Aid (Workers)	2.92	0.89	**11**	35	110	350	275	875	550	1,750

Industrial Processing Aid (ONUs) [a]	2.92	0.89	**11**	35	110	350	275	875	550	1,750
Additive (Workers)	2.92	0.89	**11**	35	110	350	275	875	550	1,750
Additive (ONUs)	2.92	0.89	**11**	35	110	350	275	875	550	1,750
Disposal: Waste Handling (Workers)	2.92	0.89	**11**	35	110	350	275	875	550	1,750
Disposal: Waste Handling (ONUs) [a]	2.92	0.89	**11**	35	110	350	275	875	550	1,750
Specialty Uses-DoD (Workers)	0.22	0.09	141	346	1,040	5,460	2,600	13,650	5,200	27,300
Specialty Uses-DoD (ONUs) [a]	0.22	0.09	141	346	1,040	5,460	2,600	13,650	5,200	27,300
Reactive Ion Etching	Negligible – highly controlled work areas with small quantities applied.									
Laboratory Chemicals	No data – exposure is low as laboratory typically uses small quantities inside a fume hood.									

Bold and highlighted in gray: Calculated MOEs were below the benchmark MOE.

* MOEs with respirator use were calculated by multiplying the MOE without a respirator by the respirator APF. OSHA's occupational safety and health standards for carbon tetrachloride include respiratory protection recommendations starting with APF =10 (any supplied-air respirator) up to APF = 10,000 for emergency or planned entry into unknown concentrations.

[a] In lieu of ONU-specific exposure data, EPA assessed ONU exposures at the worker central tendency.

4.2.4 Risk Estimation for Non-Cancer Effects Following Acute Dermal Exposures

Results from chronic inhalation studies, route-to-route extrapolation and a chronic to acute exposure uncertainty factor were used in conjunction to derive a POD for acute dermal exposures of 250 mg/kg-d (see Section 3.2.5.2.3). Table 4-9 outlines the non-cancer dermal risk estimates to workers with and without the use of gloves for all conditions of use.

Table 4-9. Risk Estimates for Acute Dermal Exposures

Condition of Use	Health Effect, Endpoint and Study	POD (mg/kg-d)	Exposure Level	Acute Retained Dose (mg/kg-d)	Benchmark MOE (= Total UF)	Worker MOE, No Gloves	Worker MOE with Gloves: 5
Manufacture	**Liver** Liver toxicity in chronic inhalation studies	250	High End	1.1	30	227	1,135
Import and repackaging							
Additive							
Processing as a Reactant							
Processing Agent/Aid							
Recycling							
Waste disposal							
Laboratory Chemicals			Central Tendency	0.37	30	676	3,380
Specialty Uses – Department of Defense Data							
Reactive Ion Etching	Negligible – highly controlled work areas with small quantities applied.						

4.2.5 Risk Estimation for Non-Cancer Effects Following Chronic Dermal Exposures

The HED_{Dermal} of 2.50 mg/kg-d for non-occluded exposures was extrapolated from the chronic inhalation $BMCL_{10[HEC]}$: 14.3 mg/m^3 for continuous exposures based on data from Nagano *et al.* (2007a). Table 4-10 outlines the non-cancer dermal risk estimates to workers for endpoints with and without the use of gloves.

Table 4-10. Risk Estimates from Chronic Dermal Exposures

Condition of Use	Health Effect, Endpoint and Study	HED (mg/kg-d)	Exposure Level	Chronic Retained Dose (mg/kg-d)	Benchmark MOE (= Total UF)	Worker MOE, No Gloves	Worker MOE with Gloves:
Manufacture	**Liver** Liver toxicity from chronic inhalation studies	2.50	High End	1.1	30	**2**	40 (PF =20)
Import and repackaging							
Additive							
Processing as a Reactant							
Processing Agent/Aid							
Recycling			Central Tendency	0.37	30	**7**	35 (PF =5)
Waste disposal							
Laboratory Chemicals							
Specialty Uses – Department of Defense Data							
Reactive Ion Etching	Negligible – highly controlled work areas with small quantities applied.						

Bold and highlighted in gray: Calculated MOEs were below the benchmark MOE.

4.2.6 Risk Estimation for Cancer Effects Following Chronic Inhalation Exposures

EPA estimated the added cancer risks and MOEs for liver tumors associated with chronic exposures to carbon tetrachloride in the workplace. The added cancer risk estimation for carbon tetrachloride was calculated by multiplying the occupational scenario-specific estimates (*i.e.*, LADC) for both workers and occupational non-users by EPA's inhalation unit risk (IUR) to estimate the added cancer risk. Added cancer risks were expressed as number of cancer cases per million. MOEs for liver tumors are based on a cancer benchmark MOE of 300 Table 4-11 and

Table 4-12 outline the cancer risk estimates to workers from inhalation exposures for the conditions of use for carbon tetrachloride.

In general terms, the exposure frequency (*i.e.*, the amount of days per year for workers or occupational non-users exposed to carbon tetrachloride) was considered to be 250 days per year and the occupational exposure duration was 40 years over a 70-year lifespan. It is recognized that these exposure assumptions are likely yielding conservative cancer risk estimates, but EPA does not have additional information for further refinement.

Table 4-11. Risk Estimates for Cancer Effects from Chronic Inhalation Exposures for Workers Based on IUR of 6 × 10^{-6} per µg/m^3 and Benchmark Risk = 1 in 10^4

Condition of Use	Chronic, Cancer Exposures		Calculated Cancer Risk without Respirator		Calculated Cancer Risk with Respirator (Worker)*					
	LADC (mg/m^3)				APF =10		APF =25		APF =50	
	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency
Manufacturing - 8-hr TWA (Workers)	0.47	0.07	**3E-03**	**4E-04**	**3E-04**	4E-05	1E-04	2E-05	6E-05	8E-06
Manufacturing - 8-hr TWA (ONUs)	0.12	0.05	**7E-04**	**3E-04**	7E-05	3E-05	3E-05	1E-05	1E-05	6E06
Manufacturing - 12-hr TWA (Workers)	0.85	0.07	**5E-03**	**4E-04**	**5E-04**	4E-05	**2E-04**	2E-05	1E-04	8E-06
Manufacturing - 12-hr TWA (ONUs)	0.15	0.06	**9E-04**	**4E-04**	9E-05	4E-05	4E-05	2E-05	2E-05	8E-06
Import/Repackaging (Workers)	0.34	0.08	**2E-03**	**5E-04**	**2E-04**	5E-05	8E-05	2E-05	4E-05	10E-06
Import/Repackaging (ONUs) [a]	0.34	0.08	**2E-03**	**5E-04**	**2E-04**	5E-05	8E-05	2E-05	4E-05	10E-06
Processing as Reactant/Intermediate – 8-hr TWA (Workers)	0.47	0.07	**3E-03**	**4E-04**	**3E-04**	4E-05	1E-04	2E-05	6E-05	8E-06
Processing as Reactant/Intermediate – 8-hr TWA (ONUs)	0.18	0.07	**1E-03**	**4E-04**	1E-04	4E-05	4E-05	2E-05	2E-05	8E-06
Processing as Reactant/Intermediate – 12-hr TWA (Workers)	0.85	0.07	**5E-03**	**4E-04**	**5E-04**	4E-05	**2E-04**	2E-05	1E-04	8E-06
Processing as Reactant/Intermediate – 12-hr TWA (ONUs)	0.23	0.09	**1E-03**	**5E-04**	1E-04	5E-05	5E-05	2E-05	3E-05	1E-05
Industrial Processing Aid (Workers)	0.34	0.08	**2E-03**	**5E-04**	**2E-04**	5E-05	8E-05	2E-05	4E-05	10E-06

Condition of Use	Chronic, Cancer Exposures LADC (mg/m^3)		Calculated Cancer Risk without Respirator		Calculated Cancer Risk with Respirator (Worker)*					
					APF =10		APF =25		APF =50	
	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency
Industrial Processing Aid (ONUs) [a]	0.34	0.08	**2E-03**	**5E-04**	**2E-04**	5E-05	8E-05	2E-05	4E-05	10E-06
Additive (Workers)	0.34	0.08	**2E-03**	**5E-04**	**2E-04**	5E-05	8E-05	2E-05	4E-05	10E-06
Additive (ONUs) [a]	0.34	0.08	**2E-03**	**5E-04**	**2E-04**	5E-05	8E-05	2E-05	4E-05	10E-06
Disposal: Waste Handling (Workers)	0.34	0.08	**2E-03**	**5E-04**	**2E-04**	5E-05	8E-05	2E-05	4E-05	10E-06
Disposal: Waste Handling (ONUs) [a]	0.34	0.08	**2E-03**	**5E-04**	**2E-04**	5E-05	8E-05	2E-05	4E-05	10E-06
Specialty Uses-DoD (Workers)	0.026	0.008	**2E-04**	5E-05	2E-05	5E-06	8E-06	2E-06	4E-06	1E-06
Specialty Uses-DoD (ONUs)[a]	0.026	0.008	**2E-04**	5E-05	2E-05	5E-06	8E-06	2E-06	4E-06	1E-06
Reactive Ion Etching	Negligible - Highly controlled work areas with small quantities applied									
Laboratory Chemicals	No data – exposure is low as laboratory typically uses small quantities inside a fume hood.									

Bold and highlighted in gray: Calculated extra-cancer risk are greater than the benchmark cancer. Extra cancer risk was calculated as follows: "Central Tendency LADC (µg/m^3)" or "High-end LADC (µg/m^3)" × IUR (*i.e.*, 6×10^{-6} per µg/m^3)

*Cancer risks with respirator use were calculated by dividing the cancer risk without a respirator by the respirator APF.

[a]In lieu of ONU-specific exposure data, EPA assessed ONU exposures at the worker central tendency.

Table 4-12. Risk Estimates for Cancer Effects from Chronic Inhalation Exposures for Workers Based on Liver Cancer POD of 6 mg/m^3 and Benchmark MOE = 300

Condition of Use	Chronic, Cancer Exposures		Calculated Cancer MOE without Respirator		Calculated Cancer MOE with Respirator (Worker)*					
	LADC (mg/m^3)				APF =10		APF =25		APF =50	
	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency
Manufacturing - 8-hr TWA (Workers)	0.47	0.07	**13**	**86**	**130**	860	325	2,150	650	4,300
Manufacturing - 8-hr TWA (ONUs)	0.12	0.05	**50**	**120**	500	1,200	1,250	3,000	2,500	6,000
Manufacturing - 12-hr TWA (Workers)	0.85	0.07	**7**	**86**	**70**	860	**175**	2,150	350	4,300
Manufacturing - 12-hr TWA (ONUs)	0.15	0.06	**40**	**100**	400	1,000	1,000	2,500	2,000	5,000
Import/Repackaging (Workers)	0.34	0.08	**18**	**75**	**180**	750	450	1,875	900	3,750
Import/Repackaging (ONUs) [a]	0.34	0.08	**18**	**75**	**180**	750	450	1,875	900	3,750
Processing as Reactant/Intermediate – 8-hr TWA (Workers)	0.47	0.07	**13**	**86**	**130**	860	325	2,150	650	4,300
Processing as Reactant/Intermediate – 8-hr TWA (ONUs)	0.18	0.07	**33**	**86**	330	860	825	2,150	1,650	4,300
Processing as Reactant/Intermediate – 12-hr TWA (Workers)	0.85	0.07	**7**	**86**	**70**	860	**175**	2,150	350	4,300
Processing as Reactant/Intermediate – 12-hr TWA (ONUs)	0.23	0.09	**26**	**67**	**260**	670	650	1,675	1,300	3,350
Industrial Processing Aid (Workers)	0.34	0.08	**18**	**75**	**180**	750	450	1,875	900	3,750

Condition of Use	Chronic, Cancer Exposures LADC (mg/m^3)		Calculated Cancer MOE without Respirator		Calculated Cancer MOE with Respirator (Worker)*					
					APF =10		APF =25		APF =50	
	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency
Industrial Processing Aid (ONUs) [a]	0.34	0.08	**18**	**75**	**180**	750	450	1,875	900	3,750
Additive (Workers)	0.34	0.08	**18**	**75**	**180**	750	450	1,875	900	3,750
Additive (ONUs) [a]	0.34	0.08	**18**	**75**	**180**	750	450	1,875	900	3,750
Disposal: Waste Handling (Workers)	0.34	0.08	**18**	**75**	**180**	750	450	1,875	900	3,750
Disposal: Waste Handling (ONUs) [a]	0.34	0.08	**18**	**75**	**180**	750	450	1,875	900	3,750
Specialty Uses-DoD (Workers)	0.026	0.008	**231**	750	2,310	7,500	5,775	18,750	11,550	37,500
Specialty Uses-DoD (ONUs)[a]	0.026	0.008	**231**	750	2,310	7,500	5,775	18,750	11,550	37,500
Reactive Ion Etching	Negligible - Highly controlled work areas with small quantities applied									
Laboratory Chemicals	No data – exposure is low as laboratory typically uses small quantities inside a fume hood.									

Bold and highlighted in gray: Calculated MOEs are below the benchmark MOE. MOE was calculated as follows: Cancer POD ÷ "Central Tendency LADC (mg/m^3)" or "High-end LADC (mg/m^3)"

* MOEs with respirator use were calculated by multiplying the MOE without a respirator by the respirator APF.

[a] In lieu of ONU-specific exposure data, EPA assessed ONU exposures at the worker central tendency.

Figure 4-1 through Figure 4-4 present the incremental individual lifetime cancer risks for the 95th percentile/high-end and 50th percentile/central tendency exposures to carbon tetrachloride occurring in occupational exposure scenarios. The figures consist of graphical representations of the cancer risks presented in Table 4-11 by COU.

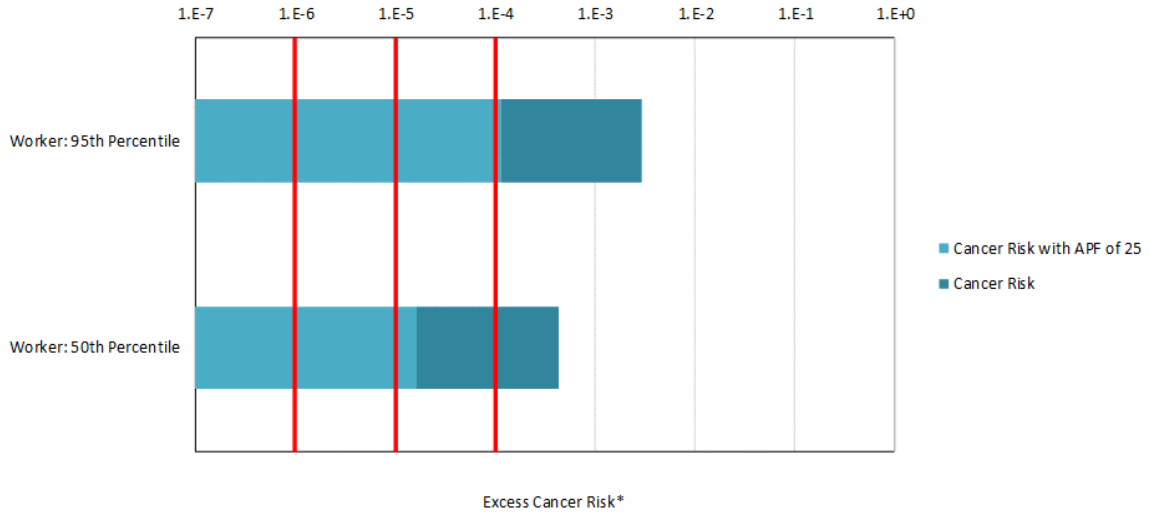


Figure 4-1. Cancer Risk Estimates for Occupational Use (*i.e.*, Workers) of Carbon Tetrachloride in Manufacturing and Processing as Reactant/Intermediate Based on Monitoring Data 8 hr TWA

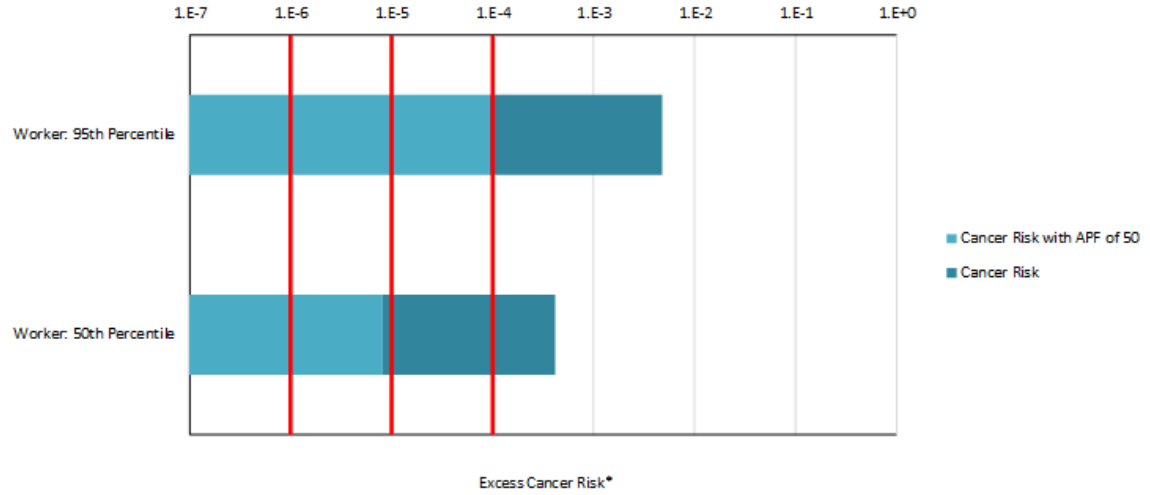


Figure 4-2. Cancer Risk Estimates for Occupational Use (*i.e.*, Workers) of Carbon Tetrachloride in Manufacturing and Processing as Reactant/Intermediate Based on Monitoring Data 12 hr TWA

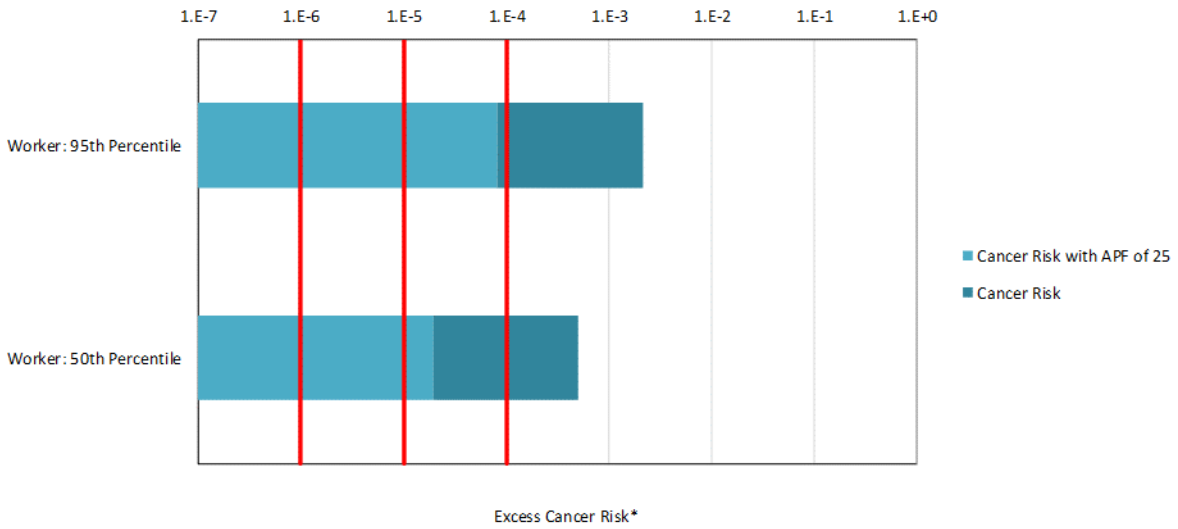


Figure 4-3. Cancer Risk Estimates for Occupational Use (*i.e.*, Workers) of Carbon Tetrachloride in Import, Processing Agent, Additive and Disposal/Recycling Based on Surrogate Modeling Data

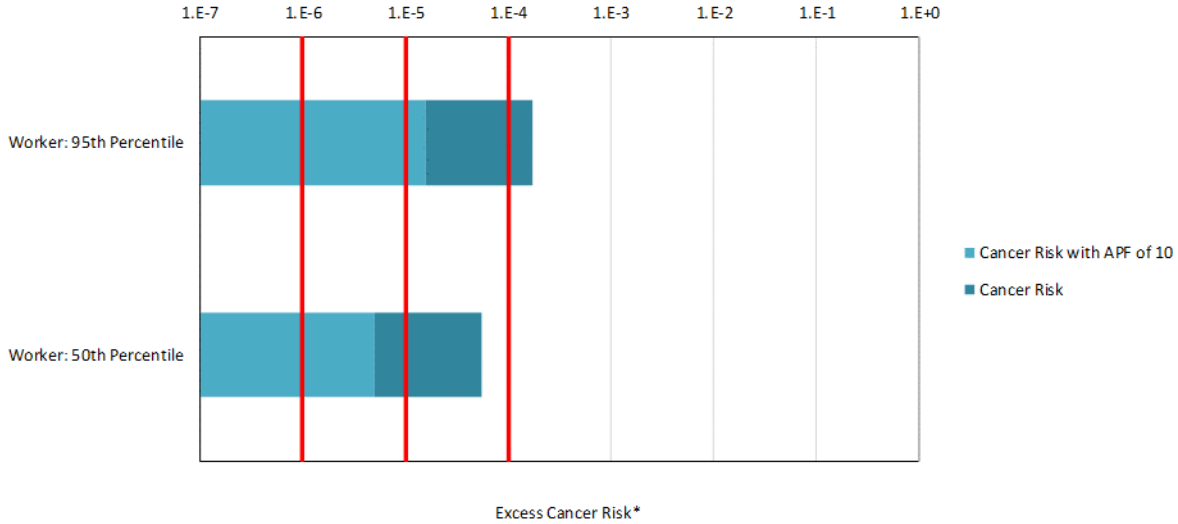


Figure 4-4. Cancer Risk Estimates for Occupational Use (*i.e.*, Workers) of Carbon Tetrachloride in Specialty Uses-DoD Based on Monitoring Data

4.2.7 Risk Estimations for Cancer Effects Following Chronic Dermal Exposures

EPA estimated the added cancer risks and MOEs for liver tumors associated with chronic dermal exposures to carbon tetrachloride in the workplace. The added cancer risk estimation for carbon tetrachloride was calculated by multiplying the occupational scenario-specific dermal exposure estimates for workers by the derived CSF_{Dermal} to estimate the added cancer risk. The CSF_{Dermal} was extrapolated from the EPA's inhalation unit risk (IUR) of 6×10^{-6} per $\mu g/m^3$ for continuous lifetime exposure resulting in a derived CSF_{Dermal} of 8×10^{-2} per mg/kg for non-occluded exposures (see Section 0). The estimated MOEs for liver tumors are based on a benchmark MOE

of 300 Table 4-13 and Table 4-14 outline the cancer dermal risk estimates to workers for endpoints with and without gloves.

Table 4-13. Risk Estimates for Cancer Effects from Chronic Dermal Exposures for Workers; Benchmark Risk = 1 in 10^4

Conditions of Use	Exposure Level	No Gloves	Gloves:
Manufacture	High End	**3E-2**	**1E-03 (PF =20)**
Import and repackaging			
Additive			
Processing as a Reactant			
Processing Agent/Aid			
Recycling			
Waste disposal			
Laboratory Chemicals			
Specialty Uses – Department of Defense Data			
Manufacture	Central Tendency	**8E-3**	**4E-04 (PF =20)**
Import and repackaging			
Additive			
Processing as a Reactant			
Processing Agent/Aid			
Recycling			
Waste disposal			
Laboratory Chemicals			
Specialty Uses – Department of Defense Data			
Reactive Ion Etching	Negligible - Highly controlled work areas with small quantities applied		

Bold and highlighted in gray: Calculated extra-cancer risk are greater than the benchmark cancer.

Table 4-14. Risk Estimates for Cancer Effects from Chronic Dermal Exposures for Workers Based on Liver Cancer POD and Benchmark MOE = 300

Conditions of Use	Exposure Level	No Gloves	Gloves:
Manufacture	High End (0.39 mg/kg-d)	**3.6**	**72 (PF =20)**
Import and repackaging			
Additive			
Processing as a Reactant			
Processing Agent/Aid			
Recycling			
Waste disposal			
Laboratory Chemicals			
Specialty Uses – Department of Defense Data			
Manufacture	Central Tendency (0.10 mg/kg-d)	**14**	**280 (PF =20)**
Import and repackaging			
Additive			
Processing as a Reactant			
Processing Agent/Aid			

Conditions of Use	Exposure Level	No Gloves	Gloves:
Recycling			
Waste disposal			
Laboratory Chemicals			
Specialty Uses – Department of Defense Data			
Reactive Ion Etching	Negligible - Highly controlled work areas with small quantities applied		

Bold and highlighted in gray: Calculated MOEs are below the benchmark MOE

4.2.8 Summary of Non-cancer and Cancer Estimates for Inhalation and Dermal Exposures

Table 4-15 presents a summary of the MOEs and estimated cancer risks for the inhalation and dermal exposures from the COUs for carbon tetrachloride.

Table 4-15. Summary of Estimated Non-cancer and Cancer Risks from Inhalation and Dermal Exposures[1]

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4	Occupational Exposure Scenario/ Category in Current Engineering Assessment (Table 2-6)	Exposure Type and Population	Exposure Levels	Risk estimates for No-PPE			Risk estimates with PPE (Workers Only)**		
						Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation /dermal benchmark MOE = 30)	Cancer Risk (CR) or Cancer MOE (cancer risk benchmark 1 in 10^4; benchmark MOE = 300)	Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation/dermal benchmark MOE = 30)	Cancer Risk (CR) of 1 in 10^4; Cancer Benchmark MOE = 300
Manufacturing	Domestic Manufacture	Domestic Manufacture	Domestic Manufacturing (Section 2.4.1.7.1)	8-hr TWA (Workers)	Central Tendency	474	41	**CR = 4E-04 MOE = 86**	N/A	N/A	CR = 4E-05 (APF =10); MOE = 860 (APF =10)
					High -End	90	**8**	**CR = 3E-03 MOE = 13**	N/A	80 (APF =10)	CR = 1E-04 (APF =25); MOE = 325 (APF = 25)
				12-hr TWA (Workers)	Central Tendency	620	53	**CR = 4E-04 MOE = 86**	N/A	N/A	CR = 4E-05 (APF =10); MOE = 860 (APF = 10)
					High -End	65	**6**	**CR = 5E-03 MOE = 7**	N/A	60 (APF = 10)	CR = 1E-04 (APF = 50); MOE = 350 (APF = 50)
				8-hr TWA (ONUs)	Central Tendency	720	62	**CR = 3E-04 MOE = 120**	N/A	N/A	N/A
					High -End	360	31	**CR = 7E-04 MOE = 50**	N/A	N/A	N/A
				12 hr TWA (ONUs)	Central Tendency	470	40	**CR = 4E-04 MOE = 100**	N/A	N/A	N/A
					High -End	238	**20**	**CR = 9E-04 MOE = 40**	N/A	N/A	N/A

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4	Occupational Exposure Scenario/ Category in Current Engineering Assessment (Table 2-6)	Exposure Type and Population	Exposure Levels	Risk estimates for No-PPE			Risk estimates with PPE (Workers Only)**		
						Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation /dermal benchmark MOE = 30)	Cancer Risk (CR) or Cancer MOE (cancer risk benchmark 1 in 10^4; benchmark MOE = 300)	Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation/dermal benchmark MOE = 30)	Cancer Risk (CR) of 1 in 10^4; Cancer Benchmark MOE = 300
				Dermal (Workers)	Central Tendency	676	**7**	**CR = 8E-03 MOE =14**	N/A	35 (PF = 5)	**CR = 4E-04 (PF = 20); MOE =280 (PF = 20)**
					High -End	227	**2**	**CR = 3E-02 MOE = 3.6**	N/A	40 (PF = 20)	**CR = 1E-03 (PF =20); MOE = 72 (PF = 20)**
	Import	Import	Import and Repackaging (Section 2.4.1.7.2)	8 hr TWA (Workers)	Central Tendency	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	CR = 5E-05 (APF =10); MOE = 750 (APF = 10)
					High -End	123	**11**	**CR = 2E-03 MOE = 18**	N/A	110 (APF =10)	CR = 8E-05 (APF =25); MOE = 450 (APF = 25)
				8 hr TWA (ONUs)	Central Tendency[a]	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	N/A
					High - End[a]	123	**11**	**CR = 2E-03 MOE = 18**	N/A	N/A	N/A
				Dermal (Workers)	Central Tendency	676	**7**	**CR = 8E-03 MOE =14**	N/A	35 (PF = 5)	**CR = 4E-04 (PF = 20); MOE =280 (PF = 20)**
					High -End	227	**2**	**CR = 3E-02 MOE = 3.6**	N/A	40 (PF = 20)	**CR = 1E-03 (PF =20); MOE = 72 (PF = 20)**

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4	Occupational Exposure Scenario/ Category in Current Engineering Assessment (Table 2-6)	Exposure Type and Population	Exposure Levels	Risk estimates for No-PPE			Risk estimates with PPE (Workers Only)**		
						Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation /dermal benchmark MOE = 30)	Cancer Risk (CR) or Cancer MOE (cancer risk benchmark 1 in 10^4; benchmark MOE = 300)	Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation/dermal benchmark MOE = 30)	Cancer Risk (CR) of 1 in 10^4; Cancer Benchmark MOE = 300
Processing	Processing as a reactant/ intermediate	Hydrochlorofluorocarbons (HCFCs), Hydrofluorocarbon (HFCs) and Hydrofluoroolefin (HFOs) Perchloroeth-ylene (PCE)	Processing as Reactant/ Intermediate* (Section 2.4.1.7.3)	8-hr TWA (Workers)	Central Tendency	474	41	**CR = 4E-04 MOE = 86**	N/A	N/A	CR = 4E-05 (APF =10); MOE = 860 (APF = 10)
					High -End	90	**8**	**CR = 3E-03 MOE = 13**	N/A	80 (APF =10)	CR = 1E-04 (APF =25); MOE = 325 (APF = 25)
				12-hr TWA (Workers)	Central Tendency	620	53	**CR = 4E-04 MOE = 86**	N/A	N/A	CR = 4E-05 (APF =10); MOE = 860 (APF = 10)
					High -End	65	**6**	**CR = 5E-03 MOE = 7**	N/A	60 (APF = 10)	CR = 1E-04 (APF =50); MOE = 350 (APF = 50)
				8-hr TWA (ONUs)	Central Tendency	720	62	**CR = 4E-04 MOE = 86**	N/A	N/A	N/A
					High -End	360	31	**CR = 1E-03 MOE = 33**	N/A	N/A	N/A
				12 hr TWA (ONUs)	Central Tendency	470	40	**CR = 5E-04 MOE = 67**	N/A	N/A	N/A
					High -End	238	**20**	**CR = 1E-03 MOE = 26**	N/A	N/A	N/A
				Dermal (Workers)	Central Tendency	676	**7**	**CR = 8E-03 MOE =14**	N/A	35 (PF = 5)	**CR = 4E-04 (PF = 20); MOE =280 (PF = 20)**
					High -End	227	**2**	**CR = 3E-02 MOE = 3.6**	N/A	40 (PF = 20)	**CR = 1E-03 (PF =20); MOE = 72**

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4	Occupational Exposure Scenario/ Category in Current Engineering Assessment (Table 2-6)	Exposure Type and Population	Exposure Levels	Risk estimates for No-PPE			Risk estimates with PPE (Workers Only)**		
						Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation /dermal benchmark MOE = 30)	Cancer Risk (CR) or Cancer MOE (cancer risk benchmark 1 in 10^4; benchmark MOE = 300)	Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation/dermal benchmark MOE = 30)	Cancer Risk (CR) of 1 in 10^4; Cancer Benchmark MOE = 300
											(PF = 20)
		Reactive ion etching (*i.e.*, semi-conductor manufacturing)	Reactive ion etching (*i.e.*, semi-conductor manufacturing) (Section 2.4.1.7.5)	Negligible - Highly controlled work areas with small quantities applied							
	Incorporation into Formulation, Mixture or Reaction Products	Petrochemicals -derived manufacturing; Agricultural products manufacturing; Other basic organic and inorganic chemical manufacturing.	Processing as Reactant/ Intermediate (Section 2.4.1.7.3)	8-hr TWA (Workers)	Central Tendency	474	41	**CR = 4E-04 MOE = 86**	N/A	N/A	CR = 4E-05 (APF =10); MOE = 860 (APF = 10)
					High -End	90	**8**	**CR = 3E-03 MOE = 13**	N/A	80 (APF =10)	CR = 1E-04 (APF =25); MOE = 325 (APF = 25)
				12-hr TWA (Workers)	Central Tendency	620	53	**CR = 4E-04 MOE = 86**	N/A	N/A	CR = 4E-05 (APF =10); MOE = 860 (APF = 10)
					High -End	65	**6**	**CR = 5E-03 MOE = 7**	N/A	60 (APF = 10)	CR = 1E-04 (APF =50); MOE = 350 (APF = 50)
				8-hr-TWA (ONUs)	Central Tendency	720	62	**CR = 4E-04 MOE = 86**	N/A	N/A	N/A
					High -End	360	31	**CR = 1E-03 MOE = 33**	N/A	N/A	N/A
				12 hr- TWA (ONUs)	Central Tendency	470	40	**CR = 5E-04 MOE = 67**	N/A	N/A	N/A
					High -End	238	**20**	**CR = 1E-03**	N/A	N/A	N/A

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4	Occupational Exposure Scenario/ Category in Current Engineering Assessment (Table 2-6)	Exposure Type and Population	Exposure Levels	Risk estimates for No-PPE			Risk estimates with PPE (Workers Only)**		
						Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation /dermal benchmark MOE = 30)	Cancer Risk (CR) or Cancer MOE (cancer risk benchmark 1 in 10^4; benchmark MOE = 300)	Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation/dermal benchmark MOE = 30)	Cancer Risk (CR) of 1 in 10^4; Cancer Benchmark MOE = 300
								MOE = 26			
				Dermal (Workers)	Central Tendency	676	**7**	**CR = 8E-03 MOE =14**	N/A	35 (PF = 5)	**CR = 4E-04 (PF = 20); MOE =280 (PF = 20)**
					High -End	227	**2**	**CR = 3E-02 MOE = 3.6**	N/A	40 (PF = 20)	**CR = 1E-03 (PF =20); MOE = 72 (PF = 20)**
			Industrial Processing Agent/Aid (Section 2.4.1.7.6)	8 hr TWA (Workers)	Central Tendency	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	CR = 5E-05 (APF =10); MOE = 750 (APF = 10)
					High -End	123	**11**	**CR = 2E-03 MOE = 18**	N/A	110 (APF =10)	CR = 8E-05 (APF =25); MOE = 450 (APF = 25)
				8 hr TWA (ONUs)	Central Tendency[a]	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	N/A
					High -End[a]	123	**11**	**CR = 2E-03 MOE = 18**	N/A	N/A	N/A
				Dermal (Workers)	Central Tendency	676	**7**	**CR = 8E-03 MOE =14**	N/A	35 (PF = 5)	**CR = 4E-04 (PF = 20); MOE =280 (PF = 20)**
					High -End	227	**2**	**CR = 3E-02 MOE = 3.6**	N/A	40 (PF = 20)	**CR = 1E-03 (PF =20); MOE = 72 (PF = 20)**
			Additive	8 hr TWA (Workers)	Central Tendency	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	CR = 5E-05 (APF =10);

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4	Occupational Exposure Scenario/ Category in Current Engineering Assessment (Table 2-6)	Exposure Type and Population	Exposure Levels	Risk estimates for No-PPE			Risk estimates with PPE (Workers Only)**		
						Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation /dermal benchmark MOE = 30)	Cancer Risk (CR) or Cancer MOE (cancer risk benchmark 1 in 10^4; benchmark MOE = 300)	Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation/dermal benchmark MOE = 30)	Cancer Risk (CR) of 1 in 10^4; Cancer Benchmark MOE = 300
			(Section 2.4.1.7.7)								MOE = 750 (APF = 10)
					High -End	123	**11**	**CR = 2E-03 MOE = 18**	N/A	110 (APF =10)	CR = 8E-05 (APF =25); MOE = 450 (APF = 25)
				8 hr TWA (ONUs)	Central Tendency[a]	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	N/A
					High - End[a]	123	**11**	**CR = 2E-03 MOE = 18**	N/A	N/A	N/A
				Dermal (Workers)	Central Tendency	676	**7**	**CR = 8E-03 MOE =14**	N/A	35 (PF = 5)	**CR = 4E-04 (PF = 20); MOE =280 (PF = 20)**
					High -End	227	**2**	**CR = 3E-02 MOE = 3.6**	N/A	40 (PF = 20)	**CR = 1E-03 (PF =20); MOE = 72 (PF = 20)**
	Processing - Repackaging	Laboratory Chemicals	Import and Repackaging (Section 2.4.1.7.2)	8 hr TWA (Workers)	Central Tendency	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	CR = 5E-05 (APF =10); MOE = 750 (APF = 10)
					High -End	123	**11**	**CR = 2E-03 MOE = 18**	N/A	110 (APF =10)	CR = 8E-05 (APF =25); MOE = 450 (APF = 25)
				8 hr TWA (ONUs)	Central Tendency[a]	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	N/A
					High - End[a]	123	**11**	**CR = 2E-03 MOE = 18**	N/A	N/A	N/A

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4	Occupational Exposure Scenario/ Category in Current Engineering Assessment (Table 2-6)	Exposure Type and Population	Exposure Levels	Risk estimates for No-PPE			Risk estimates with PPE (Workers Only)**		
						Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation /dermal benchmark MOE = 30)	Cancer Risk (CR) or Cancer MOE (cancer risk benchmark 1 in 10^4; benchmark MOE = 300)	Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation/dermal benchmark MOE = 30)	Cancer Risk (CR) of 1 in 10^4; Cancer Benchmark MOE = 300
				Dermal (Workers)	Central Tendency	676	**7**	**CR = 8E-03 MOE =14**	N/A	35 (PF = 5)	**CR = 4E-04 (PF = 20); MOE =280 (PF = 20)**
					High -End	227	**2**	**CR = 3E-02 MOE = 3.6**	N/A	40 (PF = 20)	**CR = 1E-03 (PF =20); MOE = 72 (PF = 20)**
	Recycling	Recycling	Disposal/ Recycling (Section 2.4.1.7.9)	8 hr TWA (Workers)	Central Tendency	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	CR = 5E-05 (APF =10); MOE = 750 (APF = 10)
					High -End	123	**11**	**CR = 2E-03 MOE = 18**	N/A	110 (APF =10)	CR = 8E-05 (APF =25); MOE = 450 (APF = 25)
				8 hr TWA (ONUs)	Central Tendency[a]	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	N/A
					High - End[a]	123	**11**	**CR = 2E-03 MOE = 18**	N/A	N/A	N/A
				Dermal (Workers)	Central Tendency	676	**7**	**CR = 8E-03 MOE =14**	N/A	35 (PF = 5)	**CR = 4E-04 (PF = 20); MOE =280 (PF = 20)**
					High -End	227	**2**	**CR = 3E-02 MOE = 3.6**	N/A	40 (PF = 20)	**CR = 1E-03 (PF =20); MOE = 72 (PF = 20)**
Distribution in commerce	Distribution	Distribution in Commerce	Activities related to distribution (*e.g.*, loading, unloading)	Activities related to distribution (*e.g.*, loading, unloading) are considered throughout the life cycle, rather than using a single distribution scenario							

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4	Occupational Exposure Scenario/ Category in Current Engineering Assessment (Table 2-6)	Exposure Type and Population	Exposure Levels	Risk estimates for No-PPE			Risk estimates with PPE (Workers Only)**		
						Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation /dermal benchmark MOE = 30)	Cancer Risk (CR) or Cancer MOE (cancer risk benchmark 1 in 10^4; benchmark MOE = 300)	Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation/dermal benchmark MOE = 30)	Cancer Risk (CR) of 1 in 10^4; Cancer Benchmark MOE = 300
Industrial/commercial use	Petrochemicals-derived products and agricultural products manufacturing	Processing Aid	Industrial Processing Agent/ Aid (Section 2.4.1.7.6)	8 hr TWA (Workers)	Central Tendency	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	CR = 5E-05 (APF =10); MOE = 750 (APF = 10)
					High -End	123	**11**	**CR = 2E-03 MOE = 18**	N/A	110 (APF =10)	CR = 8E-05 (APF =25); MOE = 450 (APF = 25)
				8 hr TWA (ONUs)	Central Tendency[a]	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	N/A
					High - End[a]	123	**11**	**CR = 2E-03 MOE = 18**	N/A	N/A	N/A
				Dermal (Workers)	Central Tendency	676	**7**	**CR = 8E-03 MOE =14**	N/A	35 (PF = 5)	**CR = 4E-04 (PF = 20); MOE =280 (PF = 20)**
					High -End	227	**2**	**CR = 3E-02 MOE = 3.6**	N/A	40 (PF = 20)	**CR = 1E-03 (PF =20); MOE = 72 (PF = 20)**
		Additive	Additive (Section 2.4.1.7.72.4.1.7.7)	8 hr TWA (Workers)	Central Tendency	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	CR = 5E-05 (APF =10); MOE = 750 (APF = 10)
					High -End	123	**11**	**CR = 2E-03 MOE = 18**	N/A	110 (APF =10)	CR = 8E-05 (APF =25); MOE = 450 (APF = 25)
				8 hr TWA (ONUs)	Central Tendency[a]	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	N/A

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4	Occupational Exposure Scenario/ Category in Current Engineering Assessment (Table 2-6)	Exposure Type and Population	Exposure Levels	Risk estimates for No-PPE			Risk estimates with PPE (Workers Only)**		
						Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation /dermal benchmark MOE = 30)	Cancer Risk (CR) or Cancer MOE (cancer risk benchmark 1 in 10^4; benchmark MOE = 300)	Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation/dermal benchmark MOE = 30)	Cancer Risk (CR) of 1 in 10^4; Cancer Benchmark MOE = 300
					High - End[a]	123	**11**	**CR = 2E-03 MOE = 18**	N/A	N/A	N/A
				Dermal (Workers)	Central Tendency	676	**7**	**CR = 8E-03 MOE =14**	N/A	35 (PF = 5)	**CR = 4E-04 (PF = 20); MOE =280 (PF = 20)**
					High -End	227	**2**	**CR = 3E-02 MOE = 3.6**	N/A	40 (PF = 20)	**CR = 1E-03 (PF =20); MOE = 72 (PF = 20)**
	Other Basic Organic and Inorganic Chemical Manufacturing	Manufacturing of chlorinated compounds used in solvents for cleaning and degreasing Manufacturing of chlorinated compounds used in adhesives and sealants Manufacturing if chlorinated compounds used in paints and coatings Manufacturing of other chlorinated compounds (*i.e.*,	Processing as a Reactant or Intermediate (Section 2.4.1.7.3)	8-hr TWA (Workers)	Central Tendency	474	41	**CR = 4E-04 MOE = 86**	N/A	N/A	CR = 4E-05 (APF =10); MOE = 860 (APF = 10)
					High -End	90	**8**	**CR = 3E-03 MOE = 13**	N/A	80 (APF =10)	CR = 1E-04 (APF =25); MOE = 325 (APF = 25)
				12-hr TWA (Workers)	Central Tendency	620	53	**CR = 4E-04 MOE = 86**	N/A	N/A	CR = 4E-05 (APF =10); MOE = 860 (APF = 10)
					High -End	65	**6**	**CR = 5E-03 MOE = 7**	N/A	60 (APF = 10)	CR = 1E-04 (APF =50); MOE = 350 (APF = 50)
				8-hr-TWA (ONUs)	Central Tendency	720	62	**CR = 4E-04 MOE = 86**	N/A	N/A	N/A
					High -End	360	31	**CR = 1E-03 MOE = 33**	N/A	N/A	N/A

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4	Occupational Exposure Scenario/ Category in Current Engineering Assessment (Table 2-6)	Exposure Type and Population	Exposure Levels	Risk estimates for No-PPE			Risk estimates with PPE (Workers Only)**		
						Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation /dermal benchmark MOE = 30)	Cancer Risk (CR) or Cancer MOE (cancer risk benchmark 1 in 10^4; benchmark MOE = 300)	Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation/dermal benchmark MOE = 30)	Cancer Risk (CR) of 1 in 10^4; Cancer Benchmark MOE = 300
		elimination of nitrogen trichloride in the production of chlorine and caustic) Manufacturing of chlorinated compounds used in asphalt		12 hr- TWA (ONUs)	Central Tendency	470	40	**CR = 5E-04 MOE = 67**	N/A	N/A	N/A
					High -End	238	**20**	**CR = 1E-03 MOE = 26**	N/A	N/A	N/A
				Dermal (Workers)	Central Tendency	676	**7**	**CR = 8E-03 MOE =14**	N/A	35 (PF = 5)	**CR = 4E-04 (PF = 20); MOE =280 (PF = 20)**
					High -End	227	**2**	**CR = 3E-02 MOE = 3.6**	N/A	40 (PF = 20)	**CR = 1E-03 (PF =20); MOE = 72 (PF = 20)**
	Other uses	Processing aid (*i.e.*, metal recovery)	Industrial Processing Agent/Aid (Section 2.4.1.7.6)	8 hr TWA (Workers)	Central Tendency	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	CR = 5E-05 (APF =10); MOE = 750 (APF = 10)
					High -End	123	**11**	**CR = 2E-03 MOE = 18**	N/A	110 (APF =10)	CR = 8E-05 (APF =25); MOE = 450 (APF = 25)
				8 hr TWA (ONUs)	Central Tendency[a]	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	N/A
					High - End[a]	123	**11**	**CR = 2E-03 MOE = 18**	N/A	N/A	N/A
				Dermal (Workers)	Central Tendency	676	**7**	**CR = 8E-03 MOE =14**	N/A	35 (PF = 5)	**CR = 4E-04 (PF = 20); MOE =280 (PF = 20)**
					High -End	227	**2**	**CR = 3E-02**	N/A	40	**CR = 1E-03**

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4	Occupational Exposure Scenario/ Category in Current Engineering Assessment (Table 2-6)	Exposure Type and Population	Exposure Levels	Risk estimates for No-PPE			Risk estimates with PPE (Workers Only)**		
						Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation /dermal benchmark MOE = 30)	Cancer Risk (CR) or Cancer MOE (cancer risk benchmark 1 in 10^4; benchmark MOE = 300)	Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation/dermal benchmark MOE = 30)	Cancer Risk (CR) of 1 in 10^4; Cancer Benchmark MOE = 300
								MOE = 3.6		(PF = 20)	**(PF =20); MOE = 72 (PF = 20)**
		Specialty uses (*i.e.*, DoD uses)	Specialty Uses-DoD Data (Section 2.4.1.7.4)	8 hr TWA (Workers)	Central Tendency	2,000	346	CR = 5E-05 MOE = 750	N/A	N/A	N/A
					High -End	973	141	**CR = 2E-04 MOE = 231**	N/A	N/A	CR = 2E-05 (APF =10); MOE = 2,310 (APF = 10)
				8 hr TWA (ONUs)	Central Tendency[a]	2,000	346	CR = 5E-05 MOE = 750	N/A	N/A	N/A
					High -End[a]	973	141	**CR = 2E-04 MOE = 231**	N/A	N/A	N/A
				Dermal (Workers)	Central Tendency	676	**7**	**CR = 8E-03 MOE =14**	N/A	35 (PF = 5)	**CR = 4E-04 (PF = 20); MOE =280 (PF = 20)**
					High -End	227	**2**	**CR = 3E-02 MOE = 3.6**	N/A	40 (PF = 20)	**CR = 1E-03 (PF =20); MOE = 72 (PF = 20)**
	Laboratory chemicals	Laboratory Chemicals	Laboratory Chemicals (Section 2.4.1.7.8)	Dermal (Workers)	Central Tendency	676	**7**	**CR = 8E-03 MOE =14**	N/A	35 (PF = 5)	**CR = 4E-04 (PF = 20); MOE =280 (PF = 20)**
					High -End	227	**2**	**CR = 3E-02 MOE = 3.6**	N/A	40 (PF = 20)	**CR = 1E-03 (PF =20); MOE = 72 (PF = 20)**
Disposal	Disposal	Industrial pre-treatment	Disposal/ Recycling	8 hr TWA (Workers)	Central Tendency	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	CR = 5E-05 (APF =10);

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4	Occupational Exposure Scenario/ Category in Current Engineering Assessment (Table 2-6)	Exposure Type and Population	Exposure Levels	Risk estimates for No-PPE			Risk estimates with PPE (Workers Only)**		
						Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation /dermal benchmark MOE = 30)	Cancer Risk (CR) or Cancer MOE (cancer risk benchmark 1 in 10^4; benchmark MOE = 300)	Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE = 30)	Chronic Non-cancer (inhalation/dermal benchmark MOE = 30)	Cancer Risk (CR) of 1 in 10^4; Cancer Benchmark MOE = 300
		Industrial wastewater treatment	(Section 2.4.1.7.9)								MOE = 750 (APF = 10)
		Publicly owned treatment works (POTW)			High -End	123	**11**	**CR = 2E-03 MOE = 18**	N/A	110 (APF =10)	CR = 8E-05 (APF =25); MOE = 450 (APF = 25)
		Underground injection		8 hr TWA (ONUs)	Central Tendency[a]	404	35	**CR = 5E-04 MOE = 75**	N/A	N/A	N/A
		Municipal landfill									
		Hazardous landfill			High - End[a]	123	**11**	**CR = 2E-03 MOE = 18**	N/A	N/A	N/A
		Other land disposal		Dermal (Workers)	Central Tendency	676	**7**	**CR = 8E-03 MOE =14**	N/A	35 (PF = 5)	**CR = 4E-04 (PF = 20); MOE =280 (PF = 20)**
		Municipal waste incinerator									
		Hazardous waste incinerator			High -End	227	**2**	**CR = 3E-02 MOE = 3.6**	N/A	40 (PF = 20)	**CR = 1E-03 (PF =20); MOE = 72 (PF = 20)**
		Off-site waste transfer									

Bold and highlighted in gray: Calculated MOEs are below the benchmark MOE or cancer risk is greater than benchmark cancer risk.
[1]This table presents a summary of the risks for inhalation and dermal exposures by combining the risk findings for the COUs listed in Table 4-7 to Table 4-14 and the associated lifecycle stages as listed in Table 1-4 and Figure 1-1.
*Incorporation into Reaction, Mixture and Reaction Products was regrouped and accessed under Industrial Processing Agent/Aid and Processing as a Reactant or Intermediate (see Section 1.4.1, Table 1-4 and Section 2.4.1.6).
**Risk estimates were calculated for the respirator with the lowest APF that reduces exposure to levels with MOEs greater than benchmark MOE or cancer risk lower than benchmark cancer risk.
[a]In lieu of ONU-specific exposure data, EPA assessed ONU exposures at the worker central tendency.

4.3 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 exposure assessment for carbon tetrachloride, EPA analyzed reasonably available information to identify groups that may have greater exposure or susceptibility than the general population to the hazard posed by carbon tetrachloride. Exposures of carbon tetrachloride could be higher amongst workers and ONUs who use or are exposed to carbon tetrachloride as part of typical processes.

The scope of this human health assessment is limited to workers and ONUs. Thus, this Section focuses on identifying subpopulations within workers and ONUs who may have greater susceptibility to carbon tetrachloride. Assessment of susceptible subpopulations does not include children or non-workers/non-ONUs.

Some workers and ONUs may be more biologically susceptible to the effects of carbon tetrachloride due to age, alcohol consumption, nutritional status, pre-existing disease (*e.g.*, diabetes or liver disease), exposure to other chemicals, and genetic variation (described in more detail in Section 3.2.5.4).

Metabolism of carbon tetrachloride to reactive metabolites by cytochrome P450 enzymes (particularly CYP2E1 and CYP3A) is hypothesized to be a key event in the toxicity of this compound. Therefore, heterogeneity in the human population distribution of microsomal enzymes metabolizing carbon tetrachloride has influence in the susceptibility to carbon tetrachloride toxicity. Reasonably available quantitative information on the variation in human hepatic levels of the main metabolic enzyme, CYP2E1, demonstrates considerable intrahuman variability. For example, (Lipscomb et al., 1997) reported a seven-fold range in activity of CYP2E1 among hepatic microsomal samples from 23 subjects. Snawder and Lipscomb (Snawder and Lipscomb, 2000) demonstrated 12-fold differences in CYP2E1 protein content between the highest and lowest samples from 40 samples of microsomes from adult human liver donors. Consideration of this PESS quantitative information is incorporated in the uncertainty factors used for risk characterization.

In addition to differences in the metabolism due to alcohol consumption (see below and Section 3.2.5.2 for quantitative information on toxic effects from alcohol usage), exposure to other chemicals, age, nutritional status, genetic variability in CYP expression, or impaired liver function due to liver disease can increase susceptibility to carbon tetrachloride (U.S. EPA, 2010). For example, alcohol is known to induce CYP2E1 expression. Cases of acute toxicity from occupational exposures indicate that heavy drinkers are more susceptible to carbon tetrachloride

and this observation has been verified in numerous animal studies. Exposure to other chemicals that induce P450 enzymes, including isopropanol, methanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, 2-butanone, phenobarbital, methamphetamine, nicotine, trichloroethylene, polychlorinated and polybrominated biphenyls, DDT, mirex, and chlordecone have also been shown to potentiate carbon tetrachloride liver toxicity (U.S. EPA, 2010; ATSDR, 2005).

The AEGL-2 values (See Section 3.2.4.1), which are the basis for the PODs for acute inhalation exposures in this risk evaluation, were derived using an intraspecies uncertainty factor of 10 to account for individuals who may be more susceptible to the toxic effects of carbon tetrachloride, including greater potential of carbon tetrachloride-induced toxicity in individuals with histories of alcohol usage. Susceptibility to carbon tetrachloride due to elevated (*i.e.*, moderate to high) alcohol use is in agreement with the known dispositional potentiation of carbon tetrachloride toxicity by inducers of cytochrome CYP2E1 enzymes. The AEGL document states that the variability in response to carbon tetrachloride is emphasized by the fact that an estimated exposure at 63 ppm-h was fatal in a heavy drinker whereas controlled exposures at 190 ppm-h were without effect for individuals not categorized as heavy drinkers. This exposure information indicates that a three-fold exposure reduction to the NOEC value produces an extreme toxic response in heavy drinkers, suggesting that a UF of 10 for intraspecies variability is protective of heavy drinkers.

Age can influence susceptibility to carbon tetrachloride due to differences in metabolism, antioxidant responses, and reduced kidney function in older adults. While lower CYP expression may reduce susceptibility of older adults to carbon tetrachloride in some tissues, reduced kidney function and increased CYP3A activity in the liver (indicated by animal studies) suggest that older populations could be at greater risk of carbon tetrachloride-associated kidney damage (U.S. EPA, 2010).

Nutrition has also been shown to influence susceptibility to carbon tetrachloride in animals. Food restriction has been shown to increase liver toxicity of carbon tetrachloride. Diets low in antioxidants increase lipid peroxidation and liver damage in following carbon tetrachloride exposure (reversed with antioxidant supplementation) and zinc deficient diets increase carbon tetrachloride-induced liver toxicity (U.S. EPA, 2010).

EPA identified groups of individuals with greater inhalation exposure as workers in occupational scenarios. EPA examined worker exposures in this risk evaluation for several occupational scenarios (see Section 2.4.1 for these exposure scenarios).

To account for variation in sensitivity within human populations intraspecies UFs were applied for non-cancer effects. The UF values selected are described in Section 3.2.5.2.

4.4 Assumptions and Key Sources of Uncertainty

The characterization of assumptions, variability and uncertainty may raise or lower the confidence of the risk estimates. This Section describes the assumptions and uncertainties in the exposure assessment, hazard/dose-response and risk characterization.

4.4.1 Occupational Exposure Assumptions and Uncertainties

EPA addressed variability in models by identifying key model parameters to apply a statistical distribution that mathematically defines the parameter's variability. EPA defined statistical distributions for parameters using documented statistical variations where available. Uncertainty is "the lack of knowledge about specific variables, parameters, models, or other factors" and can be described qualitatively or quantitatively (U.S. EPA, 2001). The following Sections discuss uncertainties in each of the assessed carbon tetrachloride use scenarios.

One overarching uncertainty is that exposures to carbon tetrachloride from outside the workplaces are not included in the occupational assessment, which could lead to an underestimate of occupational exposure. Another overarching uncertainty is that inhalation and dermal exposures were assessed separately, which could lead to an underestimation of occupational exposure. EPA considered the reasonably available information and used the best available science to determine whether to consider aggregate or sentinel exposures for carbon tetrachloride. There is low confidence in the result of aggregating the dermal and inhalation risks for carbon tetrachloride in case of using an additive approach, due to the uncertainty in the data. EPA does not have data that could be reliably modeled into the aggregate.

Number of Workers

There are a number of uncertainties surrounding the estimated number of workers potentially exposed to carbon tetrachloride, as outlined below.

First, BLS's OES employment data for each industry/occupation combination are only available at the 3-, 4-, or 5-digit NAICS level, rather than the full 6-digit NAICS level. This lack of granularity could result in an overestimate of the number of exposed workers if some 6-digit NAICS are included in the less granular BLS estimates but are not, in reality, likely to use carbon tetrachloride for the assessed applications. EPA addressed this issue by refining the OES estimates using total employment data from the U.S. Census's SUSB. However, this approach considers that the distribution of occupation types (SOC codes) in each 6-digit NAICS is equal to the distribution of occupation types at the parent 5-digit NAICS level. If the distribution of workers in occupations with carbon tetrachloride exposure differs from the overall distribution of workers in each NAICS, then this approach will result in inaccuracy.

Second, EPA's judgments about which industries (represented by NAICS codes) and occupations (represented by SOC codes) are associated with the uses assessed in this report are based on EPA's understanding of how carbon tetrachloride is used in each industry. Designations of which industries and occupations have potential exposures is nevertheless subjective, and some industries/occupations with few exposures might erroneously be included, or some industries/occupations with exposures might erroneously be excluded. This would result in inaccuracy but would be unlikely to systematically either overestimate or underestimate the count of exposed workers.

Worker Activities

There are various potential worker activities and/or sites within each OES that could have varying levels of exposures. If the exposure estimate is based on one or very few worker

activities or sites within the OES, it could potentially underestimate or overestimate exposures for other workers included in the same OES.

Occupational non-users (ONUs)
Exposures for occupational non-users could vary. Most data sources do not describe the proximity of these employees to the exposure source. Exposure levels for the "occupational non-user" category could have high variability depending on the specific work activity performed. It is possible that some employees categorized as "occupational non-user" have exposures similar to those in the "worker" category depending on their specific work activity pattern. ONUs are likely a heterogeneous population of workers, and some could be exposed more than just occasionally to high concentrations. It is unknown whether these uncertainties overestimate or underestimate exposures.

EPA evaluated inhalation risks for acute and chronic exposures for ONUs. However, EPA did not separately calculate inhalation risk estimates for ONUs and workers for some OES where monitoring data was unavailable. There is uncertainty in the ONU inhalation risk estimate since the modeled data does not distinguish between worker and ONU inhalation exposure estimates. While the difference between the exposures of ONUs and the exposures of workers directly handling the chemical generally cannot be quantified, ONU inhalation exposures are expected to be lower than inhalation exposures for workers directly handling the chemical. When ONU exposure data were not identified, EPA considered the ONU exposures to be equal to the central tendency risk estimates for workers when determining ONU risk attributable to inhalation. While this is likely health protective as it assumes ONU exposure is greater than that of 50% of the workers, this is highly uncertain, and EPA has low confidence in these exposure estimates for ONUs.

Analysis of Exposure Monitoring Data
This risk evaluation uses existing worker exposure monitoring data to assess exposure to carbon tetrachloride during manufacturing. Some data sources may be inherently biased. For example, bias may be present if exposure monitoring was conducted to address concerns regarding adverse human health effects reported following exposures during use.

Some scenarios have limited exposure monitoring data in literature, if any. Where there are few data points available, it is unlikely the results will be representative of worker exposure across the industry.

Where sufficient data were available, the 95th and 50th percentile exposure concentrations were calculated using available data. The 95th percentile exposure concentration is intended to represent a high-end exposure level, while the 50th percentile exposure concentration represents typical exposure level. The underlying distribution of the data, and the representativeness of the available data, are not known. Where discrete data was not available, EPA used reported statistics (*i.e.*, median, mean, 90th percentile, etc.). Since EPA could not verify these values, there is an added level of uncertainty.

EPA generally calculated ADC and LADC values assuming a high-end exposure duration of 250 days per year over 40 years and a typical exposure duration of 250 days per year over 31 years.

This assumes the workers and occupational non-users are regularly exposed during their entire working lifetime, which likely results in an overestimate. Individuals may change jobs during the course of their career such that they are no longer exposed to carbon tetrachloride, resulting in actual ADC and LADC values that are lower than the estimates presented.

Using Surrogate Monitoring Data to Assess Inhalation Exposures

Where EPA lacked inhalation monitoring data for a specific OES, EPA attempted to identify surrogate monitoring data for a carbon tetrachloride OES where the worker activities and industrial setting were expected to be similar to the OES being assessed. Due to these similarities, EPA assumed the surrogate data was representative of exposure sources, routes, and concentrations at the OES being assessed. There is some uncertainty as to the representativeness of surrogate data, EPA expects the use of such data will provide a reasonable estimate of exposure to workers.

Modeling Inhalation Exposures

The Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model was created to estimate the airborne concentration associated with generic chemical loading scenarios at industrial facilities. Specific uncertainties associated with this model are described below:

- After each loading event, the model assumes saturated air containing carbon tetrachloride that remains in the transfer hose and/or loading arm is released to air. The model calculates the quantity of saturated air using design dimensions of loading systems published in the OPW Engineered Systems catalog and engineering judgment. These dimensions may not be representative of the whole range of loading equipment used at industrial facilities handling carbon tetrachloride.
- The model estimates fugitive emissions from equipment leaks using total organic compound emission factors from EPA's Protocol for Equipment Leak Emission Estimates (U.S. EPA, 1995), and engineering judgment on the likely equipment type used for transfer (*e.g.*, number of valves, seals, lines, and connections). The applicability of these emission factors to carbon tetrachloride, and the accuracy of EPA's assumption on equipment type are not known.
- The model assumes the use of a vapor balance system to minimize fugitive emissions. Although most industrial facilities are likely to use a vapor balance system when loading/unloading volatile chemicals, EPA does not know whether these systems are used by all facilities that potentially handle carbon tetrachloride.
- The model does not account for other potential sources of exposure at industrial facilities, such as sampling, equipment cleaning, and other process activities that can contribute to a worker's overall 8-hr daily exposure. These model uncertainties could result in an underestimate of the worker 8-hr exposure.

Modeling Dermal Exposures

To assess dermal exposure, EPA used a modified equation from the *EPA/OPPT 2-Hand Dermal Exposure to Liquids* Model to calculate the dermal absorbed dose for both non-occluded and occluded scenarios. The modified equation incorporates a "fraction absorbed (fabs)" parameter to account for the evaporation of volatile chemicals and a "protection factor (PF)" to account for

glove use. PF values will vary depending on the type of glove used and the presence of employee training program.

The model considers an infinite dose scenario and does not account for the transient exposure and exposure duration effect, which likely overestimates exposures. The model assumes one exposure event per day, which likely underestimates exposure as workers often come into repeat contact with the chemical throughout their workday. Surface areas of skin exposure are based on skin surface area of hands from EPA's Exposure Factors Handbook, but actual surface areas with liquid contact are unknown and uncertain for all occupational exposure scenarios. For many scenarios, the assumption of contact over the full area of two hands likely overestimates exposures. Weight fractions are usually reported to CDR and shown in other literature sources as ranges, and EPA assessed only upper ends of ranges. While the glove protection factors are based on the ECETOC TRA model as described in Section 2.4.1.5 they are "what-if" assumptions and are highly uncertain. EPA does not know the actual frequency, type, and effectiveness of glove use in specific workplaces of the occupational exposure scenarios. Except where specified above, it is unknown whether most of these uncertainties overestimate or underestimate exposures. The representativeness of the modeling results toward the true distribution of dermal doses for the occupational scenarios is uncertain.

More details on the dermal methodology are discussed in the supplemental document *Final Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019c).

4.4.2 Environmental Exposure Assumptions and Uncertainties

As described in Appendix E and Section 2.3.1, a screening-level aquatic exposure assessment was undertaken to evaluate ecological exposures in the U.S. that may be associated with releases of carbon tetrachloride to surface waters. This assessment was intended as a first-tier, or screening-level, evaluation. The top ten (by annual release/discharge amount) facilities as reported in EPA's Discharge Monitoring Reports (DMRs) were selected for use in exposure modeling for each of five years from 2014 through 2018. Thus, not all reporting sites were modeled, and the selected sites were not cross-walked with the conditions of use included in the occupational engineering assessment.

For the purposes of this assessment, the number of release days were either 20 days or 250 days. The reported annual release amounts from DMR were divided by these numbers of release days to obtain the necessary kg/site-day release input. These assumptions are not based on associated industry-specific data or standards, but on the assumptions to capture conservative environmental concentrations for acute and chronic release scenarios. The 20 days of release is the assumption for a chronic scenario, appropriate for comparison against a chronic COC, whereas 250 days of release may be more typical for facilities that operate and release effluent frequently, such as POTWs or treatment plants.

Uncertainties in the modeled surface water concentration estimates include the variable amount of releases of carbon tetrachloride captured in the DMR database and regulated by the Office of Water's NPDES permitting process.

Lastly, some facilities releasing carbon tetrachloride, such as POTWs, may not be associated with a TSCA condition of use covered in this risk evaluation. Use of facility data to estimate environmental exposures is constrained by a number of other uncertainties including: the heterogeneity of processes and releases among facilities grouped within a given sector; assumptions made regarding sector definitions used to select facilities covered under the scope; and fluctuations in the level of production and associated environmental releases incurred as a result of changes in standard operating procedures. Nevertheless, it is important to note that the DMR dataset is based on the most comprehensive, best reasonably available data at a nationwide scale. DMR is based on representative pollutant monitoring data at facility outfalls and corresponding wastewater discharges. Any exceedances of permit levels are referred to EPA's Office Enforcement and Compliance Assurance.

4.4.3 Environmental Hazard Assumptions and Uncertainties

While the EPA has determined that sufficient data are available to characterize the overall environmental hazards of carbon tetrachloride, uncertainties exist. To begin, while reasonable attempts were made, the Agency was not able to obtain all the full scientific reports listed in ECHA, SIAP, and NICNAS on carbon tetrachloride due to challenges that include ownership of the studies by foreign sources. EPA did not use its information collection authority to obtain the full scientific reports or translate foreign language studies listed in ECHA, SIAP, and NICNAS because the robust summary endpoints from these sources align with the dataset EPA used to assess the hazards of carbon tetrachloride. Additionally, EPA has successfully obtained the full study reports for the most conservative endpoint values in the scientific literature that are driving the acute and chronic concentrations of concern.

Furthermore, EPA used sub-chronic data, measuring a developmental effect in embryo and larvae, to calculate the amphibian chronic COC, which introduces some uncertainty about whether EPA is overestimating or underestimating chronic risk. Assessment factors (AFs) were used to calculate the acute and chronic concentrations of concern for carbon tetrachloride. As described in Appendix F, AFs account for differences in inter- and intra-species variability, as well as laboratory-to-field variability and are routinely used within TSCA for assessing the hazard of new industrial chemicals (with very limited environmental test data). Therefore, there is uncertainty associated with the use of the specific AFs used in the hazard assessment. For example, a standard AF has not been established for amphibians by the EPA under TSCA, because there are few amphibian studies for industrial chemicals. It is unclear whether using an assessment factor of 10 to calculate the acute COC value for amphibians using the sub-chronic embryo-larvae test data is sufficiently protective or is overly protective of amphibian exposures to carbon tetrachloride. There are additional factors that affect the potential for adverse effects in aquatic organisms. Life-history factors and the habitat of aquatic organisms influence the likelihood of exposure above the hazard benchmark in an aquatic environment.

4.4.4 Human Health Hazard Assumptions and Uncertainties

Toxicity data are limited for dermal exposures to carbon tetrachloride and for developmental toxicity by the inhalation route. The available developmental toxicity by the inhalation route suggests that carbon tetrachloride does not induce developmental effects from single exposures during gestation (see Section 3.2.5.1.1). The available dermal data were used in a weight of evidence approach to derive points of departures (POD) for occupational dermal exposures and estimates of dermal absorption.

The main source of uncertainty for the human health hazard is the lack of evidence in support of a MOA for carcinogenesis of carbon tetrachloride for the different types of tumors observed in animal and human studies. Therefore, a low dose linear cancer risk model for carbon tetrachloride was used to calculate cancer risk for tumors other than liver, which is EPA's baseline approach to risk assessment when the MOA is unknown or not sufficiently supported by the evidence. A threshold cancer risk model was used to calculate cancer risk for liver tumors based on a regenerative hyperplasia cancer MOA for liver cancer.

Several uncertainties affected the dermal risk assessment. Evaporation from skin could occur (if in an aqueous solution, evaporation may be less likely). Route-to-route extrapolation was used to calculate a human equivalent dermal dose for acute and chronic exposures. Inhalation to dermal route-to-route extrapolation assumes that the inhalation route of exposure is most relevant to dermal exposures, as carbon tetrachloride undergoes first-pass metabolism in the liver for oral exposures.

The $BMDL_{10}$ value for continuous inhalation exposures was extrapolated to shorter exposure durations using the equation $C^n \times t = k$, where an empirical value of n was determined to be 2.5 based on rat lethality data (NRC, 2014; Ten Berge et al., 1986). The validity of this extrapolation is supported by similar time scaling processes conducted in the generation of AEGL values. Uncertainties associated to this extrapolation are discussed in U.S. EPA, (U.S. EPA, 2002) (see Section 3.2.5.2.2).

4.5 Risk Characterization Confidence Levels

4.5.1 Environmental Risk

EPA has moderate confidence in the risk estimates from the TSCA conditions of use and exposure pathways within the scope of the risk evaluation for carbon tetrachloride. EPA used high end exposures and modeled surface water concentrations and the most sensitive taxonomic groups (highest toxicity)/environmentally protective acute and chronic COCs. Uncertainties associated with risk estimates are described in Sections 4.1, 4.4.2, and 4.4.3.

4.5.2 Human Health Risk

There is medium to high confidence in the risk estimates for inhalation exposures. The PODs for non-cancer and cancer effects from acute or chronic exposures are rated with at least medium confidence (see Section 3.2.5.3). Exposure estimates from monitoring/surrogate monitoring data (*i.e.*, manufacturing and processing COUs) are based on a robust monitoring dataset (*i.e.*, > 100 data points), reflecting high confidence in resulting exposure estimates. Exposure estimates for all the other COUs are based on modeling or monitoring data with limited datapoints (*i.e.*, OBOD cleanup process in DoD). There is congruency between the exposure estimates based on the limited monitoring data for the OBOD cleanup (*i.e.*, a process that last 1-2 hrs/day) and estimates based on the *Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model* for worker exposure during container and truck unloading activities that occur at industrial facilities. The fact that there is congruency in the resulting exposure estimates suggest at least medium confidence in those exposure estimates.

There is low confidence in the risk estimates for dermal exposures. The lack of quantitative data on dermal absorption for carbon tetrachloride affects the derivation of accurate dermal PODs and the modeling of dermal exposures. The conservative assumptions used to derive the PODs and exposure estimate are likely to result in risk overestimations.

4.6 Aggregate or Sentinel Exposures

Section 6(b)(4)(F)(ii) of TSCA requires the EPA, as a part of the risk evaluation, to describe whether aggregate or sentinel exposures under the conditions of use were considered and the basis for their consideration. The EPA has defined aggregate exposure as "*the combined exposures to an individual from a single chemical substance across multiple routes and across multiple pathways*" (40 CFR § 702.33). In this risk evaluation exposure is limited to exposure to carbon tetrachloride by both inhalation and dermal contact only. Inhalation exposure is specified by the air concentration encountered as a function of time during the workday. Dermal contact is characterized by the surface area of skin (hands) exposed, and the duration of the dermal exposure. For workplace exposures inhalation and dermal exposures are assumed to be only simultaneous (both end at the end of the task, shift, or workday).

Quantitative information on the dermal absorption of carbon tetrachloride is limited. This data limitation hinders the accuracy of estimated internal doses from dermal exposures. On the other hand, carbon tetrachloride is identified and labeled as a skin irritant and sensitizer, which suggests that workers are less likely to not be wearing gloves when handling the chemical. Based on this assumption, the occurrence of aggregate exposures including dermal exposures without gloves is expected to be highly unlikely especially for chronic aggregate exposures.

EPA has determined that using the high-end risk estimate for inhalation and dermal risks separately as the basis for the unreasonable risk determination is a best available science approach. There is low confidence in the result of aggregating the dermal and inhalation risks for this chemical if EPA uses an additive approach, due to the uncertainty in the data. EPA does not have data that could be reliably modeled for the aggregate exposure, which would be a more accurate approach than adding, such as through a PBPK model. Using an additive approach to aggregate risk in this case could result in an overestimate of risk. Given all the limitations that exist with the data, EPA's approach is the best available science.

The EPA defines sentinel exposure as "*the exposure from a single chemical substance that represents the plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures"* (40 CFR § 702.33). In this risk evaluation, the EPA considered sentinel exposure the highest exposure given the details of the conditions of use and the potential exposure scenarios – for example, workers who perform activities with higher exposure potential, or certain physical factors like body weight or skin surface area exposed. EPA characterized high-end exposures in evaluating exposure using both monitoring data and modeling approaches. Where statistical data are available, EPA typically uses the 95th percentile value of the available dataset to characterize high-end exposure for a given condition of use.

Greater inhalation exposures to carbon tetrachloride are estimated for the Domestic Manufacturing and Processing as Reactant/Intermediate COUs than all the other COUs in this risk evaluation (see Table 4-7 and Table 4-8).

5 Unreasonable Risk Determination

5.1 Overview

In each risk evaluation under TSCA Section 6(b), EPA determines whether a chemical substance presents an unreasonable risk of injury to health or the environment, under the conditions of use. These determinations do not consider costs or other non-risk factors. In making these determinations, EPA considers relevant risk-related factors, including, but not limited to: the effects of the chemical substance on health and human exposure to such substance under the conditions of use (including cancer and non-cancer risks); the effects of the chemical substance on the environment and environmental exposure under the conditions of use; the population exposed (including any potentially exposed or susceptible subpopulations (PESS)); the severity of hazard (including the nature of the hazard, the irreversibility of the hazard); and uncertainties. EPA also takes into consideration the Agency's confidence in the data used in the risk estimate. This includes an evaluation of the strengths, limitations, and uncertainties associated with the information used to inform the risk estimate and the risk characterization. This approach is in keeping with the Agency's final rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726).[22]

This section describes the final unreasonable risk determinations for the conditions of use in the scope of the risk evaluation. The final unreasonable risk determinations are based on the risk estimates in the final risk evaluation, which may differ from the risk estimates in the draft risk evaluation due to peer review and public comments. Therefore, the final unreasonable risk determinations of some conditions of use may differ from those in the draft risk evaluation.

5.1.1 Human Health

EPA's risk evaluation identified liver toxicity and cancer adverse effects from chronic inhalation and dermal exposures to carbon tetrachloride. EPA did not identify risks from acute exposures for central nervous system depression, which is the most sensitive endpoint for non-cancer effects from acute exposures. The health risk estimates for all conditions of use are in Section 4.5 (Table 4-8 and Table 4-11).

For the carbon tetrachloride risk evaluation, EPA identified as Potentially Exposed or Susceptible Subpopulations: workers and ONUs, including men, women of reproductive age, and adolescents, who metabolize carbon tetrachloride to reactive metabolites faster than others, including those with elevated (moderate-high) alcohol usage, older adults, and those with antioxidant or zinc deficient diets.

EPA evaluated exposures to workers and ONUs using reasonably available monitoring and modeling data for inhalation and dermal exposures, as applicable. For example, EPA assumed that ONUs do not have direct contact with carbon tetrachloride; therefore, non-cancer effects and cancer from dermal exposures to carbon tetrachloride are not expected and were not evaluated. The description of the data

[22] This risk determination is being issued under TSCA Section 6(b) and the terms used, such as unreasonable risk, and the considerations discussed are specific to TSCA. Other statutes have different authorities and mandates and may involve risk considerations other than those discussed here.

used for human health exposure is in Section 2.4. Uncertainties in the analysis are discussed in Section 4.4 and considered in the unreasonable risk determination for each condition of use presented below, including the fact that the dermal model used does not address variability in exposure duration and frequency.

EPA did not evaluate risks to the general population from any conditions of use and the unreasonable risk determinations do not account for any risks to the general population. Additional details regarding the general population are in Section 1.4.3.

5.1.1.1 Non-Cancer Risk Estimates

The risk estimates of non-cancer effects, described with MOEs, refers to adverse health effects associated with health endpoints other than cancer, including to the body's organ systems, such as reproductive/developmental effects, cardiac and lung effects, and kidney and liver effects. The MOE is the point of departure (POD) (an approximation of the no-observed adverse effect level (NOAEL) or benchmark dose level (BMDL)) for a specific health endpoint divided by the exposure concentration for the specific scenario of concern. Section3.2.5 presents the PODs for non-cancer effects for carbon tetrachloride and Section 4.2 presents the MOEs for non-cancer effects.

The MOEs are compared to a benchmark MOE. The benchmark MOE accounts for the total uncertainty in a POD, including, as appropriate: (1) the variation in sensitivity among the members of the human population (*i.e.*, intrahuman/intraspecies variability); (2) the uncertainty in extrapolating animal data to humans (*i.e.*, interspecies variability); (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure (*i.e.*, extrapolating from subchronic to chronic exposure); and (4) the uncertainty in extrapolating from a lowest observed adverse effect level (LOAEL) rather than from a NOAEL. A lower benchmark MOE (*e.g.*, 30) indicates greater certainty in the data (because fewer of the default UFs relevant to a given POD as described above were applied). A higher benchmark MOE (*e.g.*, 1000) would indicate more uncertainty for specific endpoints and scenarios. However, these are often not the only uncertainties in a risk evaluation. The benchmark MOE for acute and chronic non-cancer risks for carbon tetrachloride is 10 and 30, respectively (accounting for interspecies and intraspecies variability). Additional information regarding the benchmark MOE is in Section 4.2.1.

5.1.1.2 Cancer Risk Estimates

EPA presents in this risk evaluation two approaches for assessment of carcinogenic risk from carbon tetrachloride: a linear extrapolation approach for adrenal gland and brain tumors in conjunction with a threshold approach for assessing risks for liver tumors. This is based on considerations for the modes of action for the different cancers evaluated. More information on the reasons for the two approaches and the overall cancer mode of action conclusions are in Section 3.2.4.3.

For adrenal gland and brain tumors, EPA used a linear extrapolation approach. The basis for this approach is described in detail in Section 3.2.4.3.2, with the cancer inhalation unit risk and dermal slope factor described in Section 3.2.5.2.5. Using this approach, cancer risk estimates represent the incremental increase in probability of an individual in an exposed population developing cancer over a lifetime (excess lifetime cancer risk (ELCR)) following exposure to the chemical. Standard cancer benchmarks used by EPA and other regulatory agencies are an increased cancer risk above benchmarks

ranging from 1 in 1,000,000 to 1 in 10,000 (*i.e.*, $1x10^{-6}$ to $1x10^{-4}$) depending on the subpopulation exposed.[23]

EPA, consistent with 2017 NIOSH guidance,[24] used $1x10^{-4}$ as the benchmark for the purposes of this unreasonable risk determination for individuals in industrial and commercial work environments. It is important to note that $1x10^{-4}$ is not a bright line and EPA has discretion to make unreasonable risk determinations based on other cancer risk benchmarks as appropriate.

For liver tumors, EPA used a threshold approach for assessing risks. Section 3.2.5.2.6 presents the PODs for liver cancer effects for carbon tetrachloride and Section 4.2 presents the MOEs for liver cancer effects. Like non-cancer effects, the MOE for cancer effects are compared to a benchmark MOE. The benchmark MOE for liver cancer risks for carbon tetrachloride is 300 (accounting for interspecies and intraspecies variability).

5.1.1.3 Determining Unreasonable Risk of Injury to Health

Calculated risk estimates (MOEs or added cancer risk estimates) can provide a risk profile by presenting a range of estimates for different health effects for different conditions of use. A calculated MOE that is less than the benchmark MOE supports a determination of unreasonable risk of injury to health, based on non-cancer or certain cancer effects. Similarly, a calculated added cancer risk estimate that is greater than the cancer benchmark supports a determination of unreasonable risk of injury to health from cancer. Whether EPA makes a determination of unreasonable risk depends upon other risk-related factors, such as the endpoint under consideration, the reversibility of effect, exposure-related considerations (*e.g.*, duration, magnitude, or frequency of exposure, or population exposed), and the confidence in the information used to inform the hazard and exposure values. A calculated MOE greater than the benchmark MOE or a calculated added cancer risk estimate less than the benchmark, alone do not support a determination of no unreasonable risk, since EPA may consider other risk-based factors when making an unreasonable risk determination.

When making an unreasonable risk determination based on injury to workers' health (who are one example of PESS), EPA also makes assumptions regarding workplace practices and the implementation of the required hierarchy of controls from OSHA. EPA assumes that feasible exposure controls, including engineering controls, administrative controls, or use of personal protective equipment (PPE) are implemented in the workplace. EPA's decisions for unreasonable risk to workers are based on high end exposure estimates, in order to capture not only exposures for PESS but also to account for the uncertainties related to whether or not workers are using PPE. However, EPA does not consider that

[23] As an example, when EPA's Office of Water in 2017 updated the Human Health Benchmarks for Pesticides, the benchmark for a "theoretical upper-bound excess lifetime cancer risk" from pesticides in drinking water was identified as 1 in 1,000,000 to 1 in 10,000 over a lifetime of exposure (EPA. Human Health Benchmarks for Pesticides: Updated 2017 Technical Document (pp.5). (EPA 822-R -17 -001). Washington, DC: U.S. Environmental Protection Agency, Office of Water. January 2017. https://www.epa.gov/sites/production/files/2015-10/documents/hh-benchmarks-techdoc.pdf). Similarly, EPA's approach under the Clean Air Act to evaluate residual risk and to develop standards is a two-step approach that "includes a presumptive limit on maximum individual lifetime [cancer] risk (MIR) of approximately 1 in 10 thousand" and consideration of whether emissions standards provide an ample margin of safety to protect public health "in consideration of all health information, including the number of persons at risk levels higher than approximately 1 in 1 million, as well as other relevant factors" (54 FR 38044, 38045, September 14, 1989).

[24] NIOSH Current intelligence bulletin 68: NIOSH chemical carcinogen policy (Whittaker et al., 2016).

ONUs use PPE. EPA recognizes that OSHA's PEL for carbon tetrachloride is 10 ppm. California adopted a PEL of 2 ppm and the American Conference of Governmental Industrial Hygienists (ACGIH™) adopted a Threshold Limit Value™ (TLV™) of 5 ppm. For each condition of use, based on the reasonably available information and professional judgment, EPA assumes the use of respirators with an APF of 50, and gloves with a PF of 5. Once EPA has applied the appropriate PPE assumption for a particular condition of use in each unreasonable risk determination, EPA also assumes that the PPE is used in a manner that achieves the stated APF or PF.

In the carbon tetrachloride risk characterization, central nervous system effects and liver toxicity were identified as the most sensitive endpoints for non-cancer adverse effects from acute or chronic inhalation and dermal exposures for all conditions of use. EPA also considered cancer risks estimates from chronic dermal or inhalation exposures in the unreasonable risk determination. The carbon tetrachloride risk determination considers the uncertainties associated with the reasonably available information to justify the linear cancer dose-response model and the threshold dose-response model when compared to other available models. The cancer analysis is described in Section3.2.5.

When making a determination of unreasonable risk, the Agency has a higher degree of confidence where uncertainty is low. Similarly, EPA has high confidence in the hazard and exposure characterizations when, for example, the basis for characterizations is measured or monitoring data or a robust model and the hazards identified for risk estimation are relevant for conditions of use. Where EPA has made assumptions in the scientific evaluation, whether or not those assumptions are protective is also a consideration. Additionally, EPA considers the central tendency and high-end exposure levels when determining the unreasonable risk. High-end risk estimates (*e.g.*, 95th percentile) are generally intended to cover individuals or sub-populations with greater exposure (PESS) and central tendency risk estimates are generally estimates of average or typical exposure. EPA may make a determination of no unreasonable risk for conditions of use where the substance's hazard and exposure potential, or where the risk-related factors described previously, lead the Agency to determine that the risks are not unreasonable.

5.1.2 Environment

EPA calculated a risk quotient (RQ) to compare environmental concentrations against an effect level. The environmental concentration is determined based on the levels of the chemical released to the environment (*e.g.*, surface water, sediment, soil, biota) under the conditions of use, based on the fate properties, release potential, and reasonably available environmental monitoring data. The effect level is calculated using concentrations of concern that represent hazard data for aquatic and sediment-dwelling, organisms. Section 4.1 provides more detail regarding the risk quotient for carbon tetrachloride.

5.1.2.1 Determining Unreasonable Risk of Injury to the Environment

An RQ equal to 1 indicates that the exposures are the same as the concentration that causes effects. An RQ less than 1, when the exposure is less than the effect concentration, supports a determination that there is no unreasonable risk of injury to the environment. An RQ greater than 1, when the exposure is greater than the effect concentration, supports a determination that there is unreasonable risk of injury to the environment. Consistent with EPA's human health evaluations, other risk-based factors may be considered (*e.g.*, confidence in the hazard and exposure characterization, duration, magnitude, uncertainty) for purposes of making an unreasonable risk determination.

EPA considered effects on aquatic organisms. Carbon tetrachloride is not expected to partition to or be retained in sediment and is expected to remain in aqueous phase due to its water solubility and low partitioning to organic matter. EPA provides estimates for environmental risk in Section 4.1 and Table 4-2.

5.2 Detailed Unreasonable Risk Determinations by Conditions of Use

Table 5-1. Categories and Subcategories of Conditions of Use Included in the Scope of the Risk Evaluation

Life Cycle Stage	Category [a]	Subcategory [b]	Unreasonable Risk	Detailed Risk Determination
Manufacture	Domestic manufacture	Domestic manufacture	Yes	Sections 5.2.1.1 and 5.2.2
	Import	Import	Yes	Sections 5.2.1.2 and 5.2.2
Processing	Processing as a reactant or intermediate	Hydrochlorofluorocarbons (HCFCs), Hydrofluorocarbon (HFCs),Hydrofluoroolefin (HFOs), and Perchloroethylene (PCE)	Yes	Sections 5.2.1.3 and 5.2.2
		Reactive ion etching (*i.e.*, semiconductor manufacturing)	No	Sections 5.2.1.4 and 5.2.2
	Processing - incorporation into formulation, mixture or reaction products	Petrochemicals-derived manufacturing; Agricultural products manufacturing; Other basic organic and inorganic chemical manufacturing	Yes	Sections 5.2.1.5 and 5.2.2
	Repackaging	Laboratory chemicals	Yes	Sections 5.2.1.6 and 5.2.2
	Recycling	Recycling	Yes	Sections 5.2.1.7 and 5.2.2
Distribution in commerce	Distribution	Distribution	No	Sections 5.2.1.8 and 5.2.2

Table 5-1. Categories and Subcategories of Conditions of Use Included in the Scope of the Risk Evaluation

Life Cycle Stage	Category [a]	Subcategory [b]	Unreasonable Risk	Detailed Risk Determination
Industrial/ commercial use [c]	Petrochemicals-derived products and agricultural products manufacturing	Processing aid	Yes	Sections 5.2.1.9 and 5.2.2
	Additive	Additive	Yes	Sections 5.2.1.10 and 5.2.2
	Other basic organic and inorganic chemical manufacturing	Including chlorinated compounds used in solvents, adhesives, asphalt, and paints and coatings	Yes	Sections 5.2.1.11 and 5.2.2
	Metal recovery	Metal recovery	Yes	Sections 5.2.1.12 and 5.2.2
	Specialty uses by the Department of Defense	Specialty uses by the Department of Defense	Yes	Sections 5.2.1.13 and 5.2.2
	Laboratory Chemical	Laboratory Chemical	Yes	Sections 5.2.1.14 and 5.2.2
Disposal	Disposal	Industrial pre-treatment	Yes	Sections 5.2.1.15 and 5.2.2
		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		

Table 5-1. Categories and Subcategories of Conditions of Use Included in the Scope of the Risk Evaluation

Life Cycle Stage	Category [a]	Subcategory [b]	Unreasonable Risk	Detailed Risk Determination

[a] These categories of conditions of use appear in the Life Cycle Diagram, reflect CDR codes, and broadly represent additional information regarding all conditions of use of carbon tetrachloride.

[b] These subcategories reflect more specific information regarding the conditions of use of carbon tetrachloride.

[c] Although EPA has identified both industrial and commercial uses here for purposes of distinguishing scenarios in this document, the Agency interprets the authority over "any manner or method of commercial use" under TSCA Section 6(a)(5) to reach both.

5.2.1 Human Health

5.2.1.1 Manufacture – Domestic Manufacture – Domestic Manufacture (Domestic manufacture)

Section 6(b)(4)(A) unreasonable risk determination for domestic manufacture of carbon tetrachloride: **Presents an unreasonable risk of injury to health (workers and ONUs).**

For workers, EPA found that there was an unreasonable risk of cancer effects from dermal exposures at the central tendency and high-end, even when assuming use of PPE. For ONUs, EPA found that there was an unreasonable risk of cancer from chronic inhalation exposures at the central tendency and high-end and non-cancer effects from chronic (liver toxicity) inhalation exposures at the high-end.

EPA's determination that the domestic manufacturing of carbon tetrachloride presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-15) and other considerations. As explained in Section 5.1, EPA considered the health effects of carbon tetrachloride, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.4):

- For workers, when assuming use of gloves with PF of 20, the risk estimates of cancer effects (from both approaches) for dermal exposures at the high-end support an unreasonable risk determination.
- For workers, when assuming the use of respirators with APF of 50, the risk estimates of cancer effects (from both approaches) and non-cancer effects from chronic inhalation exposures at the high-end do not support an unreasonable risk determination. The risk estimates of non-cancer effects from acute inhalation exposures at the central tendency and high-end do not support an unreasonable risk determination.
- For ONUs, the risk estimates of cancer effects (from both approaches) at the central tendency and high-end support an unreasonable risk determination.
- For ONUs, the risk estimates of non-cancer effects from acute (CNS) inhalation exposures at the high-end do not support an unreasonable risk determination.
- Cancer risks were assessed using two approaches: linear extrapolation and threshold. The unreasonable risk determination is based on the risk estimates derived from both approaches.

- Inhalation exposures were assessed using personal breathing zone monitoring data from two sources for workers and ONUs. The data are directly applicable to this condition of use; however, the data may not be representative of exposures across the range of facilities that manufacture carbon tetrachloride.
- Dermal exposures were assessed using modeled data.

In summary, the risk estimates, the health effects of carbon tetrachloride, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from domestic manufacturing of carbon tetrachloride.

5.2.1.2 Manufacture – Import – Import (Import)

Section 6(b)(4)(A) unreasonable risk determination for import of carbon tetrachloride: **Presents an unreasonable risk of injury to health (workers and ONUs).**

For workers, EPA found that there was an unreasonable risk of cancer effects from dermal exposures at the central tendency and high-end, even when assuming use of PPE. For ONUs, EPA found that there was an unreasonable risk of cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the import of carbon tetrachloride presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-15) and other considerations. As explained in Section 5.1, EPA considered the health effects of carbon tetrachloride, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.4), including uncertainties related to the exposures for ONUs:

- For workers, when assuming use of gloves with PF of 20, the risk estimates of cancer effects (from both approaches) for dermal exposures at the high-end support an unreasonable risk determination.
- For workers, when assuming the use of respirators with APF of 50, the risk estimates of cancer effects (from both approaches) and non-cancer effects from chronic inhalation exposures at the high-end do not support an unreasonable risk determination. The risk estimates of non-cancer effects from acute inhalation exposures at the central tendency and high-end do not support an unreasonable risk determination.
- For ONUs, the risk estimates of cancer effects (from both approaches) at the central tendency support an unreasonable risk determination.
- For ONUs, the risk estimates of non-cancer effects from acute (CNS) and chronic (liver toxicity) inhalation exposures at the central tendency do not support an unreasonable risk determination.
- Based on EPA's analysis, the data for worker and ONU inhalation exposures could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency risk estimates from inhalation exposures when determining ONUs' unreasonable risk.
- Cancer risks were assessed using two approaches: linear extrapolation and threshold. The unreasonable risk determination is based on the risk estimates derived from both approaches.
- Inhalation exposures were assessed using surrogate data from two sources. Carbon tetrachloride may be imported into the United States in bulk containers and may be repackaged into smaller

containers for resale. EPA assumed the worker unloading activity will result in exposures similar to unloading/loading activities at manufacturing sites; however, the data may not be representative of the work activities and exposures across the range of importing facilities.
- Dermal exposures were assessed using modeled data.

In summary, the risk estimates, the health effects of carbon tetrachloride, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from import of carbon tetrachloride.

5.2.1.3 Processing – Processing as a reactant in the production of hydrochlorofluorocarbon, hydrofluorocarbon, hydrofluoroolefin, and perchloroethylene

Section 6(b)(4)(A) unreasonable risk determination for processing carbon tetrachloride as a reactant in the production of hydrochlorofluorocarbon, hydrofluorocarbon, hydrofluoroolefin, and perchloroethylene: **Presents an unreasonable risk of injury to health (workers and ONUs).**

For workers, EPA found that there was an unreasonable risk of cancer effects from dermal exposures at the central tendency and high-end, even when assuming use of PPE. For ONUs, EPA found that there was an unreasonable risk of cancer from chronic inhalation exposures at the central tendency and high-end and non-cancer effects from chronic (liver toxicity) inhalation exposures at the high-end.

EPA's determination that the processing of carbon tetrachloride as a reactant in the production of hydrochlorofluorocarbon, hydrofluorocarbon, hydrofluoroolefin, and perchloroethylene presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-15) and other considerations. As explained in Section 5.1, EPA considered the health effects of carbon tetrachloride, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.4):

- For workers, when assuming use of gloves with PF of 20, the risk estimates of cancer effects (from both approaches) for dermal exposures at the high-end support an unreasonable risk determination.
- For workers, when assuming the use of respirators with APF of 50, the risk estimates of cancer effects (from both approaches) and non-cancer effects from chronic inhalation exposures at the high-end do not support an unreasonable risk determination. The risk estimates of non-cancer effects from acute inhalation exposures at the central tendency and high-end do not support an unreasonable risk determination.
- For ONUs, the risk estimates of cancer effects (from both approaches) at the central tendency and high-end support an unreasonable risk determination.
- For ONUs, the risk estimates of non-cancer effects from acute (CNS) inhalation exposures at the high-end do not support an unreasonable risk determination.
- Cancer risks were assessed using two approaches: linear extrapolation and threshold. The unreasonable risk determination is based on the risk estimates derived from both approaches.
- EPA recognizes that the manufacturing setting and associated worker activities are similar for both the manufacture and processing as a reactant or intermediate of carbon tetrachloride. Therefore, inhalation exposures for this condition of use were assessed

using personal breathing zone monitoring data from two sources for workers and ONUs in a manufacturing setting; however, the data may not be representative of the work activities and exposures across the range of processing facilities.
- Dermal exposures were assessed using modeled data.

In summary, the risk estimates, the health effects of carbon tetrachloride, the exposures, and consideration of uncertainties support EPA's determination that there is unreasonable risk of injury to health (workers and ONUs) from processing carbon tetrachloride as a reactant in the production of hydrochlorofluorocarbon, hydrofluorocarbon, hydrofluoroolefin, and perchloroethylene.

5.2.1.4 Processing – Processing as reactant/intermediate in reactive ion etching

Section 6(b)(4)(A) unreasonable risk determination for processing of carbon tetrachloride as a reactant/intermediate in reactive ion etching (*e.g.*, semiconductor manufacture): Does not present an unreasonable risk of injury to health (workers and ONUs).

A quantitative evaluation of the occupational exposures attributable to this condition of use is not included in the risk evaluation because EPA estimates that worker exposures to carbon tetrachloride during reactive ion etching are negligible. Due to the performance requirements of products typically produced using this technique, carbon tetrachloride is typically applied in small quantities under a fume hood and/or inside a highly controlled work area (a Class 1 clean room), thus eliminating or significantly reducing the potential for exposures (Section 2.4.1.7.5).

5.2.1.5 Processing – Incorporation into formulation, mixture or reaction products-Petrochemicals-derived manufacturing, agricultural products manufacturing, and other basic organic and inorganic chemical manufacturing

Section 6(b)(4)(A) unreasonable risk determination for processing carbon tetrachloride into a formulation, mixture or reaction product – Petrochemicals-derived manufacturing; Agricultural products manufacturing; Other basic organic and inorganic chemical manufacturing: **Presents an unreasonable risk of injury to health (workers and ONUs).**

For workers, EPA found that there was an unreasonable risk of cancer effects from dermal exposures at the central tendency and high-end, even when assuming use of PPE. For ONUs, EPA found that there was an unreasonable risk of cancer from chronic inhalation exposures at the central tendency and high-end and non-cancer effects from chronic (liver toxicity) inhalation exposures at the high-end.

EPA's determination that the processing of carbon tetrachloride into a formulation, mixture or reaction product (petrochemicals-derived manufacturing; agricultural products manufacturing; other basic organic and inorganic chemical manufacturing) presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-15) and other considerations. As explained in Section 5.1, EPA considered the health effects of carbon tetrachloride, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.4):

- For workers, when assuming use of gloves with PF of 20, the risk estimates of cancer effects (from both approaches) for dermal exposures at the high-end support an unreasonable risk determination.
- For workers, when assuming the use of respirators with APF of 50, the risk estimates of cancer effects (from both approaches) and non-cancer effects from chronic inhalation exposures at the high-end do not support an unreasonable risk determination. The risk estimates of non-cancer effects from acute inhalation exposures at the central tendency and high-end do not support an unreasonable risk determination.
- For ONUs, the risk estimates of cancer effects (from both approaches) at the central tendency and high-end support an unreasonable risk determination.
- For ONUs, the risk estimates of non-cancer effects from acute (CNS) inhalation exposures at the high-end do not support an unreasonable risk determination.
- Cancer risks were assessed using two approaches: linear extrapolation and threshold. The unreasonable risk determination is based on the risk estimates derived from both approaches.
- EPA recognizes that the manufacturing setting and associated worker activities are similar for the manufacture of carbon tetrachloride, processing as a reactant or intermediate, and processing of carbon tetrachloride into a formulation, mixture or reaction product. Therefore, to assess inhalation exposures, EPA assessed this condition of use under the Processing as a Reactant exposure scenario using personal breathing zone monitoring data from two sources for workers and ONUs in a manufacturing setting; however, the data may not be representative of the work activities and exposures across the range of processing facilities.
- Dermal exposures were assessed using modeled data.

In summary, the risk estimates, the health effects of carbon tetrachloride, the exposures, and consideration of uncertainties support EPA's determination that there is unreasonable risk of injury to health (workers and ONUs) from processing of carbon tetrachloride into a formulation, mixture or reaction product (other basic organic and inorganic chemical manufacturing).

5.2.1.6 Processing – Repackaging of carbon tetrachloride for use in laboratory chemicals

Section 6(b)(4)(A) unreasonable risk determination for repackaging of carbon tetrachloride for use in laboratory chemicals: **Presents an unreasonable risk of injury to health (workers and ONUs).**

For workers, EPA found that there was an unreasonable risk of cancer effects from dermal exposures at the central tendency and high-end, even when assuming use of PPE. For ONUs, EPA found that there was an unreasonable risk of cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the repackaging of carbon tetrachloride for use in laboratory chemicals presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-15) and other considerations. As explained in Section 5.1, EPA considered the health effects of carbon tetrachloride, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.4), including uncertainties related to the exposures for ONUs:

- For workers, when assuming use of gloves with PF of 20, the risk estimates of cancer effects (from both approaches) for dermal exposures at the high-end support an unreasonable risk determination.
- For workers, when assuming the use of respirators with APF of 50, the risk estimates of cancer effects (from both approaches) and non-cancer effects from chronic inhalation exposures at the high-end do not support an unreasonable risk determination. The risk estimates of non-cancer effects from acute inhalation exposures at the central tendency and high-end do not support an unreasonable risk determination.
- For ONUs, the risk estimates of cancer effects (from both approaches) at the central tendency support an unreasonable risk determination.
- For ONUs, the risk estimates of non-cancer effects from acute (CNS) and chronic (liver toxicity) inhalation exposures at the central tendency do not support an unreasonable risk determination.
- Based on EPA's analysis, the data for worker and ONU inhalation exposures could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency risk estimates from inhalation exposures when determining ONUs' unreasonable risk.
- Cancer risks were assessed using two approaches: linear extrapolation and threshold. The unreasonable risk determination is based on the risk estimates derived from both approaches.
- Inhalation exposures were assessed using surrogate data from two sources. The exposure sources, routes, and exposure levels are similar to those at an import/repackaging facility, where unloading and handling are the key worker activities. Carbon tetrachloride may be imported into the United States in bulk containers and may be repackaged into smaller containers for resale. EPA assumed the worker unloading activity will result in exposures similar to unloading/loading activities at manufacturing sites; however, the data may not be representative of the work activities and exposures across the range of repackaging facilities.
- Dermal exposures were assessed using modeled data.

In summary, the risk estimates, the health effects of carbon tetrachloride, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from repackaging of carbon tetrachloride for use in laboratory chemicals.

5.2.1.7 Processing – Recycling (Processing as recycling)

Section 6(b)(4)(A) unreasonable risk determination for recycling of carbon tetrachloride: **Presents an unreasonable risk of injury to health (workers and ONUs).**

For workers, EPA found that there was an unreasonable risk of cancer effects from dermal exposures at the central tendency and high-end, even when assuming use of PPE. For

ONUs, EPA found that there was an unreasonable risk of cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the recycling of carbon tetrachloride presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-15) and other considerations. As explained in Section 5.1, EPA considered the health effects of carbon tetrachloride, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.4), including uncertainties related to the exposures for ONUs:

- For workers, when assuming use of gloves with PF of 20, the risk estimates of cancer effects (from both approaches) for dermal exposures at the high-end support an unreasonable risk determination.
- For workers, when assuming the use of respirators with APF of 50, the risk estimates of cancer effects (from both approaches) and non-cancer effects from chronic inhalation exposures at the high-end do not support an unreasonable risk determination. The risk estimates of non-cancer effects from acute inhalation exposures at the central tendency and high-end do not support an unreasonable risk determination.
- For ONUs, the risk estimates of cancer effects (from both approaches) at the central tendency support an unreasonable risk determination.
- For ONUs, the risk estimates of non-cancer effects from acute (CNS) and chronic (liver toxicity) inhalation exposures at the central tendency do not support an unreasonable risk determination.
- Based on EPA's analysis, the data for worker and ONU inhalation exposures could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency risk estimates from inhalation exposures when determining ONUs' unreasonable risk.
- Cancer risks were assessed using two approaches: linear extrapolation and threshold. The unreasonable risk determination is based on the risk estimates derived from both approaches.
- Inhalation exposures were assessed using surrogate data from two sources. The exposure sources, routes, and exposure levels are similar to those at an import/repackaging facility, where unloading and handling are the key worker activities. Carbon tetrachloride may be imported into the United States in bulk containers and may be repackaged into smaller containers for resale. EPA assumed the worker unloading activity will result in exposures similar to unloading/loading activities at manufacturing sites; however, the data may not be representative of the work activities and exposures across the range of recycling facilities.
- Dermal exposures were assessed using modeled data.

In summary, the risk estimates, the health effects of carbon tetrachloride, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from recycling of carbon tetrachloride.

5.2.1.8 Distribution in Commerce

Section 6(b)(4)(A) unreasonable risk determination for distribution in commerce of carbon tetrachloride: Does not present an unreasonable risk of injury to health (workers and ONUs).

For the purposes of the unreasonable risk determination, distribution in commerce of carbon tetrachloride is the transportation associated with the moving of carbon tetrachloride in commerce. The loading and unloading activities are associated with other conditions of use. EPA assumes transportation of carbon tetrachloride is in compliance with existing regulations for the transportation of hazardous materials, and emissions are therefore minimal (with the exception of spills and leaks, which are outside the scope of the risk evaluation). Based on the limited emissions from the transportation of chemicals, EPA determines there is no unreasonable risk of injury to health (workers and ONUs) from the distribution in commerce of carbon tetrachloride.

5.2.1.9 Industrial/Commercial Use – Industrial processing aid in the manufacture of petrochemicals-derived products and agricultural products

Section 6(b)(4)(A) unreasonable risk determination for the industrial and commercial use of carbon tetrachloride as an industrial processing aid in the manufacture of petrochemicals-derived products and agricultural products: **Presents an unreasonable risk of injury to health (workers and ONUs).**

For workers, EPA found that there was an unreasonable risk of cancer effects from dermal exposures at the central tendency and high-end, even when assuming use of PPE. For ONUs, EPA found that there was an unreasonable risk of cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the industrial and commercial use of carbon tetrachloride in the manufacture of petrochemicals-derived products and agricultural products presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-15) and other considerations. As explained in Section 5.1, EPA considered the health effects of carbon tetrachloride, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.4), including uncertainties related to the exposures for ONUs:

- For workers, when assuming use of gloves with PF of 20, the risk estimates of cancer effects (from both approaches) for dermal exposures at the high-end support an unreasonable risk determination.
- For workers, when assuming the use of respirators with APF of 50, the risk estimates of cancer effects (from both approaches) and non-cancer effects from chronic inhalation exposures at the high-end do not support an unreasonable risk determination. The risk estimates of non-cancer effects from acute inhalation exposures at the central tendency and high-end do not support an unreasonable risk determination.
- For ONUs, the risk estimates of cancer effects (from both approaches) at the central tendency support an unreasonable risk determination.
- For ONUs, the risk estimates of non-cancer effects from acute (CNS) and chronic (liver toxicity) inhalation exposures at the central tendency do not support an unreasonable risk determination.
- Based on EPA's analysis, the data for worker and ONU inhalation exposures could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency risk estimates from inhalation exposures when determining ONUs' unreasonable risk.
- Cancer risks were assessed using two approaches: linear extrapolation and threshold. The unreasonable risk determination is based on the risk estimates derived from both approaches.

- Inhalation exposures were assessed using surrogate data from two sources. The exposure sources, routes, and exposure levels are similar to those at an import/repackaging facility, where unloading and handling are the key worker activities. Carbon tetrachloride may be imported into the United States in bulk containers and may be repackaged into smaller containers for resale. EPA assumed the worker unloading activity will result in exposures similar to unloading/loading activities at manufacturing sites; however, the data may not be representative of the work activities and exposures across the range of facilities using carbon tetrachloride as a processing aid.
- Dermal exposures were assessed using modeled data.

In summary, the risk estimates, the health effects of carbon tetrachloride, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from the industrial and commercial use of carbon tetrachloride as an industrial processing aid in the manufacture of petrochemicals-derived products and agricultural products.

5.2.1.10 Industrial/Commercial Use – Additive

Section 6(b)(4)(A) unreasonable risk determination for the industrial and commercial use of carbon tetrachloride as an additive: **Presents an unreasonable risk of injury to health (workers and ONUs).**

For workers, EPA found that there was an unreasonable risk of cancer effects from dermal exposures at the central tendency and high-end, even when assuming use of PPE. For ONUs, EPA found that there was an unreasonable risk of cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the industrial and commercial use of carbon tetrachloride as an additive presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-15) and other considerations. As explained in Section 5.1, EPA considered the health effects of carbon tetrachloride, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.4), including uncertainties related to the exposures for ONUs:

- For workers, when assuming use of gloves with PF of 20, the risk estimates of cancer effects (from both approaches) for dermal exposures at the high-end support an unreasonable risk determination.
- For workers, when assuming the use of respirators with APF of 50, the risk estimates of cancer effects (from both approaches) and non-cancer effects from chronic inhalation exposures at the high-end do not support an unreasonable risk determination. The risk estimates of non-cancer effects from acute inhalation exposures at the central tendency and high-end do not support an unreasonable risk determination.
- For ONUs, the risk estimates of cancer effects (from both approaches) at the central tendency support an unreasonable risk determination.
- For ONUs, the risk estimates of non-cancer effects from acute (CNS) and chronic (liver toxicity) inhalation exposures at the central tendency do not support an unreasonable risk determination.
- Based on EPA's analysis, the data for worker and ONU inhalation exposures could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty,

EPA considered the workers' central tendency risk estimates from inhalation exposures when determining ONUs' unreasonable risk.

- Cancer risks were assessed using two approaches: linear extrapolation and threshold. The unreasonable risk determination is based on the risk estimates derived from both approaches.
- Inhalation exposures were assessed using surrogate data from two sources. The exposure sources, routes, and exposure levels are similar to those at an import/repackaging facility, where unloading and handling are the key worker activities. Carbon tetrachloride may be imported into the United States in bulk containers and may be repackaged into smaller containers for resale. EPA assumed the worker unloading activity will result in exposures similar to unloading/loading activities at manufacturing sites; however, the data may not be representative of the work activities and exposures across the range of facilities using carbon tetrachloride as an additive.
- Dermal exposures were assessed using modeled data.

In summary, the risk estimates, the health effects of carbon tetrachloride, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from the industrial and commercial use of carbon tetrachloride as an additive.

5.2.1.11 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, asphalt, and elimination of nitrogen trichloride in the production of chlorine and caustic)

Section 6(b)(4)(A) unreasonable risk determination for the industrial and commercial use of carbon tetrachloride in other basic organic and inorganic chemical manufacturing (manufacturing of chlorinated compounds used in solvents for cleaning and degreasing, adhesives and sealants, paints and coatings, asphalt, and elimination of nitrogen trichloride in the production of chlorine and caustic): **Presents an unreasonable risk of injury to health (workers and ONUs).**

For workers, EPA found that there was an unreasonable risk of cancer effects from dermal exposures at the central tendency and high-end, even when assuming use of PPE. For ONUs, EPA found that there was an unreasonable risk of cancer from chronic inhalation exposures at the central tendency and high-end and non-cancer effects from chronic (liver toxicity) inhalation exposures at the high-end.

EPA's determination that the industrial and commercial use of carbon tetrachloride in other basic organic and inorganic chemical manufacturing (manufacturing of chlorinated compounds used in solvents for cleaning and degreasing, adhesives and sealants, paints and coatings, asphalt, and elimination of nitrogen trichloride in the production of chlorine and caustic) presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-15) and other considerations. As explained in Section 5.1, EPA considered the health effects of carbon tetrachloride, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.4):

- For workers, when assuming use of gloves with PF of 20, the risk estimates of cancer effects (from both approaches) for dermal exposures at the high-end support an unreasonable risk determination.
- For workers, when assuming the use of respirators with APF of 50, the risk estimates of cancer effects (from both approaches) and non-cancer effects from chronic inhalation exposures at the high-end do not support an unreasonable risk determination. The risk estimates of non-cancer effects from acute inhalation exposures at the central tendency and high-end do not support an unreasonable risk determination.
- For ONUs, the risk estimates of cancer effects (from both approaches) at the central tendency and high-end support an unreasonable risk determination.
- For ONUs, the risk estimates of non-cancer effects from acute (CNS) inhalation exposures at the high-end do not support an unreasonable risk determination.
- Cancer risks were assessed using two approaches: linear extrapolation and threshold. The unreasonable risk determination is based on the risk estimates derived from both approaches.
- EPA recognizes that the manufacturing setting and associated worker activities are similar for the manufacture of carbon tetrachloride, processing as a reactant or intermediate, and industrial and commercial use of carbon tetrachloride in other basic organic and inorganic chemical manufacturing. Therefore, to assess inhalation exposures, EPA assessed this condition of use under the Processing as a Reactant exposure scenario using personal breathing zone monitoring data from two sources for workers and ONUs in a manufacturing setting; however, the data may not be representative of the work activities and exposures across the range of facilities that use carbon tetrachloride in chemical manufacturing.
- Dermal exposures were assessed using modeled data.

In summary, the risk estimates, the health effects of carbon tetrachloride, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from the industrial and commercial use of carbon tetrachloride in other basic organic and inorganic chemical manufacturing (manufacturing of chlorinated compounds used in solvents for cleaning and degreasing, adhesives and sealants, paints and coatings, asphalt, and elimination of nitrogen trichloride in the production of chlorine and caustic).

5.2.1.12 Industrial/Commercial Use – Metal Recovery

Section 6(b)(4)(A) unreasonable risk determination for the industrial and commercial use of carbon tetrachloride in metal recovery: **Presents an unreasonable risk of injury to health (workers and ONUs).**

For workers, EPA found that there was an unreasonable risk of cancer effects from dermal exposures at the central tendency and high-end, even when assuming use of PPE. For ONUs, EPA found that there was an unreasonable risk of cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the industrial and commercial use of carbon tetrachloride in metal recovery presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-15) and other considerations. As explained in Section 5.1, EPA considered the health effects of carbon tetrachloride, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.4), including uncertainties related to the exposures for ONUs:

- For workers, when assuming use of gloves with PF of 20, the risk estimates of cancer effects (from both approaches) for dermal exposures at the high-end support an unreasonable risk determination.
- For workers, when assuming the use of respirators with APF of 50, the risk estimates of cancer effects (from both approaches) and non-cancer effects from chronic inhalation exposures at the high-end do not support an unreasonable risk determination. The risk estimates of non-cancer effects from acute inhalation exposures at the central tendency and high-end do not support an unreasonable risk determination.
- For ONUs, the risk estimates of cancer effects (from both approaches) at the central tendency support an unreasonable risk determination.
- For ONUs, the risk estimates of non-cancer effects from acute (CNS) and chronic (liver toxicity) inhalation exposures at the central tendency do not support an unreasonable risk determination.
- Based on EPA's analysis, the data for worker and ONU inhalation exposures could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency risk estimates from inhalation exposures when determining ONUs' unreasonable risk.
- Cancer risks were assessed using two approaches: linear extrapolation and threshold. The unreasonable risk determination is based on the risk estimates derived from both approaches.
- Inhalation exposures were assessed using surrogate data from two sources. The exposure sources, routes, and exposure levels are similar to those at an import/repackaging facility, where unloading and handling are the key worker activities. Carbon tetrachloride may be imported into the United States in bulk containers and may be repackaged into smaller containers for resale. EPA assumed the worker unloading activity will result in exposures similar to unloading/loading activities at manufacturing sites; however, the data may not be representative of the work activities and exposures across the range of facilities that use carbon tetrachloride in metal recovery.
- Dermal exposures were assessed using modeled data.

In summary, the risk estimates, the health effects of carbon tetrachloride, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from the industrial and commercial use of carbon tetrachloride in metal recovery.

5.2.1.13 Industrial/Commercial Use – Specialty Uses – Department of Defense

Section 6(b)(4)(A) unreasonable risk determination for the industrial and commercial use of carbon tetrachloride in specialty uses by the Department of Defense: **Presents an unreasonable risk of injury to health (workers).**

For workers, EPA found that there was an unreasonable risk of cancer effects from dermal exposures at the central tendency and high-end, even when assuming use of PPE. For ONUs, EPA did not identify an unreasonable risk of cancer from chronic inhalation exposures and non-cancer effects (CNS and liver toxicity) from acute and chronic inhalation exposures.

EPA's determination that the industrial and commercial use of carbon tetrachloride in specialty uses by Department of Defense presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-15) and other considerations. As explained in Section 5.1, EPA considered the health effects of carbon tetrachloride, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.4), including uncertainties related to the exposures for ONUs:

- For workers, when assuming use of gloves with PF of 20, the risk estimates of cancer effects (from both approaches) for dermal exposures at the high-end support an unreasonable risk determination.
- For workers, when assuming the use of respirators with APF of 50, the risk estimates of cancer effects (from both approaches) and non-cancer effects from chronic inhalation exposures at the high-end do not support an unreasonable risk determination. The risk estimates of non-cancer effects from acute inhalation exposures at the central tendency and high-end do not support an unreasonable risk determination.
- For ONUs, the risk estimates of cancer effects (from both approaches) for inhalation exposures and non-cancer effects from acute (CNS) and chronic (liver toxicity) inhalation exposures at the central tendency do not support an unreasonable risk determination.
- Cancer risks were assessed using two approaches: linear extrapolation and threshold. The unreasonable risk determination is based on the risk estimates derived from both approaches.
- Based on EPA's analysis, the data for worker and ONU inhalation exposures could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency risk estimates from inhalation exposures when determining ONUs' unreasonable risk.
- Inhalation exposures were assessed using personal breathing zone monitoring data provided by the Department of Defense.
- Dermal exposures were assessed using modeled data.

In summary, the risk estimates, the health effects of carbon tetrachloride, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to

health (workers) from the industrial and commercial use of carbon tetrachloride in specialty uses by Department of Defense.

5.2.1.14 Industrial/Commercial Use – Laboratory Chemical

Section 6(b)(4)(A) unreasonable risk determination for the industrial and commercial use of carbon tetrachloride as a laboratory chemical: **Presents an unreasonable risk of injury to health (workers).**

For workers, EPA found that there was an unreasonable risk of cancer effects from dermal exposures at the central tendency and high-end, even when assuming use of PPE.

Due to expected safety practices when using carbon tetrachloride in a laboratory setting, where carbon tetrachloride is applied in small quantities under a fume hood, EPA does not expect there to be inhalation exposures to workers and ONUs. Thus, EPA did not evaluate inhalation exposures to workers or ONUs for this condition of use. EPA's determination that the industrial and commercial use of carbon tetrachloride as a laboratory chemical presents an unreasonable risk is based on the comparison of the dermal risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-15) and other considerations. As explained in Section 5.1, EPA considered the health effects of carbon tetrachloride, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.4):

- For workers, when assuming use of gloves with PF of 20, the risk estimates of cancer effects (from both approaches) for dermal exposures at the high-end support an unreasonable risk determination.
- Cancer risks were assessed using two approaches: linear extrapolation and threshold. The unreasonable risk determination is based on the risk estimates derived from both approaches.
- Dermal exposures were assessed using modeled data.

In summary, the risk estimates, the health effects of carbon tetrachloride, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers) from the industrial and commercial use of carbon tetrachloride as a laboratory chemical.

5.2.1.15 Disposal – Disposal

Section 6(b)(4)(A) unreasonable risk determination for the disposal of carbon tetrachloride: **Presents an unreasonable risk of injury to health (workers and ONUs).**

For workers, EPA found that there was an unreasonable risk of cancer effects from dermal exposures at the central tendency and high-end, even when assuming use of PPE. For ONUs, EPA found that there was an unreasonable risk of cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the disposal of carbon tetrachloride presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-15) and other considerations. As explained in Section 5.1, EPA considered the health effects of carbon tetrachloride, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.4), including uncertainties related to the exposures for ONUs:

- For workers, when assuming use of gloves with PF of 20, the risk estimates of cancer effects (from both approaches) for dermal exposures at the high-end support an unreasonable risk determination.
- For workers, when assuming the use of respirators with APF of 50, the risk estimates of cancer effects (from both approaches) and non-cancer effects from chronic inhalation exposures at the high-end do not support an unreasonable risk determination. The risk estimates of non-cancer effects from acute inhalation exposures at the central tendency and high-end do not support an unreasonable risk determination.
- For ONUs, the risk estimates of cancer effects (from both approaches) at the central tendency support an unreasonable risk determination.
- For ONUs, the risk estimates of non-cancer effects from acute (CNS) and chronic (liver toxicity) inhalation exposures at the central tendency do not support an unreasonable risk determination.
- Based on EPA's analysis, the data for worker and ONU inhalation exposures could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency risk estimates from inhalation exposures when determining ONUs' unreasonable risk.
- Cancer risks were assessed using two approaches: linear extrapolation and threshold. The unreasonable risk determination is based on the risk estimates derived from both approaches.
- Inhalation exposures were assessed using surrogate data from two sources. The exposure sources, routes, and exposure levels are similar to those at an import/repackaging facility, where unloading and handling are the key worker activities. Carbon tetrachloride may be imported into the United States in bulk containers and may be repackaged into smaller containers for resale. EPA assumed the worker unloading activity will result in exposures similar to unloading/loading activities at manufacturing sites; however, the data may not be representative of the work activities and exposures across the range of disposal facilities
- Dermal exposures were assessed using modeled data.

In summary, the risk estimates, the health effects of carbon tetrachloride, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from the disposal of carbon tetrachloride.

5.2.2 Environment

6(b)(4)(A) unreasonable risk determination for **all conditions** of use of carbon tetrachloride: Does not present an unreasonable risk of injury **to the environment**.

For all conditions of use, the RQ values (Table 4-2) do not support an unreasonable risk determination in water for acute and chronic exposures to carbon tetrachloride for amphibians, fish, and aquatic invertebrates. To characterize the exposure to carbon tetrachloride by aquatic organisms, modeled data were used to represent surface water concentrations near facilities actively releasing carbon tetrachloride to surface water. EPA considered the biological relevance of the species to determine the concentrations of concern for the location of surface water concentration data to produce RQs, as well as timing and seasonality of the exposure. While the RQ was exceeded (RQ>1) from chronic exposure of carbon tetrachloride to amphibians at five facilities, additional characterization of risk based on seasonable exposure data indicated one of the exceedances did not occur during time periods relevant to amphibian

development. For the four facilities with RQ exceedances relevant to amphibian development during two separate reporting periods, risk was not consistent across facilities, and it is not possible to predict with any certainty whether risk will or will not occur during months key to amphibian development in future years. Uncertainties related to these particular estimates are discussed in section 4.4.2 and 4.4.3. EPA's analysis indicates that significant environmental exposures are not expected to exceed the acute and chronic COCs for aquatic species, as presented in Section 4.1.1.

The toxicity of carbon tetrachloride to sediment-dwelling invertebrates is similar to the toxicity to aquatic invertebrates. Carbon tetrachloride is most likely present in the pore waters and not absorbed to the sediment organic matter because carbon tetrachloride has low partitioning to organic matter. The concentrations in sediment pore water are similar to or less than the concentrations in the overlying water, and concentrations in the deeper part of sediment are lower than the concentrations in the overlying water. Therefore, for sediment-dwelling organisms the risk estimates, based on the highest ambient surface water concentration, do not support an unreasonable risk determination to sediment-dwelling organisms from acute or chronic exposures. While EPA identified one low quality study on sediment-dwelling organisms, there is uncertainty due to the lack of ecotoxicity studies specifically for sediment-dwelling organisms and limited sediment monitoring data.

Based on its physical-chemical properties, carbon tetrachloride does not partition to or accumulate in soil. Therefore, the physical-chemical properties of carbon tetrachloride do not support an unreasonable risk determination to terrestrial organisms from exposure to carbon tetrachloride through soil and land-applied biosolids.

In summary, the risk estimates, the environmental effects of carbon tetrachloride, the exposures, physical-chemical properties of carbon tetrachloride and consideration of uncertainties support a determination that there is no unreasonable risk for the environment from all conditions of use of carbon tetrachloride.

5.3 Changes to the Unreasonable Risk Determination from Draft Risk Evaluation to Final Risk Evaluation

In this final risk evaluation, EPA made changes to the unreasonable risk determination for carbon tetrachloride, as a result of the analysis following peer review and public comment. There are four types of changes: an updated dermal model, the addition of a threshold approach for cancer risks, use of surrogate data in place of modeled data, refinement of the unreasonable risk determination for injury to the environment for all conditions of use, and clarification of the unreasonable risk determinations for processing carbon tetrachloride for incorporation into formulation, mixtures, or reaction products.

In the final risk evaluation, EPA used a dermal model for all conditions of use that was updated from the draft risk evaluation based on peer review comments, which resulted in changes from the preliminary unreasonable risk determinations for most conditions of use. Peer review recommendations also included identifying a threshold POD for cancer. EPA found that the threshold approach is most relevant for liver carcinogenicity, while the linear extrapolation approach (consistent with draft risk evaluation) is most appropriate for adrenal gland and brain

carcinogenicity. The risk determinations for cancer for all conditions of use are therefore based on the risk estimates for both of these approaches.

Additionally, in the draft risk evaluation, EPA evaluated the import/repackaging of carbon tetrachloride using modeled data; however, the surrogate data provided by HSIA was found to be adequate for this condition of use and other conditions of use with similar worker activities. EPA has developed an occupational scenario using this surrogate data, and therefore the import/repackaging of carbon tetrachloride as well as conditions of use with similar worker activities have a final unreasonable risk determination that is different from the preliminary unreasonable risk determination in the draft risk evaluation.

EPA has also further refined the final unreasonable risk determination for all conditions of use for risk of injury to the environment, and therefore provides greater detail regarding unreasonable risks to the environment than the preliminary determination presented in the draft risk evaluation. Specifically, in the final risk evaluation, EPA qualitatively evaluated the soil and land-applied biosolids pathways and is now issuing a risk determination for terrestrial organisms.

EPA uses representative Occupational Exposure Scenarios to generate risk estimates. Sometimes the same Exposure Scenario is used for several conditions of use, and sometimes unreasonable risk determinations are based on multiple exposure scenarios. EPA makes an unreasonable risk determination for each condition of use within the scope of the risk evaluation. For further clarity, EPA is now issuing a single unreasonable risk determination for Processing – Incorporation into formulation, mixture or reaction products-Petrochemicals-derived manufacturing, agricultural products manufacturing, and other basic organic and inorganic chemical manufacturing, for which two preliminary unreasonable risk determinations were presented in the draft risk evaluation. This condition of use was evaluated under two exposure scenarios, both of which used HSIA monitoring data.

Table 5-2. Updates in Presentation of Unreasonable Risk Determinations Between Draft and Final Risk Evaluations

Unreasonable Risk Determinations in Final Risk Evaluation	**Unreasonable Risk Determinations in Draft Risk Evaluation** (emphasis added)
• Processing for incorporation into formulation, mixtures or reaction products (Petrochemicals-derived manufacturing; Agricultural products manufacturing; Other basic organic and inorganic chemical manufacturing)	• Processing for incorporation into formulation, mixtures or reaction products (Petrochemicals-derived manufacturing; Agricultural products manufacturing) • Processing for incorporation into formulation, mixtures or reaction products (Other basic organic and inorganic chemical manufacturing)

5.4 Unreasonable Risk Determination Conclusion

5.4.1 No Unreasonable Risk Determinations

TSCA Section 6(b)(4) requires EPA to conduct risk evaluations to determine whether chemical substances present unreasonable risk under their conditions of use. In conducting risk evaluations, "EPA will determine whether the chemical substance presents an unreasonable risk of injury to health or the environment under each condition of use within the scope of the risk evaluation…" 40 CFR 702.47. Pursuant to TSCA Section 6(i)(1), a determination of "no unreasonable risk" shall be issued by order and considered to be final agency action. Under EPA's implementing regulations, "[a] determination by EPA that the chemical substance, under one or more of the conditions of use within the scope of the risk evaluations, does not present an unreasonable risk of injury to health or the environment will be issued by order and considered to be a final Agency action, effective on the date of issuance of the order." 40 CFR 702.49(d).

EPA has determined that the following conditions of use of carbon tetrachloride do not present an unreasonable risk of injury to health or the environment:

- Processing as a reactant/intermediate in reactive ion etching (*i.e.*, semiconductor manufacturing) (Section 5.2.1.4, Section 5.2.2, Section 4, Section 3, and Section 2.4.1.7.5)
- Distribution in commerce (Section 5.2.1.8, Section 5.2.2, Section 4, Section 3)

This subsection of the final risk evaluation therefore constitutes the order required under TSCA Section 6(i)(1), and the "no unreasonable risk" determinations in this subsection are considered to be final agency action effective on the date of issuance of this order. All assumptions that went into reaching the determinations of no unreasonable risk for these conditions of use, including any considerations excluded for these conditions of use, are incorporated into this order.

The support for each determination of "no unreasonable risk" is set forth in Section 5.2 of the final risk evaluation, "Detailed Unreasonable Risk Determinations by Condition of Use." This subsection also constitutes the statement of basis and purpose required by TSCA Section 26(f).

5.4.2 Unreasonable Risk Determinations

EPA has determined that the following conditions of use of carbon tetrachloride present an unreasonable risk of injury:

- Domestic Manufacture
- Import (including loading/unloading and repackaging)
- Processing as a reactant in the production of hydrochlorofluorocarbons, hydrofluorocarbon, hydrofluoroolefin, and perchloroethylene
- Processing for incorporation into formulation, mixtures or reaction products (petrochemicals-derived manufacturing; agricultural products manufacturing; other basic organic and inorganic chemical manufacturing)
- Repackaging for use in laboratory chemicals
- Recycling
- Industrial/commercial use as an industrial processing aid in the manufacture of petrochemicals-derived products and agricultural products
- Industrial/commercial use as an additive
- Industrial/commercial use in the manufacture of other basic chemicals (including chlorinated compounds used in solvents, adhesives, asphalt, and paints and coatings)

- Industrial/commercial use in metal recovery
- Specialty uses by the Department of Defense
- Industrial/commercial use as a laboratory chemical
- Disposal

EPA will initiate TSCA Section 6(a) risk management actions on these conditions of use as required under TSCA Section 6(c)(1). Pursuant to TSCA Section 6(i)(2), the "unreasonable risk" determinations for these conditions of use are not considered final agency action.

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7 APPENDICES

Appendix A REGULATORY HISTORY

A.1 Federal Laws and Regulations

Table 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).

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
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) (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	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
	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 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)

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
		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 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.	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, 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	In 2015, EPA published updated AWQC for carbon tetrachloride, including recommendations for "water +

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
	health that may be expected from the presence of pollutants in any body of water.	organism" and "organism only" human health criteria for states and authorized tribes to consider when adopting criteria into their water quality standards. See 80 FR 36986 (June 29, 2015); https://www.regulations.gov/document?D=EPA-HQ-OW-2014-0135-0182.
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 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).	Carbon tetrachloride is designated as a toxic pollutant under Section 307(a)(1) of the CWA and as such is subject to effluent limitations.
SDWA - Section 1412	Requires EPA to publish a non-enforceable maximum contaminant level goals (MCLGs) for a contaminant which EPA makes a determination that the contaminant 1. may have an adverse effect on the health of persons; 2. is known to occur or there is a substantial	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 (40 CFR 141.50; 40 CFR

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
	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.	141.61; 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 knowledge of a release of a hazardous substance above the reportable quantity threshold.	Carbon tetrachloride is a hazardous substance under CERCLA. Releases of carbon tetrachloride in excess of 10 pounds must be reported (40 CFR 302.4).
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 261.33(f)), and spent degreasing solvent (F001) (40

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
		CFR 261.31(a)) (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). 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).

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
		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 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 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 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 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

Country/Organization	Requirements and Restrictions
	(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.
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 LIST OF SUPPLEMENTAL DOCUMENTS

1. Associated Systematic Review Data Quality Evaluation and Data Extraction Documents- Provides additional detail and information on individual study evaluations and data extractions including criteria and scoring results.
    a. *Final Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Fate and Transport Studies. Docket EPA-HQ-OPPT-2019-0499 (*U.S. EPA, 2019f*).*

    b. *Final Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Physical Chemical Properties Studies Docket EPA-HQ-OPPT-2019-0499* (U.S. EPA, 2019k).

    c. *Final Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Releases and Occupational Exposure Data Common Sources. Docket EPA-HQ-OPPT-2019-0499* (U.S. EPA, 2019i).

    d. *Final Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Releases and Occupational Exposure Data. Docket EPA-HQ-OPPT-2019-0499* (U.S. EPA, 2019h).

    e. *Final Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Hazard Studies. Docket EPA-HQ-OPPT-2019-0499* (U.S. EPA, 2019g).

    f. *Final Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies – Animal and Invitro Studies. Docket EPA-HQ-OPPT-2019-0499* (U.S. EPA, 2019e).

    g. *Final Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies - Epidemiological Studies. Docket EPA-HQ-OPPT-2019-0499* (U.S. EPA, 2019j).

    h. *Final Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies. Docket EPA-HQ-OPPT-2019-0499* (U.S. EPA, 2019l).

2. *Final Risk Evaluation for Carbon Tetrachloride, Supplemental File on Releases and Occupational Exposure Assessment, EPA-HQ-OPPT-2019-0499* (U.S. EPA, 2019c) - provides additional details and information on the environmental release and occupational exposure assessment, including process information, estimates of number of sites and workers, summary of monitoring data, and exposure modeling equations, inputs and outputs.

3. *Final Risk Evaluation for Carbon Tetrachloride, Supplemental File on Occupational Exposure Risk Calculator, EPA-HQ-OPPT-2019-0499* (U.S. EPA, 2019b).

4. *Final Risk Evaluation for Carbon Tetrachloride Supplemental File: Benchmark Dose Modeling and Source Code for PBPK Model for Derivation of the IRIS Reference Concentration (POD for Chronic Inhalation Exposures) and Inhalation Unit Risk, EPA-HQ-OPPT-2019-0499* (U.S. EPA, 2019d).

Appendix C FATE AND TRANSPORT

Table C-1. Biodegradation Study Summary for Carbon Tetrachloride

Study Type (year)	Initial Concentration	Inoculum Source	(An)aerobic Status	Duration	Result	Comments	Affiliated Reference	Data Quality Evaluation Results of Full Study Report
Water								
Anaerobic biodegradation using unadapted methanogenic granular sludge both with and without a co-substrate.	<7.5 µmol/L	activated sludge, industrial, nonadapted	anaerobic	15 days	Biodegradation parameter: percent removal: 100%/5-11d in unadapted sludge; 100%/5-8d in unadapted sludge + cosubstrate; 100%/15-16d in autoclaved sludge	The reviewer agreed with this study's overall quality level.	(Van Eekert et al., 1998)	High
Other	≤149 µg/L	activated sludge, adapted	anaerobic	54 days	Biodegradation parameter: percent removal by radiolabel: 100%/16d	The reviewer agreed with this study's overall quality level.	(Bouwer and McCarty, 1983)	High
Other	≤16 µg/L	activated sludge, adapted	anaerobic	19 months	Biodegradation parameter: concentration in column effluent (initial concentration: 16 µg/L, liquid retention: 2 days): <0.1 µg/L	The reviewer agreed with this study's overall quality level.	(Bouwer and McCarty, 1983)	High

Study Type (year)	Initial Concentration	Inoculum Source	(An)aerobic Status	Duration	Result	Comments	Affiliated Reference	Data Quality Evaluation Results of Full Study Report
Static-culture, flask-screening method	5 mg/L	sewage, domestic, non-adapted	Aerobic	7 days, then three additional 7-day periods for "subcultures" (total test time was 28 days)	Biodegradation parameter: percent removal: Avg. 89%/7 days	The reviewer agreed with this study's overall quality level.	(Tabak et al., 1981)	High
Transformation under sulfate reducing conditions in an anaerobic continuously fed packed-bed reactor	2.5-56.6 µmol/L	anaerobic micro-organisms	anaerobic	13 days (variable electron donors); 27 days to 30 weeks(inhibition - variable concentration)	Biodegradation parameter: percent removal via dechlorination: 100%/30 weeks; transformation products included chloroform and dichloro-methane.	The reviewer agreed with this study's overall quality level.	(de Best et al., 1997)	High
Soil								
Other	100 mg/kg	Microbial colonies on agar plates revealed that autoclave controls were devoid of microbial activity.	not specified	7 days	Biodegradation parameter: half-life: 50%/5 days	The reviewer agreed with this study's overall quality level.	(Anderson et al., 1991)	Medium

Table C-2. Photolysis Study Summary for Carbon Tetrachloride

Study Type (year)	Wavelength Range	Duration	Result	Comments	Affiliated Reference	Data Quality Evaluation Results of Full Study Report
Air						
Calculation	195 - 225 nm	Not reported	Photodegradation parameter: atmospheric lifetime or residence time: 30-50 years	The reviewer agreed with this study's overall quality level.	(Molina and Rowland, 1974)	High
Photochemical oxidation using photolysis of nitrous acid in air as a source of hydroxyl radicals	360 nm	Not reported	Photodegradation parameter: Tropospheric lifetime: >330 years	The reviewer agreed with this study's overall quality level.	(Cox et al., 1976)	High
Absorption	160-275	700 seconds	Photodegradation parameter: absorption: threshold wavelength = 253 nm	The reviewer agreed with this study's overall quality level.	(Hubrich and Stuhl, 1980)	High
Water						
Reductive dechlorination in aqueous solution with ferrous and sulfide ions in the absence and presence of light	Visible light; 530±20 lux	33 days	Photodegradation parameter: percent transformation via reductive dechlorination: 84%/33d (Ferrous; dark); 99.9%/33d (Ferrous; light)	The reviewer agreed with this study's overall quality level.	(Doong and Wu, 1992)	High

Table C-3. Hydrolysis Study Summary for Carbon Tetrachloride

Study Type (year)	pH	Temperature	Duration	Results	Comments	Affiliated Reference	Data Quality Evaluation Results of Full Study Report
Calculation; Review paper including calculated kh and t(1/2) at 298K and pH 7 for carbon tetrachloride	7	298K	Not reported	Hydrolysis parameter: half-life (298K and 1ppm): 7000 years.	The reviewer agreed with this study's overall quality level.	(Mabey and Mill, 1978)	Medium

Table C-4. Sorption Study Summary for Carbon Tetrachloride

Study Type (year)	Sorbent Source	Sorbent Qualities (clay/silt/sand, OC, pH)	Duration	Results	Comments	Affiliated Reference	Data Quality Evaluation Results of Full Study Report
Partitioning based on measurements in sediments of Scheldt Estuary and water Southern North Sea	Water salinity range 1.45-20.8 g/L Scheldt estuary and Belgian continental shelf sediments	Not reported		Sorption parameter: log Koc(sw,eq.): 1.67	The reviewer agreed with this study's overall quality level.	(Roose et al., 2001)	High
Equilibrium and two-site models applied to field and laboratory experiments to determine transport behavior (including Kd)	Breakthrough curves measured under water-saturated, steady-flow conditions in glass columns with aquifer material from site at Borden, Ontario and synthetic groundwater prepared from organic-free water; field experiments at site in Borden, Ontario	organic carbon 0.018-0.020 wt%, pH 8.2-8.3		Sorption parameter: Kd: 0.019-0.168 (g/g); Retardation factors obtained from column experiments conducted at high velocities were lower than those obtained at low velocities	The reviewer agreed with this study's overall quality level.	(Ptacek and Gillham, 1992)	High
Sorption isotherms in lignite and peat soil	lignite sample collected from Oberlausitz area in Saxony, Germany;	Carbon content lignite: 53.5% peat 46.1%; moisture content		Sorption parameter: log Kf: lignite and peat, respectively: 2.29, 1/n = 0.916 and 1.59, 1/n = 0.879	The reviewer agreed with this study's overall quality level.	(Endo et al., 2008)	High

Study Type (year)	Sorbent Source	Sorbent Qualities (clay/silt/sand, OC, pH)	Duration	Results	Comments	Affiliated Reference	Data Quality Evaluation Results of Full Study Report
	Pahokee peat soil purchased from International Humic Substances Society	11.1±0.4% 10.2±0.2%					
Column sorption of Carbon tetrachloride	Sandy soil samples sieved through a 0.425-mm sieve and retained by a 0.250-mm sieve	97.6% sand 2.4% clay; OC below the detection limit of 0.03%		Sorption parameter: Kd: 0.39 L/kg; retardation factor (Rf) 2.64	The reviewer agreed with this study's overall quality level.	(Zhao et al., 1999)	High
No guideline cited; batch equilibrium soil sorption study	McLaurin sandy Loam from Stone County, MS. Air dried and sieved to 2 mm	0.66±0.04%, pH 4.43 +/- 0.03		Sorption parameter: Koc: 48.89 +/-16.16; Sorption parameter: Kp: 0.323 +/-0.107	The reviewer agreed with this study's overall quality level. Study reported in ECHA (ECHA, 2017a)	(Walton et al., 1992)	High
Sorption on wastewater solids (isotherm test)	Wastewater solids collected from three different municipal WWTP near Cincinnati OH, Volatile suspended solids ranged from 65-85%	Not applicable		Sorption parameter: log Kp: primary sludge, mixed-liquor solids and digested, sludge, respectively: 2.66, 2.80, 2.49	The reviewer agreed with this study's overall quality level.	(Dobbs et al., 1989)	High
No guideline cited; batch equilibrium soil sorption study	Captina silt loam from Roane County, TN. Air dried and sieved to 2 mm	1.49±0.06%, pH 4.97±0.08		Sorption parameter: Koc: 143.6 +/-32.11; Sorption parameter: Kp: 2.140 +/-0.478	The reviewer agreed with this study's overall quality level. Study reported in ECHA (ECHA, 2017a)	(Walton et al., 1992)	High

Study Type (year)	Sorbent Source	Sorbent Qualities (clay/silt/sand, OC, pH)	Duration	Results	Comments	Affiliated Reference	Data Quality Evaluation Results of Full Study Report
Column desorption study using contaminated aquifer sediments	T17; T18; T19: 3 sediment cores from aquifer in Hanford known to contain ` and CHCl3; samples were stored at 4degC; OC determined using ASTM standard procedure; groundwater from Hanford site	T17; T18; T19: OC 0.059%, 0.017%, 0.088%; gravel 58.97%, 1.85%, 8.16%; Sand 25.6%, 835.%, 9.53%; silt 6.02%, 10.2%, 45.5%; clay: 1.97%, 4.42%, 36.7%, respectively		Sorption parameter: Kd: T17 core sample and T18 core sample, respectively: 0.367, 1.44	The reviewer agreed with this study's overall quality level.	(Riley et al., 2010)	High
Batch equilibration studies in a stratigraphic column for the determination of sorption coefficients Koc and Kd in soils representing three horizons	Soil samples from University of Nebraska's South Central Research and Extension Center in Clay County, NE; hasting series: fine, montmorillonitic, mesic Udic Argiustoll	% silt and sand not reported. Total clay content (g/kg) = 265.7±22.6 Modern A horizon, 330.4±16.2 Buried A, 273.7±30.4 Loess C horizon. Organic carbon (g/kg): 14.9±2.6 Modern A, 5.3±0.6 Buried A, 1.4±0.5 Loess C		Sorption parameter: log Koc: Modern A horizon, Buried A and Loess C horizon sites, respectively: 1.74 (±0.04), 1.89 (±0.10), 2.43 (±0.18)	The reviewer agreed with this study's overall quality level.	(Duffy et al., 1997)	High

Study Type (year)	Sorbent Source	Sorbent Qualities (clay/silt/sand, OC, pH)	Duration	Results	Comments	Affiliated Reference	Data Quality Evaluation Results of Full Study Report
Vapor sorption of carbon tetrachloride in high organic soils	Peat reference sample from International Humic Substances Society collected from Everglades Fl; extracted peat from 0.1M NaOH extraction of reference peat soil; muck soil from Michigan State University Research Farm Lainsburg, MI	Carbon content (from cited source): extracted peat 64.0%, peat 57.1%, muck 53.1%, cellulose 44.4%; oxygen content: extracted peat 28.9%, peat 33.9%, muck 37.5%, cellulose 49.4%; ash content: extracted peat 15.0%, peat 13.6%, muck 18.5%		Sorption parameter: Kom: peat and muck respectively: 44.6, 27.8	The reviewer agreed with this study's overall quality level. A previous study was cited for several details, HERO ID 3566467, Rutherford, D. W., *et al.* (1992). "Influence of soil organic matter composition on the partition of organic compounds."	(Rutherford and Chiou, 1992)	High
Sorption of Carbon tetrachloride in high organic soil and cellulose	Peat reference sample from International Humic Substances Society collected from Everglades, Fl; extracted peat from 0.1M NaOH extraction of reference peat soil; muck soil from Michigan	Carbon content: extracted peat 64.0%, peat 57.1%, muck 53.1%, cellulose 44.4%; oxygen content: extracted peat 28.9%, peat 33.9%, muck 37.5%,		Sorption parameter: Kom: peqt, peat, muck, and cellulose respectively: 73.5, 44.6, 27.8, and 1.75	The reviewer agreed with this study's overall quality level.	(Rutherford et al., 1992)	High

Study Type (year)	Sorbent Source	Sorbent Qualities (clay/silt/sand, OC, pH)	Duration	Results	Comments	Affiliated Reference	Data Quality Evaluation Results of Full Study Report
	State University Research Farm Lainsburg, MI; cellulose from Aldrich	cellulose 49.4%; ash content: extracted peat 15.0%, peat 13.6%, muck 18.5%, cellulose 0.0%					
ASTM, 1993. Standard Test Method for Determining a Sorption Constant (Koc) for an Organic Chemical in Soil and Sediments	Sediments collected from a chloroform and carbon tetrachloride contaminated sandy aquifer in Schoolcraft Michigan	Silty/fine sand; Medium sand; Coarse sand; Very coarse sand		Sorption parameter: Kd: Silty/fine sand, Medium sand, Coarse sand, and Very coarse sand, respectively: 0.162, 0.233, 0.494, 0.376	The reviewer agreed with this study's overall quality level.	(Zhao et al., 2005)	High
Sorption on aquifer materials	Column with low organic carbon aquifer materials Rabis, Vejen, and Vasby; groundwater from municipal drinking water plant in Denmark spiked influent carbon tetrachloride conc 26 µg/L	OC 0.007-0.025%; 63-90% coarse sand; 8-34% fine sand; 0-2% silt; 1-2% clay		Sorption parameter: Kd: 0.02 - 0.11; Rf = 1.10-1.46	The reviewer agreed with this study's overall quality level. The reviewer noted: Quantitative Kd data for carbon tetrachloride was not reported; however, the Rf was reported.	(Larsen et al., 1992)	High
Adsorption/desorption in soil	EPA standard soil (FW Enviresponse, Inc.) sieved to	OC 0.8%; sand 56.4% clay 28.9%, silt 14.7%		Sorption parameter: Monolayer adsorption capacity Xm: 7.3;	The reviewer agreed with this study's overall quality level.	(Thibaud et al., 1992)	High

Study Type (year)	Sorbent Source	Sorbent Qualities (clay/silt/sand, OC, pH)	Duration	Results	Comments	Affiliated Reference	Data Quality Evaluation Results of Full Study Report
	210-250 um analyzed by Soil Testing Laboratory of Texas A&M University			Sorption parameter: adsorption capacity at saturation Xa: 39.2			
Forced gradient test	Sand aquifer in Borden, Ontario composed of fine to medium grained sand; aquifer is unconfined, water table fluctuates over the year; aquifer is 10 m thick underlain by thick silty clay aquitard, within 2-3m of the aquifer is a plume of contaminants	silty clay		Sorption parameter: Kd: 0.03-0.24, Rf: .2-2.3	The reviewer agreed with this study's overall quality level.	(Mackay et al., 1994)	High
Calculation; Carbon tetrachloride concentrations in air and soil gas for determination of soil flux and partial atmospheric lifetime	Site characteristics: boreal, temperate, and tropical forests, temperate grasslands	Not reported	2 weeks monitoring data	Sorption parameter: τ-soil (partial lifetime of atmospheric carbon tetrachloride due to soil removal): 90 years	The reviewer agreed with this study's overall quality level; partial lifetime calculation based on 2 weeks monitoring data from several different regions.	(Happell and Roche, 2003)	High
Calculation; Carbon tetrachloride concentrations in air and soil gas for	boreal forest soil in Alberta, Canada; sub-tropical forest	Not reported		Sorption parameter: τ-soil (partial lifetime of atmospheric carbon	The reviewer agreed with this study's overall quality level.	(Happell et al., 2014)	High

Study Type (year)	Sorbent Source	Sorbent Qualities (clay/silt/sand, OC, pH)	Duration	Results	Comments	Affiliated Reference	Data Quality Evaluation Results of Full Study Report
determination of soil flux	soil in South Florida, tropical forest soil in Puerto Rico			tetrachloride due to soil removal): 245 years			
Determination of Freundlich sorption constants in silty loam clay	Hastings silty clay loams; Overton silty clay loams	1% sand, 31% clay, 2.6% OC (Hastings); 15% sand, 34% clay, 1.8% OC (Overton)		Sorption parameter: Koc: 45; Sorption parameter: Kf: 0.62 (Hastings); 1.18 (Overton)	The reviewer agreed with this study's overall quality level.	(Rogers and McFarlane, 1981)	Medium
Batch sorption using aquifer solids to determine equilibrium distribution coefficient Kd	Site Moffett Field, CA: core material from heterogeneous aquifer composed of sand and gravel with interspersed layers of silts and clays	organic carbon content, foc: 0.08-0.16%		Sorption parameter: Kd: 1.0 ± 0.2, Rf = 6 ± 1.0	The reviewer agreed with this study's overall quality level.	(Harmon et al., 1992)	Medium
Adsorption isotherms obtained from batch methods	A: Black soil I, B: Black soil II, C: Gray soil, D: Brown soil I, E: Brown soil II	A: 4.9%, B: 3.2%, C: 0.5%, D: 0.4%, E: 0.1%		Sorption parameter: Henry's partition coefficient k (amount adsorbed/equilibrium concentration): Black soil I, Black soil II, Gray soil, Brown soil I, Brown soil II, respectively: 0.7, 0.4, 0.1, <0.05, <0.05	The reviewer agreed with this study's overall quality level.	(Urano and Murata, 1985)	Medium
Other	Eglin-Florida Soil	OC 1.6%; 91.7% sand, 6.3% silt, 2.0% clay, pH 4.7		Sorption parameter: Henry's isotherm constant K: 1.123	The reviewer downgraded this study's overall quality rating. They noted: No controls	(Peng and Dural, 1998)	Low

Study Type (year)	Sorbent Source	Sorbent Qualities (clay/silt/sand, OC, pH)	Duration	Results	Comments	Affiliated Reference	Data Quality Evaluation Results of Full Study Report
				Sorption parameter: normalized isotherm constant Ki: 0.375	or analytical details were reported.		
	Times Beach Missouri Soil	OC 2.4%; 11.4% sand, 35.2% silt, 33.4% clay, pH 6.9		Sorption parameter: Henry's isotherm constant K: 1.695 Sorption parameter: normalized isotherm constant Ki: 0.301	The reviewer downgraded this study's overall quality rating. They noted: No controls or analytical details were reported.	(Peng and Dural, 1998)	Low
Sorption/partitioning experiments using water and soil	32 normal soils from diverse geographic regions in US and China; soil samples collected from A horizon and 1m below land surface	Organic carbon: 0.16-6.09% for soils		Sorption parameter: Koc: 45-74 (range); 60±7 (avg.)	The reviewer downgraded this study's overall quality rating. They noted: Limited data was reported; no details on specific GC methods, extraction efficiency, mass balance or controls.	(Kile et al., 1995)	Low
Other	Visalia-California Soil	OC 1.7%; 45.1% sand, 35.2% silt, 21.7% clay, pH 8.1		Sorption parameter: Henry's isotherm constant K: 1.483 Sorption parameter: normalized isotherm constant Ki: 0.459	The reviewer downgraded this study's overall quality rating. They noted: No controls or analytical details were reported.	(Peng and Dural, 1998)	Low
Sorption/partitioning experiments using water and suspended river solids	5 river suspended-solid samples collected from locations in Illinois River IL,	Organic carbon: 0.38-2.87%		Sorption parameter: Koc: 49-89	The reviewer downgraded this study's overall quality rating. They noted: Limited data was reported; no	(Kile et al., 1995)	Low

Study Type (year)	Sorbent Source	Sorbent Qualities (clay/silt/sand, OC, pH)	Duration	Results	Comments	Affiliated Reference	Data Quality Evaluation Results of Full Study Report
	Mississippi River MO, and Yellow River China				details on specific GC methods, extraction efficiency, mass balance or controls.		
Sorption/partitioning experiments using water and suspended river solids	4 contaminated bed sediment and soil samples collected from locations in LA, MA, and MN	Organic carbon: 1.56-5.27%		Sorption parameter: Koc: 133-665	The reviewer downgraded this study's overall quality rating. They noted: Limited data was reported; no details on specific GC methods, extraction efficiency, mass balance or controls.	(Kile et al., 1995)	Low
Sorption/partitioning experiments using water and sediment	36 bed sediments from diverse geographic regions in US and China; sediments collected from rivers, freshwater lakes, and marine/bay harbors	Organic carbon: 0.11-4.73% for bed sediment		Sorption parameter: Koc: 66-119 (range); 102±11 (avg.)	The reviewer downgraded this study's overall quality rating. They noted: Limited data was reported; no details on specific GC methods, extraction efficiency, mass balance or controls.	(Kile et al., 1995)	Low
Partitioning in clays	clay:water			Sorption parameter: Kgm (adsorption equilibrium constant gas/mineral): 90 at 0%RH; 3.6 at 80%RH	The reviewer agreed with this study's overall quality level.	(Cabbar et al., 1998)	Low
Vapor sorption of carbon tetrachloride using synthetic clay pellets	Synthetic clay: montmorillonite-type natural clay and humic acid			Sorption parameter: coefficient that considers: (1) adsorption from the vapor phase to the pure mineral surface; (2) adsorptions on the	The reviewer downgraded this study's overall quality rating. They noted: Study details were not provided, and results	(Cabbar, 1999)	Low

Study Type (year)	Sorbent Source	Sorbent Qualities (clay/silt/sand, OC, pH)	Duration	Results	Comments	Affiliated Reference	Data Quality Evaluation Results of Full Study Report
				surface of a water film that is adsorbed on the mineral; (3) dissolution into an adsorbed water film and soil organic carbon: 39.9(5%); 9.7(20%); 5.8(40%); 4.8(60%); 3.6(80%) for pure clay; 36.3(0%), 21.6(5%); 9.95(20%); 6.32(40%); 5.05(60%); 3.38(80%) for 2%humic acid-clay pellet; 21.8(0%), 15.65(5%); 9.49(20%); 7.21(40%); 5.49(60%); 3.50 (80%) for 2% humic acid-clay pellet	were not environmentally relevant.		
Sorption/desorption of organic vapors on single particles using an electrodynamic thermogravimetric analyzer	Spherocarb, montmorillonite, and Carbopack particles	0.63, 0.62, 0.95 g/cm^3		Sorption parameter: The isothermal adsorption and desorption of organic vapors on a single soil particle was studied. Xa amount of contaminant adsorbed per gram of soil was reported. Xa = 0.012 - 0.347	The test method was not relevant to conceptual model for this compound.	(Tognotti et al., 1991)	Unacceptable

Table C-5. Other Fate Endpoints Study Summary for Carbon Tetrachloride

System	Study Type (year)	Results	Comments	Affiliated Reference	Data Quality Evaluation Results of Full Study Report
Non-guideline; Sorption/desorption in Biomass: Air-biomass and water-biomass (wood) partitioning	Partitioning measured using tree cores and tree cuttings from hybrid poplar tree trunks; Kaw: Partitioning between air and biomass (organic matter from trees); Klw: partitioning between water (internal aqueous solution) and biomass (dry wood)	Parameter: Kaw(L/g): air:tree-core (sorption): 0.055±0.008; air:tree-cutting (sorption): 0.042±0.007; air:tree-cutting (desorption): 0.072±0.008; Parameter: Klw(L/g): water:biomass: 0.0593±0.0066 (measured) 0.0239 (calculated)	The reviewer agreed with this study's overall quality level.	(Ma and Burken, 2002)	High
Non-guideline; Lab-scale batch experiments using a bioreactor to simulate the fate of VOCs in wastewater treatment plants (WWTP) and fugacity model predictions of VOCs in WWTP	Concentrations in air, water and sludge phases analyzed under four different operational circumstances evaluating single and combined effects of aeration and sludge addition on phase distributions; sludge added prior to experiments; aeration 3rd-10th hr.	Parameter: partitioning: The concentrations of the VOCs in the air, water, and sludge phases of the bioreactor were analyzed regularly. Mass distributions indicated that carbon tetrachloride was mainly present in the water phase throughout the four treatment stages; less than 0.1% of the total mass was subject to biological sorption and/or degradation by the sludge; water aeration resulted in increased partitioning to the air phase with a negative impact on biological	The reviewer agreed with this study's overall quality level.	(Chen et al., 2014)	High

System	Study Type (year)	Results	Comments	Affiliated Reference	Data Quality Evaluation Results of Full Study Report
		removal; carbon tetrachloride mass distribution throughout the 4 stages: >99% water, >10 - 0.1% sludge			
Measurement of organic chemical effect on soil microbial respiration and correlation to structure activity analysis	Over a 7-day period soils were examined for chemical effects on microbial respiration; soils moistened with DI water for an 80% base saturation; no amendments were added	Parameter: effect on soil microbial respiration: No difference in the silt loam; no effect on the CO2 efflux from soils in the silt loam; observed decrease in CO2 efflux from the sandy loam soils during the course of the 6-day period but no significant difference on the final day of the experiment. SAR analysis showed no linear correlation with log Kow, water solubility, vapor pressure, HLC, or acute tox to chemical effects on soil microbial respiration	The reviewer downgraded this study's overall quality rating. They noted: Study details not reported (*i.e.*, Analytical methodology) limited study evaluation. Study results not relevant to a specific/designated Fate endpoint.	(Walton et al., 1989)	Low
Anaerobic abiotic transformation in the presence of sulfide and sulfide minerals	Time-series experiment under aseptic conditions in flame-sealed glass ampules; temp dependence assessed at 37.5, 50.0, and 62.7degC; pH effect was observed over pH 6-10	Parameter: abiotic dechlorination (50 °C): 75% conversion to carbon dioxide; 20% conversion to chloroform	Testing conditions were not reported, and data provided were insufficient to interpret results. Figures referenced in the text were not provided.	(Kriegman-King and Reinhard, 1991)	Unacceptable

Appendix D RELEASES TO THE ENVIRONMENT

This appendix provides a summary of the releases of carbon tetrachloride to the environment reported in 2018 TRI.

Table D-1. Summary of Carbon Tetrachloride Releases to the Environment Reported in 2018 TRI (lbs)

	Number of Facilities	Air Releases		Water Releases	Land Disposal			Other Releases[a]	Total On- and Off-Site Disposal or Other Releases[b, c]
		Stack Air Releases	Fugitive Air Releases		Class I Under-ground Injection	RCRA Subtitle C Landfills	All other Land Disposal[a]		
Totals 2018	49	116,710	59,355	1,704	15,088	29,140	29,532	146	251, 674
		176,065			73,760				

Data source: 2018 TRI Data (U.S. EPA, 2018e) covering the 2017 reporting cycle.
[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] These release quantities do include releases due to one-time events not associated with production such as remedial actions or earthquakes.
[c] Counts release quantities once at final disposition, accounting for transfers to other TRI reporting facilities that ultimately dispose of the chemical waste.

Appendix E SURFACE WATER ANALYSIS FOR CARBON TETRACHLORIDE

EPA identified additional data on ecological hazards requiring an update of the analysis of carbon tetrachloride releases and surface water concentrations (see Appendix H). In order to update the analysis, EPA expanded the release data as reported by facilities in the Discharge Monitoring Reports (in EPA's ECHO) to five years of releases (2014 through 2018) and expanded the number of facilities releasing carbon tetrachloride in any given year in order to capture the range and variability of releases. Releases or loadings of carbon tetrachloride (in lbs/yr or kg/yr) used in estimating carbon tetrachloride stream concentrations were averaged over the five-year period. The identified facilities represent, on average, 94% of total annual carbon tetrachloride releases from the manufacture, import, and use of carbon tetrachloride in the United States.

Table E-1. E-FAST Model Input Parameters Used to Estimate Carbon Tetrachloride Surface Water Concentrations

NPDES	Facility Name	E-FAST Model Parameters				
		Release to Wastewater (kg/day)	Wastewater Treatment Removal (%)	Days of Release (days/yr)		7Q10 Streamflow[a] (MLD)
				Acute Scenario	Chronic Scenario	
TX0021458	Fort Bend County WCID2	25.4	0	20	250	9.69
AL0001961	AKZO Chemicals, Inc.	114.7	0	20	250	1.85E+04
LA0000329	Honeywell, Baton Rouge	4.0	0	20	250	2.47E+05[b]
LA0005401	ExxonMobil, Baton Rouge	2.0	0	20	250	2.47E+05
OH0029149	Gabriel Performance	3.8	0	20	250	4.23
WV0004359	Natrium Plant	5.9	0	20	250	8.40E+03
CA0107336	Sea World, San Diego	1.2	0	20	250	--[c]
OH0007269	Dover Chemical Corp	36.1[b]	0	20	250	14.4
LA0006181	Honeywell, Geismar	3.7	0	20	250	2.47E+05
LA0038245	Clean Harbors, Baton Rouge	6.6	0	20	250	2.47E+05
TX0119792	Equistar Chemicals LP	13.6	0	20	250	1.53E+02[b]

WV0001279	Chemours Chemicals LLC	2.1	0	20	250	9.98E+03
TX0007072	Eco Services Operations	5.3	0	20	250	5.40
KY0024082	Barbourville STP	1.8	0	20	250	19.88
WA0030520	Central Kitsap WWTP	1.2	0	20	250	--[c]
MO0002526	Bayer Crop Science	1.0	0	20	250	8.47E+01
KY0027979	Eddyville STP	1.3	0	20	250	4.87
KY0103357	Richmond Silver Creek STP	0.6	0	20	250	9.60[b]
KY0003603	Arkema Inc.	0.4	0	20	250	2.31E+04
KY0091561	Caveland Environmental Auth	0.6	0	20	250	3.59E+02
LA0002933	Occidental Chem Corp, Geismar	0.2	0	20	250	2.47E+05

[a] The 7Q10 streamflow values for NPDES facilities are built into the E-FAST model. Those that were not found in the model are noted.
[b] Facilities not in the E-FAST NPDES database used proxy facilities discharging to the same receiving waterbody. LA0036421 was proxy for LA0000329; TX0003531 was proxy for TX0119792; KY0079898 was proxy for KY0103357.
[c] The receiving waterbody for CA0107336 is the Pacific Ocean and the receiving water body for WA0030520 is Port Orchard Bay. E-FAST model applies a dilution factor of 1 to discharges to oceans and bays.

Table E-2. Releases of Carbon Tetrachloride to Surface Waters[a]

NPDES	Facility Name	Total Pounds Discharged Per Year (lbs/yr)						
		2014	2015	2016	2017	2018	5yr Mean	5yr Median
TX0021458	Fort Bend County WCID2	81	134	25	19	21	56	61
AL0001961	AKZO Chemicals, Inc.	56	110	115	284	700	250	320
LA0000329	Honeywell, Baton Rouge	20	24	0	0	0	8.8	0
LA0005401	ExxonMobil, Baton Rouge	0	22	0	0	0	4.4	0
OH0029149	Gabriel Performance	14	21	1.2	2.4	3.7	8.5	3.7
WV0004359	Natrium Plant	13	14	12	12	14	13	13
CA0107336	Sea World, San Diego	0	14	0	0	0	2.8	0
OH0007269	Dover Chemical Corp	320[b]	13	19	48	0	79	19

LA0006181	Honeywell, Geismar	0	9.8	9.8	11	9.9	8.1	9.8
LA0038245	Clean Harbors, Baton Rouge	0	8.9	17	26	21	15	17
TX0119792	Equistar Chemicals LP	0	0	78	16	56	30	16
WV0001279	Chemours Chemicals LLC	0	0	0	0	23	4.7	0
TX0007072	Eco Services Operations	3.6	5.5	18	9.1	22	12	9.1
KY0024082	Barbourville STP	0	0	0	0	19	3.9	0
WA0030520	Central Kitsap WWTP	0	0	0	0	13	2.6	0
MO0002526	Bayer Crop Science	0	0	0	0	11	2.2	0
KY0027979	Eddyville STP	0	0	0	5.0	9.7	2.9	0
KY0103357	Richmond Silver Creek STP	0	0	0	0	7.0	1.4	0
KY0003603	Arkema Inc.	0	0	0	0	4.9	0.98	0
KY009161	Caveland Environmental Auth	0	0	0	2.4	4.2	1.3	0
LA0002933	Occidental Chem Corp, Geismar	0	0	0	0	2.6	0.52	0

[a]2014 to 2018 data from the EPA ECHO website
[b]A 2014 accidental spill/release of carbon tetrachloride likely contributed to the larger release of the chemical compared to the following 4 years; noncompliance and spills are not in the scope of this risk evaluation. (https://www.timesreporter.com/article/20140716/news/140719487)

Table E-3. Surface Water Carbon Tetrachloride Concentrations for Acute (20 day) and Chronic (250 day) Scenarios and Comparison with Amphibian Concentration of Concern[a]

NPDES	Facility Name	Amount Discharged for 20 days (kg/day)	20 Day Stream Conc. (µg/L)	Days Acute COC[b] Exceeded (PDM)	Amount Discharged for 250 days (kg/day)	250 Day Stream Conc. (µg/L)	Days Chronic COC[c] Exceeded (PDM)
TX0021458	Fort Bend County WCID2	N/A	N/A	N/A	0.10	10	0
AL0001961	AKZO Chemicals, Inc.	5.7	3.1E-01	0	0.46	2.5E-02	0
LA0000329	Honeywell, Baton Rouge	0.20	8.1E-04	0	0.02	6.5E-05	0
LA0005401	ExxonMobil, Baton Rouge	0.01	4.0E-04	0	0.01	3.2E-05	0
OH0029149	Gabriel Performance	0.19	45	0	0.02	3.6	2
WV0004359	Natrium Plant	0.29	3.4E-02	0	0.02	2.9E-03	0
CA0107336	Sea World, San Diego	6.3E-02	1.5E-01	0	5.0E-03	1.2E-02	0
OH0007269	Dover Chemical Corp	1.8	1.3E+2	0	0.14	10	15
LA0006181	Honeywell, Geismar	0.18	7.3E-04	0	0.02	6.1E-05	0
LA0038245	Clean Harbors, Baton Rouge	0.33	1.3E-03	0	0.03	1.0E-04	0
TX0119792	Equistar Chemicals LP	0.68	4.4	0	0.05	3.5E-01	0
WV0001279	Chemours Chemicals LLC	0.11	1.1E0-02	0	0.01	8.0E-04	0
TX0007072	Eco Services Operations	0.26	49	0	0.02	3.9	2
KY0024082	Barbourville STP	N/A	N/A	N/A	0.01	3.5E-01	0
WA0030520	Central Kitsap WWTP	0.06	7.0E+01	N/A	0.01	5.8E-01	0
MO0002526	Bayer Crop Science	0.05	5.9E-01	0	0.0	4.7E-02	0
KY0027979	Eddyville STP	N/A	N/A	N/A	0.01	1.0	1
KY0103357	Richmond Silver Creek STP	N/A	N/A	N/A	0.0	3.1E-01	0
KY0003603	Arkema Inc.	0.02	9.5E-04	0	0.0	8.7E-05	0
KY009161	Caveland Environmental Auth	0.03	8.4E-02	0	0.0	5.6E-03	0

NPDES	Facility Name	Amount Discharged for 20 days (kg/day)	20 Day Stream Conc. (µg/L)	Days Acute COC[b] Exceeded (PDM)	Amount Discharged for 250 days (kg/day)	250 Day Stream Conc. (µg/L)	Days Chronic COC[c] Exceeded (PDM)
LA0002933	Occidental Chem Corp, Geismar	0.01	4.9E-05	0	0.0	4.0E-06	0

[a] Loadings used to estimate carbon tetrachloride surface water concentrations were averaged over the 2014 to 2018 five year period.
[b]Acute COC = 90 µg/L
[c]Chronic COC = 3 µg/L

Table E-4. Surface Water Carbon Tetrachloride Concentrations for Acute (20 day) and Chronic (250 day) Scenarios and Comparison with Algal Concentration of Concern[a]

NPDES	Facility Name	Amount Discharged for 20 days (kg/day)	20 Day Stream Conc. (µg/L)	Days Algal COC[b] Exceeded (PDM)	Amount Discharged for 250 days (kg/day)	250 Day Stream Conc. (µg/L)	Days Algal COC[b] Exceeded (PDM)
TX0021458	Fort Bend County WCID2	N/A	N/A	N/A	0.10	10	0
AL0001961	AKZO Chemicals, Inc.	5.7	3.1E-01	0	0.46	2.5E-02	0
LA0000329	Honeywell, Baton Rouge	0.20	8.1E-04	0	0.02	6.5E-05	0
LA0005401	ExxonMobil, Baton Rouge	0.01	4.0E-04	0	0.01	3.2E-05	0
OH0029149	Gabriel Performance	0.19	45	2	0.02	3.6	2
WV0004359	Natrium Plant	0.29	3.4E-02	0	0.02	2.9E-03	0
CA0107336	Sea World, San Diego[b]	6.3E-02	1.5E-01	0	5.0E-03	1.2E-02	0
OH0007269	Dover Chemical Corp	1.8	1.3E+2	8	0.14	10	3
LA0006181	Honeywell, Geismar	0.18	7.3E-04	0	0.02	6.1E-05	0
LA0038245	Clean Harbors, Baton Rouge	0.33	1.3E-03	0	0.03	1.0E-04	0
TX0119792	Equistar Chemicals LP	0.68	4.4	1	0.05	3.5E-01	0
WV0001279	Chemours Chemicals LLC	0.11	1.1E0-02	0	0.01	8.0E-04	0
TX0007072	Eco Services Operations	0.26	49	2	0.02	3.9	0
KY0024082	Barbourville STP	N/A	N/A	N/A	0.01	3.5E-01	0
WA0030520	Central Kitsap WWTP	0.06	7.0E+01	N/A	0.01	5.8E-01	0
MO0002526	Bayer Crop Science	0.05	5.9E-01	0	0.0	4.7E-02	0
KY0027979	Eddyville STP	N/A	N/A	N/A	0.01	1.0	0
KY0103357	Richmond Silver Creek STP	N/A	N/A	N/A	0.0	3.1E-01	0
KY0003603	Arkema Inc.	0.02	9.5E-04	0	0.0	8.7E-05	0
KY009161	Caveland Environmental Auth	0.03	8.4E-02	0	0.0	5.6E-03	0

NPDES	Facility Name	Amount Discharged for 20 days (kg/day)	20 Day Stream Conc. (µg/L)	Days Algal COC[b] Exceeded (PDM)	Amount Discharged for 250 days (kg/day)	250 Day Stream Conc. (µg/L)	Days Algal COC[b] Exceeded (PDM)
LA0002933	Occidental Chem Corp, Geismar	0.01	4.9E-05	0	0.0	4.0E-06	0

[a] Loadings used to estimate carbon tetrachloride surface water concentrations were averaged over the 2014 to 2018 five year period.
[b]Algal COC = 7 µg/L

Table E-5. Surface Water Carbon Tetrachloride Concentrations for Acute (20 day) and Chronic (250 day) Scenarios and Comparison with Algal Concentration of Concern[a]

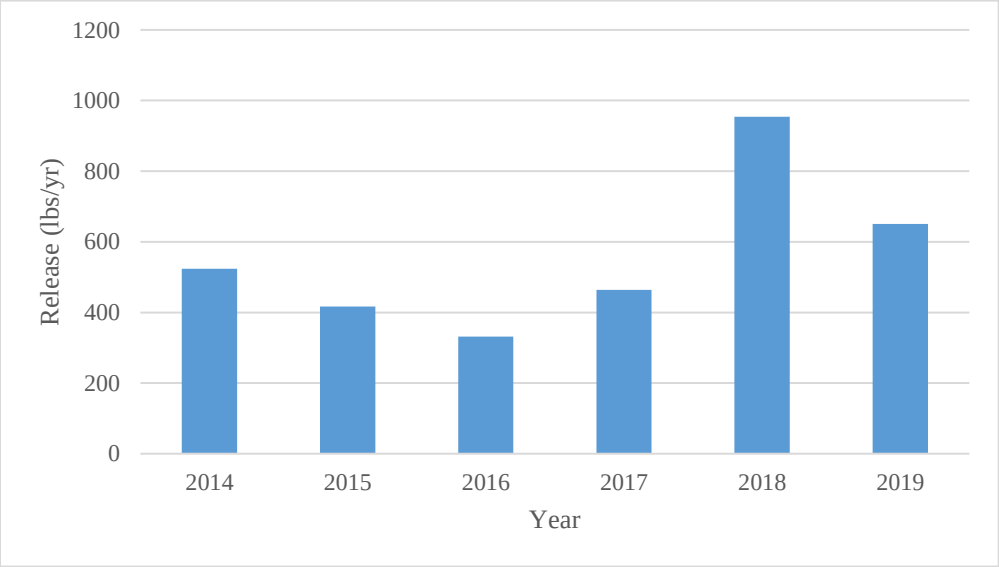
NPDES	Facility Name	Amount Discharged for 20 days (kg/day)	20 Day Stream Conc. (µg/L)	Days Algae COC[b] Exceeded (PDM)	Amount Discharged for 250 days (kg/day)	250 Day Stream Conc. (µg/L)	Days Algae COC[c] Exceeded (PDM)
TX0021458	Fort Bend County WCID2	N/A	N/A	N/A	0.10	10	0
AL0001961	AKZO Chemicals, Inc.	5.7	3.1E-01	0	0.46	2.5E-02	0
LA0000329	Honeywell, Baton Rouge	0.20	8.1E-04	0	0.02	6.5E-05	0
LA0005401	ExxonMobil, Baton Rouge	0.01	4.0E-04	0	0.01	3.2E-05	0
OH0029149	Gabriel Performance	0.19	45	2	0.02	3.5	0
WV0004359	Natrium Plant	0.29	3.4E-02	0	0.02	2.9E-03	0
CA0107336	Sea World, San Diego	6.3E-02	1.5E-01	0	5.0E-03	1.2E-02	0
OH0007269	Dover Chemical Corp	1.8	1.3E+2	8	0.14	10	3
LA0006181	Honeywell, Geismar	0.18	7.3E-04	0	0.02	6.7E-05	0
LA0038245	Clean Harbors, Baton Rouge	0.33	1.3E-03	0	0.03	1.05E-04	0
TX0119792	Equistar Chemicals LP	0.68	4.4	1	0.05	3.5E-01	0
WV0001279	Chemours Chemicals LLC	0.11	1.1E-02	0	0.01	8.0E-04	0
TX0007072	Eco Services Operations	0.26	49	2	0.02	3.9	0
KY0024082	Barbourville STP	N/A	N/A	N/A	0.01	3.5E-01	0
WA0030520	Central Kitsap WWTP	N/A	N/A	N/A	0.01	5.8E-01	0
MO0002526	Bayer Crop Science	0.05	5.9E-01	0	0.0	4.7E-02	0
KY0027979	Eddyville STP	N/A	N/A	N/A	0.01	1.0	0
KY0103357	Richmond Silver Creek STP	N/A	N/A	N/A	0.0	3.1E-01	0
KY0003603	Arkema Inc.	0.02	9.5E-04	0	0.0	8.7E-05	0
KY009161	Caveland Environmental Auth	0.03	8.4E-02	0	0.0	5.6E-03	0

NPDES	Facility Name	Amount Discharged for 20 days (kg/day)	20 Day Stream Conc. (µg/L)	Days Algae COC[b] Exceeded (PDM)	Amount Discharged for 250 days (kg/day)	250 Day Stream Conc. (µg/L)	Days Algae COC[c] Exceeded (PDM)
LA0002933	Occidental Chem Corp, Geismar	0.01	4.9E-5	0	0.0	4.0E-06	0

[a] Loadings used to estimate carbon tetrachloride surface water concentrations were averaged over the 2014 to 2018 five year period.
[b,c]Algal COC = 7 µg/L

In addition to the facilities listed above, there are other facilities that also discharge carbon tetrachloride as reported in the Discharge Monitoring Report database. However, only two other facilities to those listed in Table E-1. E-FAST Model Input Parameters Used to Estimate Carbon Tetrachloride Surface Water Concentrations discharge for more than one year and in general, over the five-year period, a total of 196 facilities report discharges only for one year. For each year, the number of facilities discharging carbon tetrachloride varies: 31 facilities in 2014, 38 in 2015, 41, in 2016 to 49 in 2017 and 42 in 2018 and 39 in 2019. The total annual surface water releases per year for 2014 through 2019 are presented below in Figure E-1.

Figure E-1. Total Annual Facility Releases of Carbon Tetrachloride per Discharge Monitoring Report Data



Appendix F ENVIRONMENTAL HAZARDS & RISK

F.1 Systematic Review

EPA reviewed ecotoxicity studies for carbon tetrachloride according to the data quality evaluation criteria found in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). The detailed data quality evaluation results of the 15 on-topic studies for carbon tetrachloride environmental hazard are presented in the document *Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Hazard Studies* (U.S. EPA, 2019g). The data quality extraction results for carbon tetrachloride environmental hazard are presented in Table F-1.

Table F-1. Aquatic Toxicity Studies Evaluated for Carbon Tetrachloride

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Fish								
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	24-hour	LD_{50} = 4.75 mL/kg body weight	1.6-5.0 mL/kg	Intraperitoneal, Nominal	Mortality	(Weber et al., 1979)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	24-hour	LOAEL = 0.2 mL/kg body weight	0, 0.2, 2.0 mL/kg	Intraperitoneal, Nominal	Plasma clearance of sulfobromophthalein	(Weber et al., 1979)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	48-hour	LOAEL = 2 mL/kg body weight	0, 2.0 mL/kg	Intraperitoneal, Nominal	Plasma clearance of sulfobromophthalein	(Weber et al., 1979)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	96-hour	LOAEL = 2 mL/kg body weight	0, 2.0 mL/kg	Intraperitoneal, Nominal	Plasma clearance of sulfobromophthalein	(Weber et al., 1979)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	24-hour	LOAEL = 1 mL/kg body weight	0, 1.0, 2.0 mL/kg	Intraperitoneal, Nominal	Glutamic pyruvic transaminase activity	(Weber et al., 1979)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	48-hour	LOAEL = 1 mL/kg body weight	0, 1.0, 2.0 mL/kg	Intraperitoneal, Nominal	Glutamic pyruvic transaminase activity	(Weber et al., 1979)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	24-hour	LOAEL = 1 mL/kg body weight	0, 1.0, 2.0 mL/kg	Intraperitoneal, Nominal	Increased body weight gain	(Weber et al., 1979)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	24-hour	NOAEL = 2 mL/kg body weight	0, 2.0 mL/kg	Intraperitoneal, Nominal	Plasma osmolality	(Weber et al., 1979)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	24-hour	LOAEL = 2 mL/kg body weight	0, 2.0 mL/kg	Intraperitoneal, Nominal	Plasma protein concentration	(Weber et al., 1979)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	24-hour	LOAEL = 2 mL/kg body weight	0, 2.0 mL/kg	Intraperitoneal, Nominal	Rate of urinary excretion	(Weber et al., 1979)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	23-day	LC_{50} = 2.02 mg AI/L	0, 0.024, 0.070, 1.11, 5.61, 10.9, 45.8 mg/L	Flow-through, Measured	Mortality	(Black et al., 1982)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	27-day	LC_{50} = 1.97 mg AI/L	0, 0.024, 0.070, 1.11, 5.61, 10.9, 45.8 mg/L	Flow-through, Measured	Mortality	(Black et al., 1982)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	23-day	LC_{100} = 45.8 mg AI/L	0, 0.024, 0.070, 1.11, 5.61, 10.9, 45.8 mg/L	Flow-through, Measured	Mortality	(Black et al., 1982)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	27-day	LC_{100} = 10.9 mg AI/L	0, 0.024, 0.070, 1.11, 5.61, 10.9, 45.8 mg/L	Flow-through, Measured	Mortality	(Black et al., 1982)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	16-day	NOAEL = 8 mg AI/L	0, 8 mg/L	Renewal, Nominal	Lipid peroxidation	(Bauder et al., 2005)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	4-day	LOAEL = 0.04 mg AI/L	0, 0.04 mg/L	Static, Nominal	Induction of genes for lipid-binding proteins and enzymes of glycolysis and energy metabolism	(Koskinen et al., 2004)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	3-month	NOAEL = 1 mL/kg body weight	0 (blank control), 0 (solvent control), 1 mL/kg body weight (one injection every 21 days)	Intraperitoneal, Nominal, Solvent: DMSO	Hepatic lesions	(Kotsanis and Metcalfe, 1988)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	6-month	NOAEL = 1 mL/kg body weight	0 (blank control), 0 (solvent control), 1 mL/kg body weight (one injection every 21 days)	Intraperitoneal, Nominal, Solvent: DMSO	Hepatic lesions	(Kotsanis and Metcalfe, 1988)	High
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	6-month	NOAEL = 1 mL/kg body weight	0 (blank control), 0 (solvent control), 1 mL/kg body weight (one injection every 21 days)	Intraperitoneal, Nominal, Solvent: DMSO; Partial hepatectomy at 4 months	Hepatic lesions	(Kotsanis and Metcalfe, 1988)	High
Common carp (*Cyprinus carpio*)	Fresh	3-day	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Lactate dehydrogenase activity	(Jia et al., 2013)	High
Common carp (*Cyprinus carpio*)	Fresh	3-day	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Serum total protein	(Jia et al., 2013)	High
Common carp (*Cyprinus carpio*)	Fresh	3-day	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Serum albumin	(Jia et al., 2013)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Common carp (*Cyprinus carpio*)	Fresh	3-day	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Superoxide dismutase activity	(Jia et al., 2013)	High
Common carp (*Cyprinus carpio*)	Fresh	3-day	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Catalase activity	(Jia et al., 2013)	High
Common carp (*Cyprinus carpio*)	Fresh	3-day	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Glutathione peroxidase activity	(Jia et al., 2013)	High
Common carp (*Cyprinus carpio*)	Fresh	3-day	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Total antioxidant capacity	(Jia et al., 2013)	High
Common carp (*Cyprinus carpio*)	Fresh	3-day	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Concentration of reduced glutathione in blood	(Jia et al., 2013)	High
Common carp (*Cyprinus carpio*)	Fresh	3-day	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Concentration of malondialdehyde in blood	(Jia et al., 2013)	High
Common carp (*Cyprinus carpio*)	Fresh	3-day	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Liver weight (relative to body weight)	(Jia et al., 2013)	High
Common carp (*Cyprinus carpio*)	Fresh	3-day	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Glutamic pyruvic transaminase activity	(Jia et al., 2013)	High
Common carp (*Cyprinus carpio*)	Fresh	3-day	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Glutamic-oxaloacetic transaminase activity	(Jia et al., 2013)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Total antioxidant capacity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Superoxide dismutase activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Glutathione peroxidase activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Catalase activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Concentration of reduced glutathione in blood	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Concentration of malondialdehyde in blood	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Cytochrome P450 2E1 level in liver	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Toll-like receptor 4 protein level in liver	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Glutamic-oxaloacetic transaminase activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Glutamic pyruvic transaminase activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Liver histopathology	(Jia et al., 2014)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Nuclear factor-κB cREL subunit gene expression	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Tumor necrosis factor gene expression	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Inducible nitric oxide synthase gene expression	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Interleukin 1 beta gene expression	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Interleukin 6 gene expression	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Arachis oil	Interleukin 12b gene expression	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	16-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Hepatocyte viability	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	0-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Hepatocyte viability	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	2-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Hepatocyte viability	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	1-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Hepatocyte viability	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	4-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Hepatocyte viability	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	8-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Hepatocyte viability	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	0-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 3 activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	1-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 3 activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	2-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 3 activity	(Jia et al., 2014)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Common carp (*Cyprinus carpio*)	Fresh	8-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 3 activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	4-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 3 activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	16-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 3 activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	0-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 8 activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	1-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 8 activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	2-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 8 activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	4-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 8 activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	8-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 8 activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	16-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 8 activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	0-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 9 activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	1-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 9 activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	2-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 9 activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	4-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 9 activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	8-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 9 activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	16-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	*In vitro*, Nominal	Caspase 9 activity	(Jia et al., 2014)	High
Common carp (*Cyprinus carpio*)	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	*In vitro*, Nominal	Adenosine triphosphate in liver	(Liu et al., 2015)	High
Common carp (*Cyprinus carpio*)	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	*In vitro*, Nominal	Glutamic pyruvic transaminase activity	(Liu et al., 2015)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Common carp (*Cyprinus carpio*)	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	*In vitro*, Nominal	Glutamic-oxaloacetic transaminase activity	(Liu et al., 2015)	High
Common carp (*Cyprinus carpio*)	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	*In vitro*, Nominal	Alkaline phosphatase activity	(Liu et al., 2015)	High
Common carp (*Cyprinus carpio*)	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	*In vitro*, Nominal	Lactate dehydrogenase activity	(Liu et al., 2015)	High
Common carp (*Cyprinus carpio*)	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	*In vitro*, Nominal	Malondialdehyde content in liver	(Liu et al., 2015)	High
Common carp (*Cyprinus carpio*)	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	*In vitro*, Nominal	Superoxide dismutase activity	(Liu et al., 2015)	High
Common carp (*Cyprinus carpio*)	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	*In vitro*, Nominal	Glutathione peroxidase activity	(Liu et al., 2015)	High
Common carp (*Cyprinus carpio*)	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	*In vitro*, Nominal	Glutathione S-transferase activity	(Liu et al., 2015)	High
Common carp (*Cyprinus carpio*)	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	*In vitro*, Nominal	Catalase activity	(Liu et al., 2015)	High
Common carp (*Cyprinus carpio*)	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	*In vitro*, Nominal	Concentration of reduced glutathione in liver	(Liu et al., 2015)	High
Common carp (*Cyprinus carpio*)	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	*In vitro*, Nominal	Total antioxidant capacity	(Liu et al., 2015)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 5 mL/kg body weight (30% v/v solution)	0, 5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Olive oil	Catalase activity	(Liu et al., 2015)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 5 mL/kg body weight (30% v/v solution)	0, 5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Olive oil	Total antioxidant capacity	(Liu et al., 2015)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 5 mL/kg body weight (30% v/v solution)	0, 5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Olive oil	Superoxide dismutase activity	(Liu et al., 2015)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 5 mL/kg body weight (30% v/v solution)	0, 5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Olive oil	Malondialdehyde content in liver	(Liu et al., 2015)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 5 mL/kg body weight (30% v/v solution)	0, 5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Olive oil	Glutathione peroxidase activity	(Liu et al., 2015)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 5 mL/kg body weight (30% v/v solution)	0, 5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Olive oil	Glutamic-oxaloacetic transaminase activity	(Liu et al., 2015)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 5 mL/kg body weight (30% v/v solution)	0, 5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Olive oil	Lactate dehydrogenase activity	(Liu et al., 2015)	High
Common carp (*Cyprinus carpio*)	Fresh	72-hour	LOAEL = 5 mL/kg body weight (30% v/v solution)	0, 5 mL/kg body weight (30% v/v solution)	Intraperitoneal, Nominal, Solvent: Olive oil	Glutamic pyruvic transaminase activity	(Liu et al., 2015)	High
Bluegill (*Lepomis macrochirus*)	Fresh	21-day	BCF = 30	0.0523 mg AI/L	Flow-through, Measured, Solvent: Acetone	Residue, whole body	(Barrows et al., 1980)	High
Bluegill (*Lepomis macrochirus*)	Fresh	24-hour	LC_{50} = 38 mg/L	Not reported	Static, Nominal, Solvent: Not specified	Mortality	(Buccafusco et al., 1981)	Low
Bluegill (*Lepomis macrochirus*)	Fresh	96-hour	LC_{50} = 27 mg/L	Not reported	Static, Nominal, Solvent: Not specified	Mortality	(Buccafusco et al., 1981)	Low
Fathead minnow (*Pimephales promelas*)	Fresh	96-hour	LC_{50} = 41.4 mg AI/L	<1.70, 8.62-9.2, 12.5-15, 21.3-29.6, 36.2-46.3, 81.8-84.9 mg/L	Flow-through, Measured	Mortality	(Geiger et al., 1990)	High
Fathead minnow (*Pimephales promelas*)	Fresh	96-hour	EC_{50} = 20.8 mg AI/L	<1.70, 8.62-9.2, 12.5-15, 21.3-29.6, 36.2-46.3, 81.8-84.9 mg/L	Flow-through, Measured	Loss of equilibrium	(Geiger et al., 1990)	High
Fathead minnow (*Pimephales promelas*)	Fresh	96-hour	LC_{50} = 43.3 mg AI/L (Rep 1)	0, 9.7, 10.5, 19.6, 37.1, 73.2, 181.0 mg/L	Flow-through, Measured	Mortality	(Kimball, 1978)	High
Fathead minnow (*Pimephales promelas*)	Fresh	96-hour	LC_{50} = 42.9 mg AI/L (Rep 2)	0, 9.7, 10.5, 19.6, 37.1, 73.2, 181.0 mg/L	Flow-through, Measured	Mortality	(Kimball, 1978)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Fathead minnow (*Pimephales promelas*)	Fresh	>7 days	NOAEL = 37.1 mg AI/L	0, 9.7, 10.5, 19.6, 37.1, 73.2, 181.0 mg/L	Flow-through, Measured	Mortality	(Kimball, 1978)	High
Fathead minnow (*Pimephales promelas*)	Fresh	>7 days	LOAEL = 73.2 mg AI/L	0, 9.7, 10.5, 19.6, 37.1, 73.2, 181.0 mg/L	Flow-through, Measured	Mortality	(Kimball, 1978)	High
Fathead minnow (*Pimephales promelas*)	Fresh	>7 days	MATC = 52.1 mg AI/L	0, 9.7, 10.5, 19.6, 37.1, 73.2, 181.0 mg/L	Flow-through, Measured	Mortality	(Kimball, 1978)	High
Fathead minnow (*Pimephales promelas*)	Fresh	>7 days	LC_{100} = 73.2 mg AI/L	0, 9.7, 10.5, 19.6, 37.1, 73.2, 181.0 mg/L	Flow-through, Measured	Mortality	(Kimball, 1978)	High
Fathead minnow (*Pimephales promelas*)	Fresh	96-hour	LC_{50} = 10.4 mg AI/L	Not reported	Static, Measured	Mortality	(Brooke, 1987)	High
Fathead minnow (*Pimephales promelas*)	Fresh	96-hour	LC_{50} = 41.4 mg AI/L	Not reported	Flow-through, Measured	Mortality	(Brooke, 1987)	High
Fathead minnow (*Pimephales promelas*)	Fresh	5-day	LC_{100} = 62.8 mg AI/L	0, 0.015, 0.065, 0.72, 9.32, 24.2, 45.0, 62.8 mg/L	Flow-through, Measured	Mortality	(Black et al., 1982)	High
Fathead minnow (*Pimephales promelas*)	Fresh	9-day	LC_{100} = 62.8 mg AI/L	0, 0.015, 0.065, 0.72, 9.32, 24.2, 45.0, 62.8 mg/L	Flow-through, Measured	Mortality	(Black et al., 1982)	High
Fathead minnow (*Pimephales promelas*)	Fresh	5-day	LC_{50} = 16.25 mg AI/L	0, 0.015, 0.065, 0.72, 9.32, 24.2, 45.0, 62.8 mg/L	Flow-through, Measured	Mortality	(Black et al., 1982)	High
Fathead minnow (*Pimephales promelas*)	Fresh	9-day	LC_{50} = 4 mg AI/L	0, 0.015, 0.065, 0.72, 9.32, 24.2, 45.0, 62.8 mg/L	Flow-through, Measured	Mortality	(Black et al., 1982)	High
Japanese medaka (*Oryzias latipes*)	Fresh	10-day	LC_{50} = 96 mg AI/L	0, 58, 70, 84, 101, 121, 145 mg/L	Renewal, Nominal	Mortality	(Schell, 1987)	High
Japanese medaka (*Oryzias latipes*)	Fresh	10-day	LC_{100} = 145 mg AI/L	0, 58, 70, 84, 101, 121, 145 mg/L	Renewal, Nominal	Mortality	(Schell, 1987)	High
Japanese medaka (*Oryzias latipes*)	Fresh	10-day	NOEC = 70 mg AI/L; LOEC = 84 mg AI/L	0, 58, 70, 84, 101, 121, 145 mg/L	Renewal, Nominal	Mortality	(Schell, 1987)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Mozambique tilapia (*Oreochromis mossambicus*)	Fresh	24-hour	LOAEL = 9 mg/L	0, 9 mg/L	Static, Nominal	Malondialdehyde content in liver	(de Vera and Pocsidio, 1998)	High
Mozambique tilapia (*Oreochromis mossambicus*)	Fresh	48-hour	NOAEL = 9 mg/L	0, 9 mg/L	Static, Nominal	Malondialdehyde content in liver	(de Vera and Pocsidio, 1998)	High
Mozambique tilapia (*Oreochromis mossambicus*)	Fresh	72-hour	NOAEL = 9 mg/L	0, 9 mg/L	Static, Nominal	Malondialdehyde content in liver	(de Vera and Pocsidio, 1998)	High
Mozambique tilapia (*Oreochromis mossambicus*)	Fresh	96-hour	LOAEL = 9 mg/L	0, 9 mg/L	Static, Nominal	Malondialdehyde content in liver	(de Vera and Pocsidio, 1998)	High
Mozambique tilapia (*Oreochromis mossambicus*)	Fresh	168-hour	LOAEL = 9 mg/L	0, 9 mg/L	Static, Nominal	Malondialdehyde content in liver	(de Vera and Pocsidio, 1998)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Hematocrit	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Red blood cell count	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Muscle water content	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Sodium concentration in blood	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Potassium concentration in blood	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Sodium/potassium ratio in blood	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Chloride concentration in blood	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the gill, sum	(Chen et al., 2004)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the gill, circulatory disturbance	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the gill, regenerative	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the gill, proliferation	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the trunk kidney, inflammation	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the trunk kidney, sum	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the trunk kidney, circulatory disturbance	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the liver, regenerative	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the trunk kidney, proliferation	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the liver, inflammation	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the liver, sum	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Calcium concentration in blood	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Magnesium concentration in blood	(Chen et al., 2004)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Bicarbonate concentration in blood	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Phosphate concentration in blood	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Iron concentration in blood	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Total iron binding capacity	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Percent saturation of iron binding	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Anion gap	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Total protein	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Glucose	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Cholesterol	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Bilirubin	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Alanine transaminase activity	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Aspartate aminotransferase activity	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Alkaline phosphatase activity	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Creatine kinase activity	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the liver, circulatory disturbance	(Chen et al., 2004)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the liver, proliferation	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the spleen, inflammation	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Body weight	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the spleen, circulatory disturbance	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the spleen, regenerative	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the spleen, proliferation	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the gill, inflammation	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL /kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the spleen, sum	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the head kidney, circulatory disturbance	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the head kidney, regenerative	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the trunk kidney, regenerative	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the head kidney, proliferation	(Chen et al., 2004)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the head kidney, inflammation	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the head kidney, sum	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the intestine, regenerative	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the intestine, circulatory disturbance	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the intestine, proliferation	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the intestine, inflammation	(Chen et al., 2004)	High
Nile tilapia (*Oreochromis niloticus*)	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intraperitoneal, Nominal	Histological changes in the intestine, sum	(Chen et al., 2004)	High
Tidewater silversides (*Menidia beryllina*)	Salt	96-hour	LC_{50} = 150 mg/L	0, 75, 100, 125, 200, 320 mg/L	Static, Nominal, Solvent: Not specified	Mortality	(Dawson et al., 1977)	Medium
Bluegill (*Lepomis macrochirus*)	Fresh	96-hour	LC_{50} = 125 mg/L	0, 75, 100, 125, 200, 320 mg/L	Static, Nominal, Solvent: Not specified	Mortality	(Dawson et al., 1977)	Medium
Fish (species not reported)	Not reported	48-hour	LC_{50} = 38 mg AI/L	Not reported	Static, Measured	Mortality	(Freitag et al., 1994)	High
Aquatic Invertebrates								
Water flea (*Daphnia magna*)	Fresh	24-hour	LC_{50} = 35 mg AI/L	Not reported	Static, Nominal, Solvent: Unknown	Mortality	(LeBlanc, 1980)	High
Water flea (*Daphnia magna*)	Fresh	48-hour	LC_{50} = 35 mg AI/L	Not reported	Static, Nominal, Solvent: Unknown	Mortality	(LeBlanc, 1980)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Water flea (*Daphnia magna*)	Fresh	48-hour	NOEC = 7.7 mg AI/L	Not reported	Static, Nominal, Solvent: Unknown	Mortality	(LeBlanc, 1980)	High
Water flea (*Daphnia magna*)	Fresh	0.25-hour	NOAEL = 37.5 mg AI/L LOAEL = 75 mg AI/L	0, 2.34375, 4.6875, 9.375, 18.75, 37.5, 75 mg/L	Static, Nominal	Phototactic response	(Martins et al., 2007a)	High
Water flea (*Daphnia magna*)	Fresh	3.5-hour	NOAEL = 37.5 mg AI/L LOAEL = 75 mg AI/L	0, 2.34375, 4.6875, 9.375, 18.75, 37.5, 75 mg/L	Static, Nominal	Phototactic response	(Martins et al., 2007a)	High
Water flea (*Daphnia magna*)	Fresh	24-hour	LOAEL = 2.3 mg AI/L	0, 2.34375, 4.6875, 9.375, 18.75, 37.5, 75 mg/L	Static, Nominal	Phototactic response	(Martins et al., 2007a)	High
Water flea (*Daphnia magna*)	Fresh	48-hour	NOAEL = 18.75 mg AI/L LOAEL = 37.5 mg AI/L	0, 2.34375, 4.6875, 9.375, 18.75, 37.5, 75 mg/L	Static, Nominal	Phototactic response	(Martins et al., 2007a)	High
Water flea (*Daphnia magna*)	Fresh	3.5-hour	LC_0 = 75 mg AI/L	0, 75 mg/L	Static, Nominal	Mortality	(Martins et al., 2007b)	High
Water flea (*Daphnia magna*)	Fresh	3.5-hour	NOAEL = 75 mg AI/L	0, 75 mg/L	Static, Nominal	Oxygen consumption	(Martins et al., 2007b)	High
Water flea (*Daphnia magna*)	Fresh	15-minute	NOAEL = 75 mg AI/L	0, 75 mg/L	Static, Nominal	Oxygen consumption	(Martins et al., 2007b)	High
Water flea (*Daphnia magna*)	Fresh	24-hour	EC_{50} = 20 mg AI/L	Not reported	Static, Measured	Immobilization	(Freitag et al., 1994)	High
Scud (*Gammarus pseudolimnaeus*)	Fresh	96-hour	LC_{50} = 11.1 mg AI/L	Not reported	Flow-through, Measured	Mortality	(Brooke, 1987)	High
Ostracod (*Cypris subglobosa*)	Fresh	24-hour	EC_{50} = 301 mg AI/L	Not reported	Renewal, Nominal	Immobilization	(Khangarot and Das, 2009)	High
Ostracod (*Cypris subglobosa*)	Fresh	48-hour	EC_{50} = 181 mg AI/L	Not reported	Renewal, Nominal	Immobilization	(Khangarot and Das, 2009)	High
Flatworm (*Dugesia japonica*)	Fresh	7-day	LC_{50} = 0.2 mg AI/L	Not reported	Renewal, Nominal	Mortality	(Yoshioka et al., 1986)	Unacceptable
Flatworm (*Dugesia japonica*)	Fresh	7-day	EC_{50} = 1.5 mg AI/L	Not reported	Renewal, Nominal	Abnormal regeneration	(Yoshioka et al., 1986)	Unacceptable
Ciliate (*Tetrahymena pyriformis*)	Fresh	24-hour	EC_{50} = 830 mg AI/L	Not reported	Static, Nominal, Solvent: unknown	Population growth rate	(Yoshioka et al., 1985)	Unacceptable

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Midge (*Chironomus tentans*)	Fresh	24-hour	LOAEL = 0.02 mg AI/L	0, 0.02, 0.2, 2 mg/L	Static, Nominal, Solvent: acetone	Gene expression - heat shock protein and hemoglobin	(Lee et al., 2006)	Low
Midge (*Chironomus tentans*)	Fresh	48-hour	NOAEL = 2 mg AI/L	0, 0.02, 0.2, 2 mg/L	Static, Nominal, Solvent: acetone	Body fresh weight	(Lee et al., 2006)	Low
Midge (*Chironomus tentans*)	Fresh	48-hour	NOAEL = 0.2 mg AI/L LOAEL = 2 mg AI/L	0, 0.02, 0.2, 2 mg/L	Static, Nominal, Solvent: acetone	Body dry weight	(Lee et al., 2006)	Low
Yellow fever mosquito (*Aedes aegypti*)	Fresh	24-hour	LC_{50} = 224 mg AI/L	Not reported	Static, Nominal	Mortality	(Richie et al., 1984)	High
Yellow fever mosquito (*Aedes aegypti*)	Fresh	0.5-hour	LC_{50} = 467 mg AI/L	Not reported	Static, Nominal	Mortality	(Richie et al., 1984)	High
Yellow fever mosquito (*Aedes aegypti*)	Fresh	1-hour	LC_{50} = 375 mg AI/L	Not reported	Static, Nominal	Mortality	(Richie et al., 1984)	High
Algae								
Green algae (*Chlamydomonas reinhardtii*)	Fresh	72-hour	EC_{50} = 0.25 mg AI/L	Not reported	Static, Measured	Biomass	(Brack and Rottler, 1994)	High
Green algae (*Chlamydomonas reinhardtii*)	Fresh	72-hour	EC_{10} = 0.07 mg AI/L	Not reported	Static, Measured	Biomass	(Brack and Rottler, 1994)	High
Green algae (*Pseudokirchneriella subcapitata*)	Fresh	48-hour	EC_{50} = 23.59 mg AI/L	Not reported	Static, Nominal	Growth	(Tsai and Chen, 2007)	High
Algae (*Desmodesmus subspicatus*)	Fresh	72-hour	EC_{50} = 21 mg/L	Not reported	Static, Measured	Inhibition	(Freitag et al., 1994)	High
Marine bacterium (*Photobacterium phosphoreum*)	Salt	15-minute	EC_{50} = 5 mg/L	Not reported	Static, Measured	Bioluminescence	(Freitag et al., 1994)	Medium
Activated sludge microorganisms	Fresh	5-day	EC_{50} > 1000 mg/L	Not reported	Static, Measured	O_2 consumption	(Freitag et al., 1994)	High
Amphibians								

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Bullfrog (*Rana catesbeiana*)	Fresh	4-day	LC_{50} = 1.5 mg AI/L	0, 0.026, 0.060, 1.18, 7.81, 65.7 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High
Bullfrog (*Rana catesbeiana*)	Fresh	8-day	LC_{50} = 0.9 mg AI/L	0, 0.026, 0.060, 1.18, 7.81, 65.7 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High
Bullfrog (*Rana catesbeiana*)	Fresh	4-day	LC_{100} = 65.7 mg AI/L	0, 0.026, 0.060, 1.18, 7.81, 65.7 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High
Bullfrog (*Rana catesbeiana*)	Fresh	8-day	LC_{100} = 7.81 mg AI/L	0, 0.026, 0.060, 1.18, 7.81, 65.7 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High
Pickerel frog (*Lithobates palustris*)	Fresh	4-day	LC_{50} = 3.62 mg AI/L	0, 0.020, 0.032, 0.69, 4.98, 92.5 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High
Pickerel frog (*Lithobates palustris*)	Fresh	8-day	LC_{50} = 2.37 mg AI/L	0, 0.020, 0.032, 0.69, 4.98, 92.5 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High
Fowler's toad (*Anaxyrus bufo*)	Fresh	3-day	LC_{50} >92 mg AI/L	0, 0.020, 0.032, 0.69, 4.98, 92.5 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High
Fowler's toad (*Anaxyrus bufo*)	Fresh	7-day	LC_{50} = 2.83 mg AI/L	0, 0.020, 0.032, 0.69, 4.98, 92.5 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High
Bullfrog (*Rana catesbeiana*)	Fresh	8-day	LC_{10} = 0.113 mg AI/L	0, 0.026, 0.060, 1.18, 7.81, 65.7 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High
Bullfrog (*Rana catesbeiana*)	Fresh	8-day	LC_{01} = 0.0236 mg AI/L	0, 0.026, 0.060, 1.18, 7.81, 65.7 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High
Pickerel frog (*Lithobates palustris*)	Fresh	8-day	LC_{10} = 0.4357 mg AI/L	0, 0.020, 0.032, 0.69, 4.98, 92.5 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High
Pickerel frog (*Lithobates palustris*)	Fresh	8-day	LC_{01} = 0.1096 mg AI/L	0, 0.020, 0.032, 0.69, 4.98, 92.5 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Pickerel frog (*Lithobates palustris*)	Fresh	4-day	LC_{100} = 92.5 mg AI/L	0, 0.020, 0.032, 0.69, 4.98, 92.5 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High
Pickerel frog (*Lithobates palustris*)	Fresh	8-day	LC_{100} = 92.5 mg AI/L	0, 0.020, 0.032, 0.69, 4.98, 92.5 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High
Fowler's toad (*Anaxyrus bufo*)	Fresh	7-day	LC_{100} = 92.5 mg AI/L	0, 0.020, 0.032, 0.69, 4.98, 92.5 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High
Bullfrog (*Rana catesbeiana*)	Fresh	8-day	LOEC = 0.060 mg AI/L	0, 0.026, 0.060, 1.18, 7.81, 65.7 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High
Pickerel frog (*Lithobates palustris*)	Fresh	8-day	LOEC = 92.5 mg AI/L	0, 0.020, 0.032, 0.69, 4.98, 92.5 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High
Fowler's toad (*Anaxyrus bufo*)	Fresh	7-day	LOEC = 92.5 mg AI/L	0, 0.020, 0.032, 0.69, 4.98, 92.5 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Birge et al., 1980)	High
Pickerel frog (*Lithobates palustris*)	Fresh	4.5-day	LC_{50} = 3.62 mg AI/L	Not reported	Flow-through, Measured	Teratogenesis Leading to Mortality	(Black et al., 1982)	High
Pickerel frog (*Lithobates palustris*)	Fresh	8.5-day	LC_{50} = 2.37 mg AI/L	Not reported	Flow-through, Measured	Teratogenesis Leading to Mortality	(Black et al., 1982)	High
Fowler's toad (*Anaxyrus bufo*)	Fresh	3-day	LC_{50} > 92 mg AI/L	Not reported	Flow-through, Measured	Teratogenesis Leading to Mortality	(Black et al., 1982)	High
Fowler's toad (*Anaxyrus bufo*)	Fresh	7-day	LC_{50} = 2.83 mg AI/L	Not reported	Flow-through, Measured	Teratogenesis Leading to Mortality	(Black et al., 1982)	High
European common frog (*Rana temporaria*)	Fresh	9-day	LC_{50} = 1.16 mg AI/L	0, 0.010, 0.076, 0.67, 10.7, 24.0, 41.2 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Black et al., 1982)	High
European common frog (*Rana temporaria*)	Fresh	9-day	LC_{100} = 41.2 mg AI/L	0, 0.010, 0.076, 0.67, 10.7, 24.0, 41.2 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Black et al., 1982)	High
European common frog (*Rana temporaria*)	Fresh	9-day	LC_{10} = 0.025 mg AI/L	0, 0.010, 0.076, 0.67, 10.7, 24.0, 41.2 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Black et al., 1982)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
European common frog (*Rana temporaria*)	Fresh	9-day	LC_{01} = 0.0011 mg AI/L	0, 0.010, 0.076, 0.67, 10.7, 24.0, 41.2 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Black et al., 1982)	High
European common frog (*Rana temporaria*)	Fresh	5-day	LC_{50} = 4.56 mg AI/L	0, 0.010, 0.076, 0.67, 10.7, 24.0, 41.2 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Black et al., 1982)	High
Leopard frog (*Lithobates pipiens*)	Fresh	9-day	LC_{50} = 1.64 mg AI/L	0, 0.010, 0.076, 0.67, 10.7, 24.0, 41.2 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Black et al., 1982)	High
Leopard frog (*Lithobates pipiens*)	Fresh	9-day	LC_{10} = 0.0339 mg AI/L	0, 0.010, 0.076, 0.67, 10.7, 24.0, 41.2 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Black et al., 1982)	High
Leopard frog (*Lithobates pipiens*)	Fresh	9-day	LC_{01} = 0.0014 mg AI/L	0, 0.010, 0.076, 0.67, 10.7, 24.0, 41.2 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Black et al., 1982)	High
Leopard frog (*Lithobates pipiens*)	Fresh	5-day	LC_{50} = 6.77 mg AI/L	0, 0.010, 0.076, 0.67, 10.7, 24.0, 41.2 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Black et al., 1982)	High
Northwestern salamander (*Ambystoma gracile*)	Fresh	5.5-day	LC_{50} = 9.01 mg AI/L	0, 0.010, 0.076, 0.67, 10.6, 24.2, 41.8 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Black et al., 1982)	High
Northwestern salamander (*Ambystoma gracile*)	Fresh	9.5-day	LC_{50} = 1.98 mg AI/L	0, 0.010, 0.076, 0.67, 10.6, 24.2, 41.8 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Black et al., 1982)	High
African clawed frog (*Xenopus laevis*)	Fresh	2-day	LC_{50} > 27 mg AI/L	0, 0.004, 0.073, 0.60, 10.5, 27.2 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Black et al., 1982)	High
African clawed frog (*Xenopus laevis*)	Fresh	6-day	LC_{50} = 22.42 mg AI/L	0, 0.004, 0.073, 0.60, 10.5, 27.2 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	(Black et al., 1982)	High

F.2 Hazard Identification- Aquatic

Relevant data from the screened literature are summarized in Table 3-1 as ranges (min-max) in the risk evaluation. Studies with data quality evaluation results of 'medium' to 'high' were used to characterize the environmental hazards of carbon tetrachloride. Table 3-1 provides the species, media, duration, endpoint, effects, etc. for all toxicity studies that were evaluated.

Toxicity to Aquatic Organisms

For the aquatic environment, the hazard endpoint for fish, from acute exposure durations (24-96-h LC_{50}) to carbon tetrachloride, ranges from 10.4 - 150 mg/L (data quality evaluation scores for each citation are in the parenthesis) (Freitag et al., 1994) (high); (Schell, 1987) (high); (Brooke, 1987) (high); (Kimball, 1978) (high); (Geiger et al., 1990) (high); (Buccafusco et al., 1981) (low); and (Dawson et al., 1977) (medium). The hazard endpoint for aquatic invertebrates, from acute exposure durations (24-48-h L/EC50) to carbon tetrachloride, ranges from 11.1 - 301 mg/L (LeBlanc, 1980) (high); (Freitag et al., 1994) (high); (Brooke, 1987) (high); (Khangarot and Das, 2009) (high); and (Richie et al., 1984) (high). The hazard endpoint for aquatic plants, from acute exposure durations (72-hr EC50) to carbon tetrachloride, ranges from 0.25 – 23.59 mg/L (Brack and Rottler, 1994) (high); (Freitag et al., 1994) (high); and (Tsai and Chen, 2007) (high).

There were no chronic studies that encompassed amphibian metamorphoses and adult reproductive stages of the amphibian life-cycle. However, amphibian embryo and larvae were the most sensitive organisms to sub-chronic exposures of carbon tetrachloride in the aquatic environment. In two sub-chronic studies that EPA assigned an overall quality level of high, amphibian embryos and larvae were exposed to carbon tetrachloride for 2 to 9 days under flow-through conditions (Black et al., 1982; Birge et al., 1980). The study authors combined embryo-larval lethality and teratogenesis effect concentrations to establish a 10% impairment value (LC_{10}). The LC_{10} hazard endpoint for amphibian embryo-larval stages, from sub-chronic exposure durations to carbon tetrachloride, ranges from 0.025 to 0.436 mg/L (Birge et al., 1980); and (Black et al., 1982).

The hazard endpoint for fish, from chronic exposure durations (27-day LC_{50}) to carbon tetrachloride, is 1.97 mg/L (Black et al., 1982) (high). The hazard endpoint for aquatic invertebrates, from chronic exposure durations to carbon tetrachloride, is 1.1 mg/L. This is calculated by applying an acute to chronic ratio (ACR) of 10 to the lowest acute aquatic invertebrate endpoint value (11.1 mg/L (Brooke, 1987) (high)). The hazard endpoint for algae, from chronic exposure durations (72-hr EC_{10}) to carbon tetrachloride, is 0.07 mg/L (Brack and Rottler, 1994) (high).

Toxicity to Sediment and Terrestrial Organisms

All of 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, except one low quality study on *Chironomus tentans* (Lee et al., 2006). Lee *et al*., examined body weight and expression of two genes that are general biomarkers for stress (*i.e.*, heat shock protein and hemoglobin) after an acute exposure to carbon tetrachloride. The lowest effect level (LOEL) for mRNA expression of the heat shock protein and hemoglobin

genes in larvae was 0.02 mg/L carbon tetrachloride; the LOEL for dry body weight was 2 mg/L carbon tetrachloride. Since the heat shock protein and hemoglobin genes are general biomarkers that cannot be attributed to an adverse outcome pathway, the sediment-dwelling organism COC were calculated based on body dry weight and an AF of 5 for acute COC and an ACR of 10 for chronic COC.

No relevant (on-topic) toxicity data were available for carbon tetrachloride to birds. There were limited hazard studies for sediment and terrestrial organisms because exposure to carbon tetrachloride by these organisms was not likely due to the physical- chemical, and fate properties of the chemical.

F.3 Weight of the Scientific Evidence

During the data integration stage of systematic review, EPA analyzed, synthesized, and integrated the data/information. This involved weighing the scientific evidence for quality and relevance, using a Weight of the Scientific Evidence (WoE) approach (U.S. EPA, 2018a).

During data evaluation, studies were rated high, medium, low, or unacceptable for quality based on the TSCA criteria described in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). Only data/information rated as high, medium, or low for quality was used for the environmental risk assessment (unless otherwise noted). Any information rated as unacceptable was not used. While integrating environmental hazard data for carbon tetrachloride, EPA gave more weight to relevant data/information rated high or medium for quality. The ecological risk assessor decided if data/information were relevant based on whether it has biological, physical-chemical, and environmental relevance (U.S. EPA, 1998):

- Biological relevance: correspondence among the taxa, life stages, and processes measured or observed and the assessment endpoint.
- Physical-chemical relevance: correspondence between the chemical or physical agent tested and the chemical or physical agent constituting the stressor of concern.
- Environmental relevance: correspondence between test conditions and conditions in the region of concern (U.S. EPA, 1998).

This WoE approach was used to assess hazard data (Appendix F.2) and develop COCs as described in Appendix F.4. Where high or medium quality studies were available for a taxonomic group, low quality studies were not used to derive COCs. Additionally, where multiple toxicity values were reported within a study for the same species (*e.g.*, multiple EC_{50}s with different durations), they were summarized as ranges (min-max) in the Appendix Table F-2 and the higher quality or more relevant citation was used. If quality and relevance were equal, the lowest toxicity endpoint value for acute and chronic exposures were used to derive acute and chronic COCs.

Certain environmental studies on carbon tetrachloride were of high quality but were not biologically relevant for purposes of environmental hazard assessment due to the reported endpoints (*e.g.*, glutamic pyruvic transaminase activity, serum total protein, catalase activity, sodium concentration in blood, whole body residue). These studies (Chen et al., 2004); (de Vera and Pocsidio, 1998); (Barrows et al., 1980); (Liu et al., 2015); (Jia et al., 2013); (Kotsanis and Metcalfe, 1988); (Weber et al., 1979); (Koskinen et al., 2004); (Bauder et al., 2005); (Martins et

al., 2007a)) are contained within the on-topic data evaluation section of Appendix F.1, but were not used within the risk evaluation process. During risk evaluation, EPA made refinements to the conceptual models resulting in the elimination of the terrestrial exposure pathway and studies that are not biologically relevant from further analysis. Thus, environmental hazard data sources on terrestrial organisms and on metabolic endpoints were considered out of scope and excluded from data quality evaluation.

Environmental test data are reported from the Japanese Ministry of the Environment (MOE). EPA obtained the Japanese MOE test data in Japanese (not English). Since studies in a foreign language are generally excluded from evaluation (although there are exceptions on a case-by-case basis) and the Japanese test data are not driving the environmental assessment, EPA decided not to translate the Japanese test data into English or use the test data in this risk evaluation. EPA acknowledges the studies exist and are included in carbon tetrachloride's docket.

To assess aquatic toxicity from acute exposures, data for four taxonomic groups were available: amphibians, fish, aquatic invertebrates, and algae. For each taxonomic group, data were available for multiple species, and were summarized in Table 3-1. as ranges (min-max).

There were no chronic studies that encompassed amphibian metamorphoses and adult reproductive stages of the amphibian life-cycle. However, amphibian embryo and larvae were the most sensitive life stages to sub-chronic exposures of carbon tetrachloride in the aquatic environment. In two sub-chronic studies that EPA assigned an overall quality level of high, amphibian embryos and larvae were exposed to carbon tetrachloride for 2 to 9 days under flow-through conditions (Black et al., 1982; Birge et al., 1980). The study authors combined embryo-larval lethality and teratogenesis effect concentrations to establish a 10% impairment value (LC_{10}) in *Lithobates palustris* (Birge et al., 1980) and *Rana temporaria* and *Lithobates pipiens* (Black et al., 1982), at carbon tetrachloride concentrations ranging from 0.025 – 0.436 mg/L.

EPA considered the sub-chronic hazard LC_{50}s and LC_{10}s for amphibians for teratogenicity leading to mortality to estimate acute and chronic hazard values for amphibians, respectively. To assess aquatic toxicity from acute and chronic exposures, EPA used and rounded the lowest LC_{50} to 0.9 mg/L and LC_{10} to 0.03 mg/L, respectively, from two high quality 9-day amphibian studies (Black et al., 1982; Birge et al., 1980). When comparing these values to the other acute and chronic data from fish and aquatic invertebrates, amphibians were again the most sensitive taxonomic group. Therefore, the amphibian 9-day lowest LC_{50} of 0.9 mg/L and LC_{10} of 0.03 mg/L were used to derive an acute COC in Appendix Section F.6 and chronic COC in Appendix Section F.7. These values were from two scientific articles that EPA assigned an overall quality level of high and represented seven amphibian species with LC_{50} values, and four amphibian species with LC_{10} values.

The 72-hour algal EC_{10} of 0.072 mg/L represented the most sensitive toxicity value derived from the available algal toxicity data to carbon tetrachloride and this value was used to derive an algal COC as described in Appendix Section F.8. This value is from one algal study that EPA assigned an overall quality of high.

Lastly, a LOEL of 2 mg/L for body dry weight from one low quality study on *Chironomus tentans* (Lee et al., 2006) was used to support the risk characterization of sediment-dwelling organisms.

F.4 Benchmark Dose Modeling and Species Sensitivity Distributions

Benchmark Dose Modeling

Benchmark dose modeling is the preferred method used in human health fields to predicting toxicity effect values for a given endpoint and study. It's utility translates to ecotoxicity studies, where it can be used to generate LC_x or EC_x values that remove biases due to experimental design (*e.g.*, what concentrations are chosen), provide for the inclusion of all toxicity data points, and allow for model fitting specific to the shape of different dose-response curves, as compared to traditional LOEC/NOEC methodologies. EPA examined whether benchmark dose modeling could be applied to the toxicity data from (Black et al., 1982; Birge et al., 1980) used to derive the acute and chronic concentrations of concern using the peer reviewed BMDS software (U.S. EPA, 2019a). Because the BMDS software requires a measure of error for model calculation, it was not possible to apply these methods with the data provided by (Birge et al., 1980) and (Black et al., 1982). Specifically, EPA was not able to back-calculate a measure of error for either paper because the experiments utilized one tank replicate per concentration. However, EPA has high confidence in the toxicity values provided by both papers because the study authors applied an appropriate modeling technique (log-probit analysis) to generate their LC_{10} and LC_{50} point of departure estimates for fish and amphibian species.

Species Sensitivity Distributions

Amphibians were the most sensitive taxa to carbon tetrachloride exposure. Because little is known about differences in sensitivity for amphibians, EPA explored the use of species sensitivity distributions (SSDs) as an additional line of evidence for how carbon tetrachloride exposure could affect this vulnerable taxonomic group. SSDs utilize toxicity estimates (ECx, LC_x) from multiple, single-species tests to predict a hazardous concentration (HCp) protective of a certain percentage (p) of the larger taxonomic group and can be used to examine the distribution of a toxicity dataset.

To examine the amphibian toxicity data, SSDs were generated using the SSD Toolbox, a resource created by EPA's Office of Research and Development (ORD) (Etterson, 2019).There was insufficient data (n = 4 species) to examine the LC_{10} data used to calculate the chronic concentration of concern for amphibians using an SSD. There was enough data (n = 7 species) to examine LC_{50} from the 4-days post-hatch exposure. Using the three best-fitting distributions, the model averaged HC_5 (the predicted hazardous concentration intended to be protective of 95% of amphibians) was = 0.42 mg/L +/- 0.36 SE. Although 7 species were not enough to capture the total variation in sensitivity to carbon tetrachloride across amphibians, the SSD showed that the model frog *Xenopus laevis* appeared to be less sensitive than other species (Figure F-1). The American bullfrog (*Rana catesbiana*) and the European common frog (*Rana temporaria*) were the most sensitive species in the dataset (Figure F-1). The SSD provided a useful line of evidence that EPA used to visually assess the distribution of the available amphibian toxicity data. However, due to underlying uncertainties including unknown total variation in amphibian sensitivity, a small sample size (n = 7 species, from n = 2 studies), large variation surrounding

the HC_5, and possible differences across amphibian life stages, EPA used the more conservative concentration of concern (0.09 mg/L versus the HC_5 of 0.42 mg/L) generated by the traditional approach to assess risk due to acute exposure.

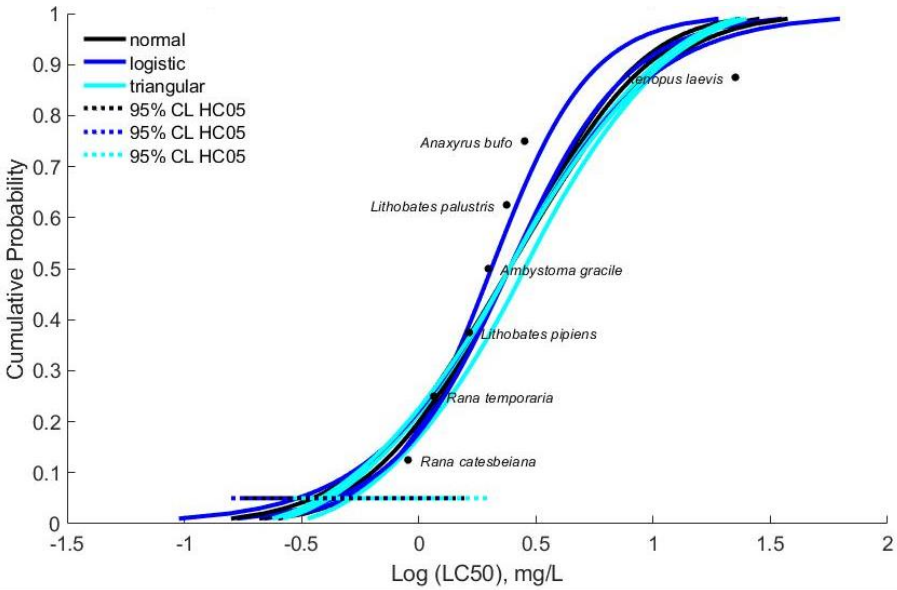


Figure F-1. Species Sensitivity Distribution (SSD) for Amphibian Species Using LC_{50}s From (Etterson, 2019)

Note: The data in this figure includes LC_{50}s for seven amphibian species from (Birge et al., 1980) and (Black et al., 1982). A black dot indicates the toxicity value reported for a given species. Colored lines represent model fit with log, normal, or triangular distributions. The dotted horizontal lines represent the 95% confidence intervals around the modeled HC_5. The HC_5 was calculated using a model average of the best-fitting log, normal, and triangular distributions.

F.5 Concentrations of Concern

EPA calculated screening-level acute and chronic COCs for aquatic species based on the environmental hazard data for carbon tetrachloride, using EPA methods (U.S. EPA, 2012b); (U.S. EPA, 2013). While there was data representing amphibians, fish, aquatic invertebrates, and aquatic plants, the data were not robust enough to apply species sensitivity distribution analyses. Therefore, EPA chose to establish the COC as protective cut-off standards above which exposures to carbon tetrachloride are expected to cause effects for each taxonomic group in the aquatic environment. The acute, chronic, and algal COCs for carbon tetrachloride are based on the lowest toxicity value in the dataset. For the aquatic environment, EPA derived acute and a chronic COCs for amphibians as well as a COC for algae to serve as representative COCs for all aquatic taxa.

After weighing the scientific evidence and selecting the appropriate toxicity values from the integrated data to calculate COCs, EPA applied an assessment factor (AF) according to EPA methods (U.S. EPA, 2012b); (U.S. EPA, 2013), when possible. The application of AFs provides a lower bound effect level that would likely encompass more sensitive species not represented by the available experimental data. AFs also account for differences in inter- and intra-species variability, as well as laboratory-to-field variability. 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. The assessment factors are standardized in risk assessments conducted under TSCA, since the data available for most industrial chemicals are limited. For fish and aquatic invertebrates (*e.g.*, *Daphnia sp.*), the acute hazard values were divided by an AF of 5 and the chronic hazard values were divided by an AF of 10. For algal species, the hazard values were divided by an AF of 10. For amphibians, EPA does not have a standardized AF. The greater level of uncertainty (*i.e.*, unknown inter-species variability) associated with the sub-chronic endpoints in the amphibian studies necessitates the use of a more protective AF of 10. As such, for the acute and chronic COCs derived from amphibian data, an AF of 10 was used (U.S. EPA, 2013, 2012b).

F.6 Hazard Estimation for Acute Exposure Durations

The lowest acute toxicity value for aquatic organisms (*i.e.*, most sensitive species) for carbon tetrachloride is from a 9-day amphibian toxicity study where the LC_{50} is 0.9 mg/L (Black et al., 1982; Birge et al., 1980). The lowest value was then divided by the AF of 10.

Acute COC
The acute COC = (0.9 mg/L) / (AF of 10) = 0.09 mg/L x 1,000 = 90 µg/L or 90 ppb

The acute COC of 90 µg/L, derived from an experimental amphibian endpoint, is used as the conservative (screening-level) hazard level in this risk evaluation for carbon tetrachloride.

F.7 Hazard Estimation for Chronic Exposure Durations

The lowest chronic toxicity value for aquatic organisms (*i.e.*, most sensitive species) for carbon tetrachloride is from a 9-day amphibian toxicity study where the LC_{10} is 0.03 mg/L (Black et al., 1982). The chronic COC was derived from the lowest chronic toxicity value from the amphibian LC_{10} (for developmental effects and mortality in frogs). Throughout the systematic review process, these two studies were both assigned a quality level of high (Black et al., 1982; Birge et al., 1980). The LC_{10} was then divided by an assessment factor of 10, and then multiplied by 1,000 to convert from mg/L to µg/L, or ppb.

Chronic COC
The chronic COC = (0.03 mg/L) / (AF of 10) = 0.003 mg/L x 1,000 = 3 µg/L or ppb

The amphibian chronic COC for carbon tetrachloride is 3 µg/L is used as the lower bound hazard level in this risk evaluation for carbon tetrachloride.

F.8 Hazard Estimation for Algal Toxicity

Given that the hazard endpoints for aquatic plants (72-hr EC_{10}/NOEC)) exposed to carbon tetrachloride ranges from ranges from 0.0717 - 2.2 mg/L (Brack and Rottler, 1994), 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:

Algal Toxicity COC
The 72-hr algal toxicity 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 an experimental algal endpoint, is used as the lower bound hazard level for algal toxicity in this risk evaluation for carbon tetrachloride.

F.9 Hazard Estimation for Sediment-Dwelling Organism Toxicity

Only one low quality study on Chironomus tentans (Lee et al., 2006) was available for sediment-dwelling organisms. Since the heat shock protein and hemoglobin genes are general biomarkers that cannot be attributed to an adverse outcome pathway, the sediment-dwelling organism COC were calculated based on a 2 mg/L carbon tetrachloride LOEL for body dry weight and an AF of 5 for acute COC and an ACR of 10 for chronic COC.

Acute COC
The acute COC = (2.0 mg/L) / (AF of 5) = 0.4 mg/L x 1,000 = 400 µg/L or 400 ppb

Chronic COC
400 µg/L / (ACR of 10) = 40 µg/L or 40 ppb

F.10 Summary of Environmental Hazard Assessment

The derived amphibian acute COC (90 µg/L) and chronic COC (3 µg/L) are based on environmental toxicity endpoint values from (Black et al., 1982; Birge et al., 1980) and algal COC (7 µg/L) is based on environmental toxicity endpoint values from (Brack and Rottler, 1994). The data represent the lowest bound of all carbon tetrachloride data available in the public domain and provide the most conservative hazard values. The full study reports for all on-topic citations in this risk evaluation were systematically reviewed and described in the *Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Hazard Studies* (U.S. EPA, 2019g).

F.11 Site-Specific Seasonal Risk Determination for Chronic Exposure

For the five facilities where chronic risk to aquatic organisms was identified, EPA examined whether releases occurred during months the were ecologically relevant to amphibian development (April – August at the Ohio facilities or March – August in Texas facilities). Where releases occurred, EPA calculated surface water concentrations using E-FAST and associated, site-specific RQs to determine whether risk was/was not indicated at the facilities during these key time periods. Risk was not indicated during time periods relevant to amphibian development at Eco Services Operations Facility (RQs < 1 for the three years where monitoring information was available). At the other four facilities, risk was indicated (RQs > 1) during the time periods relevant to amphibian development for at least 2 separate reporting periods. At the OH 0028149 and the TX0007072 facilities, the 20-day stream concentrations also exceed the unadjusted amphibian endpoint (*e.g.*, 30 µg/L the amphibian LC_{10}). However, risk was not consistent or

predictable across years or facilities (*e.g.*, some years no releases of carbon tetrachloride occurred, or RQs < 1). Thus, it is important to acknowledge that the timing of future exposures is an uncertainty in the risk evaluation. Facilities do not release carbon tetrachloride consistently throughout the year, and it is not possible to predict whether risk will or will not occur during months key to amphibian development in future years. The specific seasonal release information and associated RQs for each of the five sites that indicated risk for development from chronic exposures to carbon tetrachloride are available in Table F-2.

Table F-2. Seasonal Risk Determinations for the Five Facilities Indicating Risk to Amphibian Development from Chronic Exposure to Carbon Tetrachloride

NPDES	Facility Name	Monitoring Period[a]	Monitoring Period Duration (Days)	Days of Release Scenario (PDM)	Avg Daily Value (kg/day)	Stream Conc. (µg/L)	COC Type	COC (µg/L)	Days COC Exceeded (PDM)	RQ[b]
TX0021458	Fort Bend County WCID2	**5/31/2014**	92	20	1.2E-01	1.24E+01	Chronic Amphibian	3	0	**4.1E+00**
		8/31/2014	92		1.5E-01	1.55E+01			0	**5.2E+00**
		7/31/2015	92		1.5E-01	1.45E+01			0	**4.8E+00**
		4/30/2016	89		3.0E-02	3.09E+00			0	**1.0E+00**
		7/31/2016	92		3.0E-02	3.46E+00			0	**1.2E+00**
		4/30/2017	89		2.0E-02	2.38E+00			0	7.9E-01
		7/31/2017	92		2.0E-02	1.83E+00			0	6.1E-01
		4/30/2018	89		2.0E-02	2.48E+00			0	8.3E-01
		7/31/2018	92		3.0E-02	3.46E+00			0	**1.2E+00**
OH00029149	Gabriel Performance	3/31/2014	31	20.0	0.0E+00	1.00E-02	Chronic Amphibian	3	0	3.6E-03
		6/30/2014	30		4.0E-02	9.93E+00			1	**3.3E+00**
		3/31/2015	31		8.0E-02	1.84E+01			2	**6.2E+00**
		6/30/2017	30		1.0E-02	2.84E+00			0	9.5E-01
		3/31/2018	31		1.0E-02	2.84E+00			0	9.5E-01
OH0007269	Dover Chemical Corp	**4/30/2015**	30	20	9.0E-02	5.97E+00	Chronic Amphibian	3	0	**2.0E+00**
		7/31/2017	31		7.0E-01	4.86E+01			7	**1.6E+01**
TX0119792	Equistar Chemicals LP	8/31/2016	365	20	0.0E+00	5.9E-01	Chronic Amphibian	3	0	2.0E-01
		8/31/2017	365		0.0E+00	9.78E-02			0	3.0E-02
		8/31/2018	365		0.0E+00	3.9E-01			0	1.3E-01
TX0007072	Eco Services Operations	7/31/2014	181	20	1.0E-02	1.68E+00	Chronic Amphibian	3	0	5.6E-01

		7/31/2015	183		1.0E-02	2.52E+00			0	8.4E-01
		7/31/2016	183		2.0E-02	3.35E+00			0	**1.1E+00**
		3/31/2017	182		2.0E-02	4.20E+00			0	**1.4E+00**
		9/30/2018	183		3.0E-02	5.04E+00			0	**1.7E+00**

[a] Spring, summer, and fall months are included (3/31 through 9/30) as available. Missing time periods within one permit represent either no discharge of carbon tetrachloride or no sampling data reported. The monitoring periods that indicated risk to amphibian development from exposure to carbon tetrachloride (RQ > 1) and are indicated in bold.

Appendix G HUMAN HEALTH HAZARDS

This appendix provides a high-level summary of the human health animal and *in vitro* (genotoxicity) studies that were evaluated in the systematic review process. The appendix summarizes and presents study findings in Tables.

Table G-1. Summary of Reviewed Human Health Animal Studies for Carbon Tetrachloride

Target Organ/ System[1]	Study Type	Species/ Strain/Sex (Number/ group)[2]	Exposure Route	Doses/ Concentrations[3]	Duration[4]	Effect Dose or Concentration (Sex)	Effect[6]	Reference	Data Quality Evaluation[8]
Mortality	Chronic	Mouse, Crj:BDF1 (SPF), M/ F (n=100/ group)	Inhalation, vapor, whole body	0, 32, 160, 801 mg/m^3 (0, 5, 25, 125 ppm)	6 hours/ day, 5 days/ week for 104 weeks	NOAEL = 32 mg/m^3 (F), LOAEL = 160 mg/m^3 (F)	Reduced survival late in study (because of liver tumors)	(Nagano et al., 2007a)	High
Mortality	Short-term (1-30 days)	Rat, Wistar, M (n=10/group)	Inhalation	0, 63,80 mg/kg-bw/day	6 hours/day, 5 days/week for 4 weeks	NOAEL = 80 mg/m^3	No effect on general condition of rats; no significant effects on body weight that were considered treatment-related.	(Civo Institute Tno, 1985)	High
Mortality	Other	Guinea pig (n=20)	Dermal	0.5 or 2.0 mL (260 mg/cm^3)	Once; contact for 5 days	LOAEL = 260 mg/ cm^3 [i]	5 of 20 animals died	(Wahlberg and Boman, 1979)	Medium
Mortality	Other	Guinea pig, Hartley, M (n=~4/group)	Dermal (intact and abraded skin)	0.5 mL undiluted (15,000 mg/kg)	Once	LD50 = 15,000 mg/kg-bw/day	Reduced survival	(Roudabush et al., 1965)	Unacceptable
Mortality	Other	Rabbit, white, M/ F (n=~4/group)	Dermal (abraded skin)	0.5 mL undiluted (15,000 mg/kg)	Once	LD50= 15,000 mg/kg-day [iii]	Reduced survival	(Roudabush et al., 1965)	Unacceptable
Hepatic	Chronic	Mouse, Crj:BDF1 (SPF), M/ F (n=100/ group)	Inhalation, vapor, whole body	0, 32, 160, 801 mg/m^3 (0, 5, 25, 125 ppm)	6 hours/ day, 5 days/ week for 104 weeks	NOAEL = 32 mg/m^3, LOAEL = 160 mg/m^3	Incidence of hepatocellular adenoma or carcinoma	(Nagano et al., 2007a)	High

Target Organ/ System[1]	Study Type	Species/ Strain/Sex (Number/ group)[2]	Exposure Route	Doses/ Concentrations[3]	Duration[4]	Effect Dose or Concentration (Sex)	Effect[6]	Reference	Data Quality Evaluation[8]
Hepatic	Chronic	Rat, F344/DuCrj (SPF), M/ F (n=100/group)	Inhalation, vapor, whole body	0, 32, 160, 801 mg/m^3 (0, 5, 25, 125 ppm)	6 hours/ day, 5 days/ week for 104 weeks	NOAEL = 160 mg/m^3, LOAEL = 801 mg/m^3	Incidence of hepatocellular adenoma or carcinoma	(Nagano et al., 2007a)	High
Hepatic	Chronic	Rat, F344/DuCrj (SPF), M/ F (n=100/group)	Inhalation, vapor, whole body	0, 31, 157 or 786 mg/m^3 (0, 5, 25 or 125 ppm)	6 hours/ day, 5 days/ week for 104 weeks	NOAEL = 31 mg/m^3, LOAEL = 157 mg/m^3	Increased AST, ALT, LDH, GPT, BUN, CPK; lesions in the liver (fatty changes, fibrosis)	(Nagano et al., 2007a)	High
Hepatic	Chronic	Mouse, Crj:BDF1 (SPF), M/F (n= 100/group)	Inhalation, vapor, whole body	0, 31, 157 or 786 mg/m^3 (0, 5, 25 or 125 ppm)	6 hours/ day, 5 days/ week for 104 weeks	LOAEL=31 mg/m^3 (M)	Reduced survival late in study (because of liver tumors); increased ALT, AST, LDH, ALP, protein, total bilirubin, and BUN; decreased urinary pH; increased liver weight; lesions in the liver (degeneration)	(Nagano et al., 2007a)	High
Hepatic	Chronic	Mouse, BDF1, M/ F (n=20/group)	Inhalation, vapor, whole body	0, 63, 189, 566, 1699, or 5096 mg/m^3 (0, 10, 30, 90, 270, or 810 ppm)	6 hours/ day, 5 days/ week for 13 weeks	LOAEL = 63 mg/m^3	Slight cytological alterations in the liver; cytoplasmic globules	(Nagano et al., 2007b)	High

Target Organ/ System[1]	Study Type	Species/ Strain/Sex (Number/ group)[2]	Exposure Route	Doses/ Concentrations[3]	Duration[4]	Effect Dose or Concentration (Sex)	Effect[6]	Reference	Data Quality Evaluation[8]
Hepatic	Chronic	Rat, F344, M/ F (n=20/group)	Inhalation, vapor, whole body	0, 63, 189, 566, 1699, 5096 mg/m^3 (0, 10, 30, 90, 270, 810 ppm)	6 hours/ day, 5 days/ week for 13 weeks	NOAEL = 63 mg/m^3 (F), LOAEL = 189 mg/m^3 (F)	Increased liver weight; large droplet fatty change in liver	(Nagano et al., 2007b)	High
Hepatic	Chronic	Rat, F344, M/ F (n=20/group)	Inhalation, vapor, whole body	0, 63, 189, 566, 1699, or 5096 mg/m^3 (0, 10, 30, 90, 270, or 810 ppm)	6 hours/ day, 5 days/ week for 13 weeks	LOAEL = 63 mg/m^3	Increased liver weight; fatty change in liver	(Nagano et al., 2007b)	High
Hepatic	Chronic	Rat, albino, M/ F (n=30-50/group)	Inhalation, vapor, whole body	0, 31, 63, 157, 315, 629, 1258 or 2516 mg/m^3 (0, 5, 10, 25, 50, 100, 200 or 400 ppm)	7 hours/ day, 5 days/ week for 6 months	NOAEL = 31 mg/m^3, LOAEL = 63 mg/m^3	Increased liver weight; fatty degeneration in liver	(Adams et al., 1952)	Low
Hepatic	Chronic	Guinea pig, M/ F (n=10-18/group)	Inhalation, vapor, whole body	0, 31, 63, 157, 315, 629, 1258 or 2516 mg/m^3 (0, 5, 10, 25, 50, 100, 200 or 400 ppm)	7 hours/ day, 5 days/ week for 6 months	NOAEL = 31 mg/m^3, LOAEL = 63 mg/m^3	Increased liver weight; fatty degeneration in liver	(Adams et al., 1952)	Low
Hepatic	Chronic	Rabbit, albino, M/ F (n=2-4/ group)	Inhalation, vapor, whole body	0, 31, 63, 157, 315, 630, 1260 or 2520 mg/m^3 (0, 5, 10, 25, 50, 100, 200 or 400 ppm)	7 hours/ day, 5 days/ week for 6 months	NOAEL = 63 mg/m^3, LOAEL = 157 mg/m^3	Increased liver weight; fatty degeneration and slight cirrhosis in liver	(Adams et al., 1952)	Low
Hepatic	Chronic	Monkey, rhesus, M/ F (n=2-4/ group)	Inhalation, vapor, whole body	0, 31, 63, 157, 315 or 630 mg/ m^3 (0, 5, 20, 25, 50 or 100 ppm)	7 hours/ day, 5 days/ week for 6 months	NOAEL = 315 mg/m^3 , LOAEL = 629 mg/m^3	Slight fatty degeneration and increased lipid content in liver	(Adams et al., 1952)	Low

Target Organ/ System[1]	Study Type	Species/ Strain/Sex (Number/ group)[2]	Exposure Route	Doses/ Concentrations[3]	Duration[4]	Effect Dose or Concentration (Sex)	Effect[6]	Reference	Data Quality Evaluation[8]
Hepatic	Chronic	Mouse, CD-1, M/ F (n=40/group)	Oral, gavage (corn oil vehicle)	0, 12, 120, 540 or 1200 mg/kg-bw/day	7 days/ week for 13 weeks	LOAEL = 12 mg/kg-bw/day	Increased liver weight, ALT, AST, ALP, LDH, 5'-nucleotidase; fatty change, hepato-cytomegaly, necrosis, and hepatitis	(Hayes et al., 1986)	Medium
Hepatic	Subchronic	Mouse, CD-1, M/ F (n=40/group)	Oral, gavage (corn oil vehicle)	0, 625, 1250, 2500 mg/kg-bw/day	7 days/ week for 90 days	LOAEL = 625 mg/kg-bw/day	Increased liver weight, ALT, AST, ALP, LDH, 5'-nucleotidase; fatty change, hepato-cytomegaly, necrosis, and hepatitis	(Hayes et al., 1986)	Medium
Hepatic	Subchronic	Rat, F344/ Crl, M (n=10/ group)	Inhalation, whole body	0, 31, 126, or 629 mg/m^3 (0, 5, 20 or 100 ppm)	6 hours/ day, 5 days/ week for 12 weeks	NOAEL = 126 mg/m^3 (M), LOAEL = 629 mg/m^3 (M)	Increased ALT, SDH; necrosis in liver	(Benson and Springer, 1999)	High
Hepatic	Subchronic	Mouse, B6C3F1, M (n=10/group)	Inhalation, whole body	0, 31, 126, or 629 mg/m^3 (0, 5, 20 or 100 ppm)	6 hours/ day, 5 days/ week for 12 weeks	NOAEL = 31 mg/m^3 (M), LOAEL = 126 mg/m^3 (M)	Increased ALT, SDH; necrosis and cell proliferation in liver	(Benson and Springer, 1999)	High

Target Organ/ System[1]	Study Type	Species/ Strain/Sex (Number/ group)[2]	Exposure Route	Doses/ Concentrations[3]	Duration[4]	Effect Dose or Concentration (Sex)	Effect[6]	Reference	Data Quality Evaluation[8]
Hepatic	Subchronic	Hamster, Syrian, M (n=10/group)	Inhalation, whole body	0, 31, 127 or 636 mg/m^3 (0, 5, 20 or 100 ppm)	6 hours/ day, 5 days/ week for 12 weeks	NOAEL = 126 mg/m^3 (M), LOAEL = 629 mg/m^3 (M)	Increased ALT, SDH; necrosis and cell proliferation in liver	(Benson and Springer, 1999)	High
Hepatic	Subchronic	Rat, Sprague Dawley, M (n=15-16/ group)	Oral, gavage (corn oil vehicle)	0, 1, 10 or 33 mg/kg-bw/day	5 days/ week for 12 weeks	NOAEL = 1 mg/kg-bw/day (M), LOAEL = 10 mg/kg-bw/day (M)	Two- to three-fold increase in SDH; mild centrilobular vacuolization in liver	(Bruckner et al., 1986)	High
Hepatic	Subchronic	Rat, F344, M (n=48/group; 6/ group and sacrifice time; sacrificed at intervals from 1 to 15 days post exposure)	Oral, gavage (corn oil vehicle)	0, 20 or 40 mg/kg-bw/day	5 days/ week for 12 weeks	LOAEL = 20 mg/kg-bw/day (M)	Increased liver weight, ALT, AST, LDH; reduced liver CYP450; cirrhosis, necrosis, and degeneration in liver	(Allis et al., 1990)	Medium
Hepatic	Subchronic	Mouse, CD-1, M/ F (n=24/group)	Oral, gavage (corn oil vehicle)	0, 1.2, 12 or 120 mg/kg-bw/day	5 days/ week for 12 weeks	NOAEL = 1.2 mg/kg-bw/day, LOAEL = 12 mg/kg-bw/day	Increased ALT; mild to moderate hepatic lesions (hepato-cytomegaly, necrosis, inflammation)	(Condie et al., 1986)	High
Hepatic	Subchronic	Rat, Sprague-Dawley, M (n=5/group)	Oral, gavage (corn oil vehicle)	0, 50, or 2000 mg/kg-bw/day	72 hours	LOAEL = 50 mg/kg-bw/day	Increased ALT, AST, and ALP	(Sun et al., 2014)	High

Target Organ/ System[1]	Study Type	Species/ Strain/Sex (Number/ group)[2]	Exposure Route	Doses/ Concentrations[3]	Duration[4]	Effect Dose or Concentration (Sex)	Effect[6]	Reference	Data Quality Evaluation[8]
Hepatic	Acute	Guinea pig, albino (n=20)	Dermal	513 mg/cm^2	15 minutes to 16 hours	LOAEL = 513 mg/cm^2 (ATSDR)	Hydropic changes, slight necrosis	(Kronevi et al., 1979)	Unacceptable
Hepatic	Acute	Rat, Sprague-Dawley, M (n=5/group)	Oral, gavage (corn oil vehicle)	0, 50, or 2000 mg/kg-bw/day	6 hours, 24 hours	NOAEL = 50 mg/kg-bw/day	Weight loss; increased ALP; decreased cholesterol, triglycerides, and glucose; liver histopathology (centrilobular necrosis and degeneration; cytoplasmic vacuolization); increased BUN	(Sun et al., 2014)	High
Renal	Chronic	Rat, F344, M/ F (n=20/group)	Inhalation, vapor, whole body	0, 63, 189, 566, 1699, 5096 mg/m^3 (0, 10, 30, 90, 270, 810 ppm)	6 hours/ day, 5 days/ week for 13 weeks	NOAEL = 1699 mg/m^3, LOAEL =5096 mg/m^3	Histopathological lesions, kidney glomerulosclerosis	(Nagano et al., 2007b)	High
Renal	Chronic	Rat, F344/DuCrj (SPF), M/ F (n=100/ group)	Inhalation, vapor, whole body	0, 31, 157 or 786 mg/m^3 (0, 5, 25 or 125 ppm)	6 hours/ day, 5 days/ week for 104 weeks	NOAEL = 31 mg/m^3 LOAEL = 157 mg/m^3	Lesions in the kidney (progressive glomerulo-nephrosis)	(Nagano et al., 2007a)	High

Target Organ/ System[1]	Study Type	Species/ Strain/Sex (Number/ group)[2]	Exposure Route	Doses/ Concentrations[3]	Duration[4]	Effect Dose or Concentration (Sex)	Effect[6]	Reference	Data Quality Evaluation[8]
Renal	Chronic	Mouse, Crj:BDF1 (SPF), M/ F (n=100/ group)	Inhalation, vapor, whole body	0, 31, 157 or 786 mg/m^3 (0, 5, 25 or 125 ppm)	6 hours/ day, 5 days/ week for 104 weeks	NOAEL = 31 mg/m^3, LOAEL = 157 mg/m^3	Increased ALT, AST, LDH, ALP, protein, total bilirubin, and BUN; lesions in the kidney (protein casts); benign pheochro-mocytoma (males)	(Nagano et al., 2007a)	High
Renal	Acute (<24 hr)	Rat, Sprague-Dawley, M (n=5/group)	Oral, gavage (corn oil vehicle)	Oral, gavage (corn oil vehicle)	Not Reported	NOAEL = 50 mg/kg-bw/day	Weight loss; increased ALP; decreased cholesterol, triglycerides, and glucose; liver histopathology (centrilobular necrosis and degeneration; cytoplasmic vacuolization); increased BUN	(Sun et al., 2014)	High
Skin	Other	Guinea pig, albino (n=20)	Dermal	513 mg/cm^2	15 minutes to 16 hours	LOAEL = 513 mg/cm^2	Karyopynosis, spongiosis, perinuclear edema	(Kronevi et al., 1979)	Unacceptable
Skin	Other	Guinea pig, Hartley, M (n=6/group)	Dermal (intact and abraded skin)	120 mg/kg-bw/day	Once, 24 hours	LOAEL = 120 mg/kg-bw/day	Primary irritation	(Roudabush et al., 1965)	Unacceptable

Target Organ/ System[1]	Study Type	Species/ Strain/Sex (Number/ group)[2]	Exposure Route	Doses/ Concentrations[3]	Duration[4]	Effect Dose or Concentration (Sex)	Effect[6]	Reference	Data Quality Evaluation[8]
Skin	Other	Rabbit, white, M/ F (n=6/group)	Dermal (intact and abraded skin)	120 mg/kg-bw/day	Once, 24 hours	LOAEL = 120 mg/kg-bw/day	Primary irritation	(Roudabush et al., 1965)	Unacceptable
Develop-mental Effects	Developmental	Rat, F344, F (n=12-14/ group)	Oral, gavage (corn oil vehicle)	0, 25, 50 or 75 mg/kg-bw/day	GDs 6-15	NOAEL = 25 mg/kg-bw/day (F), LOAEL = 50 mg/kg-bw/day (F)	Piloerection; markedly increased full-litter resorption	(Narotsky et al., 1997)	High
Develop-mental Effects	Developmental	Rat, F344, F (n=12-14/ group)	Oral, gavage (10% Emulphor vehicle)	0, 25, 50 or 75 mg/kg-bw/day	GDs 6-15	NOAEL = 25 mg/kg-bw/day (F), LOAEL = 50 mg/kg-bw/day (F)	Piloerection; markedly increased full-litter resorption	(Narotsky et al., 1997)	High
Body weight	Chronic	Rat, F344/DuCrj (SPF), M/ F (n=100/ group)	Inhalation, vapor, whole body	0, 32, 160, 801 mg/m^3 (0, 5, 25, 125 ppm)	6 hours/ day, 5 days/ week for 104 weeks	NOAE L= 32 mg/m^3, LOAEL = 160 mg/m^3	Reduced body weight gain	(Nagano et al., 2007a)	High
Body weight	Chronic	Mouse, Crj:BDF1 (SPF), M/F (n= 100/group)	Inhalation, vapor, whole body	0, 32, 160, 801 mg/m^3 (0, 5, 25, 125 ppm)	6 hours/ day, 5 days/ week for 104 weeks	NOAEL = 32 mg/m^3, LOAEL = 160 mg/m^3	Reduced body weight gain	(Nagano et al., 2007a)	High
Body Weight	Subchronic	Rat, Sprague-Dawley, M (n=5/group)	Oral, gavage (corn oil vehicle)	0, 50, or 2000 mg/kg-bw/day	72 hours	NOAEL = 50 mg/kg-bw/day	Weight loss	(Sun et al., 2014)	High

Target Organ/ System[1]	Study Type	Species/ Strain/Sex (Number/ group)[2]	Exposure Route	Doses/ Concentrations[3]	Duration[4]	Effect Dose or Concentration (Sex)	Effect[6]	Reference	Data Quality Evaluation[8]
Body Weight	Subchronic	Rat, Wistar, M (n=10/group)	Inhalation	0, 63,80 mg/kg-bw/day	6 hours/day, 5 days/week for 4 weeks	NOAEL = 80 mg/m^3	No effect on general condition of rats; no significant effects on body weight that were considered treatment-related.	(Civo Institute Tno, 1985)	High
Body Weight	Acute (<24 hr)	Rat, Sprague-Dawley, M (n=5/group)	Oral, gavage (corn oil vehicle)	0, 50, or 2000 mg/kg-bw/day	6 hours, 24 hours	NOAEL = 50 mg/kg-bw/day	Weight loss; increased ALP; decreased cholesterol, triglycerides, and glucose; liver histopathology (centrilobular necrosis and degeneration; cytoplasmic vacuolization); increased BUN	(Sun et al., 2014)	High
Immune	Chronic	Mouse, Crj:BDF1 (SPF), M/F (n= 100/ group)	Inhalation, vapor, whole body	0, 32, 160, 801 mg/m^3 (0, 5, 25, 125 ppm)	6 hours/ day, 5 days/ week for 104 weeks	NOAEL = 160 mg/m^3, LOAEL = 801 mg/m^3	Lesions in the spleen (extra medullary hemato-poiesis)	(Nagano et al., 2007a)	High

Table G-2. Summary of Reviewed Genotoxicity Studies for Carbon Tetrachloride

Target Organ/ System	Study Type	Species/Strain/Cell Type (Number/group if relevant)	Exposure Route	Doses/ Concentrations	Duration	Effect Concentration/ Result	Effect Measured	Reference	Data Quality Evaluation
Genotoxicity	Acute	Mouse lymphoma L5178/TK+/- cells	*In vitro*	0, 4.38, 6.55, 8.76 mmol/L (+S9)	3 hours	Positive at 6.55 and 8.76 mmol/L[a] (at relative toxicities of 6% and 16%, respectively)	Alkaline unwinding of DNA (ratio of ssDNA and dsDNA); cell viability	(Garberg et al., 1988)	Unacceptable
Genotoxicity	Acute	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 <3 replicates /group	*In vitro*	0, 0.005, 0.01, 0.05, 0.1, 0.2, 0.5, 1, 2, 5% (±S9)[b]	24 hours	Weakly positive[c] in TA 98 (-S9) at ≥ 1%; negative in TA 98 (+S9); negative in TA 100, TA 1535, and TA 1537 (± S9)	Reverse mutation (gas exposure method)	(Araki et al., 2004)	High
Genotoxicity	Acute	*Escherichia coli* strains WP2/*uvrA*/pKM101, WP2/pKM101 <3 replicates /group	*In vitro*	0, 0.005, 0.01, 0.05, 0.1, 0.2, 0.5, 1, 2, 5% (±S9)[b]	24 hours	Weakly positive[c] at 2% in WP2/*uvrA*/pKM101 (±S9); positive at ≥ 0.1% (-S9) and ≥ 0.2% (+S9) in WP2/pKM101[d]	Reverse mutation (gas exposure method)	(Araki et al., 2004)	High

[a] The test substance was positive at toxic concentrations only. However, the criteria for a positive response in this assay included increases in the relative fraction of ssDNA that is greater than the increase in relative toxicity (at toxicities of 5% to 50%), if this occurs at two or more concentrations.
[b] Tests were also conducted with glutathione-supplemented S9 mix.
[c] A result was considered positive if a two-fold increase in the number of revertants was observed.
[d] Data for *E.coli* strain WP2/pKM101 were based on <3 measurements (statistical analyses were not performed).

Appendix H GENOTOXICITY

The *in vitro* and *in vivo* genotoxicity databases for carbon tetrachloride, including their limitations are described below.

H.1 *In vitro* Genotoxicity and Mutation

Bacterial mutagenicity with reference to strains more capable to detect oxidative damage

Many experiments have tested carbon tetrachloride for mutagenesis in standard salmonella reverse mutation assays. Eastmond (2008) observes: "While carbon tetrachloride has consistently been negative in studies using Salmonella and certain strains of *E. coli*, at high exposure concentrations, it has been reported to produce differential DNA repair and mutations in the WP2 strain of *E. coli*, a strain that is particularly sensitive to oxidative mutagens (Araki et al., 2004; De Flora et al., 1984)." EPA IRIS (U.S. EPA, 2010) further notes that because the WP2 strains of *E. coli* have an AT base pair at the critical mutation site within the *trpE* gene, they have been recommended for screening oxidizing mutagens (Martínez et al., 2000; Gatehouse et al., 1994). In contrast, using *E. coli* strains that are more sensitive to oxidative mutagens, increases in DNA repair were reported by De Flora (1984) and increases in reverse mutation were reported by Araki (2004) and Norpoth (1980). In the De Flora (1984) study, carbon tetrachloride was more toxic to the *E. coli* strain CM871 (uvrA- recA- lexA-) than it was to the isogenic repair-proficient WP2 strain or WP67 (uvrA- polA-). Although a similar pattern was seen in the presence of metabolic activation, carbon tetrachloride was more active in the absence of activation.

Bacterial test strains

Although carbon tetrachloride has been evaluated many times in the standard Salmonella test strains, it has not been tested in either TA102 or TA104 and only a few times in the *E. coli* WP2 strains, the strains that would be the most sensitive to the oxidative DNA damage likely to be generated during carbon tetrachloride toxicity.

Based on OECD relevant guidance as to selection of bacterial strains, standard Salmonella test strains "may not detect certain oxidizing mutagens, cross-linking agents, and hydrazines. Such substances may be detected by *E.coli* WP2 strains or *S. typhimurium* TA102…" OECD's recommended combination of strains includes *E. coli* WP2 strains or *S. typhimurium* TA102 (OECD Guideline for Testing of Chemicals. Bacterial Reverse Mutation Test. Report 471, adopted 21 July 1997). Additionally, a statistically significant but well less than a two-fold increase for *E. coli* WP2uvrA was reported by Norpoth (1980) at high levels (about 25,000 ppm) in another gas-phase exposure study.

In vitro genotoxicity studies for carbon tetrachloride in mammalian cells

As discussed below, *in vitro* studies of carbon tetrachloride genotoxic effects in metabolically competent liver cells will be of most importance. Studies in lung and kidney cells may provide supplemental information, while studies in other cell types may not allow for metabolism believed to be necessary for carbon tetrachloride toxicity/carcinogenicity.

Metabolism induction

According to the EPA IRIS Assessment (U.S. EPA, 2010), "when standard inducing procedures (Arochlor 1254 or the combination of phenobarbitone and beta-naphthoflavone) have been used,

the levels of CYP2E1 in the rat liver are markedly suppressed (Burke et al., 1994). This would lead to a decrease in CYP2E1 in the S9 used for the test and could potentially contribute to the observed negative results." However, mammalian cell test strains using lymphocytes, ovary cells, lung cells, or kidney cells may not closely resemble liver cells in the ability to metabolize carbon tetrachloride. The kidney and lung do have P450 metabolic capability that has been evaluated for carbon tetrachloride and this has been used in the development of PBPK models. Using *in vitro* measurements with p-nitrophenol as a reference compound, (Yoon et al., 2007) has estimated CYP2E1 activity (Vmax – nmole/min/g) in the lung and kidney as approximately 6% and 5% of that in the liver. Accordingly, cells from these other tissues may not be similar to liver cells in the metabolism of carbon tetrachloride.

Mammalian cell mutagenesis tests

There are no mutagenesis tests identified in mammalian liver, kidney or lung cells *in vitro*. OECD now recommends *in vitro* mammalian cell gene mutation tests using the *hprt* or *xprt* genes (OECD TG 476). The OECD cited tests include lung cell lines (V79 and CHL) that could be examined for CYP2E1 competence.

Chromosomal changes

In the absence of mutation studies, the current review focuses on chromosomal aberration and micronucleus studies in mammalian cells *in vitro* – using cells from (1) liver, (2) kidney, or lung which also show some CYP2E1 activity, or (3) cells with CYP2E1 capability is added. These are extracted from EPA IRIS Assessment (U.S. EPA, 2010) below.

Table H-1. Bacterial mutagenesis data in systems believed relevant to detection of oxidative damage to DNA – excerpted from the EPA IRIS Assessment

Test system	Endpoint	Test conditions	Results with metabolic activation	Results without metabolic activation		Reference
Escherichia coli WP2*uvr*A/pKM101	Reverse mutation	Gas phase exposure in a gas sampling bag for 24 hrs	±	±	10,000 ppm	(Araki et al., 2004)
E. coli WP2/pKM101	Reverse mutation	Gas phase exposure in a gas sampling bag for 24 hrs	+	+[a]	5,000 ppm	(Araki et al., 2004)
E. coli WP2*uvr*A	Reverse mutation	Gas phase exposure in a desiccator	ND	±	25,000 ppm	(Norpoth et al., 1980)

"+" = positive results; "-" = negative results; "±" = equivocal or weakly positive; "ND" = No Data

[a] Results similar with or without GSH added to the S9 mix. Positive response is based on the magnitude of response as statistical analyses were not performed.

Table H-2. Chromosomal changes in *in vitro* studies mammalian cells from liver, kidney or lung; or cells with CYP2E1 genetic capability added – excerpted from the EPA IRIS Assessment

Test system	Endpoint	Test conditions	Results with metabolic activation	Results without metabolic activation		Reference
RL_1 cultured cell line derived from rat liver	Chromosomal aberrations	Assay conducted in sealed flasks	–	ND	0.02 µg/mL in DMSO	(Dean and Hodson-Walker, 1979)
V79 Chinese hamster lung cell line	Aneuploidy	3-Hr incubation	+	ND	246 µg/mL	(Onfelt, 1987)
V79 Chinese hamster lung cell line	c-Mitosis (spindle disturbance)	30-Min incubation	± (T)	ND	492 µg/mL	(Onfelt, 1987)
h2E1 cell line (cDNA for CYP2E1)	Micronucleus formation	Immunofluorescent labeling of kinetochore proteins	+ (T)	ND	308 µg/mL	(Doherty et al., 1996)
Study in CYP2E1 competent cells. Quoting EPA (2010): "Doherty *et al*. (1996) reported that carbon tetrachloride induced micronuclei in two human lymphoblastoid cell lines—one expressing CYP2E1 (h2E1) and the other expressing CYP1A2, 2A6, 3A4, and 2E1 and microsomal epoxide hydrolase (MCL-5)—but not the CYP1A1-expressing AHH-1 cell line. Treatment of the cells with 10 mM carbon tetrachloride resulted in five- and nine-fold increases in micronucleated cells in the h2E1 and the MCL-5 cell lines, respectively. The increases occurred mostly in kinetochore-positive micronuclei, indicating an origin from chromosome loss. Smaller increases (~two- to four-fold) in micronuclei originating from chromosomal breakage (kinetochore-negative) were also seen." At the 10 mM high concentration, there was indication of substantial toxicity, but this study indicates a dose response trend down to 1 mM concentration, where toxicity was less evident.						
MCL-5 cell line (cDNA for CYPs 1A2, 2A6, 3A4, and 2E1, and epoxide hydrolase)	Micronucleus formation	Immunofluorescent labeling of kinetochore proteins	+ (T)	ND	308 µg/mL	(Doherty et al., 1996)
See comment above						

"+" = positive results; "-" = negative results; "±" = equivocal or weakly positive; "T" = Toxicity; "ND" = No Data.

H.2 *In vivo* Genotoxicity

Mutation studies

Three studies using the *lacL* or *lacZ* genes in the liver in transgenic mice are available and reported negative or inconclusive results. These studies use single or in one case five exposures to carbon tetrachloride, a limitation for a study methodology in which longer term exposures are generally recommended. Additionally, two studies reported an increase in mutation frequency after single exposures, increases that while limited in magnitude, indicate a need for more definitive studies.

Chromosomal studies

Two studies reported positive results in micronucleus experiments, while two others were negative. Two studies of chromosomal aberration or damage after single high dose carbon tetrachloride exposures were negative. Use of maximal doses may not increase (or even reduce) sensitivity due to reduction of CYP2E1 activity with high carbon tetrachloride doses.

DNA breakage

A number of *in vivo* comet and other DNA breakage assays have been performed with rodent liver cell lines and appear mostly, but not uniformly, negative. These studies were primarily conducted using high single dose injection or gavage dosing. There are general reservations about interpreting DNA breakage data in the presence of toxicity. OECD Test Guideline 489 notes that "Fragmentation of the DNA can be caused not only by chemically-induced genotoxicity, but also during the process of cell death, *i.e.*, apoptosis and necrosis. It is difficult to distinguish between genotoxicity and apoptosis/necrosis by the shape of the nucleus and comet tail after electrophoresis…"

Unscheduled DNA Synthesis (UDS)

A number of rodent experiments assessed UDS in the liver, generally after single oral or injection exposures. Test results were generally, but not uniformly, negative. OECD test guideline 486 notes that the UDS test responds positively only to substances that induce DNA damage that is repaired by nucleotide excision repair. It is not clear that this is a sensitive test for potential carbon tetrachloride induced DNA damage, including oxidative damage. The OECD guideline also comments that "The UDS test should not be considered as a surrogate test for a gene mutation test."

Summary of in vivo genotoxicity evidence

Optimal *in vivo* studies of carbon tetrachloride mutagenesis or chromosomal alterations are not available. While the available *in vivo* database does not on balance demonstrate carbon tetrachloride genotoxicity, neither does it represent a fully sensitive body of studies to test for such effects.

Table H-3. *In vivo* mutation and chromosomal change studies for carbon tetrachloride in liver tissue – excerpted from EPA IRIS Assessment

Test system	Endpoint	Test conditions	DNA adducts IRIS (2010) descriptor	Dose	Reference
Mouse (B6C3F$_1$, *lacI* transgenic; Big Blue™, male)	Mutations in *lacI* transgene in liver	The target *lacI* gene is recovered from genomic DNA after five daily doses and the animals sacrificed 7 d after the first dose	IRIS: – (T)	35 mg/kg-day (5 times)	(Mirsalis et al., 1994)
Comment: Original article not reviewed. This non-positive test used 5 administrations of a relevant dose of carbon tetrachloride (a much lower dose than used in many shorter term *in vivo* experiments. The sensitivity of this experiment could have been strengthened if carbon tetrachloride were administered for a longer period.					
Mouse (CD2F$_1$ *lacZ* transgenic, Mutamouse™, male)	Mutations in the *lacz* transgene in liver	The target *lacz* gene is recovered from genomic DNA after a single dose with the animals being sacrificed 14 d later	IRIS: – (T)	80 mg/kg by oral gavage in corn oil	(Tombolan et al., 1999)
Comment: The carbon tetrachloride data was generated as a adjuct of a study with a differenet research focus, and were thus limited in scope. Carbon tetrachloride mutation frequency exceeded controls by 60% of which was not indicated as significant. Use of only a single test administration limits the sensitivity of these results. This study should not be judged as a specificlly negative finding.					
Mouse (CD2F$_1$ *lacZ* transgenic, Mutamouse™, male)	Mutations in the *lacz* transgene in liver	The target *lacz* gene is recovered from genomic DNA after dosing with the animals being sacrificed 7, 14, or 28 d later	IRIS: – (T)	1,400 mg/kg by oral gavage	(Hachiya and Motohashi, 2000)
Comment: Increases in mutation frequency, some more that twice the control rate were seen in some test groups. While the author inferred that the results”were not biologically significant,” this study is not a ”negative” result. Use of only a single test administration limits the sensitivity of these results. The high dose used may not contribute to sensitivity as CYP2E1 activity can be degreaded at high dose.					
Mouse (CD-1, male)	Chromosomal fragments and bridges in liver	Anaphase analysis of squash preparations prepared 72 hrs after dosing	–	8,000 mg/kg	(Curtis and Tilley, 1968)

Test system	Endpoint	Test conditions	DNA adducts IRIS (2010) descriptor	Dose	Reference
Rat (F344, male)	Chromosomal aberrations in liver	Analyzed primary hepatocytes cultured for 48 hrs from rats sacrificed 0–72 hrs after dosing	–	1,600 mg/kg by oral gavage in corn oil	(Sawada et al., 1991)
Rat (F344, male)	Micronucleus formation in liver	Analyzed primary hepatocytes cultured for 48 hrs from rats sacrificed 0–72 hrs after dosing	–	1,600 mg/kg by oral gavage in corn oil	(Sawada et al., 1991)
Rat (Wistar, male)	Micronucleus formation in liver	Analyzed primary hepatocytes harvested 72 hrs after dosing, an optimal time to detect micronuclei.	± (T)	3,200 mg/kg by oral gavage in corn oil	(Van Goethem et al., 1993)
Rat (Wistar, male)	Micronucleus formation in liver	Analyzed primary hepatocytes harvested 72 hrs after dosing, an optimal time to detect micronuclei. Increase was in both centromere-lacking (5.5-fold) and centromere-containing (3.6-fold) micronuclei.	+ (T)	3,200 mg/kg by oral gavage in corn oil	(Van Goethem et al., 1995)
Mouse (CBAxC575BL/6, male)	Micronucleus formation and ploidy levels in liver	Analyzed primary hepatocytes from rats sacrificed 5 d after dosing and compared with a partially hepatectomized control.	–	15-Min inhalation at 0.05–0.1 mL/5 L	(Uryvaeva and Delone, 1995)

"+" = positive results; "-" = negative results; "±" = equivocal or weakly positive; "T" = Toxicity

Appendix I CANCER MOA ANALYSIS FOR LIVER AND ADRENAL TUMORS

Cancer MOA Analysis for Liver Tumors

The MOA for carbon tetrachloride-induced liver tumors is supported by experimental evidence which is presented below for each of the key events in the MOA as stated above. The evidence in support of the MOA for carbon tetrachloride-induced liver tumors is summarized below from the 2010 IRIS Toxicological Review for carbon tetrachloride.

1) Metabolism to the trichloromethyl radical by CYP2E1 and subsequent formation of the trichloromethyl peroxy radical

The metabolism of carbon tetrachloride to trichloromethyl and trichloromethyl peroxy radicals is an obligatory step in carbon tetrachloride's MOA. There is considerable evidence that the initial step in biotransformation of carbon tetrachloride is reductive dehalogenation: reductive cleavage of one carbon-chlorine bond to yield chloride ion and the trichloromethyl radical (Reinke and Janzen, 1991; Tomasi et al., 1987; Mccay et al., 1984; Mico and Pohl, 1983; Slater, 1982; Poyer et al., 1980; Lai et al., 1979; Poyer et al., 1978). The fate of the trichloromethyl radical is dependent on the availability of oxygen and includes several alternative pathways for anaerobic or aerobic conditions. Under aerobic conditions, the trichloromethyl radical can be trapped by oxygen to form the trichloromethyl peroxy radical, which can bind to tissue proteins (Galelli and Castro, 1998; Packer et al., 1978) or decompose to form phosgene ($COCl_2$) (Pohl et al., 1984) and an electrophilic form of chlorine (Pohl et al., 1984). The trichloromethyl peroxy radical is the primary initiator of lipid peroxidation that occurs from exposure to carbon tetrachloride (Boll et al., 2001; Mccay et al., 1984; Rao and Recknagel, 1969).

Further support for metabolism of carbon tetrachloride as a key event is based on the following: (1) reactive metabolites are present in the liver (Stoyanovsky and Cederbaum, 1999; Connor et al., 1986), (2) CYP450 inhibitors prevent carbon tetrachloride-induced liver damage (Martínez et al., 1995; Letteron et al., 1990; Mourelle et al., 1988; Bechtold et al., 1982; Weddle et al., 1976), (3) treatment of knockout mice specific for CYP2El (cyp2el-/-) with carbon tetrachloride does not result in hepatocellular cytotoxicity as compared to wild type (cyp2el+/+) mice, and (4) treatment with compounds that induce CYP450s result in potentiating effects to carbon tetrachloride-induced toxicity.

2) Radical-induced mechanisms leading to hepatocellular cytotoxicity

Under aerobic conditions, the trichloromethyl radical is converted to the more reactive trichloromethyl peroxy radical. The trichloromethyl peroxy radical can attack polyenoic (polyunsaturated) fatty acids in the cellular membrane, forming fatty acid free radicals that initiate subsequent autocatalytic lipid peroxidation through a chain reaction.

Numerous studies have demonstrated the occurrence of lipid peroxidation following carbon tetrachloride exposure, either by detection of conjugated dienes (a characteristic marker of lipid

peroxidation) in liver lipids (Tribble et al., 1987; Lee et al., 1982; Recknagel and Glende, 1973; Rao and Recknagel, 1969), increased exhalation of ethane or pentane (end degradation products of peroxidized T-3 and T-6 polyunsaturated fatty acids, respectively) in treated rats (Younes and Siegers, 1985; Gee et al., 1981), or occurrence of reactive aldehydes, such as malonaldehyde and 4-hydroxyalkenals, frequently measured as thiobarbituric acid-reactive substances (TBARS) (De Zwart et al., 1997; Gassó et al., 1996; Ichinose et al., 1994; Fraga et al., 1987; Comporti, 1985; Comporti et al., 1984). TBARS form when the oxidation of the fatty acid progresses from the hydroperoxide, facilitated by the oxidation of Fe^{2+} to Fe^{3+} in a Fenton reaction, leading to breaks in the fatty acid chain and the formation of aldehydes from the fatty acid fragments (Klaassen, 1986). Among the many different aldehydes formed from lipid peroxidation are 4-hydroxynonenal and malondialdehyde.

Evidence of the relationship between hepatotoxicity and lipid peroxidation was also reported by (Younes and Siegers, 1985). These researchers found that administration of an iron-chelating agent, deferoxamine, suppressed both lipid peroxidation (ethane exhalation) and hepatotoxicity (serum ALT and SDH levels) in GSH-depleted mice treated with carbon tetrachloride. This result suggests that the observed hepatotoxic effect was secondary to lipid peroxidation. Administration of the antioxidant vitamin E (α-tocopherol) was shown to reduce lipid peroxidation (pentane exhalation) and metabolism (chloroform generation) in another rat study (Gee et al., 1981).

3) Sustained regenerative and proliferative changes in the liver in response to hepatotoxicity

As summarized below, several subchronic inhalation and oral studies demonstrate that carbon tetrachloride produces hepatic toxicity and regenerative responses. In rodents exposed to carbon tetrachloride vapor for 12 weeks to 6 months, LOAELs for tissue damage were reported at concentrations ranging from 4 to 42 ppm (adjusted to continuous exposure) and for hyperplasia/ regeneration at concentrations ranging from 4 to 20 ppm (adjusted). Thus, results of subchronic exposure studies are consistent with results of the Nagano study in rats, showing cytotoxicity at ≥10 ppm (≥2 ppm adjusted) and hyperplasia/proliferation at ≥30 ppm (≥5.4 ppm adjusted) after 13 weeks of exposure (Nagano et al., 2007b) and cytotoxicity and hyperplasia/regeneration at ≥25 ppm (≥4.5 ppm adjusted) after 104 weeks of exposure (Nagano et al., 2007a). In rats and mice exposed orally to carbon tetrachloride for 12–17 weeks, LOAELs for tissue necrosis ranged from 8.6 to 80 mg/kg-d and for hyperplasia/regeneration ranged from 12 to 71 mg/kg-d. Durations of the subchronic studies were too short to evaluate tumor formation; thus, data from subchronic studies do not allow for further definition of the dose-response relationship and time course for cytotoxicity and tumor formation.

Table I-1. Subchronic and Chronic Inhalation and Oral Studies Showing that Carbon Tetrachloride Produces Hepatic Toxicity and Regenerative Responses

Species	Exposure Regimen	Hepatic Effects	Hyperplasia/ Regenerative Effects	Reference
Sprague-Dawley rat	Oral, 12 weeks, 24 mg/kg/day	Necrosis	Bile duct hyperplasia	(Bruckner et al., 1986)
Fischer 344 rat	Oral, 12 weeks, 14 mg/kg/day	Necrosis		(Allis et al., 1990)
Sprague-Dawley rat (male)	Oral, 13 weeks, 71/mg/kg/day	Necrosis	Nodular hepatic, bile duct, and oval cell hyperplasia	(Koporec et al., 1995)
CD-1 mouse	Oral, 13 wks 12 mg/kg-d	Necrosis	Bile duct hyperplasia	(Hayes et al., 1986)
CD-1 mouse	Oral, 12 wks 8.6 mg/kg/day	Necrosis		(Condie et al., 1986)
Strain A mouse	Oral, 120 d (30 doses) 80 mg/kg/day	Necrosis		(Eschenbrenner and Miller, 1946)
B6C3F1 mouse	Oral, 78 wks, 892 mg/kg/day		Bile duct proliferation	(NCI, 1977, 1976a, b)
Fischer 344 rat (male)	Inhalation, 12 wks 18 ppm	Necrosis	BrdU-negative hepatocytes	(Benson and Springer, 1999)
B6C3F1 mouse (male)	Inhalation, 12 wks 4 ppm	Necrosis	BrdU-positive hepatocytes	(Benson and Springer, 1999)
Syrian hamster (male)	Inhalation, 12 wks 18 ppm	Necrosis	BrdU-positive hepatocytes	(Benson and Springer, 1999)
Wistar rat	Inhalation, 6 months 42 ppm	Necrosis		(Adams et al., 1952)
Hartley guinea pig	Inhalation, 13 wks 10 ppm (continuous)	Hepatocellular degeneration	Hepatocellular regeneration	(Prendergast, 1967)

Hartley guinea pig; Sprague-Dawley or Long-Evans rat	Inhalation, 6 wks 20 ppm	Necrosis, hepatocellular degeneration	Hepatocellular regeneration, bile duct proliferation	(Prendergast, 1967)
Fischer 344 rat	Inhalation, 13 wks 2 ppm		Mitosis, bile duct proliferation, foci	(Nagano et al., 2007b)
BDF_1 mouse	Inhalation, 13 wks 5–48 ppm		Bile duct proliferation: 5 ppm, female; 16 ppm, male; mitosis: 16 ppm, male; 48 ppm, female; foci: 48 ppm both sexes	(Nagano et al., 2007b)
Fischer 344 rat	Inhalation, 104 wks 5–22 ppm		Foci: 5 ppm, female; 22 ppm, male	(Nagano et al., 2007a)
BDF_1 mouse	Inhalation, 104 wks 5 ppm	Degeneration in males; necrosis in females		(Nagano et al., 2007a)

Based on the reasonably available information described above, EPA has concluded that there is significant evidence to support key events (1) and (2) for being broadly responsible for carbon tetrachloride's main biological effects and toxicity in the liver.

A complication in this MOA sequence is that CYP450 metabolism of carbon tetrachloride to reactive radicals and subsequent processes of lipid peroxidation leading to the formation of additional radicals (linked to carbon tetrachloride through chemical processes, but not direct metabolites of carbon tetrachloride) could be proposed as a key event for other potential MOAs that may be considered. Specifically, these reactive radicals have the ability to chemically interact with DNA, and thus metabolism of carbon tetrachloride would likely be a first step in hypotheses about potential genotoxic effects of carbon tetrachloride (discussed further below). Metabolism of carbon tetrachloride to reactive molecules is thus not necessarily probative of the nature of the subsequent biological effects that lead to the development of cancer. Additionally, as discussed in some detail in the EPA IRIS Assessment (U.S. EPA, 2010), the specific biological interactions between the reactive compounds resulting from carbon tetrachloride

exposure and the occurrence of cytotoxicity has itself a complicated and long history in the study of carbon tetrachloride toxicology. Strong inferences can be made in favor of lipid peroxidation being the product interaction of carbon tetrachloride metabolites with constituents of cellular/intracellular lipid membranes and a proximate cause of carbon tetrachloride cytotoxicity. While other data indicates importance of direct interactions of carbon tetrachloride metabolites with biomolecules, for example those within the endoplasmic reticulum where highly reactive carbon tetrachloride metabolites will have direct potential for chemical interactions. Biological processes subsequent to damage induced by free radical interactions including disruption of calcium homeostasis have also been proposed as more proximate causes of cytotoxicity, and yet there remain questions regarding whether, changes in calcium homeostasis are a cause of cytotoxicity or are themselves the result of cytotoxic processes.

Accordingly, the evaluation of the evidence in support of a cytotoxicity and regenerative proliferation based MOA for carbon tetrachloride induced liver tumors depends primarily on an empirical examination of evidence of association of those processes and not on a more detailed (mechanistic) understanding of the specific biological processes involved in toxicity.
Carbon tetrachloride is one of the most classical liver toxicants in studies using high single or limited duration dosing (*e.g.*, gavage or intraperitoneal doses in the range of 0.5-5 g/kg-d have been amply demonstrated to induce acute carbon tetrachloride hepatotoxicity, and indeed are often used in mechanistic studies specifically as a reliable tool to induce such toxicity. However, chronic bioassays of carbon tetrachloride tumorigenesis utilize lower doses, *e.g.*, calculated alveolar inhaled doses of carbon tetrachloride in the Nagano (2007a) cancer bioassay were equal or less than approximately 100 mg/kg-d in the rat and 200 mg/kg-d in the mouse (calculated for illustration of magnitude of dose ranges, not as a metric for quantitative risk assessment). Additionally, while the inhaled carbon tetrachloride delivered in the Nagano (2007a) bioassay was delivered over a daily period of 6 hours, a larger number of toxicity studies used a gavage dosing technique which would lead to different dosing dynamics than would an inhalation study. For example, in a study by Bruckner (1990) peak blood concentrations and hepatotoxicity were substantially higher in rats receiving gastric bolus doses of carbon tetrachloride than those receiving more prolonged gastric (both gastric exposures using an aqueous vehicle) or receiving equivalent calculated alveolar doses of carbon tetrachloride by inhalation exposures. The authors suggest that caution is needed in inferring comparability of toxicity finding in studies using bolus administration of carbon tetrachloride versus those using a continuous means of administration. A subchronic exposure study from the same laboratory (Koporec et al., 1995) reported similar toxicity for carbon tetrachloride delivered by either corn oil or aqueous gavage infusion. Accordingly, the review here addressing cancer MOA specifically with reference to the (Nagano et al., 2007a) inhalation study will focus observations from the major inhalation studies of the toxicity of this compound and specifically, the Nagano subchronic and chronic bioassays as well as the subchronic study of (Benson and Springer, 1999).

Accordingly, the focus here is an evaluation of data regarding whether "sustained regenerative and proliferative changes in the liver in response to hepatotoxicity" is a key event for cancer development. That is the focused of the analysis on whether the observed compound related tumors resulted from this hypothesized MOA and its key events. The Cancer Guidelines framework review if organized as follows:

(1) Describe the empirical data that support the occurrence the proposed key events under conditions that have been found to be carcinogenic

The (Nagano et al., 2007a) inhalation cancer bioassay is accompanied by the (Nagano et al., 2007b) subchronic (13 week) toxicity study. This study specifically investigated toxicity in the same strains of rodents, sourced contemporaneously with the cancer study it represents the most valuable data on sustained toxic responses. At that time frame, transient effects from acute lower level exposures will have resolved and may not be relevant to chronic exposures representing conditions that result from sustained exposures across the animal's lifespans.

The toxicological findings from the cancer bioassay itself while important reflect end of life phenomena and in the case of carbon tetrachloride a large fraction of the animals in the higher dose groups developed tumors, sometimes reported to have involved essentially the entire liver, thus blurring inferences on MOA from liver pathology.

This high incidence of tumors in the Nagano bioassays makes examination of the subchronic study for both mice and rats important. In these subchronic studies inhaled doses of 10, 30, 90, 270, and 810 ppm were used while the cancer bioassay (again for both sexes and species) used inhaled doses of 5, 25, and 125 ppm. Thus, while these dose ranges overlap there is not exact correspondence and the higher doses in the subchronic study far exceed bioassay doses and higher doses (270 and 810 ppm) may not be informative for effects that occurred in the cancer bioassay.

For mice the subchronic study reported serum enzymes AST, ALT, and ALP for which elevated levels can be indicative of liver toxicity and at higher levels infer frank toxicity and cell killing. In males AST was only elevated (2x or less) in the high dose groups (270 and 810 ppm) and was not elevated in females. ALT was not elevated in the 10 or 30 ppm groups of either sex but was significantly elevated (roughly 3x) in both males and females at 90 ppm and increased moderately at the high concentrations. ALP was significantly, but only slightly increased (<2x) in male mice at 30 ppm and above and was not significantly elevated in females. Both male and female mice had high incidence of tumors at 25 and 125 ppm concentrations in (Nagano et al., 2007a). The serum enzyme markers did not provide a strong indication for sustained cytotoxicity (or cell death) in those dose ranges.

Histopathological examination in the subchronic study reported cytoplasmic globules and large droplet fatty change frequently in mice at 10 ppm and above. In female mice these effects were reported at 30 ppm and above. A phenomenon termed "collapse" was common in both male and female mice at 30 ppm and above. The authors state that collapse “was characterized by the shrunken parenchymal tissue over the centrilobular area, presumably resulting from the necrotic loss of hepatocytes" and note that collapse "was accompanied by both proliferation of the bile ducts and oval cells and deposition of ceroid-like yellow pigment.”

At high concentrations (270 and 810 ppm) nuclear enlargement with atypia was reported while in males altered cell foci were seen at these concentrations, with the latter being a potentially preneoplastic effect rather than an indication of cytotoxicity. More severe liver pathology *e.g.*, necrosis or cirrhosis was not reported in these mice. The reported pathology was indicative of cellular changes due to carbon tetrachloride, but did not indicate ongoing frank cytotoxicity, cell

killing, or regenerative processes. The authors description of the "collapse" phenomenon and associated bile duct proliferation suggests that some necrotic processes may have occurred in these animals.

In the (Nagano et al., 2007a) chronic study, AST and ALT were strongly elevated (10x or more in some cases) in the male and female 25 and 125 ppm test groups; LDH was also significantly elevated but to a lesser degree as compared with controls. However, liver tumors were prevalent in these dose groups and may themselves have impacted these results. Liver histopathology in this study reported presence of ceroid, a yellow pigment, which literature indicates may result from peroxidation processes but may occur in the absence of necrosis and more severe pathology (Greaves, 2012). Hydropic change (cellular swelling) was noted in centrilobular hepatocytes at these doses. Bile duct proliferation, again at the 25 and 125 ppm doses, was significantly elevated in both sexes, but was more prevalent in the males. Neither necrosis nor cirrhosis was reported in these mice.

(Benson and Springer, 1999) exposed male mice to 0, 5, 20 or 100 ppm carbon tetrachloride 6 hours/day, 5 days/week - matching the exposure protocol of the Nagano studies but with a different mouse strain (B6C3F1 as compared to BDF1 used by Nagano). Animals were killed after 1, 4 and 12 weeks of exposure. The serum enzymes ALT and SDH were reported to be significantly elevated at all three time points at the 20 and 100 ppm concentration levels. For these groups ALT levels were generally at least 10x higher than the corresponding controls (only results for ALT were reported and only in figure form). These authors also used an automated procedure to estimate fraction of liver area and found that the percent of the hepatic parenchyma that was necrotic was significantly increased in mice at the 20 and 100 ppm dose levels for all three time points. Interestingly the strongest results were seen at the 20 ppm dose level at one week where approximately 12% of the liver was scored as necrotic. By 12 weeks, both the 20 and 100 ppm concentration groups were scored at 3-4% necrotic tissue. Finally, these authors used a BrdU technique as an indicator of replicating cells. Mice in the 20 and 100 ppm groups had significantly elevated fractions of cells BrdU positive, with levels at 20 ppm being roughly 5-10 times control levels and 20-30 times control levels at 100 ppm. (Benson and Springer, 1999) reported no significant changes in mice exposed to 5 ppm carbon tetrachloride as compared with controls.

In summary, results from the (Nagano et al., 2007b) 13-week study provided quite limited evidence for an ongoing process of cell killing and regeneration without strongly elevated serum enzymes or observed necrosis, but with proliferative indications from bile duct proliferation and the authors description of shrunken parenchymal tissue. The (Nagano et al., 2007a) chronic study reported elevation of liver enzymes in serum and bile duct proliferation but did not report necrosis. As mentioned, given the high prevalence of tumors in the same dose groups it is not feasible to interpret the toxicology findings in terms of providing data on key events for cancer development. The 12-week data from (Benson and Springer, 1999) in a different mouse strain, by contrast demonstrated strongly elevated serum enzyme levels indicative of cellular damage/killing at the 20 and 100 ppm dose levels. These results appear to be in conflict with the Nagano 13-week data which found much less indication of elevated serum levels of liver enzymes. (Benson and Springer, 1999) also reported a positive scoring of necrotic liver areas (3-4% by area at 12 weeks) in both the 20 and 100 ppm groups. In addition, these authors measured

an index of cell replication indicating a large increase in replicating hepatocytes at the same dose levels.

(2) Examine the temporal and dose-response concordance between the measures of proposed events and observed tumors

A. Temporal concordance.

To prove causality an event must necessarily precede resulting events, and therefore data from time points prior to the onset of tumors are critical for consideration of a temporal relationship. For the MOA under consideration, sustained effects on cellular proliferation are hypothesized. The subchronic duration studies comport well with these needs as both being well before observed carcinogenesis and reflecting a non-acute, presumably continuing biological process. Temporal considerations validate the relevance of the comparison between subchronic study results and carcinogenic processes as presented above. However, the fact that certain biological effects are observed at ~13 weeks and tumors are observed ~2 years is qualifying rather than probative of causation - varied biological responses may be seen in a subchronic study without generally leading to inferences about chronic tumor risks.

B. Dose response correspondence.

As the (Nagano et al., 2007b) 13-week study did not provide strong evidence of cell killing or proliferative processes, only limited dose response comparisons may be made. The liver tumors in both male and female mice were very strongly elevated in both male and female mice at both the 25 and 125 ppm doses. To the extent that (modest) increases in liver enzymes in serum were seen, they suggested a lesser response at 30 than 90 ppm, not consistent with the tumor pattern. The phenomena called "collapse" where shrunken parenchymal tissue was observed (said, without data shown, to be associated with bile duct proliferation) showed a similar dose response pattern to the tumors, but the relevance of this phenomena to the hypothesized MOA is unclear. Importantly, at 5 ppm the female mice showed a statistically elevated ($p \leq 0.05$) incidence of hepatocellular adenomas, a finding (as discussed elsewhere in this assessment) whose relevance was supported by comparisons with historical control data for the same laboratory. Neither the subchronic or chronic Nagano studies provided data on to suggest cell killing or regeneration at a dose of 5 ppm or 10 ppm (subchronic study).

The findings of (Benson and Springer, 1999) in males of a different mouse strain show a dose-response concordance with the higher dose cancer findings in (Nagano et al., 2007a). The levels of ALT are strongly elevated at both the 20 and 100 ppm concentrations (with the levels of SDH being reported to be similarly elevated, though not reported), at 12 weeks both these concentration groups also show 3-4% increases in scored necrotic cells by area. However, the BrdU cellular replication data from this study shows a different dose response with the level of replication being much higher at 100 ppm than 20 ppm not indicative of the maximal tumor response seen at those doses. The (Benson and Springer, 1999) study did not provide any data on a toxic response at 5 ppm (males only examined), the dose where elevated adenomas were seen in female, but not male mice.

(3) *Direct experimental challenge to the MOA.*

Studies with P450 metabolic inhibitors, P450 metabolic enhancers and P450 CYP2E1 knock out mice have demonstrated the predicted relationship between modulating carbon tetrachloride

metabolism and increasing (or decreasing) carbon tetrachloride liver toxicity. Thus, there is strong evidence of experimental challenge in support of the hypothesis that P450 metabolism of carbon tetrachloride is required for the occurrence of observed liver toxicity. However, as noted above, metabolism of carbon tetrachloride may be expected to affect various processes (*e.g.*, potential genotoxicity) of carbon tetrachloride and thus this line of evidence does not substantially support a cytotoxicity-based MOA over other alternative MOAs that may also involve carbon tetrachloride metabolism. There do not appear to be any studies providing and experimental challenge to the hypothesis that cytotoxicity is a key event for carbon tetrachloride carcinogenesis.

(4) Have the proposed key events been demonstrated to cause cancer in studies of other chemicals?
The EPA Cancer Guidelines recognize cell killing followed by sustained regenerative proliferation as a MOA for chemical carcinogenesis. Accordingly, no further review of the general MOA has been conducted for this assessment.

(5) Other potential MOAs.
Due to the formation of reactive free radicals (both directly from the metabolism of carbon tetrachloride and due to lipid peroxidation subsequent to interactions of carbon tetrachloride metabolites with lipids) concerns have been raised about potential genotoxic effects from carbon tetrachloride. Using radiolabeled ^{14}C, carbon tetrachloride metabolites have been shown to bind to DNA in simplified *in vitro* systems (Direnzo et al., 1982) and to bind to DNA in liver exposed *in vivo* or *ex vivo* to carbon tetrachloride (Castro et al., 1989; Diaz Gomez and Castro, 1980; Rocchi et al., 1973). However, such binding does not appear to have been chemically characterized.

A number of positive results have been reported for the production of oxidative adducts by carbon tetrachloride, suggesting a plausible genotoxic endpoint for this compound which is known to induce lipid peroxidation. It should be noted that while such processes are "indirect" in the sense that they do not result from direct interaction with carbon tetrachloride metabolites, such oxidative radicals are proposed to result from chemical processes rapidly stimulated by carbon tetrachloride after intake of the compound (Benedetti et al., 1974) and are not "secondary" to toxicological damage. However, the existing database on oxidative adducts induced by carbon tetrachloride is not fully consistent and would require further study. Finally, as discussed elsewhere in this document, there are many studies of mutation and genotoxic effects due to carbon tetrachloride. Much of this database is of questionable relevance to potential effects of metabolites of carbon tetrachloride, and while a number of positive findings have been reported, most of these studies were only conducted at high dose, often with observed cellular toxicity. Despite the numerically large database, it is not possible conclude whether or mutation or genotoxicity due to carbon tetrachloride may contribute to its carcinogenic MOA.

Cancer MOA Analysis for Adrenal Tumors

This section explores the extent to which the cytotoxicity/regenerative cell proliferation hypothesis - the most explored MOA hypothesis for carbon tetrachloride induced liver tumors -

may be supported for the pheochromocytoma endpoint. This hypothesized MOA would include the following key events:

(1) metabolism to the trichloromethyl radical by CYP450 enzymes and subsequent formation of the trichloromethyl peroxy radical,
(2) radical-induced mechanisms leading to adrenal toxicity and cell death, and
(3) sustained regenerative and proliferative changes in the adrenal gland in response to cytotoxicity.
(4) Resulting cellular proliferation increases the probability of tumor formation through replicative processes that increase the probability of mutations becoming fixed or increase the rate of clonal expansion of cells carrying somatic mutations - in both cases without hypothesizing a direct mutagenic effect from carbon tetrachloride or its metabolites.

While much more limited than in the case of the liver, there is substantial evidence to support event (1) as occurring in the adrenal gland with a range biochemical and biological events resulting from the metabolism of carbon tetrachloride in the adrenal gland. However, studies specific to carbon tetrachloride metabolism in the mouse were not identified. In the rat, Castro (1972) found that single dose intraperitoneal injection of ^{14}C labeled carbon tetrachloride resulted in binding of the labeled compound to lipids in isolated adrenal microsomal preparations. This binding, implying the formation of reactive metabolites of carbon tetrachloride which have bound to lipids, and is comparable in magnitude to the binding seen in the same study to rat liver microsomal lipids. This binding was also demonstrated in mitochondrial lipids from the adrenal gland, where it was not identified for mitochondria from the liver, demonstrating additional capabilities for metabolism. Kolby (1981) demonstrated that a single high intraperitoneal dose of carbon tetrachloride leads to a substantial reduction of P450 protein content and a reduction of P450 enzymatic activities in microsomes subsequently prepared from the adrenal gland. These results seen in the study for the guinea pig liver are in agreement with the understanding that reactive metabolites of carbon tetrachloride can damage and inactivate P450 enzymes. *In vitro* studies of carbon tetrachloride in adrenal microsomes in Kolby (1981) supported these findings and also demonstrated that carbon tetrachloride treatment of the adrenal microsomes increased lipid peroxidization, an effect that was substantiated by its elimination after treatment with EDTA. In an *in vivo* study in guinea pigs exposed to a single high intraperitoneal dose of carbon tetrachloride , Brogan *et al.*, (1984) demonstrated that the P450 activity with carbon tetrachloride was primarily present in the inner medulla tissues, with microsomes from this region showing strong inhibition of xenobiotic metabolism activity, but not reduction of steroid hydroxylase activity. *In vitro* studies in this publication showed binding of ^{14}C to microsomal proteins from inner medulla tissues as well as generation of malonaldehyde as an indicator of lipid peroxidation inferred to result subsequent to P450 metabolism of carbon tetrachloride. Further *in vitro* studies in Kolby (1994) demonstrated that carbon tetrachloride's inhibitory effect on P450 enzymes were specific to forms metabolizing xenobiotics and did not similarly affect metabolism of steroids in the gland. Covalent binding of ^{14}C labeled metabolites to microsomal protein was also demonstrated in this study.

Data specific to the adrenal gland, together with the broader database on carbon tetrachloride action in the liver and other organs plausibly supports the belief that metabolism in the adrenal

gland is required for the occurrence of toxicity or other biological effects. However, the absence of metabolic data specific to the mouse adrenal gland is a data gap in supporting this MOA step. Additionally, there are no reasonably available experimental information challenging the proposed causality between metabolism and adrenal toxicity for the adrenal gland such as there were using knock out mice and inhibitor studies for liver toxicity.

Accordingly, the focus here is an evaluation of data regarding whether "sustained regenerative and proliferative changes in the adrenal gland in response to cytotoxicity" is a key event for cancer development. That is the analysis focuses on whether the observed compound related pheochromocytomas in the mouse after carbon tetrachloride inhalation (particularly the findings in Nagano (2007a)) resulted from this process.

The Cancer Guidelines framework review is organized as follows:

(1) Describe the empirical data that support the occurrence of the proposed key events under conditions that have been found to be carcinogenic

The Nagano (2007a) inhalation cancer bioassay is accompanied by the Nagano (2007b) subchronic (13 week) toxicity study. As this study specifically investigated toxic response in the same strains of rodents, sourced contemporaneously with the cancer study it represents the most valuable data on sustained toxic responses. At that time frame, transient effects from acute exposure times will have settled while representing conditions that can be reasonably inferred to be sustained through the animal's lifespans.

The Nagano (2007b) subchronic study (for both mice and rats) used inhaled doses of 10, 30, 90, 270, and 810 ppm, while the cancer bioassay (again for both sexes and species) used inhaled doses of 5, 25, and 125 ppm. Thus, while these dose ranges overlap there is not exact correspondence and the higher doses in the subchronic study far exceed bioassay doses and may not be informative for effects that occurred in the bioassay. While Nagano (2007b) included a pathological examination of the adrenal gland, no adverse histopathological findings were reported.

Similarly, in the Nagano (2007a) chronic study, no pathological findings for the adrenal gland, apart from the excess of pheochromocytomas, were reported. It is noted that adrenal gland weights were increased in both male and female mice at the 25 and 125 ppm carbon tetrachloride inhaled concentrations. Among these, the male groups at 25 and 125 ppm and the female group at 125 ppm showed significant increase in pheochromocytomas and these groups showed approximately a doubling or greater in mean adrenal weight - a finding that was likely influenced by the tumor masses in these groups. However, the 25 ppm female group showed a significant, approximately 20%, increase in adrenal weight in the absence of tumors. While appropriate to note, these adrenal weight data don't provide information specific to the MOA under consideration.

Other studies indicate that carbon tetrachloride at sufficiently high doses is toxic to the adrenal gland. Brogan *et al.*, (1984), using a single intraperitoneal dose of 640 mg/kg-d in guinea pigs observed “transzonal cellular necrosis primarily in inner portions of the adrenal cortex and in the

medulla." No information is reasonably available regarding whether carbon tetrachloride can induce adrenal tumors in guinea pigs. Castro (1972) administered a single intraperitoneal dose of 1600 mg/kg to Sprague-Dawley rats, conditions under which liver toxicity is readily observed, with no histopathological changes in the adrenal glands. For comparison, at the airborne concentrations mice where adrenal tumors were observed in Nagano (2007a), daily alveolar inhaled doses of carbon tetrachloride were roughly 40 to 225 mg/kg. Weisburger (1977) reports elevated incidence of pheochromocytomas in male and female mice receiving high doses (up to 2500 mg/kg-d) of carbon tetrachloride, however, this compound was utilized as a positive control in this study of other carcinogens. Therefore, noncancer pathology for the positive controls was not discussed in the study. Castro (1972) and Brogan *et al.*, (1984) provide citations to older literature indicating that human ingestion of carbon tetrachloride can cause adrenal gland toxicity at high doses, and to additional studies in dogs, rats, and guinea pigs indicating the potential of carbon tetrachloride to cause adrenal toxicity. However, no data in mice is reasonably available to indicate adrenal toxicity. The subchronic (Nagano et al., 2007b) and chronic (Nagano et al., 2007a) inhalation studies examined adrenal glands and did not report necrosis or other toxicity. Accordingly, there are no data to support the hypothesis that carbon tetrachloride produces adrenal cytotoxicity or produces regenerative effects under conditions of the mouse cancer bioassay.

(2) Examine the temporal and dose-response concordance between the measures of proposed events and observed tumors

For the MOA under consideration, sustained effects on cellular proliferation are hypothesized. The design of the subchronic duration study of (Nagano et al., 2007b) fits well with the needs to generate data of temporal relevance (providing data well before observed carcinogenesis and having ability to reflect a non-acute, presumably continuing biological processes) and with multiple doses consistent of the dose range of the carcinogenesis bioassay. However, as noncancer adrenal histopathological findings were not identified in (Nagano et al., 2007b), temporal or dose-response comparisons cannot support the hypothesized MOA.

(3) Direct experimental challenge to the MOA

In contrast with the database for the liver effects of carbon tetrachloride there are not experimental studies to challenge and test the assumption that carbon tetrachloride metabolism is required for adrenal toxicity, however as discussed above this is a plausible assumption. There are no reasonably available information providing an experimental challenge to the hypothesis that cytotoxicity (which has not been documented in mice) is a key event for carbon tetrachloride carcinogenesis.

(4) Have the proposed key events been demonstrated to cause cancer in studies of other chemicals?

The EPA Cancer Guidelines recognize cell killing followed by sustained regenerative proliferation as a MOA for chemical carcinogenesis. Accordingly, no further review of the general MOA has been conducted for this assessment.

(5) Other potential MOAs

Due to the formation of reactive free radicals (both directly from the metabolism of carbon tetrachloride and due to lipid peroxidation resulting from subsequent reactions with carbon tetrachloride metabolites) concerns have been raised about potential genotoxic effects from carbon tetrachloride. Using radiolabeled ^{14}C, carbon tetrachloride metabolites have been shown to bind to DNA in simplified *in vitro* systems (Direnzo et al., 1982) and to bind to DNA in liver exposed *in vivo* or *ex vivo* to carbon tetrachloride (Castro et al., 1989; Diaz Gomez and Castro, 1980; Rocchi et al., 1973). However, such binding does not appear to have been chemically characterized.

Positive results have been reported for the production of oxidative adducts by carbon tetrachloride, suggesting a plausible genotoxic endpoint for this compound which is known to induce lipid peroxidation. It should be noted that while such processes are "indirect" in the sense that they do not result from direct interaction with carbon tetrachloride metabolites, such oxidative radicals are proposed to result from chemical processes stimulated by carbon tetrachloride very after intake of the compound rapidly (Benedetti et al., 1974) and are not "secondary" to toxicological damage. However, the existing database on oxidative adducts induced by carbon tetrachloride is not fully consistent and would require further study. Finally, as discussed elsewhere in this document, there are many studies of mutation and genotoxic effects due to carbon tetrachloride. Much of this database is of questionable relevance to potential effects of metabolites of carbon tetrachloride, and while a number of positive findings have been reported, most of these studies were only conducted at high dose, often with observed cellular toxicity. Despite the numerically large database, it is not possible conclude whether or mutation or genotoxicity due to carbon tetrachloride may contribute to its carcinogenic MOA. Alternately it has been suggested that pheochromocytomas might result as a result in some biological process secondary to the formation of liver tumors, as liver tumors were prevalent in the (Nagano et al., 2007a) dose groups where these adrenal tumors were seen.

Appendix J METHODOLOGIES AND FINDINGS FROM KEY TOXICOLOGICAL STUDIES

This appendix presents information on the methodologies and findings from the toxicological studies with acceptable data quality that were taken into consideration for hazard characterization.

J.1 (Adams et al., 1952)

(Adams et al., 1952) (data quality rating = low) conducted studies with Wistar-derived rats (15–25/sex), outbred guinea pigs (5–9/sex), outbred rabbits (1–2/sex), and Rhesus monkeys (1–2 of either sex) exposed to carbon tetrachloride vapor (>99% pure), 7 hours/day, 5 days/week for 6 months at concentrations of 5, 10, 25, 50, 100, 200, or 400 ppm (31, 63, 157, 315, 630, 1,260, or 2,520 mg/m^3). Matched control groups included unexposed and air exposed. Animals were observed frequently for appearance and general behavior and were weighed twice weekly. Selected animals were used for hematological analyses periodically throughout the study. Moribund animals and those surviving to scheduled sacrifice were necropsied. The lungs, heart, liver, kidneys, spleen, and testes were weighed, and sections from these and 10 other tissues were prepared for histopathological examination. Serum chemistry analyses were performed in

terminal blood samples and part of the liver was frozen and used for lipid analyses. In this study, the primary target of carbon tetrachloride in all species was the liver. In guinea pigs, liver effects progressed from a slight, statistically significant increase in relative liver weight in females at 5 ppm to slight-to-moderate fatty degeneration and increases in liver total lipid, neutral fat, and esterified cholesterol at 10 ppm, and cirrhosis at 25 ppm. However, the effect at the 5 ppm dose was not considered adverse, as there were no histopathological changes in the liver at 5 ppm. In the kidney, slight tubular degeneration was observed at 200 ppm and increased kidney weight was noted at 400 ppm. Mortality was increased at ≥100 ppm. A similar progression of effects was seen in rats (no effects at 5 ppm, mild liver changes at 10 ppm, cirrhosis at 50 ppm, and liver necrosis, kidney effects, testicular atrophy, growth depression, and mortality at 200 ppm and above). In rabbits, 10 ppm was without effect, 25 ppm produced an increase in liver weight and mild liver changes (mild fatty degeneration), 50 ppm produced moderate liver changes, and 100 ppm produced growth depression. Monkeys were the least sensitive species tested, with evidence of adverse effects (mild liver lesions and increased liver lipid) only at 100 ppm, the highest concentration tested. This study identified NOAEL and LOAEL values, respectively, of 5 and 10 ppm in rats and guinea pigs, 10 and 25 ppm in rabbits, and 50 and 100 ppm in monkeys, all based on hepatotoxic effects.

J.2 **(**Allis et al., 1990**)**

(Allis et al., 1990) (data quality rating = medium) conducted a study to investigate the ability of rats to recover from toxicity induced by subchronic exposure to carbon tetrachloride. Groups of 48 60-day-old male F344 rats were given 0, 20, or 40 mg/kg of carbon tetrachloride 5 days/week for 12 weeks (average daily doses of 0, 14.3, or 28.6 mg/kg-d) by oral gavage in corn oil. One day after the end of exposure, significant dose-related changes were found for relative liver weight, serum ALT, AST, and LDH (all increased), and liver CYP450 (decreased) in both dose groups. In addition, serum ALP and cholesterol were increased in the high-dose group only. In the low-dose group, histopathological examination of the liver revealed cirrhosis in 2/6 rats and vacuolar degeneration and hepatocellular necrosis in 6/6 rats. In the high-dose group, histopathological examination revealed cirrhosis (as well as degeneration and necrosis) in 6/6 rats. Serum enzyme levels and CYP450 returned to control levels within 8 days of the end of exposure. Severity of microscopic lesions declined during the post-exposure period, but cirrhosis persisted in the high-dose group through the end of the experiment. Relative liver weight decreased during the post-exposure period but did not reach control levels in the high-dose group even after 22 days. Neither of the radiolabeled tracer techniques detected a decreased functional capacity in cirrhotic livers, a finding that could not be explained by the investigators. The low dose of 14.3 mg/kg-d was a LOAEL for hepatic toxicity in this study.

J.3 **(**Benson and Springer, 1999**)**

(Benson and Springer, 1999) (data quality rating = high) exposed groups of F344/Crl rats, B6C3F1 mice, and Syrian hamsters (10 males/species) by nose only inhalation to 0, 5, 20 or 100 ppm of carbon tetrachloride for 6 hours per day, 5 days per week for 1, 4 or 12 weeks. The chamber concentrations were monitored throughout the exposure. According to study authors, the objectives of the study were three-fold. The first objective was to evaluate the metabolism of carbon tetrachloride to get an estimate of species sensitivity. These studies were conducted as either whole-body exposures (for *in vivo* metabolism) or nose only exposures (for toxicokinetic studies). *In vitro* studies using human liver microsomes were also conducted. The second

objective was to assess the genotoxic or non-genotoxic mechanisms of liver tumors for carbon tetrachloride exposure. The third objective was to compare *in vitro* and *in vivo* metabolism studies to revise the model for uptake, fate and metabolism of carbon tetrachloride to provide an estimate for a human metabolic rate constant. Cell proliferation was evaluated in these animals by implanting a minipump containing bromodeoxyuridine (BrdU) in each animal prior to necropsy. At sacrifice, blood was collected for ALT and SDH determinations, and liver sections were collected for histopathological examination and BrdU detection. In summary, (Benson and Springer, 1999) used *in vitro* data on metabolism of carbon tetrachloride by human liver microsomes, together with *in vitro* and *in vivo* rodent data, to estimate the *in vivo* human metabolic rate constants and generated experimental information that allowed expanding the rat PBPK model of (Paustenbach et al., 1988) to include parameters for the hamster.

Following repeated carbon tetrachloride inhalation exposure in the (Benson and Springer, 1999) studies, hepatocellular proliferation was reported along with necrosis and regenerative cell proliferation at 20 and 100 ppm in mice. In rats, liver microsomal protein levels were increased by 45% and 63% following 5-day inhalation exposure at 5 ppm without any change in the 12-week exposure group. In hamsters, following carbon tetrachloride inhalation exposure (100 ppm), microsomal protein levels were decreased by 33% and 54% in both the 5-day and the 12-week exposure groups. Mice did not exhibit any decrease in microsomal protein content at any concentration of exposure. Significant increases in percent BrdU positive cells in the cell proliferation assays were apparent at 20 and 100 ppm in mice and at 100 ppm in hamsters. Serum levels of ALT and SDH were significantly increased in mice at ≥20 ppm and in rats and hamsters at 100 ppm.

Cytochromes CYP2E1 and CYP2B, which are the primary enzymes responsible for biotransformation of carbon tetrachloride in rodents, were measured in all exposed and control animals in the metabolic studies (Benson and Springer, 1999). In all species, microsomal measurement of these enzymes indicated that while enzyme induction increased several fold as dose increased, catalytic activity was not significantly altered.

The rate of carbon tetrachloride metabolism was measured in rat, mouse and hamster species. The metabolic rate of carbon tetrachloride did not vary more than two-fold between the three species. A NOAEC of 5 ppm and a LOAEC of 20 ppm for hepatotoxicity was identified for mice. Hamsters and rats were less sensitive than mice, with a NOAEC of 20 ppm and a LOAEC of 100 ppm, respectively.

J.4 **(**Bruckner et al., 1986**)**

In a subchronic study by (Bruckner et al., 1986) (data quality rating = high) groups of 15–16 adult male Sprague-Dawley rats were given doses of 0, 1, 10, or 33 mg/kg of analytical-grade carbon tetrachloride by oral gavage in corn oil 5 days/week (time-weighted average doses of 0, 0.71, 7.1, or 23.6 mg/kg-d) for 12 weeks. Body weight gain was significantly reduced by 6% after 30 days and 17% after 90 days in the high dose group. In the high dose group (23.6 mg/kg-d), liver enzymes, including ALT (up to 34 times control levels), SDH (up to 50 times control levels), and ornithine-carbamyl transferase (OCT, up to 8 times control levels) were significantly elevated from week 2 through the end of exposure. In addition, significantly increased relative liver weight and degenerative lesions were observed. Reported liver lesions included lipid

vacuolization, nuclear and cellular polymorphism, bile duct hyperplasia, and periportal fibrosis. Severe degenerative changes, such as Councilman-like bodies (single-cell necrosis), deeply eosinophilic cytoplasm, and pyknotic nuclei, were occasionally noted as well. No evidence of nephrotoxicity was observed. At lower doses moderate effects were seen in animals. At 7.1 mg/kg-d, only a significant (two- to three-fold) elevation of SDH during the second half of the exposure period and the presence of mild centrilobular vacuolization in the liver was observed. Serum ALT and SDH levels returned towards control levels in both mid- and high-dose rats following a 2-week recovery period although hepatic lesions of less severity with the exception of fibrosis and bile duct hyperplasia were still present in both groups. No effects were observed in rats exposed to 0.71 mg/kg-d. This study identified a NOAEL of 0.71 mg/kg-d and a LOAEL of 7.1 mg/kg-d for carbon tetrachloride-induced liver toxicity.

J.5 **(**Condie et al., 1986**)**

A subchronic study conducted by (Condie et al., 1986) (data quality rating = high) compared the effects of two different gavage vehicles on the toxicity of carbon tetrachloride in mice. CD-1 mice (12/sex/group) were treated with 0, 1.2, 12, or 120 mg/kg of carbon tetrachloride by oral gavage in either corn oil or 1% Tween-60 aqueous emulsion 5 days/week for 12 weeks (average daily doses of 0, 0.86, 8.6, or 86 mg/kg-d). Fifteen deaths occurred during the study (6 in male mice, 9 in female mice). Of the total deaths, 8 were attributed to gavage (4 male and 4 female mice). These deaths did not appear to influence the study outcome. In the high-dose group (86 mg/kg-d) relative liver weight was significantly elevated. In addition, liver enzymes were significantly increased (ALT (77–89 times control levels in corn oil and 10–19 times control levels in Tween-60), AST (14–15 times control levels in corn oil and 3–4 times control levels in Tween-60), and LDH (12–15 times control levels in corn oil and 2–3 times control levels in Tween-60). Histopathological findings include increased incidence and severity of hepatocellular vacuolization, inflammation, hepatocytomegaly, necrosis, and portal bridging fibrosis. The only difference between oral gavage vehicles observed at 86 mg/kg-d was a greater incidence and severity of necrosis in mice given carbon tetrachloride in corn oil. The difference between vehicles was more apparent at the middle dose of 8.6 mg/kg-d. This dose produced significantly elevated ALT and mild-to-moderate liver lesions in mice gavaged with corn oil but was identified as a NOAEL for mice gavaged with Tween-60. The low dose of 0.86 mg/kg-d was identified as the NOAEL for mice gavaged with corn oil. In general, both sexes responded similarly, with severity of histopathologic changes in males slightly greater than females.

J.6 **(**Davis, 1934**)**

NAC/AEGL evaluated a series of experiments conducted by (Davis, 1934) (data quality rating = low) to determine their suitability to derive AEGL-2 values for carbon tetrachloride. In one study, three human subjects were exposed to carbon tetrachloride at 317 ppm (concentration calculated on the basis of room volume and amount of carbon tetrachloride) for 30 min. CNS effects, including nausea, vomiting, dizziness, and headaches were reported by the subjects, but clinical assessments (urinalysis, blood count, hemoglobin levels, blood pressure, and heart rate) remained normal for up to 48 h post-exposure. Similar effects were reported by subjects exposed at 1,191 ppm for 15 min, with the exception that one of the four subjects found the exposure to be intolerable after 9 min (*i.e.*, the subject experienced headache, nausea, and vomiting). Exposures at 2,382 ppm for 3-7 min produced these effects in addition to dizziness, listlessness, and sleepiness. The observed CNS effects were apparently not long-lasting but were considered

severe enough to impair escape or normal function and, therefore, a conservative endpoint (*i.e.*, hazard effect) for deriving AEGL-2 values by NAC/AEGL.

In the second experiment, four subjects (ages 35, 48, 22, and 30; gender not specified) were exposed to a carbon tetrachloride at 76 ppm for 2.5 h. There were no symptoms or signs of toxicity in any of the subjects. In a third experiment, the same subjects in the second experiment were exposed 24 hours later to carbon tetrachloride at 76 ppm for 4 h and did not have signs or symptoms. (Davis, 1934) also reported that renal effects were observed in a worker experimentally exposed to carbon tetrachloride at 200 ppm for 8 h with renal function returning to near normal 2 months after exposure.

The AEGL-2 values were derived on the basis of the highest no-effect level of 76 ppm for CNS effects in humans exposed carbon tetrachloride for 4 h. The AEGL-2 values are derived using an interspecies uncertainty factor of 1 because the study was conducted in humans, and an intraspecies uncertainty factor of 10 to account for individuals who may be more susceptible to the toxic effects of carbon tetrachloride, including greater potential of carbon tetrachloride-induced toxicity in individuals with histories of alcohol usage.

J.7 **(**Hayes et al., 1986**)**

A subchronic study in mice was conducted at higher doses by (Hayes et al., 1986) (data quality rating = medium). CD-1 mice (20/sex/group) received daily oral gavage doses of 0, 12, 120, 540, or 1,200 mg/kg-d of carbon tetrachloride in corn oil for 90 days. An untreated control group of 20 male and 20 female mice was maintained as well. Dose-related effects including increases in serum LDH, ALT, AST, ALP, and 5'-nucleotidase and a decrease in serum glucose were observed in both sexes. Treatment-related lesions were observed in the liver, including fatty change, hepatocytomegaly, karyomegaly, bile duct hyperplasia, necrosis, and chronic hepatitis associated with increases in absolute and relative liver weight. Other changes in organ weight include increases in spleen and thymus weights. No treatment-related lesions were observed in the kidney. No changes were found in urinalysis or hematology parameters. It should be noted that, compared with untreated controls, vehicle controls had significantly elevated serum LDH and ALT, altered organ weights, and increased incidence of liver lesions (*e.g.*, necrosis in 5/19 in vehicle controls versus 0/20 in untreated controls and 20/20 in the 12 mg/kg-d group). This study failed to identify a NOAEL. The low dose of 12 mg/kg-d was a LOAEL for hepatic effects.

J.8 **(**Nagano et al., 2007a**;** Nagano et al., 2007b**)**

The IRIS RfC is based on the findings from bioassays conducted by (Nagano et al., 2007b) (data quality rating = high). In one of the subchronic inhalation studies in rats, F344/DuCrj rats (10/sex/group) were subjected to whole body exposure of carbon tetrachloride vapor (purity: 99.8%) concentrations of 0, 10, 30, 90, 270, or 810 ppm (0, 63, 189, 566, 1,700, or 5,094 mg/m^3) for 6 hours/day, 5 days/week for 13 weeks. The lowest exposure concentration of 10 ppm was a LOAEC for rats for hepatic effects including increased liver weight and histopathological effects ranging from slight fatty change, cytological alteration, and granulation to ceroid deposits, fibrosis, pleomorphism, proliferation of bile ducts and cirrhosis. While small fatty droplets were not evident in male rats at any concentration, large droplets were significantly elevated at ≥ 30 ppm in both male and female rats. Different types of significantly altered cell foci (acidophilic,

basophilic, clear cell, and mixed cell foci) was evident at 810 ppm in male rats and 270 ppm in female rats. A NOAEC was not identified.

A similar whole body exposure to carbon tetrachloride (purity: 99.8%) vapor was conducted in mice (Nagano et al., 2007b) (data quality rating = high) where groups of Crj:BDF1 mice (10/sex/group) were exposed at concentrations of 0, 10, 30, 90, 270, or 810 ppm (0, 63, 189, 566, 1,700, or 5,094 mg/m^3) for 6 hours/day, 5 days/week for 13 weeks. A similar set of endpoints as that of the rat study were measured in mice. However, the incidence of altered cell foci was not significantly elevated in male mice at <270 ppm and was not noted in female mice. Additional liver lesions observed include nuclear enlargement with atypia and altered cell foci (≥270 ppm) and collapse (possibly resulting from the necrotic loss of hepatocytes) at ≥30 ppm. The lowest exposure level of 10 ppm is a LOAEC for hepatic effects (*i.e.*, slight cytological alterations) in male mice. Hepatic effects (*i.e.*, fatty change, fibrosis and cirrhosis) were observed in female mice exposed to ≥30 ppm.

Significant increases were observed in liver weights (≥10 ppm for males and ≥30 ppm for female rats) and kidney weights (≥10 ppm for male rats and ≥90 ppm for female rats). Statistically significant, exposure-related decreases in hemoglobin and hematocrit were observed at ≥90 ppm in both males and females. At 810 ppm, red blood cell count was also significantly decreased in both sexes. Serum chemistry changes included large, statistically significant, and exposure-related increases in ALT, AST, LDH, ALP, and leucine aminopeptidase (LAP) in males at ≥270 ppm and females at ≥90 ppm. In general, female mice were less sensitive to hematological alterations than male mice. Nephrotoxicity was observed at higher concentrations than toxicity to the liver, although kidney weights were increased significantly at 10 ppm in male rats and ≥90 ppm in female rats. Glomerulosclerosis was observed only at the highest concentration (810 ppm) of exposure in rats. No histopathological changes were observed in the nasal cavity, larynx, trachea or lungs of any carbon tetrachloride-exposed mouse or rat groups.

(Nagano et al., 2007a) (data quality rating = high) conducted studies with groups of F344/DuCrj rats (50/sex/group) exposed whole body to 0, 5, 25, or 125 ppm (0, 31.5, 157, or 786 mg/m^3) of carbon tetrachloride (99.8% pure) vapor for 6 hours/day, 5 days/week for 104 weeks. An increase in the severity of proteinuria in rats of both sexes was observed at the low exposure concentration of 5 ppm; however, interpretation of the observed proteinuria and the renal lesions in the F344 rat is difficult because this strain has a high spontaneous incidence of renal lesions. Increases in the incidence and severity of nonneoplastic liver lesions (*i.e.*, fatty change, fibrosis, and cirrhosis) were seen at 25 and 125 ppm in both males and females. Therefore, 5 ppm was considered a NOAEC based on liver toxicity at 25 and 125 ppm evidenced by serum chemistry changes (including significant increases in ALT, AST, LDH, LAP, and GGT) and histopathologic changes (*i.e.*, fatty change, fibrosis, and cirrhosis). Kidney effects described above were also considered for determining the NOAEC value, which is the basis of the EPA IRIS RfC.

A similar 2-year (104 week) study was conducted by the same group in Crj:BDF1 mice (Nagano et al., 2007a) (data quality rating = high). Groups of 50/sex were exposed to 0, 5, 25, or 125 ppm (0, 31.5, 157, or 786 mg/m^3) of carbon tetrachloride (99% pure) vapor for 6 hours/day, 5 days/week for 104 weeks. The 25 ppm concentration was the LOAEC in this study for effects on

the liver (*i.e.*, increased weight, serum chemistry changes indicative of damage, and lesions), kidney (*i.e.*, serum chemistry changes and lesions), and spleen (*i.e.*, lesions); decreased growth; and reduced survival. The 5 ppm concentration was the NOAEC.

J.9 (Narotsky et al., 1997)

(Narotsky et al., 1997) (data quality rating = high). In this study, groups of 12–14 timed-pregnant F344 rats received carbon tetrachloride at doses of 0, 25, 50, or 75 mg/kg-d in either corn oil or an aqueous emulsion (10% Emulphor) on GDs 6–15. Dose-related piloerection was observed in dams at ≥50 mg/kg-d for both vehicles but was seen in more animals and for longer periods in the corn oil groups. Dams exposed to 75 mg/kg-d in corn oil also exhibited kyphosis (rounded upper back) and statistically significant weight loss. Dams exposed to 50 and 75 mg/kg-d in aqueous emulsion showed only significantly reduced body weight gain. Full-litter resorption occurred with an incidence of 0/13, 0/13, 5/12 (42%), and 8/12 (67%) in the control through high-dose corn oil groups and 0/12, 0/12, 2/14 (14%), and 1/12 (8%) in the respective aqueous groups. The difference between vehicles was statistically significant at the highest dose. Among the surviving litters, there were no effects on gestation length, prenatal or postnatal survival, or pup weight or morphology. The 25 mg/kg-d dose was a NOAEL for developmental and maternal toxicity and the 50 mg/kg-d dose a LOAEL for full-litter resorption and maternal toxicity (*i.e.*, reduced maternal weight gain, and piloerection) with either corn oil or aqueous vehicle, although these effects were more pronounced with the corn oil vehicle. (U.S. EPA, 2010) noted that the NOAEL in this developmental study (25 mg/kg-d) exceeds the POD for the RfD based on liver effects by over six-fold and the LOAEL (50 mg/kg-d) by 13-fold and is consistent with developmental toxicity endpoints as less sensitive than measures of hepatotoxicity.

J.10 (Schwetz et al., 1974)

The IRIS assessment identified (Schwetz et al., 1974) (data quality rating = high) as the most detailed inhalation exposure developmental toxicity study available. In the study, groups of pregnant Sprague-Dawley rats were exposed (whole-body) by inhalation to 0, 300, or 1,000 ppm carbon tetrachloride vapor for 7 hours/day on days 6-15 of gestation. A significant increase in the serum glutamic-pyruvic transaminase activity was observed in rats exposed to 300 and 1000 ppm by the end of the exposure period. This effect was no longer observed by day 6 post exposure. The developmental effects at the LOAEC of 300 ppm consisted of decreased fetal body weight (7%) and decreased crown-rump length (3.5%). The same effects were observed at 1,000 ppm (*i.e.*, 14% decreased fetal body weight, 4.5% decreased crown-rump length) in addition to increases in sternebral anomalies (13% at 1,000 ppm vs. 2% in controls). Maternal toxicity was observed at 300 and 1,000 ppm. Food consumption and body weight were significantly reduced in treated dams compared with controls. Hepatotoxicity was indicated by significantly elevated serum ALT, gross changes in liver appearance (pale, mottled liver), and significantly increased liver weight (26% at 300 ppm and 44% at 1,000 ppm).

J.11 (Sun et al., 2014)

In this study by (Sun et al., 2014) (data quality rating = high), a total of 30 male Sprague-Dawley rats (5 rats/group) were given single oral gavage doses of carbon tetrachloride at 0, 50, or 2000 mg/kg. Rats were then sacrificed at either 6- or 24-hours post-dosing (5/group/time point). An additional group of male rats (5/group) were given oral doses of vehicle (corn oil) or carbon tetrachloride for 3-days at the same doses and sacrificed 24-hours after the third dose (72 hours).

Rats lost weight 24-hours after a single exposure to 2,000 mg/kg (or after 3 daily doses at 2,000 mg/kg). Control and low-dose animals gained weight normally. Food consumption was also decreased in high-dose rats. Significant, dose-related, increases in serum ALT (30-114%), AST (15-213%), and ALP (37-137%) were observed in both dose groups following exposure for 3 days. Twenty-four hours after exposure, ALT was significantly increased by 15% at 50 mg/kg, but not 2000 mg/kg. ALP was significantly increased by 78% at 2000 mg/kg after 24 hours. Other significant potentially exposure-related findings were limited to the high-dose group and included a 26-49% increase in BUN 6- or 24-hours after a single exposure, a 24-33% decrease in cholesterol, and a 59-69% decrease in triglycerides 24-hours after one or three exposures, and a 12-23% decrease in glucose 6- or 24-hours after a single exposure. No other consistent clinical chemistry findings were observed. No significant changes were observed in liver triglyceride levels.

Centrilobular necrosis, centrilobular degeneration, and cytoplasmic vacuolization were observed at 6- and 24-hours post-dose in all animals given a single dose of 2,000 mg/kg. In animals given 3 doses of 2,000 mg/kg carbon tetrachloride, 80% were observed with centrilobular degeneration, while 100% were observed with centrilobular necrosis and cytoplasmic vacuolization. Mean severity scores for centrilobular necrosis and degeneration were highest 24-hours after a single exposure, whereas severity scores for cytoplasmic vacuolization were highest after 3 exposures. Six hours after a single exposure to 50 mg/kg, 40% of animals (n = 2) showed minimal centrilobular necrosis. Hepatic lesions were not observed at other time points following exposure to 50 mg/kg. No hepatic lesions were observed in control groups at any time point. No exposure-related kidney lesions were observed in any group.

J.12 **(**Wahlberg and Boman, 1979**)**

In (Wahlberg and Boman, 1979) (data quality rating = medium), guinea pigs (20 animals/dose) were exposed to carbon tetrachloride by a single application of 0.5 or 2.0 ml to a 3.1 cm^2 area of skin. Application area was occluded to prevent inhalation and ingestion. Dermal contact with carbon tetrachloride occurred for 5 consecutive days to the single applied dose under occluded exposure conditions. For animals exposed to 0.5 mL, mortality was observed from day 3 (1 out of 20 animals died) to day 14. Five animals died by the end of the observation period. Among animals exposed to 2.0 mL, mortality was observed from day 1 (1 out of 20 animals died) to day 21. A total of 13 animals died in the 2.0 mL dose group by the end of the observation period.

Appendix K EVIDENCE ON LINEARITY OF THE PBPK MODEL

The appendix table below presents the external:internal dose ratios for the human PBPK model over a span of concentrations, using the model assumptions adopted by the IRIS assessment (model parameter VmaxC = 1.49 mg/hr/kg $BW^{0.70}$, continuous 24 hour/day, 7 days/week exposure), including PBPK model results for the MCA (mean arterial concentration) internal dose metric and results for the MRAMKL (mean rate of metabolism in the liver) internal dose metric. This appendix table is a modification of Tables C-6 and C-10 in the IRIS assessment.

Table K-1. Table Summarizing PBPK Model results in the IRIS Assessment Tables C-6 and C-10

EC (ppm)	EC (mg/m^3)	MCA (µmol/L)	EC/MCA	% change	MRAMKL (µmol/hr/kg liver)	EC/ MRAMKL	% change
0.1	0.6290	0.007827	80.37	--	--	--	--
0.2	1.258	0.01566	80.35	-0.02	--	--	--
0.3	1.887	0.02349	80.33	-0.05	--	--	--
0.4	2.516	0.03133	80.31	-0.07	--	--	--
0.5	3.145	0.03917	80.29	-0.10	--	--	--
0.6	3.774	0.04702	80.27	-0.12	--	--	--
0.7	4.403	0.05487	80.25	-0.15	--	--	--
0.8	5.032	0.06272	80.23	-0.17	--	--	--
0.9	5.661	0.07058	80.21	-0.20	--	--	--
1	6.290	0.07844	80.19	-0.22	1.3834	4.547	--
2	12.58	0.1573	79.99	-0.47	2.749	4.577	0.66
3	18.87	0.2365	79.80	-0.71	4.095	4.608	1.34
4	25.16	0.3161	79.60	-0.96	5.423	4.640	2.05
5	31.45	0.3962	79.39	-1.22	6.731	4.672	2.75
6	37.74	0.4766	79.19	-1.47	8.020	4.706	3.50
7	44.03	0.5575	78.98	-1.73	9.289	4.740	4.24
8	50.32	0.6388	78.78	-1.98	10.537	4.776	5.04
9	56.61	0.7205	78.57	-2.24	11.764	4.812	5.83
10	62.90	0.8027	78.36	-2.50	12.971	4.850	6.66
20	125.8	1.650	76.24	-5.14	23.832	5.279	16.10
30	188.7	2.545	74.16	-7.73	32.48	5.810	27.78

EC (ppm)	EC (mg/m^3)	MCA (µmol/L)	EC/MCA	% change	MRAMKL (µmol/hr/kg liver)	EC/ MRAMKL	% change
40	251.6	3.482	72.26	-10.09	39.11	6.434	41.50

Appendix L SUMMARY OF PUBLIC COMMENTS / RESPONSE TO COMMENTS

COMMENTS ON MOA FOR CARCINOGENICITY

EPA has received public comments from the American Chemistry Council (ACC) that provide a different evaluation scheme of the mode of action for liver tumors induced by carbon tetrachloride. This submission illustrates a recently developed quantitative MOA weight of evidence (WOE) scoring approach (EPA-HQ-OPPT-2016-0733-0066) by providing a case example for the identification of the likely operative MOA for carbon tetrachloride induced rodent liver tumor. The submission states that the case example is not intended to be a complete discussion of all available and relevant studies and an in-depth systematic review of the available literature was not conducted. The ACC submitted case example reaches a different conclusion of the carbon tetrachloride MOA, evaluating the cytotoxicity MOA to have a high positive score in their framework, while a mutagenicity MOA to have a highly negative score, which supports a threshold cytotoxicity MOA.

The quantitative MOA weight of evidence (WOE) scoring approach is intended to be a competitive evaluation of alternative MOA proposals stated in detail. In the case of carbon tetrachloride this involves a proposed sequence of events for causation of cancer by carbon tetrachloride cytotoxicity and alternately a proposed sequence of events for carbon tetrachloride cancer induction by direct mutagenicity alone. ACC states: "This approach enables a side-by-side comparison of numerical WOE confidence scores for each MOA to determine which MOA is more likely to be operative."

This approach for carbon tetrachloride does not address other important possibilities and areas of uncertainty identified in the IRIS assessment including:

- carbon tetrachloride cancer indication involves contributions from *both* cytotoxicity and mutagenicity. As oxidative damage to DNA has been implicated in carcinogenesis, EPA believes there is direct potential for this compound to contribute to both of these processes.
- Other processes not evaluated may be key to carbon tetrachloride carcinogenicity. Such processes could include: oxidative damage to DNA resulting from carbon tetrachloride metabolism and reactivity; epigenetic events related to carbon tetrachloride effects on DNA methylation; or other as yet unidentified effects of carbon tetrachloride
- EPA's (U.S. EPA, 2010) assessment concluded: (1) the MOA was unknown and (2) that there was potential for a MOA that included both low dose genotoxic effects and higher dose cytotoxicity. The submitted approach does not allow for consideration of these possibilities.

EPA uses a Bradford Hill based evidence approach for MOA evaluation under its cancer guidelines. Similarly, the submitted approach utilizes Bradford Hill considerations. However, the submitted scoring system does not provide an appropriate evaluation system for datasets showing extensive areas of uncertainty from confounding toxicity mechanisms:

I. Evaluation of the cytotoxicity MOA

A. "Essentiality"

This criterion addresses the extent that the available experimental data challenge and support the proposed causal key steps for cancer causation.

The submission cites the following experimental data as supporting qualitative evaluation of the proposed MOA (paraphrased for succinctness):

(1) Metabolism of carbon tetrachloride has been demonstrated to produce free radicals including CCl_3•, which has been detected in spin trapping studies with the liver *in vivo*, isolated liver cells, and microsomal preparations.
(2) Studies using a variety of methodologies show that carbon tetrachloride exposures can cause lipid peroxidation in the liver.
(3) A study in CYP2E1 knockout mice found that these animals avoided liver toxicity. Other studies using CYP450 inhibitors indicate that prevention of carbon tetrachloride metabolism also prevents liver toxicity. Studies with co-administration of free radical scavengers with carbon tetrachloride have reduced liver toxicity. Conversely, there is increased carbon tetrachloride cytotoxicity in hepatocyte cell lines that over express P450 enzymes.
(4) Studies using free radical scavengers or antioxidants in conjunction with carbon tetrachloride administration have shown reduced liver toxicity or lipid peroxidation. Co-administration of antioxidants (vitamin E) with carbon tetrachloride have reduced liver peroxidation.
(5) Cytosolic calcium levels have been strongly increased by carbon tetrachloride treatment.
(6) Carbon tetrachloride administration increases cell replication in liver tissue. A 1× administration of 40 mg/kg carbon tetrachloride increased BrdU uptake by cells in the peri-portal zone within one day, plateauing at 3 days.
(7) Altered hepatic foci [of the GST-P form that are believed to be indicative of carcinogenic processes] were increased by 12 weeks of carbon tetrachloride treatment. [Such foci are observed at the 25 ppm and 125 ppm inhalation exposures in Tsujimura (2008), but not significantly elevated at 5 ppm or 1 ppm.]
(8) "Hepatocellular carcinomas appear only at the high dose in rats and mid and high doses in mice, with an all or none response."

However, while these study findings inform our understanding of carbon tetrachloride carcinogenesis, much uncertainty remains.

(1) Metabolism of carbon tetrachloride to free radicals, at least substantially by CYP2E1, is responsible for observed lipid peroxidation and liver toxicity of this compound, but this does not establish relative role of cytotoxicity or genotoxicity in a cancer MOA – both processes could be driven by carbon tetrachloride metabolites and/or peroxidation products.
(2) These results suggest a hypothesis that lipid peroxidation is a specific cause of observed liver toxicity, but it is not apparent that this hypothesis has been specifically challenged. Direct liver toxicity from carbon tetrachloride metabolites is also possible. Also, importantly, a recently discovered process termed ferroptosis

describes cell death elicited by lipid peroxidation as being "genetically, biochemically, and morphologically distinct from other cell death modalities, including apoptosis, unregulated necrosis, and necroptosis" (Yang and Stockwell, 2016). As carbon tetrachloride toxicity studies have identified liver "necrosis," the above suggests that this necrosis may be distinct from a lipid driven process. On the other hand, if ferroptosis plays a role in (some) observed carbon tetrachloride cell death, the effects of such cell death may not fit with a regenerative hyperplasia (necrosis) driven MOA for cancer. A study by Siegers *et al.*, (1988) provides substantial evidence that an iron mediated lipid peroxidation process is involved in carbon tetrachloride liver toxicity. Pretreatment of rodents with the iron binding agent deferoxamine before carbon tetrachloride administration reduced both liver toxicity (indicated by plasma GPT and SDH activity levels) and lipid peroxidation (as indicated by exhaled ethane levels) (Siegers et al., 1988). The carbon tetrachloride analogue bromotrichloromethane showed the same pattern of results, while several other hepatotoxic agents did not show a reduction of liver toxicity or lipid peroxidation following deferoxamine treatment. This suggests that the response observed was specifically relevant to carbon tetrachloride's toxic MOA.

(3) The submission proposes that lipid peroxidation-induced cell death drives cellular proliferation-induced liver cancer. This conclusion ignores the carcinogenic potential of steps leading up to lipid peroxidation, including oxygen and lipid based radical reactions resulting from carbon tetrachloride metabolism, derangement of cellular calcium levels, potential enhanced cellular iron availability to catalyze oxygen-radical induced lipid peroxidation, and depletion of cellular glutathione and consequent inhibition of enzymes responsible for repair of lipid peroxides.

(4) Changes in cytosolic calcium levels occur during carbon tetrachloride toxicity, but it is not apparent that the hypothesis that elevation of cellular calcium concentrations *causes* toxicity has been experimentally challenged.

(5) Cell replication is increased early, but not immediately, in the process of carbon tetrachloride toxicity (*i.e.*, at two days). Such proliferation is proposed to be due to tissue regeneration; however, other processes might also be involved.

(6) Cytotoxic processes (considered holistically) or increased cell replication specifically can be proposed as causes of carbon tetrachloride carcinogenicity. However, these hypotheses are proposed based on broader biological considerations and not directly supported or tested by data on carbon tetrachloride.

(7) The observed tumorigenicity data have mostly shown steep dose response patterns that are interpreted in the submission as indicative of thresholds. However, the study authors of the inhalation cancer bioassay (Nagano et al., 2007a) and EPA's IRIS assessment provide a more nuanced characterization of the tumor data as being indicative of responses at some of the lower dose levels.[25]

[25] In a visual examination of the data from the Nagano (2007a) inhalation study, the male F344 rat data is strongly nonlinear with a high response at 125 ppm but no apparent response at 25 ppm. The female F344 rats also indicate a steep increase between these doses, but an apparent increase in the carcinomas at 25 ppm suggests non-threshold

(8) Data on carbon tetrachloride increased GST-P liver foci in male rats are observed in intermediate term experiments in male rats and follow a dose response pattern similar to, but distinct from, the tumor dose response seen in male rats (foci were statistically elevated at an inhaled concentration of 25 ppm, while a tumor response was not observed at that dose). In other studies, this GST-P foci protocol has been suggested as an practical indicator for carcinogenicity by either genotoxic or non-genotoxic pathways. Thus, the observation of these foci provides qualitative supporting evidence for carbon tetrachloride carcinogenicity and also support for an upward curving (but not necessarily threshold) dose response relationship in male rats. The role of this data in supporting a cytotoxic versus an alternative MOA for carbon tetrachloride is not apparent. The occurrence of liver foci after carbon tetrachloride treatment – without prior treatment by an initiating agent or use of a partial hepatectomy may be interpreted to indicate that carbon tetrachloride is a "complete carcinogen" (*i.e.*, a compound that contributes to both tumor induction and promotion).

The "Essentiality" criterion is scored in the submission as maximally high for all steps in their proposed MOA. The resulting score contributes strongly to the highly positive ranking they assign to the cytotoxicity MOA for tumors. However, a scoring problem is present in this methodology. Specifically, the "essentiality" score for each proposed key event in a pathway is assigned "the highest score achieved by any one of the unique Key Events in the pathway." This is a problematic approach because a MOA may (and usually does) involve varied events with different degrees of experimental support. Assigning the maximum score to all such events overstates the available evidence. In the case of carbon tetrachloride, this numeric process leads to strongly over-scoring the degree of experimental evidence for the cytotoxic MOA.

B. Dose-response concordance

The submission states: "Because the earlier key events are demonstrated via *in vitro* assays, the concentrations do not align with the longer term *in vivo* studies. It is clear, however, that the doses for the earlier key events are lower than those needed to elicit liver tumors … for dose concordance the precursor key events must occur earlier and at lower doses than the tumorigenic dose."

This quote does not provide a strong argument in favor of a cytotoxicity MOA. First, it is not clear to the reader that doses at which early events have been demonstrated are lower than the experimental tumorigenic doses. While it is difficult to compare *in vitro* and *in vivo* systems, with the available PK predictions, the authors could have undertaken some comparisons between molar concentrations of carbon tetrachloride in liver tissue and those used in the *in*

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behavior. In male BDF1 mice, there is a strong (essentially complete) tumor response at 25 and 125 ppm, without observed increase at 5 ppm. However, the high control tumor response observed in these male mice (approximately 50 % combined adenoma and carcinoma risk) prevents sensitive determination potential compound response at low dose. In the female BDF1 mice, there was likewise a high adenoma plus carcinoma tumor risk at the 25 ppm and 125 ppm doses, however, in this case there was also a statistically significant increased incidence of tumors (primarily adenomas) at the subtoxic 5 ppm dose level – indicating no apparent threshold for tumorigenic response in the female mice.

vitro experiments they are referring to. It is logically correct that precursor key events (if measured with sufficient sensitivity) must occur doses at least as low as tumorigenic doses. Violation of this pattern can be strong evidence *against* a MOA proposal. Such an example is presented in EPA (2010): namely tumors were observed in the female mouse inhalation bioassay at a lower concentration (25 ppm) than where substantial toxicity was observed. This provides evidence against cytotoxic effects alone providing an explanation for observed tumors.

Secondly, a showing that precursor events occur at lower doses than tumors sets a rather low bar for evaluating this dose response concordance. A range of diverse biological responses may occur at doses below those that cause frank toxicity. Knowing that a given effect occurs at a subtoxic dose is not in itself evidence that the two are related. Stronger evidence for a MOA would come from demonstrating a reasonable quantitative functional relationship between increasing levels of the proposed precursor response and increased incidence of apical toxic response.[26] The ACC materials do not present such an analysis.

The submitted example case scored dose response concordance as providing "moderate" support most of the proposed key events in the cytotoxicity MOA. In EPA's evaluation, the evidence is somewhat weaker. The data as assembled do not reveal unambiguous relationships between increasing cytotoxicity and increasing tumorigenicity. EPA (2010) has also judged that the inhalation study tumor response in the low dose (5 ppm) female mice occurred in the absence of substantial observed toxicity.

C. Temporal concordance

Temporal relationships can provide important evidence for causal relationships, as reflected in Bradford Hill's criterion: "The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay)." However, in evaluating mechanistic data, it is also true that an agent can cause a variety of biological perturbations resulting from short term exposure. That is many biological effects may occur much in advance of chronic apical effects such as cancer. The observation that a proposed precursor occurs rapidly (or even at subchronic duration) does not in itself provide much evidence for a causal relationship between the two. Specific to carbon tetrachloride, ACC's concordance table shows metabolism of carbon tetrachloride to reactive radicals, lipid peroxidation, loss of calcium homeostasis, and initial cytotoxicity all occurring within 24 hours; cellular proliferation is observed after two days; and liver tumors are observed at 2 years. This pattern of shorter term versus longer term findings may simply reflect the expected time scales for (1) prompt events of metabolism and initial chemical tissue interactions, (2) acute toxicological changes, and (3) chronic toxicity. This pattern in itself doesn't provide much information to support a MOA.

The submitted example case cites Cabre *et al*., (2001) as showing liver fibrosis, changes in glutathione pathways, and observation of products of lipid peroxidation at time periods before the occurrence of cirrhosis. These earlier events may have a role in carbon

[26] However, biological changes that are not directly related may show a common increasing relationship over a studied dose range. This could result when diverse secondary events share a common antecedent (*e.g.*, changes in metabolic patterns) or simply because an agent has multiple biological effects within the experimental dose range.

tetrachloride carcinogenesis, however, this study doesn't seem to provide evidence of a cancer MOA.

The MOA scoring process attributed maximum scores for "temporal concordance" for all five hypothesized key events in the cytotoxicity pathway, contributing heavily to high overall score assigned to the MOA. However, we believe the cited data on temporal patterns for carbon tetrachloride effects provides only marginal insight for evaluating the MOA for this compound.

II. ACC evaluation of a mutagenicity MOA

This MOA as constructed calls for direct mutagenicity by carbon tetrachloride metabolites to account for the observed cancer findings. As noted above, this inference does not agree with the conclusions about a carbon tetrachloride MOA as described by EPA (2010). The IRIS assessment suggested a multi-step MOA that may involve both mutagenicity and promotion by cytotoxic effects. Such mutagenic effects of carbon tetrachloride need not be direct (in the sense of a direct metabolite of carbon tetrachloride binding to DNA). A multistep MOA may involve oxidative DNA adducts derived through lipid peroxidation resulting from carbon tetrachloride metabolism. Such effects need not be limited to situations with carbon tetrachloride toxicity, as chemical interactions leading to ROS formation may occur in the absence of toxicity. The presence of cytotoxicity may quantitatively alter the dose response for production of DNA oxidation; however, the specific effects of toxicity processes is unknown. High doses of carbon tetrachloride may not produce maximal adduct response, as: (1) high carbon tetrachloride doses can impair CYP2E1 metabolism to species causing lipid peroxidation, and (2) cell killing at high doses will cause birth of cells not exposed to initial carbon tetrachloride doses – or prior background conditions. While there are positive studies showing increased oxidative binding following carbon tetrachloride exposure, this database is complex and sometimes inconsistent. However, with the present state of knowledge, carbon tetrachloride induced oxidative adducts may be an important contributor to carbon tetrachloride's MOA for cancer. Feasible studies using modern methods and quality assurance procedures could substantially resolve these questions.

The submitted example case statement of a mutagenicity MOA is specific and calls for proof at several stages for mutagenic processes:

(1) Metabolism of carbon tetrachloride to a reactive intermediate that leads to the formation of carbon tetrachloride-induced pro-mutagenic DNA adducts
(2) Insufficient or mis-repair of carbon tetrachloride-induced DNA adducts
(3) Early mutations induced in cancer critical genes
(4) Clonal expansion/cell proliferation to form pre-neoplastic AHF
(5) Progression and late mutations
(6) Hepatocellular carcinoma

Given the current lack of resolution on the potential for carbon tetrachloride mutagenicity at bioassay and human relevant exposure levels (see Table L-1 below) the resultant scoring for this MOA was low. However, the score derived by ACC was driven by the choice of steps included above. Note that step (1) includes both metabolism and production of pro-mutagenic DNA

adducts. This compound step would demand much evidence to satisfy. This contrasts with the accompanying hypothesized cytotoxicity MOA where step 1 was purely metabolic: “Metabolism via CYP2E1 and formation of trichloromethyl peroxy radical.” Requiring that both metabolism and DNA lesions be established in a first step for the mutagenic MOA reduces the scoring for this MOA. The decision to separately include step (2) - establishing that DNA repair is inadequate - seems both experimentally challenging and somewhat beside the point as step (3) calls for specific data on completed mutations. Note also that step (3) specifically addresses mutations in cancer critical genes, data that is rarely available from chemical mutagenesis studies.

The practical challenge for evaluating a mutagenic MOA (or a role for mutation in a multi-step MOA) is assessing the available data on mutagenesis. The attachments to this paper excerpt key data from EPA (2010) for *in vivo* and *in vitro* genotoxicity toxicity studies. These tables seek to show that while there is a large database of genotoxicity studies on carbon tetrachloride, there are also major limitations in the database. In particular there are very limited *in vitro* data that applicable to oxidative damage to DNA by carbon tetrachloride (*i.e.*, positive but limited findings in *E. coli* strains) and very limited *in vivo* mutagenesis data for carbon tetrachloride metabolizing tissues. The submitted example case has judged the carbon tetrachloride database as essentially demonstrating lack of a mutagenic effect. By comparison EPA (2010) emphasized the available data do not allow characterization of the genotoxicity at low carbon tetrachloride exposure levels or the role of such genotoxicity in a cancer MOA.

Table L-1. Summary of Reviewed Genotoxicity Studies for Carbon Tetrachloride

Target Organ/ System	Study Type	Species/Strain/ Cell Type (Number/group if relevant)	Exposure Route	Doses/ Concentrations	Duration	Effect Concentration/ Result	Effect Measured	Reference	Data Quality Evaluation
Genotoxicity	Acute	Mouse lymphoma L5178/TK+/- cells	*In vitro*	0, 4.38, 6.55, 8.76 mmol/L (+S9)	3 hours	Positive at 6.55 and 8.76 mmol/L[a] (at relative toxicities of 6% and 16%, respectively)	Alkaline unwinding of DNA (ratio of ssDNA and dsDNA); cell viability	(Garberg et al., 1988)	Unacceptable
Genotoxicity	Acute	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 <3 replicates /group	*In vitro*	0, 0.005, 0.01, 0.05, 0.1, 0.2, 0.5, 1, 2, 5% (± S9)[b]	24 hours	Weakly positive[c] in TA 98 (-S9) at ≥ 1%; negative in TA 98 (+S9); negative in TA 100, TA 1535, and TA 1537 (± S9)	Reverse mutation (gas exposure method)	(Araki et al., 2004)	High
Genotoxicity	Acute	*Escherichia coli* strains WP2/*uvrA*/pKM101, WP2/pKM101 <3 replicates /group	*In vitro*	0, 0.005, 0.01, 0.05, 0.1, 0.2, 0.5, 1, 2, 5% (±S9)[b]	24 hours	Weakly positive[c] at 2% in WP2/*uvrA*/pKM101 (±S9); positive at ≥ 0.1% (-S9) and ≥ 0.2% (+S9) in WP2/pKM101[d]	Reverse mutation (gas exposure method)	(Araki et al., 2004)	High

[a] The test substance was positive at toxic concentrations only. However, the criteria for a positive response in this assay included increases in the relative fraction of DNA that is greater than the increase in relative toxicity (at toxicities of 5% to 50%), if this occurs at two or more concentrations.
[b] Tests were also conducted with glutathione-supplemented S9 mix.
[c] A result was considered positive if a two-fold increase in the number of revertants was observed.
[d] Data for *E.coli* strain WP2/pKM101 were based on < 3 measurements (statistical analyses were not performed).