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Office of Chemical Safety and
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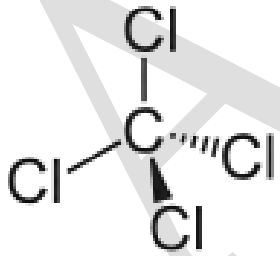
Draft Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-) CASRN: 56-23-5



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ABBREVIATIONS

°C	Degrees Celsius
AAL	Allowable Ambient Levels
ACGIH	American Conference of Government Industrial Hygienists
ADC	Average Daily Concentration
AEC	Acute Exposure Concentration
AIA	Aerospace Industries Association
AIHA	American Industrial Hygiene Association
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
STORET	STORage and RETrieval
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 draft risk evaluation for carbon tetrachloride was performed in accordance with the Frank R. Lautenberg Chemical Safety for the 21st Century Act and is being disseminated for 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. As per EPA's final rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726), EPA is taking comment on this draft, and will also obtain peer review on this draft risk evaluation for carbon tetrachloride. All conclusions, findings, and determinations in this document are preliminary and subject to comment. The final risk evaluation may change in response to public comments received on the draft risk evaluation and/or in response to peer review, which itself may be informed by the public comments. The preliminary conclusions, findings, and determinations in this draft 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 § 26(h) and (i) require EPA 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. To meet these TSCA § 26 science standards, EPA used the TSCA systematic review process described in the Application of Systematic Review in TSCA Risk Evaluations document (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) 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. As a result of this phase-out and ban, it is highly unlikely that there are any ongoing uses of carbon tetrachloride that could be considered legacy uses, and no such uses have been evaluated. 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 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).

In the problem formulation document (U.S. EPA, 2018d), EPA identified the carbon tetrachloride conditions of use and presented two conceptual models and an analysis plan for this current draft risk evaluation. These have been updated in the draft risk evaluation to remove two activities that are no longer considered conditions of use because they consist of outdated industrial/commercial processes (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 draft risk evaluation. EPA quantitatively evaluated the risk to aquatic species from exposure to surface water from water releases due to disposals of carbon tetrachloride associated with its manufacturing, processing, use, or disposal carbon tetrachloride. EPA also quantitatively evaluated the risk to workers, from inhalation and dermal exposures, and occupational non-users (ONUs)[1], 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. 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 draft risk evaluation. Further analysis was not conducted for exposure to aquatic organisms from the suspended soils or sediment pathway based on a qualitative assessment of the physical chemical properties and fate of carbon tetrachloride in the environment. However, exposures to aquatic organisms from ambient surface water were further analyzed in this draft risk evaluation to address a slight change in the environmental hazard chronic COC and the calculation of a distinct algal COC during the data quality evaluation process after the problem formulation phase. This assessment is used to inform the risk determination. 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 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

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

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. 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 highly uncertain, and EPA has low confidence in these exposure estimates for ONUs. Dermal exposures are not expected because ONUs do not typically directly handle the carbon tetrachloride, nor they are in the immediate proximity of 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 draft risk evaluation.

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 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. A distinct COC is calculated for algal toxicity. 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, 2014) 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 and dermal 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 adequate for dose-response assessment. Therefore, most of the dermal candidate values were derived by route-to-route extrapolation from the inhalation PODs mentioned above. In accordance with 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 limited supporting

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. 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 (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. Data to characterize MOA key events at low-exposure levels, however, are limited, hence the use of the baseline linear approach. EPA considered a nonlinear approach with exposures exceeding the POD (18 mg/m^3) for continuous exposure, because above this level, the fitted dose-response model better characterizes what is known about the MOA of carcinogenicity of carbon tetrachloride at higher doses (U.S. EPA, 2010). 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 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 higher levels of exposure.

Risk Characterization

This draft 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 organisms. EPA included a qualitive assessment describing carbon tetrachloride exposure from sediments and land-applied biosolids. 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 determined that there are no acute or chronic environmental risks from the TSCA conditions of use of carbon tetrachloride. Using conservative scenarios, EPA demonstrated that the surface water concentrations did not exceed the acute or chronic COCs (i.e., RQs < 1) for aquatic species for all sites except one site (i.e., acute RQ = 1.4). EPA determined there is not an acute aquatic concern for carbon tetrachloride after further review of the site, which indicated that there was a one-time elevated environmental release of carbon tetrachloride in 2014 due to an unexpected chemical spill. 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 did not identify potential risks for non-cancer liver effects but identified potential cancer risks for high-end chronic exposures.

For workers and ONUs, EPA estimated potential cancer risk 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. For workers and ONUs, EPA also estimated potential non-cancer (liver) risks resulting from acute or chronic inhalation or dermal exposures and used a Margin of Exposure (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 exposures and cancer risks were indicated for both high-end and central tendency exposures for the manufacturing and processing conditions if PPE was not used. For most industrial/commercial conditions of use, cancer risks were also identified for high-end inhalation exposure scenarios if PPE was not used. With use of expected PPE during relevant conditions of use (COUs), worker exposures were estimated to be reduced with MOEs greater than benchmark MOEs and cancer risks 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 4-13. Cancer risks for workers were identified for high-end dermal exposures for all COUs (see section 4.2.7). The dermal high-end exposures are reduced with the use of gloves (PF =5) resulting in cancer risks below the benchmark. Risks were not identified for non-cancer liver effects for workers from dermal exposures (see sections 4.2.4, 4.2.5)

For ONUs, cancer risks were indicated for inhalation occupational exposure scenarios for manufacturing and processing carbon tetrachloride conditions of use. ONUs are not expected to be using PPE to reduce exposures to carbon tetrachloride used in their vicinity. 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 4-13

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 readily available for many of the conditions of use evaluated. Therefore, there is low confidence in the ONU inhalation exposure estimates used in the risk calculations. An additional source of uncertainty in the dermal risk assessment is the inhalation to dermal route-to-route extrapolations and use of the limited available dermal data in a weight of evidence approach. Another source of uncertainty for the human health hazard is the evidence in support of a mode of action (MOA) for carcinogenesis of carbon tetrachloride at low dose levels. Therefore, a low dose linear cancer risk model for carbon tetrachloride was used to calculate cancer risk. Assumptions and key sources of uncertainty are detailed in section 4.4.

Potentially Exposed and Susceptible Subpopulations (PESS)

TSCA § 6(b)(4) requires that EPA evaluate risk to relevant PESS. In developing the risk evaluation, EPA analyzed the reasonably available information to ascertain whether some human receptor groups may have greater exposure or greater susceptibility than the general population to the hazard posed by carbon tetrachloride. EPA considered carbon tetrachloride exposures to be higher among workers using carbon tetrachloride and ONUs in the vicinity of carbon tetrachloride use than the exposures experienced by the general population. 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.

Aggregate and Sentinel Exposures

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 additivity of exposure pathways at this time within a condition of use because of the uncertainties present in the current exposure estimation procedures that may lead to an underestimate of aggregate exposure. Other identified uncertainties for performing an aggregate exposure assessment of carbon tetrachloride are discussed in section 4.6. Those uncertainties were also considered by EPA for determining not to employ additivity of exposure pathways. In this risk evaluation, EPA considered sentinel exposure the highest exposure given the details of the conditions of use and the potential exposure scenarios.

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); 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 preliminary risk determination is discussed in section 5.1.

Environmental Risks: 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 aquatic species for all but one of the sites assessed, and the exceedance at that site was due to an unexpected chemical spill. None of the sites analyzed had more than 20 days where the chronic and algal COCs were exceeded. 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. Consequently, EPA did

not further assess exposure to sediment-dwelling aquatic organisms. Therefore, in this draft risk evaluation, EPA does not find unreasonable environmental risk to aquatic species from the conditions of use for carbon tetrachloride. As explained in section 2.5.3.2 of the problem formulation (U.S. EPA, 2018d), exposure to terrestrial organisms was removed from the scope of the evaluation. This exposure pathway is considered to be covered under programs of other environmental statutes, administered by EPA, which adequately assess and effectively manage exposures and for which long-standing regulatory and analytical processes already exist. Therefore, EPA did not evaluate hazards and exposures to terrestrial organisms in this draft risk evaluation, and there is no risk determination for terrestrial organisms.

Risks of Injury to Health: EPA's preliminary determination of unreasonable risk for specific conditions of use of carbon tetrachloride listed below are based on health risks to occupational non-users. As described below, risks to workers, general population, consumers, and bystanders to consumer use either were not relevant for these conditions of use or were evaluated and not found to be unreasonable.

Risks from acute exposures include central nervous system effects that are temporarily disabling, such as dizziness. Risks from chronic exposures include liver toxicity and cancer.

Risk to Workers: EPA evaluated workers' acute and chronic inhalation and dermal occupational exposures for cancer and non-cancer risks and preliminarily determined that these risks are not unreasonable. This determination incorporates consideration of expected PPE (frequently estimated to be a respirator of APF 10, 25 or 50). A full description of EPA's preliminary determination for each condition of use is in section 5.3.

Risk to the General Population: EPA is not including in this draft risk evaluation exposure pathways under programs of other environmental statutes, administered by EPA, which adequately assess and effectively manage exposures and for which long-standing regulatory and analytical processes already exist. The Office of Chemical Safety and Pollution Prevention works closely with EPA offices that administer and implement the regulatory programs under these statutes. EPA believes this TSCA risk evaluation should focus on those exposure pathways associated with TSCA uses that are not covered under other environmental regulatory regimes administered by EPA because these pathways are likely to represent the greatest areas of concern to EPA. As described in section 2.4.3 of this draft risk evaluation, exposure pathways for carbon tetrachloride for human receptors (i.e., general population) already addressed by these other statutory programs include ambient air, drinking water, ambient water, biosolids, and disposal. Because there are no other exposure pathways impacting the general population, EPA did not evaluate hazards or exposures to the general population in this risk evaluation, and there is no risk determination for the general population.

Risks to Occupational Non-Users (ONUs): EPA evaluated ONU acute and chronic inhalation occupational exposures for cancer and non-cancer risks and preliminarily determined whether any risks indicated are unreasonable. Generally, risks identified for ONUs are linked to acute and chronic inhalation exposures. The determinations reflect the hazards associated with the occupational exposures to carbon tetrachloride and the expected absence of PPE for ONUs. The driver for EPA's determinations of unreasonable risk for ONUs is cancer from chronic inhalation exposure. The determinations reflect the severity of the hazards associated with the occupational exposures to carbon tetrachloride and the expected absence of PPE for ONUs. For dermal exposures, because ONUs are not expected to be dermally exposed to carbon tetrachloride, dermal risks to ONUs generally were not identified. ONU inhalation exposures are expected to be lower than inhalation exposures for workers directly handling

the chemical substance; however, the relative exposure of ONUs to workers in these cases cannot be quantified. To account for the fact that the monitoring data or modeling did not distinguish between worker and ONU inhalation exposure estimates, EPA considered the central tendency risk estimate when determining ONU risk. Recognizing the significant uncertainty surrounding EPA's inhalation exposure estimates for ONUs, EPA will continue to seek data on ONU inhalation exposures during the public comment period on the draft risk evaluation. In addition, because EPA is preliminarily making a finding that four COUs present an unreasonable risk for ONUs based on increased cancer risk estimate of 4×10^{-4}, EPA will further analyze this information to determine whether this four-fold difference from the cancer risk benchmark falls within the range of uncertainty for these estimates. As noted previously, EPA has low confidence in the exposure estimates for ONUs.

For ONUs, EPA preliminarily determined that the conditions of use that present unreasonable risks include the domestic manufacture of carbon tetrachloride; the processing of carbon tetrachloride as a reactant or intermediate in the production of hydrochlorofluorocarbons (HCFCs), hydrofluorocarbon (HFC), hydrofluoroolefin (HFO), and perchloroethylene (PCE); processing for incorporation into formulation, mixtures or reaction products (other basic organic and inorganic chemical manufacturing); and industrial/commercial use in the manufacture of other basic chemicals (including chlorinated compounds used in solvents, adhesives, asphalt, and paints and coatings). A full description of EPA's preliminary determination for each condition of use is in section 5.3.

Risk to Consumers and Bystanders to Consumer Use: EPA did not include any consumer uses among the conditions of use within the scope of the risk evaluation for carbon tetrachloride. 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. 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 de minimis exposure to, or otherwise insignificant risk from, 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. Therefore, EPA did not evaluate hazards or exposures to consumers or bystanders to consumer use in this risk evaluation, and there are no risk determinations for these populations.

Summary of Risk Determinations:
EPA has preliminarily determined that the following conditions of use of carbon tetrachloride do not present an unreasonable risk of injury to health. The details of these determinations are presented in Table 5-1 and section 5.3.

Conditions of Use that Do Not Present an Unreasonable Risk
• Import (including loading/unloading and repackaging) • Processing as a reactant/intermediate in reactive ion etching (i.e., semiconductor manufacturing) • Processing for incorporation into formulation, mixtures or reaction products (petrochemicals-derived manufacturing; agricultural products manufacturing) • Repackaging for use in laboratory chemicals • Recycling • Distribution in commerce

Conditions of Use that Do Not 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 in metal recovery • Industrial/commercial use as an additive • Specialty uses by the Department of Defense • Industrial/commercial use as a laboratory chemical • Disposal

EPA has preliminarily determined that the following conditions of use of carbon tetrachloride present an unreasonable risk of injury to health of occupational non-users. The details of these determinations are presented in Table 5-1 and in section 5.3.

Manufacturing Use that Presents an Unreasonable Risk to ONUs
• Domestic manufacture

Processing Use that Presents an Unreasonable Risk to ONUs
• Processing as a reactant or intermediate in the production of hydrochlorofluorocarbons (HCFCs), hydrofluorocarbon (HFCs) and hydrofluoroolefin (HFOs), and perchloroethylene (PCE) • Processing for incorporation into formulation, mixtures or reaction products (other basic organic and inorganic chemical manufacturing)

Industrial/Commercial Use that Presents an Unreasonable Risk to ONUs
• Industrial/commercial use in the manufacture of other basic chemicals (including chlorinated compounds used in solvents, adhesives, asphalt, and paints and coatings)

1 INTRODUCTION

This document presents for comment the draft 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 Agency 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, 2018d), 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*. EPA received comments on the published problem formulation for carbon tetrachloride and has considered the comments specific to carbon tetrachloride, as well as more general comments regarding EPA's chemical risk evaluation approach for developing the draft risk evaluations for the first 10 TSCA Workplan chemicals.

During problem formulation, EPA identified the carbon tetrachloride's conditions of use and presented the associated 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 formulations preliminarily concluded that further analysis was necessary for exposure pathways to workers. Further analysis was not conducted for exposure to aquatic organisms from the suspended soils or sediment pathway based on a qualitative assessment of the physical chemical properties and fate of carbon tetrachloride in the environment. However, to address a slight change in the environmental hazard chronic COC from 7 ppb to 3 ppb during the data quality evaluation process after the problem formulation phase, EPA quantitatively evaluated risk to aquatic organisms from exposure to surface water based on a conservative assessment of the available monitoring data for carbon tetrachloride to adequately evaluate any potential environmental risk to aquatic organisms posed by carbon tetrachloride.

EPA used reasonably available information consistent with the best available science for physical chemical and fate properties, potential exposures, and relevant hazards according to the systematic review process. For the human exposure pathways, EPA evaluated inhalation exposures to vapors and mists for workers and occupational non-users, and dermal exposures via skin contact with liquids for workers. EPA characterized risks to ecological receptors from exposures via surface water in the risk characterization section of this draft risk evaluation based on the analyses briefly described above.

This document is structured such that the Introduction (Section 1) 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 draft 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 draft risk evaluation. As required under TSCA 15 U.S.C. 2605(b)(4), a determination of whether the risk posed by this chemical substance is unreasonable is presented in the Risk Determination (Section 0).

As per EPA's final rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 Fed. Reg. 33726) (hereinafter "Risk Evaluation Rule"), this draft risk evaluation is subject to both public comment and peer review, which are distinct but related processes. EPA is providing 60 days for public comment, which will inform the EPA Science Advisory Committee on Chemicals (SACC) peer review process. EPA seeks public comment on all aspects of this draft risk evaluation, including all conclusions, findings, and determinations.

Peer review will be conducted in accordance with EPA's regulatory procedures for chemical risk evaluations, including using the *EPA Peer Review Handbook* and other methods consistent with section 26 of TSCA (*See* 40 CFR 702.45). As explained in the Risk Evaluation Rule, the purpose of peer review is for the independent review of the science underlying the risk assessment. Peer review will therefore address 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.

The final risk evaluation may change in response to public comments received on the draft risk evaluation and/or in response to peer review, which itself may be informed by public comments. EPA will respond to public and peer review comments received on the draft risk evaluation when it issues the final risk evaluation.

EPA solicited input on the first 10 chemicals as it developed use dossiers, scope documents, and problem formulations. At each step, EPA has 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 of carbon tetrachloride. Thus, in addition to any new comments on the draft risk evaluation, the public should re-submit or clearly identify at this point any previously filed comments, modified as appropriate, that are relevant to this risk evaluation and that the submitter feels have not been addressed. EPA does not intend to further respond to comments submitted prior to the publication of this draft risk evaluation unless they are clearly identified in comments on this draft risk evaluation.

1.1 Physical and Chemical Properties

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). Carbon tetrachloride is expected to volatilize based on its high vapor pressure (115 mm Hg at 25°C) (Lide, 1999). Carbon tetrachloride has a log K_{ow} value of 2.83 (Hansch et al., 1995), indicating that this chemical is moderately miscible in water. A summary of the physical and chemical properties of carbon tetrachloride are listed 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)

Property	Value[a]	References
Autoflammability	Not flammable	(USCG, 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, 2018d), 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) reporting data for carbon tetrachloride are provided in Table 1-2 for carbon tetrachloride from EPA's CDR database (U.S. EPA, 2017b).

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).				

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, 2018d)).

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 (2015)
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)

Authoring Organization	Assessment
California Environment Protection Agency, Office of Environmental Health Hazard Assessment	Public Health Goal for Carbon Tetrachloride (2000)
International	
Health Canada	Guidelines for Canadian Drinking Water Quality, Guideline Technical Document, Carbon Tetrachloride (2010)
Organisation for Economic Co-operation and Development's Screening Information Dataset (OECD SIDS), Co-CAM, 10-12	SIDS SIAP for Carbon Tetrachloride (2011)
World Health 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)

1.4 Scope of the Evaluation

1.4.1 Conditions of Use Included in the Risk Evaluation

TSCA § 3(4) defines the conditions of use as ''the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of." 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 releases have been evaluated in this draft risk evaluation for the following industrial/commercial uses of carbon tetrachloride:

1. Manufacture: Manufacturing
2. Manufacture: Import (including repackaging)
3. Processing: Reactant/Intermediate: Feedstock for HCFC, HFCs, HFO and PCE
4. Processing: Reactant/Intermediate: Reactive Ion Etching
5. Processing: Incorporation into Formulation, Mixture or Reaction Products
6. Industrial/Commercial Use: DoD Specialty Uses
7. Industrial/Commercial Use: Laboratory Chemical,
8. Industrial/Commercial Use Processing agent/aid
9. Industrial/Commercial Use: Additive
10. Disposal: Waste Handling

1.4.2 Subcategories Determined Not To Be Conditions of Use

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 has reviewed reasonably available information obtained or possessed by EPA

concerning activities associated with carbon tetrachloride. As a result of that review, EPA has determined uses of carbon tetrachloride that were previously thought to be a condition of use are no longer used in current practices and are not reasonably foreseen to be resumed. Consequently, EPA will not consider or 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)

Based on all present information, 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 data supporting its use in the industry and there is no significant human exposure from products used in the aerospace industry. Additionally, there are current regulatory actions (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, 2018d).

1.4.2.2 Manufacturing of Pharmaceuticals

EPA had identified uses of carbon tetrachloride as a process agent in the manufacturing of pharmaceuticals (i.e., ibuprofen) in the problem formulation (U.S. EPA, 2018d). In 1983, EPA presented a report entitled *Preliminary Study of Sources of Carbon Tetrachloride: Final Report*. This report stated that carbon tetrachloride was used as a solvent to dissolve solid reactants during the pharmaceutical manufacturing process, which included ibuprofen (U.S. EPA, 1983). However, 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). EPA found no evidence to suggest that the manufacturing of ibuprofen, or any other pharmaceuticals, still utilizes carbon tetrachloride or that such use is reasonably foreseen to resume. Accordingly, EPA no longer considers use as a process agent in the manufacturing of pharmaceuticals to be a condition of use of carbon tetrachloride and does not evaluate it in this draft risk evaluation.

1.4.2.3 Exclusions During Problem Formulation

In problem formulation, EPA removed from the risk evaluation any activities and exposure pathways 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. For example, 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, 2018d).

In addition, 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 further evaluation or inclusion in the risk evaluation. These activities and 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 no approved consumer uses for carbon tetrachloride. 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).

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.

Based on the information identified by EPA, carbon tetrachloride is not a direct reactant or additive in the formulation of solvents for cleaning and degreasing, adhesives and sealants or paints and coatings. Because industrial, commercial, and consumer use of such products (solvents for cleaning/degreasing, adhesives/sealants, and paints/coatings) would present only de minimis exposure 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 EPA has not considered or evaluated these conditions of use or associated hazards or exposures in the risk evaluation for carbon tetrachloride.

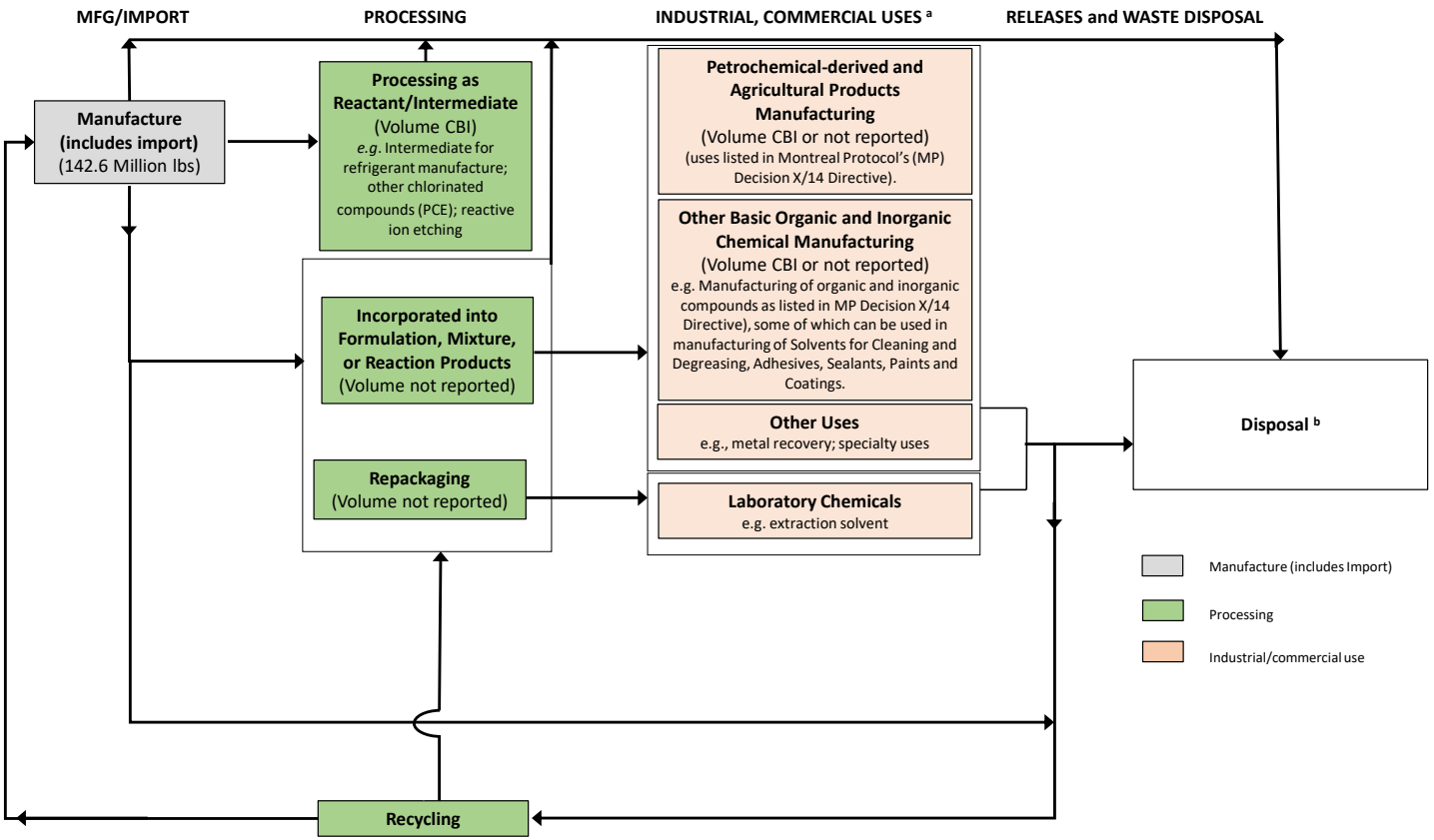


Figure 1-1. Carbon Tetrachloride Life Cycle Diagram

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

1114 **Table 1-4. Categories and Subcategories of Conditions of Use Included in the Scope of the**
1115 **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.
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)
		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
Disposal	Disposal[c]	Industrial pre-treatment	(U.S. EPA, 2017g)
		Industrial wastewater treatment	(U.S. EPA, 2017g)

		Publicly owned treatment works (POTW)	(U.S. EPA, 2017g)
		Underground injection	(U.S. EPA, 2017g)
		Municipal landfill	(U.S. EPA, 2017g)
		Hazardous landfill	(U.S. EPA, 2017g)
		Other land disposal	(U.S. EPA, 2017g)
		Municipal waste incinerator	(U.S. EPA, 2017g)
		Hazardous waste incinerator	(U.S. EPA, 2017g)
		Off-site waste transfer	(U.S. EPA, 2017g)

[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.

1.4.3 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, 2018d). 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 potential risk to aquatic organisms from carbon tetrachloride. The conceptual models for this risk evaluation are shown below in Figure 1-2 and Figure 1-3.

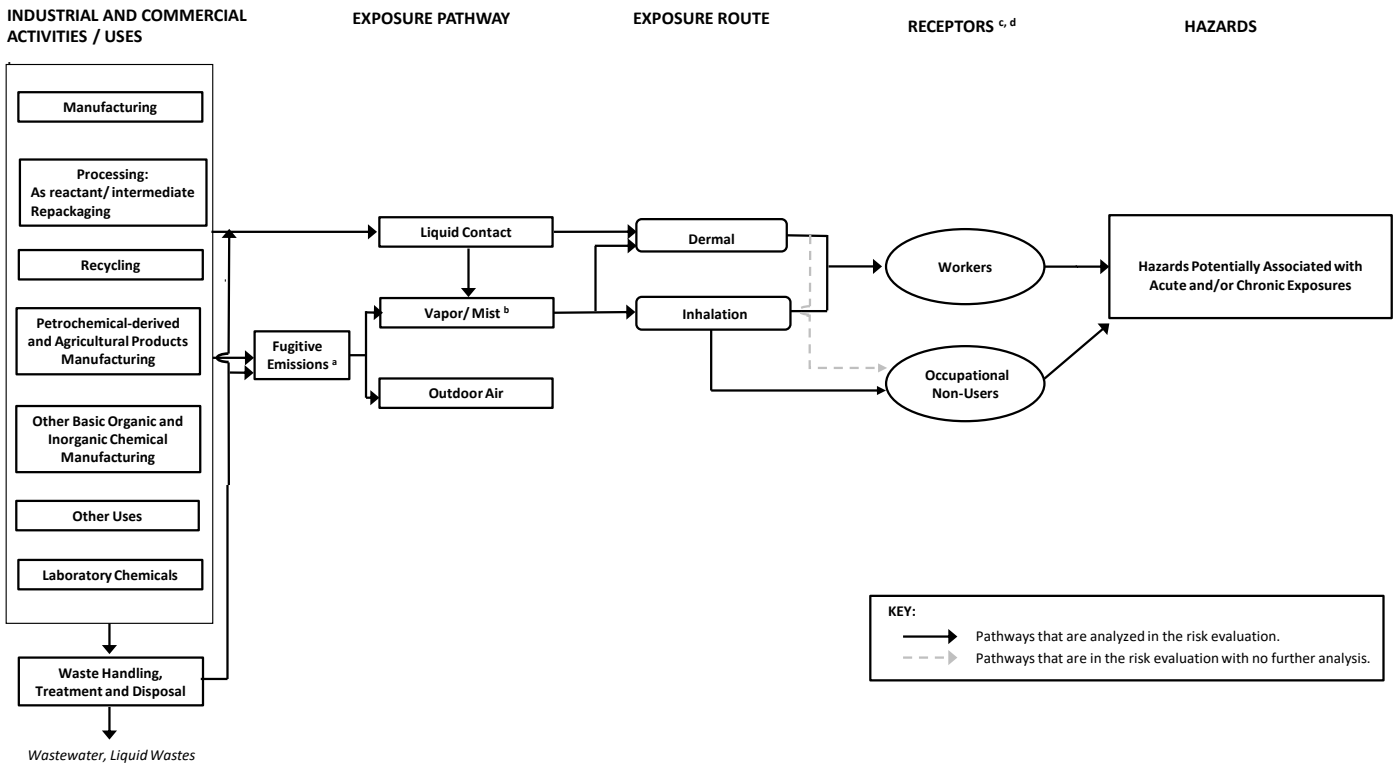


Figure 1-2. Carbon Tetrachloride Conceptual Model for Industrial/Commercial Activities and Uses: Potential Exposures and Hazards

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.

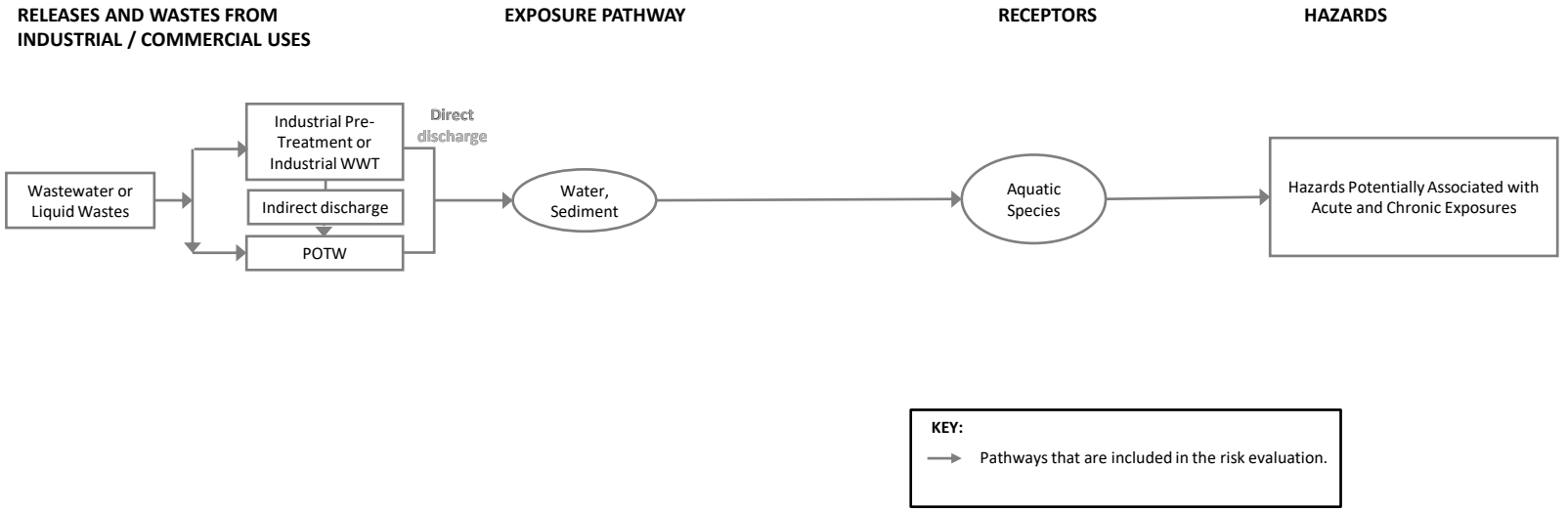


Figure 1-3. Carbon Tetrachloride Conceptual Model for Environmental Releases and Wastes: Potential Exposures and Hazards

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 will be 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 comprehensive 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.[2] 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, 2018d).

In addition to the comprehensive literature search and screening process described above, EPA leverage the information presented in previous assessments,[3] when identifying relevant key and supporting data,[4] 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 relevant 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 of 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.

[2] 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.

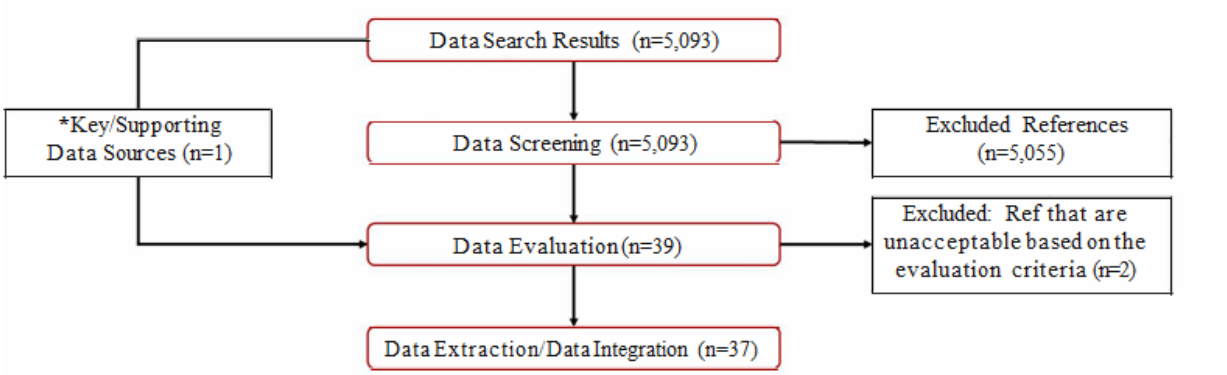
[3] Examples of existing assessments are EPA's chemical assessments (e.g. previous work plan risk assessments, problem formulation documents), ATSDR's Toxicological Profiles, EPA's IRIS assessments and ECHA's dossiers. This is described in more detail in the *Strategy for Conducting Literature Searches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

[4] 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 draft risk evaluation.

The literature flow diagrams shown in Figure 1-4, Figure 1-5, Figure 1-6, Figure 1-7 and 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 draft 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).

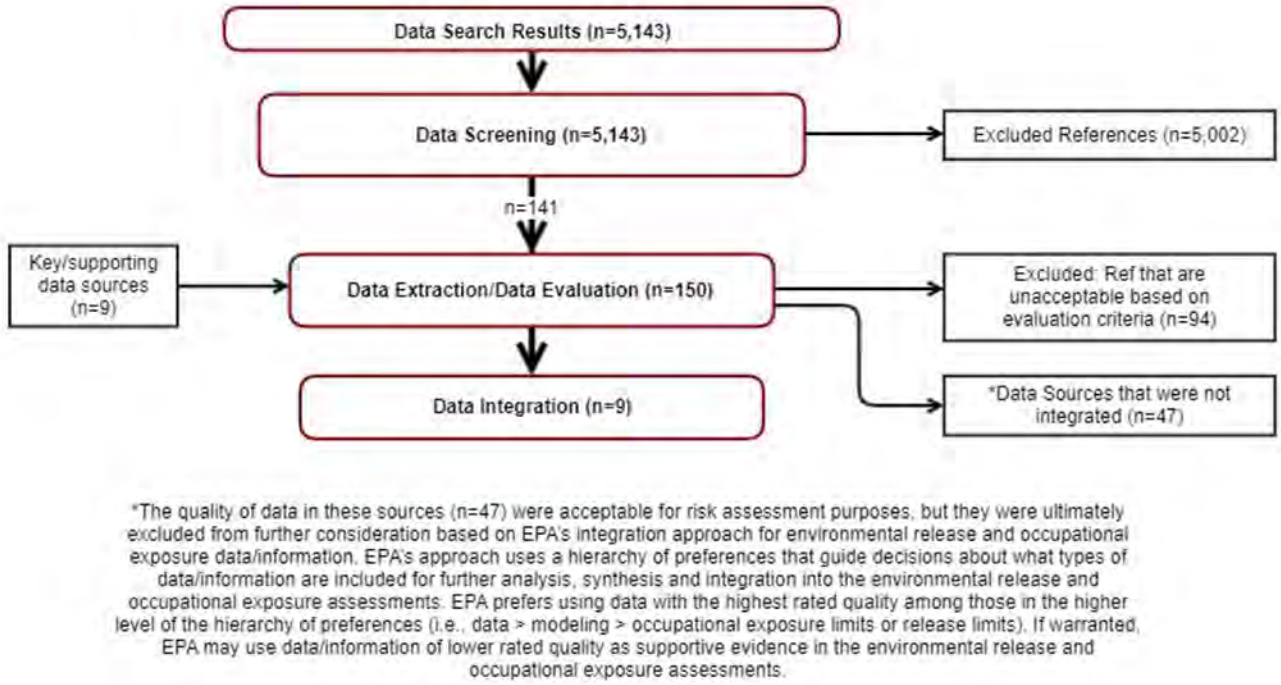


Figure 1-5. Key/Supporting Data Sources for Releases and Occupational Exposures

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 9 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 9 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).

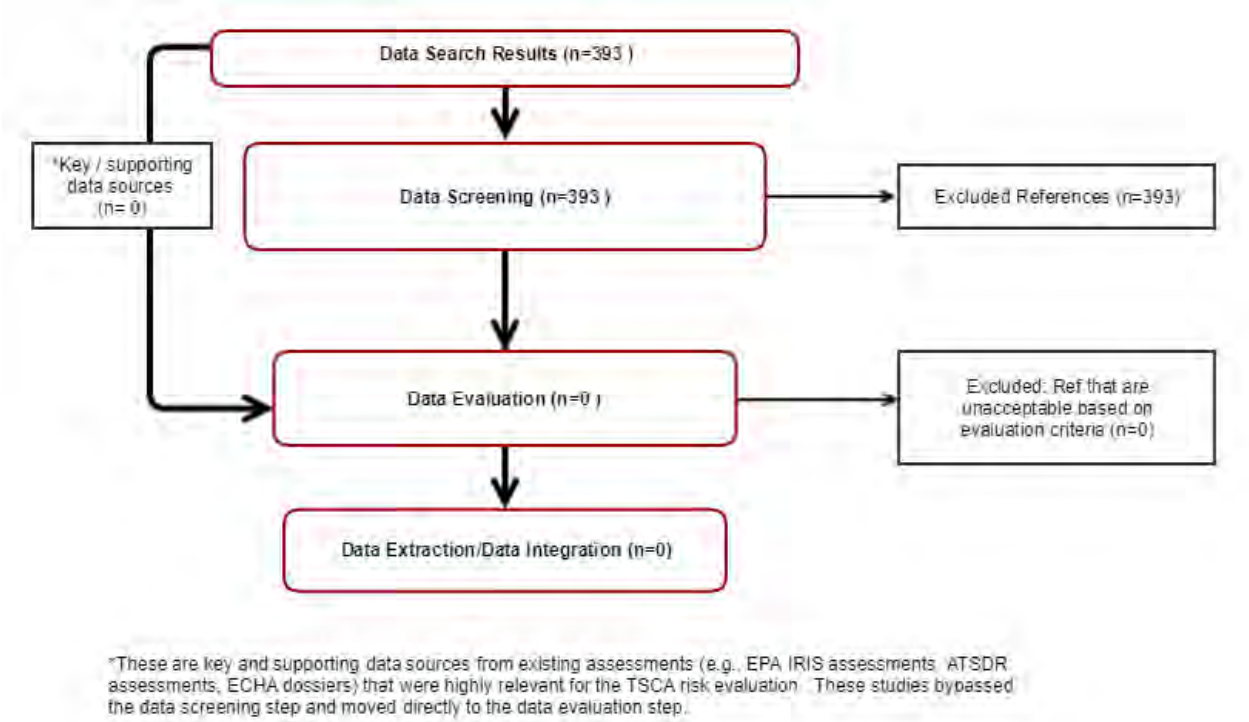


Figure 1-6. Key/Supporting Sources for Environmental Exposures

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 draft risk evaluation through the data screening process.

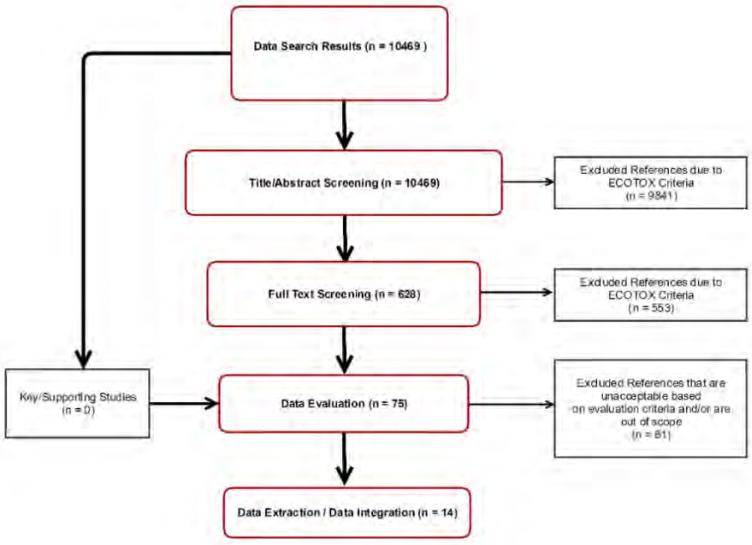


Figure 1-7. Key/Supporting Sources for Environmental Hazards

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, 2018c). 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. The terrestrial species exposure pathways were considered to be covered under programs of other environmental statues administered by EPA, which adequately assess and effectively manage such exposures (e.g., RCRA, CAA). Therefore, environmental hazard data sources on terrestrial organisms and on metabolic endpoints were excluded from data quality evaluation. 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. These studies bypassed the data screening step and moved directly to the data evaluation step.

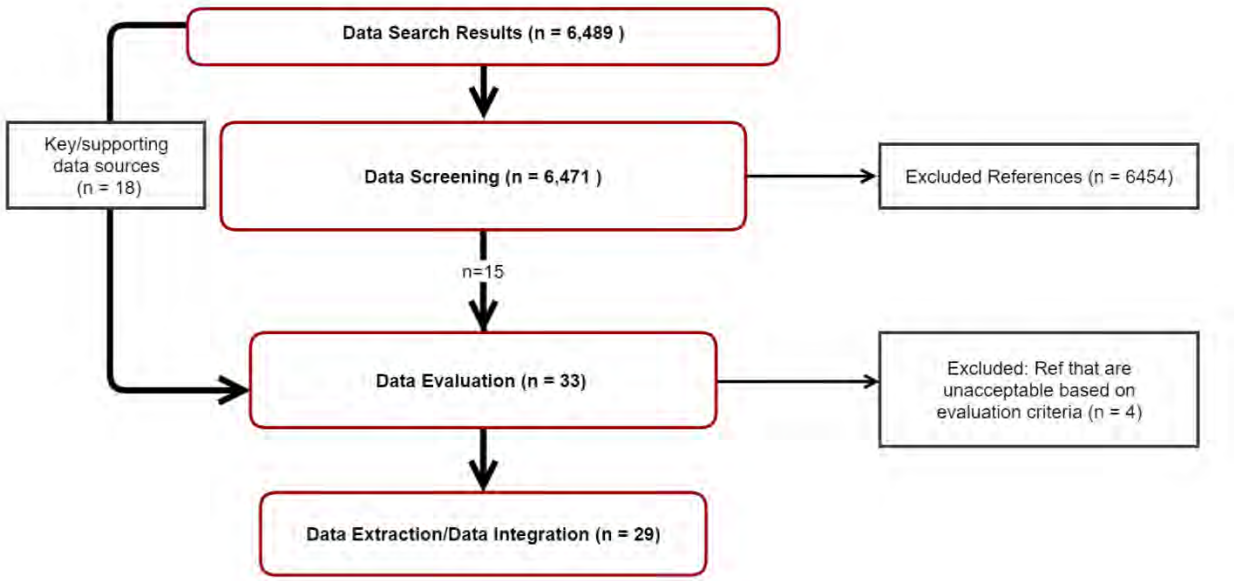


Figure 1-8. Key/Supporting Data Sources for Human Health Hazards

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. 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 draft 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, 2018e).

EPA used previous assessments to identify key and supporting information and then analyzed and synthesized available evidence regarding carbon tetrachloride's 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, *Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Fate and Transport Studies* (U.S. EPA, 2019c).

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, 2018d).

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, 2018d).

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).

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

The EPI Suite™ module that predicts biodegradation rates ("BIOWIN" module) was run using default settings to estimate biodegradation rates of carbon tetrachloride under aerobic conditions. Three of the models built into the BIOWIN module (BIOWIN 1, 2 and 6) estimate that carbon tetrachloride will not rapidly biodegrade in aerobic environments. 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.

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 one component of potential exposure and may be derived from reported data that are obtained through direct measurement, calculations based on empirical data and/or assumptions, and models.

Under the Emergency Planning and Community Right-to-Know Act (EPCRA) section 313 rule, carbon tetrachloride is a Toxics Release Inventory (TRI)-reportable substance effective January 1, 1987. The TRI database includes information on disposal and other releases of carbon tetrachloride to air, water, and land, in addition to how it is being managed through recycling, treatment, and burning for energy recovery. Facilities are required to report if they manufacture (including import) or process more than 25,000 pounds of carbon tetrachloride, or if they otherwise use more than 10,000 pounds of carbon tetrachloride.

TRI reporting by subject facilities is required by law to provide information on releases and other waste management activities of Emergency Planning and Community Right-to-Know Act (EPCRA) Section 313 chemicals (i.e., TRI chemicals) to the public for informed decision making and to assist the EPA in determining the need for future regulations. Section 313 of EPCRA and Section 6607 of the Pollution Prevention Act (PPA) require certain industrial facilities to report release and other waste management quantities of TRI-listed chemicals annually when a reporting threshold is triggered, but these statutes do not impose any monitoring burden for determining the quantities.

TRI data are self-reported by the subject facility where some facilities are required to measure or monitor emission or other waste management quantities due to regulations unrelated to the TRI Program, or due to company policies. These existing, readily available data are often used by facilities for TRI reporting purposes. When measured (e.g., monitoring) data are not "readily available," or are known to be non-representative for TRI reporting purposes, the TRI regulations require that facilities determine release and other waste management quantities of TRI-listed chemicals by making "reasonable estimates." Such reasonable estimates include a variety of different approaches ranging from published or site-specific emission factors (e.g.,

AP-42), mass balance calculations, or other engineering estimation methods or best engineering judgement. TRI reports are then submitted directly to EPA on an annual basis and must be certified by a facility's senior management official that the quantities reported to TRI are reasonable estimates as required by law.

Based on 2018 TRI (U.S. EPA, 2018f), 49 facilities reported almost 252 thousand pounds of carbon tetrachloride released into the environment. Of these environmental releases, the largest releases of over 176 thousand pounds were to air (fugitive and point source air emissions), less than 2 thousand pounds were released to water (surface water discharges), over 73 thousand pounds were released to land (of which disposal to Resource Conservation and Recovery Act (RCRA) Subtitle C landfills is the primary disposal method), and under 146 pounds were released in other forms such as indefinite storage. Carbon tetrachloride migration to groundwater from RCRA Subtitle C landfills regulated by the state/local jurisdictions will likely be mitigated by landfill design (double liner, leachate capture) and requirements to adsorb liquids onto solid absorbant and containerize prior to disposal. See Appendix D for a TRI summary table on the 2018 releases of carbon tetrachloride to various media.

2.3 Environmental Exposures

In the problem formulation (U.S. EPA, 2018d), 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, 2018d). 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 section 2.5.3.2 of the problem formulation (U.S. EPA, 2018d), which has been updated in section 4.1.2 below.

2.3.1 Environmental Exposures – Aquatic Pathway

As explained in section 2.5.3.1 of the Problem Formulation document (U.S. EPA, 2018d), 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. The fate information on carbon tetrachloride identified in the systematic review confirmed the validity of the fate values used for concluding that risk to aquatic species from sediments and solid do not need further analysis.

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 five years (2014 through 2018) EPA NPDES permit Discharge Monitoring Report (DMR) data on the top highest carbon tetrachloride releasing facilities based on the reported annual loadings (lbs/year). 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 4-2 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) to model a chronic aquatic exposure scenario and over 20 days/year to model acute aquatic exposure. 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.

In some ways, the E-FAST estimates are overestimating aquatic exposure, because carbon tetrachloride is a volatile chemical and E-FAST does not take volatilization into consideration; and for static water bodies, E-FAST does not take dilution into consideration.

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., top discharging facilities), which could result in overestimation of the water concentrations, in addition to the uncertainties associated with the E-FAST model and DMR dataset (see section 4.4.2).

2.3.2 Terrestrial Environmental Exposure

Terrestrial species populations living near industrial/commercial facilities using carbon tetrachloride may be exposed to the chemical through environmental media. Terrestrial species populations living near industrial/commercial facilities using carbon tetrachloride may be exposed via multiple routes such as ingestion of surface waters and inhalation of outdoor air. As described above, carbon tetrachloride is present and measurable through monitoring in a variety of 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 and that these existing programs and processes adequately assess and effectively manage the exposures (see section 2.5.3.2 of the problem formulation document) (U.S. EPA, 2018d). Therefore, these exposure pathways were excluded from the scope of this risk evaluation, and terrestrial environmental exposure data were not analyzed as part of this risk evaluation.

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 (ONU). Workers that 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 report. 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 that 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 work day. 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.

EPA assessed occupational exposures following the analysis plan published in section 2.6.1.2 of the problem formulation document (U.S. EPA, 2018d). EPA evaluated acute and chronic inhalation exposures to workers and ONUs in association 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, 2018d) 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 and Appendix F. 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 *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b) 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 *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b).
- **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 *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b).

The OSHA Personal Protective Equipment (PPE) Standard, 29 CFR § 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 to meet different concentration benchmarks. If the employer determines that exposures are not hazardous, OSHA does not require controls such as PPE. Conversely if the employer identifies a hazardous exposure, OSHA requires control measures.

The OSHA respirator protection standard, 29 CFR § 1910.134(a)(1), recommends 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. They 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 § 1910.1000, employers should utilize respirator protective equipment. (29 CFR § 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 *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b).

See Appendix E of the supplemental document *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b) 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' 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 are unlikely to result in a systematic underestimate or overestimate and could result in an inaccurate estimate. 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' 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' 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 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 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 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 50^{th} percentile and 95^{th} percentile. For datasets with three to five data points, central tendency exposure was calculated using the 50^{th} 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, 2019b).

EPA used exposure monitoring data and exposure models to estimate inhalation exposures for all conditions of use. 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 *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b) 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 A-1.

Equation 2-1

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

Where:

AEC = acute exposure concentration [mg/m^3]
C = contaminant concentration in air (8-hour TWA) [mg/m^3]
ED = exposure duration [hr/day]
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

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

Where:

ADC = average daily concentration (8-hr TWA) used for chronic non-cancer risk calculations
$LADC$ = lifetime average daily concentration (8-hr TWA) used for chronic cancer risk calculations
C = contaminant concentration in air (8-hr TWA)
ED = exposure duration (8 hr/day)
EF = exposure frequency (250 days/yr)
WY = exposed working years per lifetime (tenure values used to represent: 50th percentile = 31; 95th percentile = 40)

AT = averaging time, non-cancer risks (***WY*** × 250 days/yr × 8 hr/day)
AT$_c$ = averaging time, cancer risks (lifetime (***LT***) x 365 days/year x 24 hr/day; where ***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 *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b) 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, 2013a):

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).
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*.
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 ***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, ***f$_{abs}$*** ($0 \leq f_{abs} \leq 1$):

Equation 2-4

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

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 *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b).

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. Initial literature review suggests that there is unlikely to be sufficient data to justify a specific probability distribution for effective glove use for a chemical or industry. Instead, the impact of effective glove use should be 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 2-20.

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 real-world scenarios.

2.4.1.5 Consideration of Engineering Controls and Personal Protective Equipment

OSHA and NIOSH recommend 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 § 1910.134(a)(1). The PPE (e.g., respirators, gloves) could be used as the last means of control, when the other control measures cannot reduce workplace exposure to an acceptable level.

Respiratory Protection

OSHA's Respiratory Protection Standard (29 CFR § 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 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 § 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 2-2) 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 200 ppm as a maximum peak. 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 and health (IDLH) value of 200 ppm (ATSDR, 2017) 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).

Respirators should be used when effective engineering controls are not feasible as per OSHA's 29 CFR § 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 2-2 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 2-2 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 2-2. 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). The survey found that the establishments that required respirator use had the following respirator program characteristics (NIOSH, 2003):

- 59% provided training to workers on respirator use;
- 34% had a written respiratory protection program;
- 47% performed an assessment of the employees' medical fitness to wear respirators;
- 24% included air sampling to determine respirator selection.

The survey report does not provide a result for respirator fit testing or identify if fit testing was included in one of the other program characteristics. Of the establishments that had respirator use for a required purpose within the 12 months prior to the survey, NIOSH and BLS found (NIOSH, 2003):

- Non-powered air purifying respirators are most common, 94% overall and varying from 89% to 100% across industry sectors
  - A high majority use dust masks, 76% overall and varying from 56% to 88% across industry sectors of the establishments;
  - A varying fraction use half-mask respirators, 52% overall and varying from 26% to 66% across industry sectors;
  - A varying fraction use full-facepiece respirators, 23% overall and varying from 4% to 33% across industry sectors.
- Powered air-purifying respirators represent a minority of respirator use, 15% overall and varying from 7% to 22% across industry sectors;
- Supplied air respirators represent a minority of respirator use, 17% overall and varying from 4% to 37% across industry sectors.

In a more recent article, 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. Thus, the likelihood of respirator use may not be widespread or effective.

Dermal Protection

Based on a hazard assessment, employers must also determine whether employees are exposed to skin hazards (1910.32(d). The Hand Protection section of OSHA's Personal Protective Equipment Standard (29 CFR § 1910.138(a)) requires employers to select and require workers to wear gloves to prevent exposure to harmful substances identified in the hazard assessment. As with respirators, gloves 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 impervious to the hazardous chemical, and if worn on clean hands and replaced when contaminated or compromised, could provide employees with protection from hazardous substances. As described earlier, EPA is using glove protection factors developed by a conceptual model developed by Cherie et al. in this risk evaluation. Table 2-3 shows these glove protection factors (PF) and the dermal protection strategies. These values could vary depending on the type of gloves used and the presence of employee training program.

Table 2-3. 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

2.4.1.6 Regrouping of Conditions of Use for Engineering Assessment

EPA assessed the conditions of use in Table 1-4; 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 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, 2018d) 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 is evaluated in the reactant section and the latter 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 2-4 below.

Table 2-4. 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[5]	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	Industrial Processing Agent/Aid (Section 2.4.1.7.6) Additive (Section 2.4.1.7.7)

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

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4[5]	Category in Current Engineering Assessment
		inorganic chemical manufacturing.	Processing as a Reactant or Intermediate (Section 2.4.1.7.3)
	Processing - repackaging	Laboratory Chemicals	Import and Repackaging (Section 2.4.1.7.2)[6]
	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	Processing aid	Industrial Processing Agent/Aid (Section 2.4.1.7.6)
		Additive	Additive (Section 2.4.1.7.7)
	Agricultural products manufacturing	Processing aid	Industrial Processing Agent/Aid (Section 2.4.1.7.6)
	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)

[6] 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[5]	Category in Current Engineering Assessment
	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)
	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)[7]
		Industrial wastewater treatment	
		Publicly owned treatment works (POTW)	
		Underground injection	
		Municipal landfill	
		Hazardous landfill	
		Other land disposal	
		Municipal waste incinerator	

[7] 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.

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4[5]	Category in Current Engineering Assessment
		Hazardous waste incinerator	
		Off-site waste transfer	

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 for the regrouped conditions of use. The following sections 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 *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b).

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 motions 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 CCl_4.

To determine the total number of workers and ONUs, EPA used the average worker and ONUs estimates from the BLS analysis based on each site's reported NAICS code in TRI (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. To determine the total number of workers and ONUs, EPA used the average worker and ONUs estimates from the BLS analysis based on each site's reported NAICS code in TRI (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.

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 5 sites being classified under 325199 and 2 sites under 325180. There is a total of 243 workers and 115 ONUs (see Table 2-5).

Table 2-5. Estimated Number of Workers Potentially Exposed to Carbon Tetrachloride During Manufacturing

Number of Sites	Total Exposed Workers	Total Exposed Occupational Non-Users	Total Exposed
7	243	115	358

Inhalation Exposure

EPA assessed inhalation exposures during manufacturing using identified monitoring data. Table 2-6 summarizes 8-hr and 12-hr TWA samples 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 *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b)

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 "high" confidence rating through EPA's systematic review process.

Table 2-6. 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	127	0.76	4.0	High
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	246	0.50	4.8	High
AC		0.50	4.8	
ADC		0.50	4.8	
LADC		0.069	0.83	

Equations and parameters for calculation of the ADC and LADC are described in supplemental document *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b).

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[8]; or (3) import the chemical and process or use the chemical directly at the site. In case #1, there is little or negligible opportunity for exposures or releases as the containers are never opened. In case #2, the potential for exposure and release is at the site receiving carbon tetrachloride, not the "import" site and exposures/releases at the site

[8] In CDR, the reporting site is the importer of record which may be a corporate site or other entity that facilitates the import of the chemical but never actually receives the chemical. Rather, the chemical is shipped directly to the site processing or using the chemical.

receiving carbon tetrachloride are assessed in the relevant scenario based on the condition of use for carbon tetrachloride at the site. Similarly, for case #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).

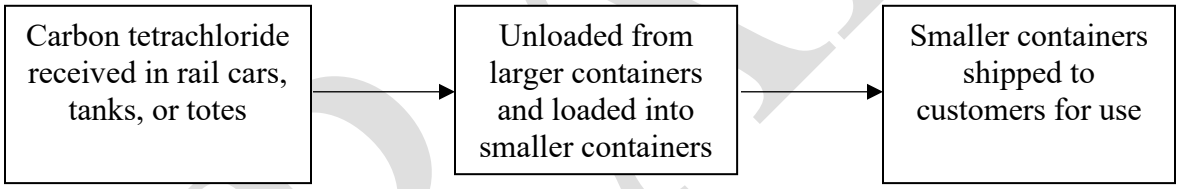


Figure 2-1. General Process Flow Diagram for Import and Repackaging

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, 2018f), 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, 2017h, 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 2-7) (U.S. BLS, 2016; U.S. Census Bureau, 2015).

Table 2-7. 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 did not identify any inhalation exposure monitoring data related to the repackaging of carbon tetrachloride. Therefore, EPA assessed inhalation exposures during repackaging using the 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 *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b).

EPA calculated 8-hr TWA exposures to workers during loading activities. The 8-hr TWA exposure is the weighted average exposure during an entire 8-hr shift, assuming zero exposures during the remainder of the shift.

presents a summary of the exposure modeling results. The model estimates a 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.

Table 2-8. Summary of Exposure Modeling Results for Import and Repackaging

Exposure Calculation	Central Tendency (mg/m^3)	High-End (mg/m^3)	Confidence Rating of Associated Air Concentration Data
Full-Shift TWA	0.057	0.30	N/A – Modeled Data
AC	0.057	0.30	
ADC	0.057	0.30	
LADC	0.0052	0.035	

2.4.1.7.3 Processing as a Reactant or Intermediate

Process Description

Processing as a reactant or intermediate is the use of carbon tetrachloride as a feedstock in the production of another chemical product via a chemical reaction in which carbon tetrachloride is consumed. 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, 2017h), 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. 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 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 911 workers and 429 ONUs (see Table 2-9).

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, 2017h; U.S. BLS, 2016).This resulted in an estimated 182 workers and 86 ONUs (see Table 2-9).

Table 2-9. Estimated Number of Workers Potentially Exposed to Carbon Tetrachloride During Processing as a Reactant

Number of Sites	Total Exposed Workers	Total Exposed Occupational Non-Users	Total Exposed
High-End			
30	911	429	1,340
Low-End			
6	182	86	268

Inhalation Exposure

EPA identified one source for inhalation exposure monitoring data related to the use of carbon tetrachloride as a reactant; however, the discrete sample values as well as the number of samples taken were not available to estimate exposure concentrations. 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 will be used to assess the inhalation exposure during the use of carbon tetrachloride as a reactant or intermediate.[9]

The manufacturing monitoring data were determined to have a "high" 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 that are the subject of the Agency's initial chemical risk evaluations. 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). These data are not distinguished among the three branches.

The following subsections provide an overview of the DoD data. EPA only used the Open Burn/Open detection (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

[9] Chlorinated hydrocarbon use means a process that produces one or more of the following products using chloroform, carbon tetrachloride, chlorinated paraffins, Hypalon®, oxybisphenoxarsine/1,3-diisocyanate, polycarbonate, polysulfide rubber, and symmetrical tetrachloropyridiene (Federal Register, Vol. 57, No. 252, December 31, 1992, 62765)

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 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 provided personal breathing zone samples for all of the DoD activities are summarized in Table 2-10. 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 2-10. 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	None Provided	Special Occasions	-	< 0.217	-	1	221	June 22, 2011

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
Torpedo Body								
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 2-11.

Table 2-11. 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 *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b).

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 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 2-12.

Table 2-12. 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 among 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, 2018g). 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 are listed below in Table 2-13.

Table 2-13. List of Approved Uses of Carbon Tetrachloride as a Process Agents 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

[1]EPA found no evidence to suggest that the manufacturing of ibuprofen, or any other pharmaceuticals, still utilizes carbon tetrachloride or that such use is reasonably foreseen to resume. Accordingly, EPA no longer considers use as a process agent in the manufacturing of pharmaceuticals to be a condition of use of carbon tetrachloride and does not evaluate it in this draft risk evaluation. See section 1.4.2.2

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 (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 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

Using 2016 CDR data and 2017 TRI data, EPA confirmed three sites that use carbon tetrachloride as a processing agent/aid.

To determine the total number of workers and ONUs, EPA used the average worker and ONUs estimates from the BLS analysis based on their NAICS codes (U.S. BLS, 2016). This resulted in an estimated 67 workers and 32 ONUs (see Table 2-14).

Table 2-14. 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
3	67	32	99

Inhalation Exposure

EPA did not find any exposure monitoring data for use of carbon tetrachloride as a processing agent/aid; therefore, exposures were assessed with the Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model.

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 carbon tetrachloride as a processing agent/aid is estimated by the Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model used 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, 2018f). 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 2-15).

Table 2-15. 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 use of carbon tetrachloride as an additive were assessed with the *Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model*.

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 the use of carbon tetrachloride as an additive is estimated by the Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model used in the import/repackaging scenario.

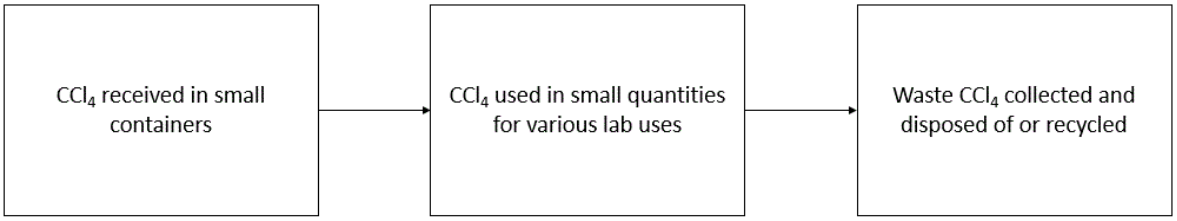
2.4.1.7.8 Laboratory Chemicals

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.



CCl_4 = carbon tetrachloride

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, 2018f, 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 87 exposed workers and ONUs (see Table 2-16).

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 2-16).

Table 2-16. 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	9	78	87
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 § 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 §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 § 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 § 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, f). See Figure 2-3 for a general depiction of the waste disposal process.

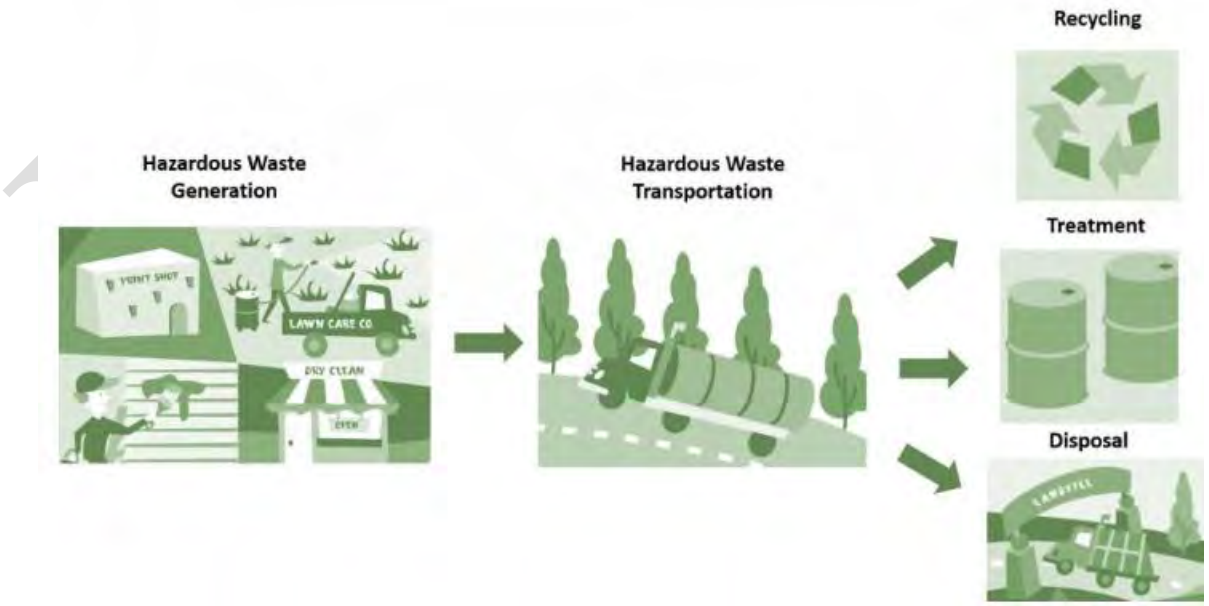


Figure 2-3. Typical Waste Disposal Process
Source: (U.S. EPA, 2017c)

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, 2018f, 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 125 workers and 63 ONUs potentially exposed at sites using carbon tetrachloride as a processing agent/aid (see Table 2-17).

Table 2-17. 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	125	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 the *Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model*. The following subsections detail the results of EPA's occupational exposure assessment for waste handling are based on modeling.

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 the disposal of carbon tetrachloride is estimated by the Tank Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model used in the import/repackaging scenario.

2.4.1.7.10 Summary of Occupational Inhalation Exposure Assessment

Table 2-18 presents the occupational exposure assessment summary for the conditions of use described by the previous sections of this draft 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 *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b).

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 2-19.

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Table 2-18. Summary of Occupational Inhalation Exposure Assessment for Workers

Condition of Use	8-Hour or 12-Hour TWA Exposures		Acute Exposures		Chronic, Non-Cancer Exposures		Chronic, Cancer Exposures		TWA Data Points	Data Type
	8 or 12-hr TWA (mg/m^3)		AC TWA (mg/m^3)		ADC TWA (mg/m^3)		LADC TWA (mg/m3)			
	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency		
Manufacturing - 8-hr TWA	4.0	0.76	4.0	0.76	4.0	0.76	0.47	0.069	127	Monitoring Data
Manufacturing - 12-hr TWA	4.8	0.50	4.8	0.50	4.8	0.50	0.83	0.069	246	Monitoring Data
Import/Repackaging	0.30	0.057	0.30	0.057	0.30	0.057	0.035	0.0052	N/A	Model
Processing as Reactant/Intermediate – 8-hr TWA	4.0	0.76	4.0	0.76	4.0	0.76	0.47	0.069	127	Surrogate Monitoring Data
Processing as Reactant/Intermediate - 12-hr TWA	4.8	0.50	4.8	0.50	4.8	0.50	0.83	0.069	246	Surrogate Monitoring Data
Specialty Uses - Department of Defense Data	0.37	0.18	0.37	0.18	0.22	0.092	0.026	0.0083	3	Monitoring Data
Reactive Ion Etching	Negligible - Highly controlled work areas with small quantities applied									
Industrial Processing Aid	0.30	0.057	0.30	0.057	0.30	0.057	0.035	0.0052	N/A	Model
Additive	0.30	0.057	0.30	0.057	0.30	0.057	0.035	0.0052	N/A	Model
Laboratory Chemicals	No data – exposure is low as laboratory typically uses small quantities on a lab bench under a fume cupboard or hood.									
Waste Handling	0.30	0.057	0.30	0.057	0.30	0.057	0.035	0.0052	N/A	Model

2881 **Table 2-19. Summary and Ranking of Occupational Exposure of Carbon Tetrachloride for Various Conditions of Use**

Occupational Exposure Scenario	Strength	Challenge	Inhalation Exposure						Representativeness	Dermal Exposure Modeling[a]		Overall Rating for Workers[b]
			Monitoring				Modeling			Worker	ONU	
			Data (#)	Surrogate	Worker	ONU	Worker	ONU				
Manufacturing	PBZ sampling High data quality	Data is provided from one source	✓ (373)	✗	✓	✗	✗	✗	Routine monitoring data available for work environment	✓	—	Higher Lower
	Source of information available directly from manufacturer CDR provided employee counts for specific manufacturing site Data from multiple facilities	Many data points were at or below the limit of detection										
Import and Repackaging	CDR provided employee counts for specific Import and Repackaging sites	No Monitoring Data EPA models are not specific to Import and Repackaging	✗	✗	✗	✗	✓	✗	Assesses exposure based on loading and unloading only. Assumes controlled and closed systems for all other operations.	✓	—	Higher Lower
	Model uses published EPA emission factors	Relies on process and protection assumptions May underestimate worker exposure										
Processing as a Reactant or Intermediate	PBZ sampling 415 data points	No monitoring data for this CoU; Surrogate data from manufacturing	✗	✓ (373)	✓	✗	✓	✗	Routine monitoring data available for work environment	✓	—	Higher

Occupational Exposure Scenario	Strength	Challenge	Inhalation Exposure						Representativeness	Dermal Exposure Modeling[a]		Overall Rating for Workers[b]
			Monitoring				Modeling			Worker	ONU	
			Data (#)	Surrogate	Worker	ONU	Worker	ONU				
	Source of information available directly from manufacturer	Data is provided from one source										Lower
	CDR provided employee counts for specific manufacturing site	Many data points were at or below the limit of detection										
	Data from multiple facilities											
Specialty Uses (Department of Defense)	PBZ sampling	All data points are at or below the limit of detection	✓ (3)	✗	✓	✗	✗	✗	Routine monitoring data available for work environment	✓	—	Higher  Lower
		Only 3 data points										
Industrial Processing Agent/Aid	CDR provided employee counts for specific industrial processing agent/aid sites	No Monitoring Data	✗	✗	✗	✗	✓	✗	Assesses exposure based on loading and unloading only. Assumes controlled and closed systems for all other operations.	✓	—	Higher  Lower
		EPA models are not specific to use as Industrial Processing Agent/Aid										
	Model uses published EPA emission factors	Relies on process and protection assumptions										
		May underestimate worker exposure										

Occupational Exposure Scenario	Strength	Challenge	Inhalation Exposure						Representativeness	Dermal Exposure Modeling[a]		Overall Rating for Workers[b]
			Monitoring				Modeling			Worker	ONU	
			Data (#)	Surrogate	Worker	ONU	Worker	ONU				
Additive	CDR provided employee counts for specific additive sites	No Monitoring Data	✗	✗	✗	✗	✓	✗	Assesses exposure based on loading and unloading only. Assumes controlled and closed systems for all other operations.	✓	—	Higher / Lower
		EPA models are not specific to use as an additive										
	Model uses published EPA emission factors	Relies on process and protection assumptions										
Disposal / Recycling	CDR provided employee counts for specific disposal/recycling sites	No Monitoring Data	✗	✗	✗	✗	✓	✗	Assesses exposure based on loading and unloading only. Assumes controlled and closed systems for all other operations.	✓	—	Higher / Lower
		EPA models are not specific to disposal/recycling										
	Model uses published EPA emission factors	Relies on process and protection assumptions										

[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 Appendix E of the document *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b).

Table 2-20 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 work day 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 are expected to come into contact with bulk liquid carbon tetrachloride during use in open systems (e.g., during solvent changeout in vapor degreasing and dry cleaning) and 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 *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b). 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 in a dilute form, there will be relatively slow uptake. If the worker is wearing a glove 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 2-20 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 2-20. Estimated Dermal Acute and Chronic Retained Doses for Workers for All Conditions of Use[10]

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-day)	CRD (mg/kg-day)	CRD (mg/kg-day)
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 problem formulation 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.

2.4.3 General Population Exposures

As explained in sections 1 and 2.5 of the problem formulation document (U.S. EPA, 2018d), EPA is not including in this draft risk evaluation exposure pathways under programs of other environmental statutes, administered by EPA, which adequately assess and effectively manage exposures and for which long-standing regulatory and analytical processes already exist. Therefore, based on information obtained by EPA and presented in section 2.5.3.2 of the problem formulation document (U.S. EPA, 2018d), 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, SDWA, and CAA).

[10] Calculation are described in Appendix E of *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b).

Because there are no other exposure pathways impacting the general population, EPA did not analyze general population exposures in the risk evaluation for carbon tetrachloride.

2.5 Other Exposure Considerations

2.5.1 Potentially Exposed or Susceptible Subpopulations

TSCA § 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 § 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 draft 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 draft 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 2605(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 to a single chemical substance that represents the plausible upper bound 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 section 2.5.3.1. of the problem formulation document) (U.S. EPA, 2018d). EPA identified the following sources of environmental hazard data for carbon tetrachloride: ECHA (2017), OECD SIDS Initial Assessment Profile (SIAP) (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, 2018e). Since only studies with data quality evaluation results of 'high' and 'medium' quality ratings were available to characterize the environmental hazards, no studies with 'low" 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, 61 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 14 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, 2019e). Relevant test data from the screened literature are summarized in 7Appendix G 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 statues administered by EPA, which adequately assess and effectively manage such exposures (e.g., RCRA and CAA). Thus, environmental hazard data sources on terrestrial organisms and on metabolic endpoints were considered out of scope and excluded from data quality evaluation.

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, 2018d). 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 of aquatic organisms in this draft risk evaluation. The derived acute COC (62 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. Further details about the environmental hazards of carbon tetrachloride are available in Appendix G.

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.

Overall Confidence in COCs

After evaluating all available carbon tetrachloride test data, 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 draft.

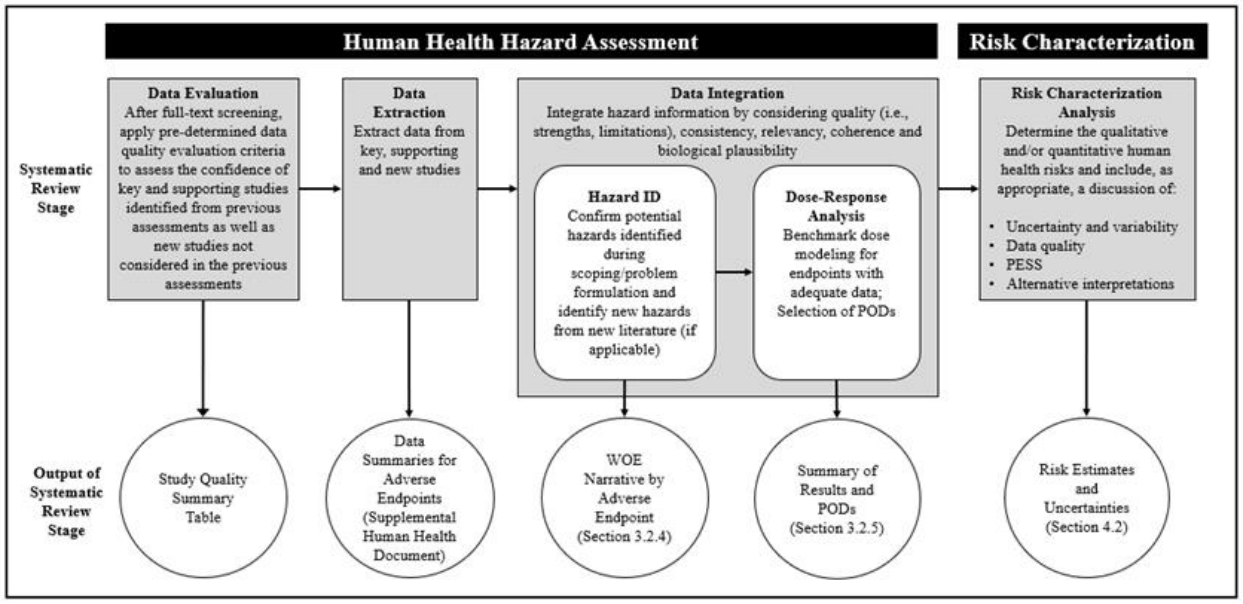

Figure 3-1. Hazard Identification and Dose-Response Process

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 (2010), the ATSDR Toxicological Profile (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 data extraction (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 draft. In data integration (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 that was rated unacceptable was considered in the risk evaluation under a weight of evidence approach, when necessary to fulfill data gaps. Information on human health hazard endpoints for all acceptable studies (with high, medium or low scores) evaluated is presented in Appendix H.

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 draft risk evaluation can be found in Appendix H, 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 value, or a lowest-observed-adverse-effect level (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 I.

The dose-response assessment used for selection of PODs for cancer and non-cancer endpoints and the benchmark dose analysis used in the draft risk evaluation are found in section 3.2.5. Development of the carbon tetrachloride hazard and dose-response assessments considered principles set forth in various risk assessment guidances/guidelines issued by the National Research Council and the EPA.

Given that the inhalation and dermal routes of exposure are the routes of concern for this risk evaluation, studies conducted via these routes of exposure were considered for POD derivation in this assessment. Nevertheless, oral exposure data are presented herein below for weight of evidence support in the selection of hazard endpoints and PODs. No acceptable toxicological data are available 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 EPA's 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 3.2.5.1 and 3.2.4.1.1).

A summary table which includes all endpoints considered for this assessment, the no-observed- or lowest-observed-adverse-effect levels (NOAEL and LOAEL) for health endpoints by target organ/system and the results of the data evaluation is provided in Appendix H. 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 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. 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.

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. 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 (i.e., anaerobic dimerization to form hexachloroethane, aerobic trapping by oxygen to form a trichloromethyl peroxy radical).

3.2.3 Hazard Identification

3.2.3.1 Non-Cancer Hazards

For non-cancer hazard characterization, EPA reviewed the reasonably available information on acute, subchronic, and chronic exposure to carbon tetrachloride via the inhalation, dermal and oral routes and evaluated the identified hazard endpoints. Studies were evaluated according to

the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a, b). The results of the data quality evaluation for the non-cancer studies are described here and included in the data extraction summary table in Appendix H.

Toxicity Following Acute Exposure

Overall, the database evaluating the acute toxicity of carbon tetrachloride is limited to numerous case reports on acute inhalation exposure of humans to carbon tetrachloride, most without adequate exposure characterization, in addition to a small number of animal studies. Human case reports following acute exposures identify liver as a primary target organ of toxicity and the kidney as an additional primary target organ of toxicity. Neurotoxicity indicated as central nervous system (CNS) depression is another primary effect of carbon tetrachloride in humans following acute exposures, with examples of neurotoxic effects including drowsiness, headache, dizziness, weakness, coma and seizures. Gastrointestinal symptoms such as nausea and vomiting, diarrhea and abdominal pain are considered another initial acute effect (U.S. EPA, 2010; ATSDR, 2005). Unmetabolized carbon tetrachloride is expected to depress the CNS, while most other toxic effects of carbon tetrachloride are related to its biotransformation products catalyzed by CYP-450 enzymes (ATSDR, 2005).

The National Advisory Committee for Acute Exposure Guideline Levels for hazardous substances (NAC/AEGL) (NRC, 2014) describe case reports of human fatalities resulting from acute exposure to carbon tetrachloride, which provide a clinical picture of dizziness, nausea, abdominal pain, oliguria, anuria, and death being attributed to renal failure and hepatotoxicity. NAC/AEGL has concluded that although data on lethality in humans following acute exposures to carbon tetrachloride are available, exposure concentration and duration information are lacking.

Hazard Effects from Acute Inhalation Exposures – Human Data

The EPA IRIS Assessment (U.S. EPA, 2010) concluded that the CNS depression is an immediate effect in acute toxicity studies in animals exposed by inhalation to relatively high concentrations of carbon tetrachloride.

Similar conclusions were reached by NAC/AEGL (NRC, 2014) based on human data. NAC/AEGL developed acute exposure guideline levels-2 (AEGL-2) (NRC, 2014) for carbon tetrachloride based on CNS effects observed in humans. AEGL-2 values are defined as the airborne concentrations of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.[11]

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

[11] Similarly, AEGL-3 values (i.e., airborne concentration above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death) were also developed on a 1-h LC_{01} (lethal concentration, 1% lethality) of 5,135.5 ppm on the basis of data from multiple studies in laboratory rats. AEGL-1 concentration values for notable discomfort, irritation, or certain asymptomatic, non-sensory (non-disabling, transient) effects were not established for carbon tetrachloride.

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 (Davis, 1934). 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, 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 end point (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 (Davis, 1934). 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.

Hazard Effects from Acute Inhalation and Oral Exposures – Animal Data

IRIS, ATSDR and AEGL have identified and evaluated a small number of available acute animal studies for carbon tetrachloride. Systematic review for this risk evaluation found that two of the main acute animal studies in those previous hazard assessments have unacceptable data quality: Hayes et al., (1986) acute study, which has an ECHA reliability = 4 and Adams et al., (1952) acute study (ECHA reliability score not available). Nevertheless, the EPA IRIS Assessment (U.S. EPA, 2010) and ATSDR profile (ATSDR, 2005) provide a weight of evidence evaluation on the effects observed in animal studies after acute oral and inhalation exposure to carbon tetrachloride. In animals acutely exposed to carbon tetrachloride, the liver appears to be the primary target organ; damage to the kidney occurs at slightly higher doses. Hepatic toxicity is frequently demonstrated by significant increases in serum enzyme activities that peak between 24 and 48 hours after dosing (U.S. EPA, 2010). Similarly, ATSDR (2005) evaluated the acute toxicity database for carbon tetrachloride and determined that hepatotoxicity appeared to be the critical effect from acute duration exposure. However, ATSDR (2005) did not derive an MRL for acute-duration inhalation exposure to carbon tetrachloride due in part to data limitations. A more recent and comprehensive review of both acute epidemiological data and animal studies by NAC/AEGL (NRC, 2014) concluded that animal inhalation toxicity data for carbon tetrachloride affirm hepatotoxic and renal effects, as well as anesthetic-like effects, as primary end points; and that findings from animal studies are consistent with those associated with human exposures.

In addition to acute toxicity data evaluated by IRIS, AEGL and ATSDR, the systematic review identified an additional study evaluating liver toxicity of carbon tetrachloride after single dose administration with high overall quality based on the quality criteria in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). In this additional 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 (Sun et al., 2014).

Table 3-1 and Table 3-2 present a summary of acute toxicity studies in humans by the inhalation route and in rats by the oral route of exposure, which are either a critical study identified for establishing AEGL values or a study published after the completion of the IRIS assessment (U.S. EPA, 2010) and NAC/AEGL (NRC, 2014).

Table 3-1. Acute Inhalation Toxicity Study in Humans (Critical Study for NAC/AEGL-2 Values)

Subjects	Exposure Route	Doses/ Concentrations	Duration	Effect Dose	Effect	Reference	Data Quality Evaluation
Four subjects (ages 35, 48, 22, and 30; gender not specified)	Inhalation	76 ppm	2.5 hrs, 4 hrs	NOAEC = 76 ppm	No CNS symptoms or signs of toxicity	(Davis, 1934)	low; basis for AEGL-2

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

Table 3-2. Acute Toxicity Oral study in Sprague-Dawley Rats with Acceptable Data Quality Not Evaluated in Previous Hazard Assessments for Carbon Tetrachloride

Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Effect Dose	Effect	Reference	Data Quality Evaluation
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 hrs 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

Hazard Effects from Oral and Inhalation Exposures During Gestation

Developmental effects from carbon tetrachloride exposures are more extensively studied by the oral route than any other route of exposure. The lowest adverse effect level for developmental hazards from oral exposures was identified in the EPA IRIS Assessment (U.S. EPA, 2010) in Narotsky (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-day 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-day for both vehicles but was seen in more animals and for longer periods in the corn oil groups. Dams exposed to 75 mg/kg-day in corn oil also exhibited kyphosis (rounded upper back) and statistically significant weight loss. Dams exposed to 50 and 75 mg/kg-day 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-day dose was a NOAEL for developmental and maternal toxicity and the 50 mg/kg-day dose a LOAEL for full-litter resorption and maternal toxicity (i.e., reduced maternal weight gain, piloerection) with either corn oil or aqueous vehicle, although these effects were more pronounced with the corn oil vehicle. EPA (2010) noted that the NOAEL in this developmental study (25 mg/kg-day) exceeds the POD for the RfD based on liver effects by over 6-fold and the LOAEL (50 mg/kg-day) by 13-fold and is consistent with developmental toxicity endpoints as less sensitive than measures of hepatotoxicity.

The IRIS assessment identified Schwetz et al. (1974) (data quality rating = high) as the most detailed inhalation exposure developmental toxicity study available. In the Schwetz et al. (1974) study, groups of pregnant Sprague-Dawley 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).

The systematic review process for this risk evaluation did not identify additional developmental toxicity data by the inhalation or oral routes for carbon tetrachloride. Table 3-3 presents the developmental toxicity studies with acceptable data quality.

Table 3-3. Developmental Toxicity Studies in Fisher 344 and Sprague-Dawley Rats with Acceptable Data Quality

Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Effect Dose	Effect	Reference	Data Quality Evaluation
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

Subchronic and Chronic Hazards from Inhalation and Oral Exposures

Consistent with human data, toxicity assays in animals exposed orally or by inhalation of sub-chronic or chronic duration identify the liver as the major target organ. While the liver appears to be the primary target organ from exposure to carbon tetrachloride by both the oral and inhalation routes, the kidney is also a target organ for carbon tetrachloride exposure.

All the key and supporting inhalation and oral studies in the EPA IRIS Assessment (U.S. EPA, 2010) were rated acceptable with low, medium or high overall quality data using the quality criteria in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). Those acceptable studies are briefly described in this section and Appendix H. The systematic review process for this risk evaluation did not identify additional subchronic and chronic toxicity data for carbon tetrachloride.

Inhalation

The IRIS assessment concluded that the liver and kidney are the most prominent targets of carbon tetrachloride in subchronic and chronic inhalation toxicity studies in animals. Renal

damage was reported less frequently in these animal studies and generally at higher concentrations than those causing liver damage. The key and supporting subchronic and chronic inhalation studies in the IRIS assessment are summarized below.

The IRIS RfC is based on the findings from bioassays conducted by Nagano (2007a) (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 (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 end points 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 (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 LAP (leucine aminopeptidase) 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 ≥ 90ppm 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/m3) 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 (fatty change, fibrosis, 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 (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 25ppm concentration was a LOAEC in this study for effects on the liver (increased weight, serum chemistry changes indicative of damage, and lesions), kidney (serum chemistry changes and lesions), and spleen (lesions); decreased growth; and reduced survival. The 5-ppm level was a NOAEC.

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 3-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 is 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 BrdU (bromodeoxyuridine) 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 2-fold between the three species. A NOAEC of 5ppm and a LOAEC of 20 ppm for hepatotoxicity was identified for mice. Hamsters and rats were less sensitive than mice, with NOAEC of 20 ppm and LOAEC of 100 ppm, respectively.

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 increase in liver weight and mild liver changes (mild fatty degeneration and(in) by histological examinations, 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.

Table 3-4 presents a summary of subchronic and chronic inhalation studies in various experimental animal species for carbon tetrachloride with acceptable data quality.

3564
3565 **Table 3-4. Subchronic and Chronic Inhalation Studies in Various Experimental Animal**
3566 **Species with Acceptable (High, Medium or Low) Data Quality**

Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Effect Dose	Effect	Reference	Data Quality Evaluation
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)	(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
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

Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Effect Dose	Effect	Reference	Data Quality Evaluation
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

Oral

U.S. EPA (2010) identifies the following subchronic oral gavage studies as supporting studies in 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. Consistent with human data, toxicity assays in animals (i.e., rats, mice) exposed orally identify the liver to be the major target organ, with oral NOAELs between 0.71 and 0.86 mg/kg. Subchronic oral studies that also examined non-hepatic endpoints (Bruckner et al., 1986; Hayes et al., 1986) did not observe effects in the kidneys or other organs. These studies are summarized below as follows.

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-day) for 12 weeks. Body weight gain in this group 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-day) liver enzymes including ALT (up to 34 times control levels), SDH (up to 50 times control levels), and 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-day only a significant (two- to threefold) 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-day. This study identified a NOAEL of 0.71 mg/kg-day and a LOAEL of 7.1 mg/kg-day for carbon tetrachloride-induced liver toxicity.

A subchronic study conducted by Condie (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-day) (Condie et al., 1986). 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-day) 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-day 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-day. 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-day 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.

A subchronic study in mice was conducted at higher doses by Hayes (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-day of carbon tetrachloride in corn oil for 90 days (Hayes et al., 1986). 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-day group). This study failed to identify a NOAEL; the low dose of 12 mg/kg-day was a LOAEL for hepatic effects.

Allis (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-day) 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 postexposure period, but cirrhosis persisted in the high-

dose group through the end of the experiment. Relative liver weight decreased during the postexposure 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-day was a LOAEL for hepatic toxicity in this study. Table 3-5 presents the subchronic oral toxicity studies with acceptable data quality.

Table 3-5. Subchronic Oral Toxicity Studies in Rats and Mice with Acceptable Quality Data

Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Effect Dose	Effect	Reference	Data Quality Evaluation
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
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
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

Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Effect Dose	Effect	Reference	Data Quality Evaluation
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

Hazard Effects from Dermal Exposures

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).

The limited number of animal studies by the dermal route, which have been cited in the previous assessments for carbon tetrachloride (see Table 1-3) were found to be acceptable with low, medium or high overall quality data based on the quality criteria in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). Those acceptable studies are briefly described in Appendix H. The systematic review process for this risk evaluation did not identify additional dermal toxicity data for carbon tetrachloride.

Among the few dermal studies, Kronevi (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. In this study, guinea pigs weighing 440 and 570 g were dermally exposed to a single application of 1 mL of carbon tetrachloride in a 3.1 cm^2 skin depot (513 mg/cm^2)[12] for 15 minutes, 1 hour, 4 hours, or 16 hours. Changes in liver morphology were observed from carbon tetrachloride exposure only in the 16 hour exposure group. At 16 hours, the study authors reported marked hydropic changes in the central two-thirds of each lobule of hepatocytes. These changes were characterized by large clear cytoplasmic spaces. There also was a tendency to necrotic lesions characterized by homogenous, slightly eosinophilic, and slightly PAS-positive structures within the cytoplasm of most of these hepatocytes. The glycogen was absent all over the specimens and the nuclei showed a tendency to degeneration. Animals exposed to the same dose levels of carbon tetrachloride for 15 minutes, 1 hr or 4 hr did not show liver morphology alterations.[13]

[12] This exposure concentration is reported in the ATSDR profile for carbon tetrachloride. The concentration estimate is based on a density value of 1.59 g/mL for carbon tetrachloride.

[13] The study authors reported marked hydropic changes in the central two-thirds of each lobule of hepatocytes. These changes were characterized by large clear cytoplasmic spaces. There also was a tendency to necrotic lesions characterized by homogenous, slightly eosinophilic, and slightly PAS-positive structures within the cytoplasm of most of these hepatocytes. The glycogen was absent all over the specimens and the nuclei showed a tendency to degeneration.

There were no reported kidney changes from dermal exposures to carbon tetrachloride in this study.

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.

Besides the few animal studies with dermal exposures, information on the toxicity of carbon tetrachloride following dermal exposure is mostly based on anecdotal evidence. For instance, the IRIS assessment describes one case report of carbon tetrachloride- induced toxicity that can at least partially be attributed to absorption across the skin (Farrell and Senseman, 1944). The worker was exposed 8 hours/day by using a fine spray of carbon tetrachloride to saturate a cloth wrapped around the fingers. Although some exposure is likely to have occurred by inhalation, absorption through the skin of the hands was considered as the primary route of exposure. After an unspecified period of time at this job, the worker showed weakness, pain in the limbs, and loss or reduction of certain reflexes. The patient lost 8 pounds in the month between onset of illness and hospitalization. The signs and symptoms of neurotoxicity reversed after several months without exposure.

presents acute toxicity dermal studies in guinea pigs with experimental observations in liver toxicity and/or toxicity progression over time.

Table 3-6. Acute Toxicity Dermal Studies in Guinea Pigs with Observations on Liver Toxicity and/or Toxicity Progression Over Time

Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations*	Duration	Effect Dose	Effect	Reference	Data Quality Evaluation
Guinea pig, albino (n=20, gender not specified)	Dermal	1 mL	15 minutes to 16 hours	LOAEL = 513 mg/ cm^2 (1 mL)	Hydropic changes, slight necrosis at 16 hrs exposure	(Kronevi et al., 1979)	Unacceptable (i.e., lack of negative controls and small number of animals)
Guinea pig (n=20, gender not specified)	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 day1 at 2.0 ml)	(Wahlberg and Boman, 1979)	Medium

*As reported by study authors: mL of highly pure carbon tetrachloride solution.

3.2.3.2 Epidemiological Data on Non-Cancer Toxicity

Epidemiological data on non-cancer effects of carbon tetrachloride published prior to 2010 have been evaluated in previous assessments (see Table 1-3). For instance, the occupational study by

Tomenson et al., (1995) (data quality = medium) was considered by EPA IRIS as the basis for the RfC derivation. The study was not selected as the basis for the RfC because exposures for almost two-thirds of the workers were estimated, so that there is some uncertainty in the study NOAEL and LOAEL values.

Tomenson et al., (1995) conducted a cross-sectional study of hepatic function in 135 carbon tetrachloride-exposed workers in three chemical plants in northwest England and in a control group of 276 unexposed workers. The exposure assessment was based on historical personal monitoring data for various jobs at the three plants. Subjects were placed into one of three exposure categories—low (≤1 ppm), medium (1.1–3.9 ppm), or high (≥4 ppm)—according to their current jobs. Overall, this study suggests an effect of occupational carbon tetrachloride exposure on the liver at exposures in the range of >1–3.9 ppm (6.3–24.5 mg/m^3); this exposure range is considered a LOAEL. The low exposure category in this study (≤1 ppm or ≤6.3 mg/m^3) is a NOAEL.

Table 3-7presents human epidemiological studies published on or after 2010 that have acceptable data quality according to the systematic review for this risk evaluation. As shown in the table, the studies do not suggest significant association between carbon tetrachloride exposure and Parkinson's Disease or autism.

Table 3-7. Acceptable Epidemiological Studies for Non-Cancer Toxicity of Carbon Tetrachloride Not Evaluated in Previously Published Hazard 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 positive, non-significant association was observed between Parkinson Disease and exposure to carbon tetrachloride	(Goldman et al., 2012)	High
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

3.2.3.3 Genotoxicity and Cancer Hazards

3.2.3.3.1 Genotoxicity

A substantial body of publications have studied genotoxic effects of carbon tetrachloride as documented in the EPA IRIS Toxicological Review of carbon tetrachloride (U.S. EPA, 2010). The results of this review, as further supported in data summaries provided in Appendix KAppendix I indicate:

- 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. The presence of cellular toxicity in a number of studies, complicates the evaluation of the database.

- Lipid peroxidation products generate compounds (e.g., reactive aldehydes) that may covalently bind to DNA.
- Measurement of genetic damage to DNA has not been well characterized at or below doses at which tumors are observed.

The systematic review did not identify additional genetic toxicity studies with carbon tetrachloride rated of medium or high overall quality based on the quality criteria in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). The *in vitro* and *in vivo* genotoxicity databases for carbon tetrachloride, including their limitations are described in Appendix I.

3.2.3.3.2 Carcinogenicity

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) inadequate evidence of carcinogenicity in humans and (2) sufficient evidence in animals by oral and inhalation exposure, i.e., hepatic tumors in multiple species (rat, mouse, and hamster) and pheochromocytomas (adrenal gland tumors) in mice."

Epidemiological Data on Carcinogenicity

The 2010 EPA IRIS assessment concluded that the evidence in humans was inadequate to show an association between exposure to carbon tetrachloride and carcinogenicity. There was some limited evidence for certain types of cancer in occupational populations thought to have had some exposure to carbon tetrachloride, including non-Hodgkin's lymphoma, lymphosarcoma and lymphatic leukemia, esophageal and cervical cancer, breast cancer, astrocytic brain cancer, and rectal cancer (U.S. EPA, 2010).

Table 3-8 presents epidemiological studies published after completion of the EPA IRIS assessment that have been found to be of acceptable data quality in the systematic review for this risk evaluation. Among the 11 studies, 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, and four studies of cancers of the nervous system.

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. However, four of these newer studies report results for cancers of the nervous system – as did one study from the IRIS assessment (Heineman et al., 1994). Three of these were specific to astrocytic brain tumors which include astrocytoma, glioma, and glioblastoma and occur in adults. The fourth was a study of neuroblastoma – a childhood cancer of the nervous system.

Table 3-8. Acceptable Epidemiological Studies for Cancer Toxicity of Carbon Tetrachloride Not evaluated in EPA IRIS Assessment

Cancer Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Brain (Neuroblastoma)	Children (75 cases, 14602 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
Brain (Glioblastoma)	8,006 men of Japanese descent from the Honolulu Heart Program (HHP) and Honolulu-Asia Aging Study (HAAS) cohorts, aged 45-68 at initial examination (1965-1968) and followed through 1998. 9 glioblastoma cases.	Usual occupation with no, low-medium, or high exposure to carbon tetrachloride, based on professional judgement; no quantification of exposure available.	Rate ratio of exposed vs unexposed was 10.09 (p=0.012). A positive, statistically significant association was found between glioblastoma and high occupational exposure vs. no exposure to carbon tetrachloride (OR=26.59; 95% CI: 2.9, 243.50).	(Nelson et al., 2012)	Medium
Brain (Glioma)	489 glioma cases, 197 meningioma cases, and 799 controls from three USA hospitals in Arizona, Massachusetts and Pennsylvania.	Occupational exposure to carbon tetrachloride via self-reported occupational history and industrial hygienist assigned level of exposure.	Carbon tetrachloride was associated with a significant increase in risk of gliomas with higher average weekly exposure (OR=7.1; 95% CI: 1.1, 45.2; p-value = 0.04) and when further controlling for lead and magnetic fields (OR=60.2; 95% CI: 2.4, 1533.8).	(Neta et al., 2012)	High
Brain (Glioma)	Non-farm workers from the Upper Midwest Health Study (798 cases and 1141 controls from Iowa, Michigan, Minnesota, and Wisconsin 1995-1997).	Carbon tetrachloride use (self-reported occupational history through 1992, using a bibliographic database of published exposure). Of 798 glioma cases, 360 interviews were conducted with proxies because the cases were deceased.	Excluding proxy-only interviews: 'Ever' vs. 'never' having carbon tetrachloride exposure was not associated with a risk of glioma (OR=0.82; 95% CI: 0.64, 1.06) and cumulative exposure was associated with decreased risk of gliomas per ppm-year with borderline significance (OR=0.98; 95% CI: 0.96, 1.00). Including proxy-only interviews: 'Ever' vs. 'never' having carbon tetrachloride exposure was significantly associated with a decreased risk of glioma (OR=0.79; 95% CI: 0.65, 0.97) and cumulative exposure was associated with a small but significant decrease in risk of gliomas per ppm-year (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. Significant trend across quintiles.	(Garcia et al., 2015)	High

Cancer Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Head/Neck	Case-control, women only, 296 cases, 775 controls, diagnosed 2001-2007, general population, 18-85 years, subset of ICARE cohort	Carbon tetrachloride, exposure qualitatively stated as ever (job with likely exposure >1month) or never	No significant association between carbon tetrachloride and head/neck cancers	(Carton et al., 2017)	Medium
Kidney	General population case-control study of kidney cancer (1217 cases; 1235 controls). Detroit (2002 - 2007) and Chicago (2003).	Job exposure matrix was used to determine years exposed, average weekly exposure and cumulative hours exposed. to carbon tetrachloride	No significant associations observed between exposure to carbon tetrachloride and kidney cancer.	(Purdue et al., 2016)	High
Lymphohematopoietic (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 hours/week) by the number of years worked in each exposed job.	Primary analysis: non-significant increase 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, a non-significant increased risk of multiple myeloma was observed in individuals ever 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).	(Gold et al., 2010)	High
Lymphohematopoietic (Mycosis Fungoides)	100 patients with Mycosis Fungoides and 2846 controls, 35-69 years of age, from Denmark, Sweden, France, Germany, Italy, and Spain, 1995-1997.	Occupational exposure to carbon tetrachloride assessed with job exposure matrix.	A positive, non-significant association was observed between Mycosis Fungoides and subjects with exposure to carbon tetrachloride >= median of control exposure vs. unexposed subjects	(Morales-Suárez-Varela et al., 2013)	High
Lung	Investigation of occupational and environmental causes or 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 self-reported 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.	(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 self-reported job histories.	Increase in OR for any exposure to carbon tetrachloride in Study II only; significant increased OR for substantial exposure in Study II and pooled analysis	(Vizcaya et al., 2013)	Medium

Animal Data on Carcinogenicity

The EPA IRIS assessment concludes that carbon tetrachloride has been shown to be a liver carcinogen in rats, mice, and hamsters in eight bioassays of various experimental design by oral

and inhalation exposure. Carbon tetrachloride has also been shown to induce pheochromocytomas in mice by oral and inhalation exposure. Information on the carcinogenic effects of carbon tetrachloride via the dermal route in humans and animals is limited or absent.

The IRIS assessment (U.S. EPA, 2010) identifies the (Nagano et al., 2007a) bioassay of carbon tetrachloride by the inhalation route described in section 3.2.3.1 (data quality = high) as a bioassay that provides data adequate for dose-response modeling. In this bioassay, 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.

Tumor incidence data for rats in the 104-week inhalation study in F344/DCR rats described above are presented in Table 3-9 (Nagano et al., 2007a). The incidence of hepatocellular adenomas and carcinomas was statistically significantly increased in male and female rats at 125 ppm. The incidence of hepatocellular carcinomas 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 incidences of liver tumors in control mice (18% in males and 4% in females for hepatocellular adenomas and 34% in males and 4% in females for hepatocellular carcinomas) were similar to historical control data for liver tumors in Crj:BDF1 mice in 20 studies at JBRC. The gender differences in unexposed mice are thought to be related to inhibition of liver tumor formation by female estrogen levels. 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 incidence of benign adrenal pheochromocytomas was significantly increased in males at 25 or 125 ppm and females at 125 ppm.

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]

	Male				Female			
Tumor	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]	32/50[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)

The systematic review did not identify additional cancer studies with carbon tetrachloride with acceptable data quality based on the quality criteria in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a).

3.2.4 Weight of Scientific Evidence

The following sections describe the weight of the scientific evidence for both non-cancer and cancer hazard endpoints. Factors considered in weighing the scientific evidence included consistency and coherence among human and animal studies, quality of the studies (such as whether studies exhibited design flaws that made them unacceptable) and biological plausibility. Relevance of data was considered primarily during the screening process but may also have been considered when weighing the evidence.

3.2.4.1 Non-Cancer Hazards

The following sections consider and describe the weight of the scientific evidence of health hazard domains discussed in section 3.2.3.1. These domains include: toxicity from acute exposure; liver effects; nervous system effects; kidney effects; and reproductive and developmental effects.

3.2.4.1.1 Acute Toxicity

EPA is basing the evidence integration for the acute toxicity of carbon tetrachloride on the conclusions of the AEGL program. NAC/AEGL evaluated reports describing nonlethal effects of acute exposure of humans to carbon tetrachloride in addition of relevant animal data to derive AEGL values. The AGL-2 values are based on observations of CNS effects (Davis, 1934), (i.e., nausea, vomiting, dizziness, and headaches) despite normal clinical assessments (i.e., urinalysis, blood count, hemoglobin levels, blood pressure, and heart rate) for individuals exposed to 317 ppm carbon tetrachloride for 30 min. The observed effects were apparently not long-lasting but are considered severe enough to impair escape or normal function. The same study also reported notable renal effects in a worker experimentally exposed to carbon tetrachloride at 200 ppm for 8 hrs.

Testing for developmental toxicity by the inhalation route is limited to one study in the rat that found effects only at high, maternally toxic exposure concentrations. Reduced fetal body weight and crown-rump length was reported in the single inhalation study (Schwetz et al., 1974) at a concentration that also produced toxicity in the dam (i.e., hepatoxicity reflected by increase in serum glutamic-pyruvic transaminase activity). This inhalation developmental toxicity study has been reviewed in the ATSDR, IRIS, and AEGL assessments. NAC/AEGL (NRC, 2014) determined that these results were inconclusive for identifying any fetal end points for deriving AEGL (acute) values. NAC/AEGL further concluded that these 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 (see section 3.2.5.1).

The systematic review did not identify additional developmental toxicity studies with carbon tetrachloride with acceptable data quality based on the quality criteria in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a).

Limited available acute animal studies by the dermal route, described above, provide evidence of mortality and liver changes from single, continuous (≥19 hrs) dermal exposure conditions. The systematic review did not identify additional dermal acute toxicity studies with carbon tetrachloride with acceptable data quality based on the quality criteria in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a).

3.2.4.1.2 Chronic Toxicity

Limited evidence from gestational exposure studies in animals suggest that developmental toxicity is not an acute effect (see section 3.2.4.1.1) nor the most sensitive effect for carbon tetrachloride. Developmental toxicity has been observed at doses accompanied by some degree of maternal toxicity. Increased resorptions were observed in developmental toxicity studies following maternal exposure to doses ≥50 mg/kg-day during pregnancy (Narotsky et al., 1997), which were attributed to maternally-mediated effects, including reduced progesterone and luteinizing hormone levels in dams. EPA (2010) concluded that the most detailed developmental toxicity study by inhalation exposure (Schwetz et al., 1974) suggests that developmental effects of carbon tetrachloride occur at concentrations toxic to the mother and at exposure concentrations higher than those associated with liver and kidney toxicity. EPA (2010) notes that the LOAEL for developmental effects (in the presence of maternal toxicity) in this study (300

ppm) was 66-fold higher than the NOAEL (5 ppm) for liver toxicity from chronic inhalation exposures identified by IRIS for the development of the RfC.

The EPA IRIS Assessment (U.S. EPA, 2010) identified the liver as the target organ for carbon tetrachloride after repeated inhalation and oral exposure in animals and humans. Limited available dermal exposure data suggest that liver changes can be induced by exposure to carbon tetrachloride through the skin in animals.

Primary animal evidence on the liver toxicity from inhalation exposures is from the chronic (104 week) inhalation toxicity study in F344/DuCrj rats (Nagano et al., 2007a). Increased incidence and severity of nonneoplastic liver lesions (fatty change, fibrosis, cirrhosis) were seen at 25 and 125 ppm in both male and female rats in this study. Fatty change in the liver of rats was selected by EPA IRIS as the specific endpoint indicative of cellular damage and most sensitive endpoint among the histopathologic changes observed in the 25-ppm group rats in the study. This critical effect is the basis for the derivation of the IRIS Inhalation Reference Concentration (RfC).

Kidney toxicity was identified as a target for carbon tetrachloride toxicity after repeated inhalation exposure (U.S. EPA, 2010). Similar to the evidence for liver toxicity, the primary evidence for kidney toxicity is the chronic (104 week) inhalation toxicity study in F344/DuCrj rats (Nagano et al., 2007a). increased severity of glomerulonephrosis, accompanied by evidence of impaired glomerular function, including increases in serum BUN, creatinine, inorganic phosphorus and proteinuria were observed following exposure to ≥25 ppm. The interpretation of the observed proteinuria in the F344 rat, a strain with a high spontaneous incidence of renal lesions, was deemed problematic and not an appropriate basis for the RfC in the IRIS assessment.

The kidney was not identified as a critical target for carbon tetrachloride toxicity following oral exposure. In oral gavage studies, no exposure-related kidney effects were observed in Sprague-Dawley rats exposed to doses up to 2,000 mg/kg-day for 1-3 days (Sun et al., 2014), Sprague-Dawley rats exposed to doses up to 33 mg/kg-day for 12 weeks (Bruckner et al., 1986), or CD-1 mice exposed to doses up to 1,200 mg/kg-day for 90 days (Hayes et al., 1986).

The systematic review did not identify additional chronic toxicity studies with carbon tetrachloride with acceptable data quality based on the quality criteria in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a).

3.2.4.2 Genotoxicity and Cancer

The available data for carbon tetrachloride do not support a conclusion that this compound induces cancer though a mutagenic mode of action, however, there are important limitations to the database. While there is little direct evidence that carbon tetrachloride induces intragenic or point mutations in mammalian systems, studies have characterized formation of DNA adducts and chromosomal damage. Lipid peroxidation products (e.g., reactive aldehydes) may contribute to observed effects. The presence of cellular toxicity complicates the evaluation of the database and genetic damage has not been well studied at or below the doses at which tumors are observed.

The EPA IRIS assessment of carbon tetrachloride classifies this compound as "likely to be carcinogenic to humans" based on sufficient evidence in animals by oral and inhalation exposure, i.e., hepatic tumors in multiple species (rat, mouse, and hamster) and pheochromocytomas (adrenal gland tumors) in male and female mice exposed by oral and inhalation exposures (U.S. EPA, 2010).

The systematic review did not identify additional genotoxicity studies with carbon tetrachloride with acceptable data quality based on the quality criteria in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a).

3.2.4.3 MOA for Carcinogenicity

This section summarizes available information on mode of action (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. The EPA IRIS assessment reviewed MOA information for liver tumors and pheochromocytomas. IRIS described evidence in support of several potential mechanisms of action (described below) but concluded that "the overall MOA for carbon tetrachloride carcinogenicity across all levels of exposure is unknown at this time" (U.S. EPA, 2010). The IRIS assessment did not review information on potential MOAs for brain cancers and the MOA for brain cancer is also unknown.

3.2.4.3.1 Mode of Action for Liver Tumors

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, and information submitted to EPA through public comment (see Appendix K) 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:

(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.

This MOA appears to play a significant role at relatively high exposures, driving the steep increase in liver tumors in this exposure range. Data to characterize key events at low-exposure

levels, however, are limited. Therefore, EPA also considered an alternate MOA that combines cytotoxic mechanisms at high doses with alternate, non-cytotoxic mechanisms as lower doses.

Based on information in the IRIS assessment and public comments EPA-HQ-OPPT-2016-0733-0066 and EPA-HQ-OPPT-2016-0733-0088, the following potential MOAs, including evidence for key events, are evaluated in Table 3-11 and Appendix K.

- Liver cytotoxic MOA (Lipid peroxidation and cytotoxicity as proposed in comments submitted by ACC)
- Combined MOA (non-cytotoxic at low dose and cytotoxic at high dose)

Table 3-11. Cytotoxic MOA (key events as proposed by EPA-HQ-OPPT-2016-0733-0066 and EPA-HQ-OPPT-2016-0733-0088)

Key Events	Supporting Evidence	Counterfactual Evidence	Data Gaps/limitations
Metabolism	There is well documented evidence in IRIS assessment and other assessments listed in Table 1-3 on the metabolism of carbon tetrachloride to the trichloromethyl radical by CYP2E1 and subsequent formation of the trichloromethyl peroxy radical	No significant evidence	No significant gaps
Lipid peroxidation and attack of cellular membranes	From EPA-HQ-OPPT-2016-0733-0066 and EPA-HQ-OPPT-2016-0733-0088: Studies of radical scavengers that are not necessarily specific to trichloromethyl peroxy or lipid peroxidative free radicals have shown that these agents confer protection against carbon tetrachloride induced liver toxicity, while another study demonstrated administration of α-tocopherol, Vitamin E antioxidant, had been shown to reduce lipid peroxidation (Gee et al., 1981). Numerous studies have demonstrated lipid peroxidation following carbon tetrachloride exposure by the detection of conjugated dienes in liver lipids, increased exhalation of ethane and pentane (end degradation products of peroxidized polyunsaturated fatty acids) or malondialdehyde and 4-HNE. Hartley et al., (1999) demonstrated the temporal	No significant evidence	From information in Appendix I: Collectively, the data indicate that carbon tetrachloride exposure can result in the formation of DNA adducts in response to two distinct pools of reactive oxygen species 1) those formed as a result of exposure to carbon tetrachloride itself or reactive metabolites thereof and 2) those formed as a result of lipid peroxidation. However, the relative contribution of each of these pathways to the overall carcinogenic potential carbon tetrachloride is currently uncertain.

Key Events	Supporting Evidence	Counterfactual Evidence	Data Gaps/limitations
	relationship between carbon tetrachloride exposure-initiated lipid peroxidation, liver damage and formation of 4-HNE and MDA protein adducts.		
Cytotoxicity due to loss of calcium homeostasis	From EPA-HQ-OPPT-2016-0733-0066 and EPA-HQ-OPPT-2016-0733-0088: Studies have reported 100-fold or more increases in cytosolic concentrations of calcium following exposure to carbon tetrachloride. Studies have demonstrated that effect of carbon tetrachloride on membrane integrity and the active transport that may be by the NADPH-cytochrome P-450 electron-transport chain in liver endoplasmic reticulum, a distance away from the nucleus (Mccay et al., 1984; Slater and Sawyer, 1977; Recknagel and Glende, 1973), which appear to be secondary to lipid peroxidation.	Low-dose exposed female mice displayed an increase incidence of liver adenomas that occurred in the absence of hepatocellular cytotoxicity, suggesting that more than one mechanism may be responsible for carbon tetrachloride-induced liver carcinogenesis	It is uncertain if disruption of calcium homeostasis is a major driver of carcinogenesis.
Regenerative Proliferation	Increased hepatocellular toxicity in animals occurred with a concomitant increase in regenerative cellular proliferation to compensate for necrotic or damaged tissue.	No significant evidence	No significant gaps
Liver tumors	EPA IRIS assessment (U.S. EPA, 2010) summarizes a variety of studies describing liver tumor formation in rats, mice, and hamsters by both oral and inhalation exposure	No significant evidence	No significant gaps

4017
4018 **Table 3-12. Combined MOA (non-cytotoxic at low dose and cytotoxic at high dose)**

Key Events	Supporting Evidence	Counterfactual Evidence	Data Gaps/limitations
Metabolism	There is well documented evidence in EPA IRIS assessment and other assessments listed in Table 1-3 on the metabolism of carbon tetrachloride to the trichloromethyl radical by CYP2E1 and subsequent formation of the trichloromethyl peroxy radical	No significant evidence	No significant gaps

Key Events	Supporting Evidence	Counterfactual Evidence	Data Gaps/limitations
radical-induced mechanisms (driven by non-cytotoxic mechanisms at low doses and cytotoxic mechanisms at high doses)	Multiple studies have characterized the formation of endogenously produced DNA adducts, chromosomal aberrations, and micronucleus formation. Lipid peroxidation products generate compounds (e.g. reactive aldehydes) that may covalently bind to DNA Low-dose exposed female mice displayed an increase incidence of liver adenomas that occurred in the absence of hepatocellular cytotoxicity, suggesting that more than one mechanism may be responsible for carbon tetrachloride-induced liver carcinogenesis.	Carbon tetrachloride has consistently been negative in studies using Salmonella and certain strains of E. coli, at high exposure concentrations.	Measurement of genetic damage to DNA has not been well characterized at or below doses at which tumors are observed. Technical challenges for the evaluation the genotoxicity of carbon tetrachloride are summarized in Appendix I. It is unknown what are the major radical-induced mechanisms driving carcinogenesis.
Regenerative Proliferation after cytotoxicity at high-dose exposures only	Increased hepatocellular toxicity in animals occurred with a concomitant increase in regenerative cellular proliferation to compensate for necrotic or damaged tissue for high- dose exposed animals.	Low-dose exposed female mice displayed an increase incidence of liver adenomas that occurred in the absence of hepatocellular cytotoxicity, suggesting that more than one mechanism may be responsible for carbon tetrachloride-induced liver carcinogenesis.	No significant gaps
Liver tumors	The IRIS Toxicological Review of carbon tetrachloride (U.S. EPA, 2010) summarizes a variety of studies describing liver tumor formation in rats, mice, and hamsters by both oral and inhalation exposure	No significant evidence	No significant gaps

Based on the qualitative MOA WOE for the alternative MOAs, there are significant data limitations to assess within certainty the causal considerations (i.e., biological plausibility, essentiality, dose-response concordance, consistency) for the postulated non-cytotoxic and cytotoxic key events that are expected to occur after carbon tetrachloride metabolism. The available data suggest that cytotoxicity is one major mechanism in the MOA of carcinogenesis at high exposures, however data also indicate that carbon tetrachloride can induce tumors in the absence of cytotoxicity, i.e., tumorigenesis in low dose female mice. There is limited information about mechanisms at lower doses.

3.2.4.3.2 Mode of Action for Pheochromocytomas (Adrenal Tumors)

EPA has reviewed the available literature and concludes that the MOA by which carbon tetrachloride induces pheochromocytomas in mice is unknown. Animal and in vitro evidence suggests that metabolism is an important contributor to the toxicity of carbon tetrachloride in the adrenal gland ((U.S. EPA, 2010) (see page 168)).

Pheochromocytomas are relatively rare in people. Only a small number of chemicals have been associated with pheochromocytomas in mice, and there does not appear to be a common mechanism shared across these chemicals (U.S. EPA, 2010). Several potential MOAs for induction of pheochromocytomas in mice have been hypothesized but not experimentally supported, including endocrine disturbances, uncoupling of oxidative phosphorylation, disturbances in calcium homeostasis, impaired mitochondrial function, and hepatoxicity (Greim et al., 2009).

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 3.2.3 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

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 h (Davis, 1934). EPA considers that the acute NOEL 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-3 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 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). Among the reasonably available developmental toxicity data for carbon tetrachloride, Schwetz et al., (1974) is the only developmental study by the inhalation route with acceptable data quality. This inhalation developmental study has been reviewed in the ATSDR, IRIS, and AEGL assessments. ATSDR, IRIS, and AEGL describe that the developmental effects (decreased fetal body weight and crown-rump length) occur at the same LOAEL that results in maternal toxicity (a NOAEL was not identified). ATSDR categorized these effects as less serious. The maternal effects were reduced body weight (decreased food consumption), increased liver weight and ALT. Based on this consideration as well as experimental variability over the 3-fold dose range, AEGL determined that these results were inconclusive for identifying any fetal end points for deriving AEGL values. They further concluded that these 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.

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. However 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.[14] 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.

3.2.5.1.2 Toxicity from Chronic Inhalation Exposures

EPA's systematic review process rated as high the overall quality of the 13-week and 104-week inhalation studies by Nagano et al., (2007a; 2007b). The IRIS assessment concluded that among the animal studies for carbon tetrachloride the most robust inhalation study was the 104-weeks (2-year) inhalation study with F344/DuCrj rats in which the lowest exposure concentration in this study, 5 ppm, was considered a NOAEL based on liver and kidney toxicity at ≥25 ppm. A human PBPK model was used in the IRIS Assessment to estimate continuous HECs (in mg/m^3) that would result in values for the internal dose metrics, equal to the $BMDL_{10}$ values for fatty changes of the liver. *The $BMDL_{10}$ based on male rat data was calculated as 14.3 mg/m^3 for continuous exposures*.

[14] 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.

The systematic review conducted did not identify information that challenges the observations or conclusions from this critical study used in the IRIS assessment to derive a reference concentration and inhalation unit risk for carbon tetrachloride.

3.2.5.1.3 Toxicity from Dermal Exposures

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 liver and kidney in addition to skin. In the study guinea pigs dermally exposed to a single application of 1 mL of carbon tetrachloride in a 3.1 cm^2 skin depot (513 mg/cm^2)[15] for 16 hours showed hydropic changes and necrosis in liver cells. Animals exposed to the same dose levels for 15 minutes, 1 hr or 4 hr did not show liver morphology alterations. The study provides suggestive evidence on the lower systemic availability of carbon tetrachloride from dermal exposures in comparison with other routes of exposure. The results of Kronevi et al., (1979) can be considered in conjunction with the findings from Wahlberg and Boman, (1979), in which guinea pigs exposed to a higher dose level of 1 mL with a similar size skin depot as Kronevi et al., (1979) did not show mortality during the first 2 days of continuous dermal exposure. Collectively, these studies provide evidence suggesting that the induction of liver toxicity in animals dermally exposed for 4 hrs to 0.5 mL carbon tetrachloride from a skin depot of 3.1 cm^2 is unlikely.

A study briefly described in the IRIS assessment: Tsuruta, (1975) (Klimisch score = 4: 'Not assignable') reports a percutaneous absorption rate for carbon tetrachloride in mice of 53.6 ± 9.3 nmoles/ minute/cm^2. This study, which is equivalent in design to OECD Guideline 427 (Skin Absorption: In Vivo Method)[16] is considered to provide an underestmation of the skin absorption rate for occluded exposures because of the possibility of carbon tetrachloride volatilization during dose preparation or application. The aspect of volatilization is not considered in this study to address potential loss of the analyte. In addition, the IRIS assessment states that Morgan et al., (1991) (Klimisch Score =3: 'Not reliable') showed that approximately one quarter of an applied volume (i.e., 0.54 mL of neat carbon tetrachloride application) was absorbed in a 24-hour period under occluded conditions.

The systematic review did not identify additional information for refining the skin absorption rate for carbon tetrachloride. Therefore, the available dermal toxicity information, with its uncertainties and limitations has been used under a weight of evidence approach in the derivation of dermal PODs for liver toxicity from acute 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 used in the derivation of PODs for chronic dermal exposures for the chemical.

[15] This exposure concentration is reported in the ATSDR profile for carbon tetrachloride. The concentration estimate is based on a density value of 1.59 g/mL for carbon tetrachloride.
[16] Equivalency based on information in ECHA dossier for carbon tetrachloride; ECHA reliability score =4.

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 and other routes of exposures 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.

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

3.2.5.2.1 PODs for Acute Inhalation Exposure

The AEGL Program identified a NOEL of 76 ppm (480 mg/m^3) for CNS effects (i.e., dizziness) in humans exposed to carbon tetrachloride for 4 hrs.[17] The resulting AEGL-2 value is 7.6 ppm (48 mg/m^3) for 4 hrs and 5.8 ppm (36 mg/m^3) for 8 hrs 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 hr for disabling effects (CNS effects such as dizziness) from elevated, but short inhalation exposures. For 12-hrs 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.

Table 3-13. 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 hr[A]	UF_H 10	10
			310 mg/m^3-12 hr		
			310 mg/m^3-12 hr		

[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).

3.2.5.2.2 PODs for Chronic Inhalation Exposure

The basis for the chronic inhalation PODs is the 104-weeks (2-year) inhalation study with F344/DuCrj rats (Nagano et al., 2007b), in which the lowest exposure concentration in this study, 5 ppm, was considered a NOAEC based on liver and kidney toxicity at ≥25 ppm. A human

[17] Transient kidney effects were also reported for acute exposures, but at higher exposure concentrations (see Section 3.2.3.1).

PBPK model was used in the IRIS Assessment to estimate HEC (in mg/m^3) consisting of *calculated* $BMDL_{10}$ for fatty changes of the liver of 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 J, below). 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 (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 MCA (mean arterial concentration) 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 J. 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 (ECs) below 95 mg/m^3. The value of the (24-hour continuous) HEC ($BMDL_{10}$) used for RfC derivation was 14.3 mg/m^3, and thus is within the linear range. This supports the use of the Haber's law equation, $C^n \times t = k$ with n=1 to estimate HEC values for non-continuous exposures.

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 in 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 exposure durations 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 (Ten Berge et al., 1986).

A benchmark MOE of 30 (based on UF_H 10 and UF_A 3) is used to evaluate risk for workers and ONUs.

Table 3-14. 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 hrs/d and 5 days per week of exposure and 26.4 mg/m^3 for 12 hrs/d 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

3.2.5.2.3 PODs for Acute Dermal Exposures

Given the limited information on non-cancer effects after acute dermal toxicity from carbon tetrachloride, the POD for acute dermal exposures is based on the only reasonably available 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 animal per dose group. However, the study findings provide a rough comparison of liver and kidney changes from acute dermal exposure to carbon tetrachloride during different time periods (i.e., 4 hrs, 19 hrs). The use of the study findings in conjunction with findings from another dermal toxicity study with similar experimental conditions and acceptable quality data (i.e., (Wahlberg and Boman, 1979)) were used to derive a POD for acute dermal exposures. An alternative approach, in which the POD for acute dermal exposures is extrapolated from the POD for chronic inhalation exposures results in a similar POD for acute exposures (2,450 mg/kg vs 2,750 mg/kg).[18] Extrapolation of the acute dermal POD from 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.

Based on the assumption that induction of liver toxicity is unlikely for animals dermally exposed for 4 hrs to 0.5 mL carbon tetrachloride from a skin depot of 3.1 cm^2 (see section 3.2.5.1), an acute dose for occluded conditions, which is associated with non-adverse liver effects was estimated. Dose for occluded exposures = [(260 mg/cm^2 × 3.1 cm^2) / 0.440 kg] – 4 hrs or 1,832 mg/kg – 4 hrs

A NOAEL value for the acute dermal exposure dose was then obtained by estimating how much of the acute dose is absorbed in 4 hrs under by using the reasonably available dermal absorption information for carbon tetrachloride. The available information includes a (underestimated) percutaneous absorption rate for carbon tetrachloride in mice of 53.6 ± 9.3 nmoles/ minute/cm^2 (Tsuruta, 1975), which shows dermal absorption of carbon tetrachloride has linear dependency to

[18] presents a POD for chronic dermal exposures of 245 mg/kg-d based on inhalation exposure information. Extrapolation of a POD for acute dermal exposures by multiplying the derived POD for chronic dermal exposures by a factor of 10 results in a POD for acute dermal exposures of 2,450 mg/kg.

the time and area of exposure and the experimental observations from Morgan et al., (1991) showing that about 25% of a total dose was absorbed in a 24-hr period under occluded conditions were used to extrapolate NOAEL for retained/absorbed carbon tetrachloride for acute dermal exposures.

By considering the reasonably available animal evidence on dermal absorption (i.e., 25% of a dermal dose is absorbed in 24 hrs, and linear time dependency for dermal absorption), a conservative assumption of 6% of an applied dose of carbon tetrachloride under occluded dermal conditions been absorbed in 4 hrs, was used to account for experimental underestimation. Therefore, the estimated NOAEL for acute (retained/absorbed) for occluded dermal exposures = 1,832 mg/kg × 0.06 = 110 mg/kg-d.

This NOAEL for acute (retained/absorbed) occluded exposures can be adjusted to a larger NOAEL value for non-occluded exposures to account for volatilization of carbon tetrachloride during non-occluded dermal exposures. Loss of carbon tetrachloride from volatilization in non-occluded scenarios results in the need for a higher amount of applied dose to reach effect levels. The supplemental file (U.S. EPA, 2019b) explains that because carbon tetrachloride is a volatile liquid, its dermal absorption depends on the type and duration of exposure. Where exposure is not occluded, only a fraction of carbon tetrachloride that comes into contact with the skin will be absorbed as the chemical readily evaporates from the skin. The default fraction of applied mass that is absorbed for carbon tetrachloride is 0.04. This fractional absorption factor is estimated based on a theoretical framework by Kasting and Miller (2006).

The NOAEL for non-occluded retained doses of carbon tetrachloride is estimated by dividing the NOAEL of 110 mg/kg-d for occluded dermal exposures by the default absorbed fraction factor of 0.04. Therefore, a NOAEL for acute non-occluded retained doses of 2,750 mg/kg was estimated.

Table 3-15. PODs for Acute Dermal Exposures (non-occluded)

Study	Study Details	Endpoint	POD	UFs/Dose Metric	Benchmark MOE
(Kronevi et al., 1979; Wahlberg and Boman, 1979)	Acute dermal studies in guinea pigs	Histopathological changes in the liver	2,750 mg/kg-d (estimated retained/absorbed dose per day)	UF_H 10 UF_A 10	100

3.2.5.2.4 PODs for Chronic Dermal Exposures

The chronic inhalation HEC was converted to a dermal HED for non-occluded retained doses by using a modified equation based on (Jongeneel, 2012) equation (Equation 3-1) for transposing an inhalation Occupational exposure level (OEL) to a dermal OEL. In the modified equation a dermal absorption factor is not used, which allows the estimation of the absorbed dermal dose instead of the OEL. This modification is necessary because dermal exposures in 2.4.1.8 are retained doses.

Equation 3-1. $HED_{Dermal} = HEC_{human,respiratory} \times V_{rate} \times T \times absorption_{(inhalation)}/absorption_{(dermal)} \times 1/bodyweight$

Equation 3-2. $HED_{Dermal} = HEC_{human,respiratory} \times V_{rate} \times T \times absorption_{(inhalation)} \times 1/bodyweight$

Where:

$HEC_{human,respiratory}$ = extrapolated $BMCL_{10[HEC]}$ of 31.1 mg/m^3 for 8 hrs/d, 5 days/week,
V_{rate} = a default worker ventilation rate of 1.25 m^3 per hour for light activities;
T = 8 hrs /day of exposure
Absorption (inhalation) = 63%; based on inhalation absorption information in (U.S. EPA, 2010)
Absorption (dermal) = 4% for non-occluded exposures, for 8-hrs exposure and absorption assumptions used to derive PODs for acute dermal exposures in section 3.2.5.2.3.
bodyweight = 80 kg.

Table 3-16. 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} = 245 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)

In the IRIS Toxicological Review of Carbon Tetrachloride (U.S. EPA, 2010) two quantitative approaches for assessment of carbon tetrachloride carcinogenicity are presented:

1- a low dose linear cancer risk model for carbon tetrachloride, which is EPA's default approach to risk assessment when the MOA is unknown. The IRIS program estimated an IUR of 6×10^{-6} per µg/m^3 for continuous lifetime exposure. The question of combining risks from the liver and adrenal tumors was considered in the IRIS Tox Review. As noted in the Tox Review, 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.

In summary, the MS-combo model could not be applied 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.

2- nonlinear approach with exposures exceeding the POD (18 mg/m^3, lower 95% bound on exposure associated with 10% extra risk) for continuous exposure, because above this level, the fitted dose-response model better characterizes what is known about the carcinogenicity of carbon tetrachloride. This threshold approach is used in this risk evaluations for high exposures based on a benchmark MOE of 30 (UF_H = 10 and UF_A = 3).

Cancer Slope Factor for Dermal Exposures

To avoid uncertainties related to the first-pass biotransformation 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 3.2.5.2.4.

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) (1/63) = 8×10^{-4} per mg/kg-d

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 (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 *Draft Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Epidemiological Studies. Docket EPA-HQ-OPPT-2019-0499* (U.S. EPA, 2019g).

For the chronic non-cancer endpoint, confidence in the Nagano et al., (2007a) the principal study is high. According to 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. The IUR is based on pheochromocytomas observed in only one of the rodent species, mice. 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 3-17. 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	4 hrs-single exposure	360	mg/m^3-8hr	10 (UF_H 10)	Study duration and endpoint relevant to worker acute exposures; in agreement with AEGL acute exposure guidelines	(Davis, 1934)
	Non-cancer	Extrapolated $BMCL_{10[HEC]}$	31.1	mg/m^3 - 8 hrs	30 (UF_H 10; UF_A 3)	POD relevant for liver effects; in agreement with IRIS non-cancer conclusions	(Nagano et al., 2007a)
	Cancer	Inhalation Unit Risk (IUR)	6×10^{-6}	$(\mu g/m^3)^{-1}$	1 in 10^4 for occupational risk	In agreement with IRIS cancer conclusions for carbon tetrachloride	(Nagano et al., 2007a)
Dermal	Short term-Liver effects	Single exposure	2,750	mg/kg-d	100 (UF_H 10; UF_A 10)	POD relevant for liver effects	(Kronevi et al., 1979) (Wahlberg and Boman, 1979)
	Non-cancer	Extrapolated Human Equivalent Dose (HED)	245	mg/kg-d	30 (UF_H 10; UF_A 3)	POD relevant for liver effects	(Nagano et al., 2007a)
	Cancer	Cancer Slope Factor (CSF)	8×10^{-4} (derived from IUR)	$(mg/kg\text{-}d)^{-1}$	1 in 10^4 for occupational risk	In agreement with IRIS cancer conclusions for carbon tetrachloride	(Nagano et al., 2007a)

Uncertainty Factors = UF_A = interspecies UF; UF_H = intraspecies UF

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. Differences in the metabolism due to alcohol consumption, 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).

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).

The AEGL-2 values (See section 3.2.3.1), which are the basis for the PODs for acute inhalation exposures in this draft 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-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.

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 represents 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 concludes that carbon tetrachloride poses a hazard to environmental aquatic receptors (section 3.1). Amphibians are the most sensitive taxa for acute and chronic exposures, respectively. For acute exposures, a hazard value of 0.9 mg/L was established for amphibians using data on teratogenesis leading to lethality in frog embryos and larvae. For acute exposures, carbon tetrachloride also has hazard values for fish as low as 10.4 mg/L and for freshwater aquatic invertebrates as low as 11.1 mg/L. 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. For chronic exposures, carbon tetrachloride also has hazard values as low as 1.97 mg/L for fish and 1.1 mg/L (acute to chronic ratio of 10) for aquatic invertebrates. 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 chronic exposure (see Appendix G.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 14 aquatic environmental hazard studies were reviewed and determined to have acceptable data quality for carbon tetrachloride. EPA's evaluation of these studies was either high or medium during data quality evaluation (Appendix G). The document Risk *Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Hazard Studies.* EPA, (2019e) 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. Given carbon tetrachloride's conditions of use under TSCA outlined during problem formulation (U.S. EPA, 2018d), EPA determined that significant environmental exposures are not expected to exceed the acute and chronic COCs for aquatic species, as presented in section 3.1.2. 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 is using the worst-case, high end exposures and modeled surface water concentrations.

At problem formulation, EPA made refinements to the conceptual models resulting in the elimination of the sediment exposure pathway from further analysis. Based on physical chemical and fate properties of carbon tetrachloride, EPA did not conduct a full quantitative assessment to further evaluated exposure to sediment-dwelling aquatic organisms through the sediment. There is no data to suggest that sediment-dwelling aquatic organisms are exposed to carbon tetrachloride.

During problem formulation, exposure pathways to terrestrial species (e.g., through soil, land-applied biosolids, and ambient air) were determined to be adequately assessed and effectively managed under programs of other environmental statutes administered by EPA. These pathways were excluded from the scope of this risk evaluation. Thus, environmental hazard data sources on terrestrial organisms were excluded from data quality evaluation.

4.1.1 Aquatic Pathway

The purpose of the environmental risk characterization is to determine whether there are risks to the aquatic environment from levels of carbon tetrachloride found in surface water based on the fate properties, relatively high potential for release, and the availability of environmental monitoring data and hazard 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. Due to the physical, chemical, and fate properties of carbon tetrachloride in the environment (*e.g.,* volatility, water solubility) and a quantitative comparison of hazards and exposures for aquatic organisms, EPA has high confidence that there are no environmental risks to the aquatic species posed by carbon tetrachloride under the conditions of use within the scope of the risk evaluation. The results of the analyses are presented in Appendix E and Appendix G.

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

RQ = Environmental Concentration / 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. The environmental concentration for surface water is determined based on experimental test data of carbon tetrachloride (Appendix E and Appendix G).

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

Environmental Toxicity	Most Sensitive Test	Assessment Factor**	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

*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 G, EPA used model exposure data that was calculated from E-FAST, monitored data from Discharge Monitoring Reports (DMR), and aquatic COCs from the available hazard data to determine the risk of carbon tetrachloride to aquatic species 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, or an RQ ≥ 1 and 20 days or more of exceedance for the chronic and algal COCs suggest the potential for environmental risks posed by carbon tetrachloride.

EPA used the acute COC (90 µg/L), chronic COC (3 µg/L), and algal COC (7 µg/L) based on environmental toxicity LC_{50} from (Brack and Rottler, 1994), LC_{10} from (Black et al., 1982; Birge et al., 1980), and EC_{10} from (Brack and Rottler, 1994) endpoint values, respectively, to represent

the lowest bound of all carbon tetrachloride data available in the public domain and provide the most conservative hazard values.

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 Publicly-Owned Treatment Works (POTWs). EPA compiled five years of carbon tetrachloride NPDES permit Discharge Monitoring Report (DMR) release data (2014 through 2018). 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 the Probabilistic Dilution Model (PDM) in E-FAST to estimate site-specific receiving water concentrations of carbon tetrachloride at the point of discharge. Based on carbon tetrachloride 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. The largest releases of carbon tetrachloride were modeled for releases over 20 days and 250 days per year as estimates of releases that could lead to chronic risk. The 20-day 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 and the 250-day time frame represents annual full-time industrial operations. The surface water concentrations are summarized in Table 4-2 below.

Table 4-2. Modeled Facilities Showing Acute, Chronic, Algae Risk from the Release of Carbon Tetrachloride; RQ Greater Than One are Shown in Bold

NPDES	Facility Name	Amount Discharged for 20 days (kg/day)	20 Day Stream Conc. (µg/L)	Days Acute COC[a] Exceeded (PDM)	RQ for Amphibian Acute COC (90 µg/L)	RQ for Algae COC (7 µg/L)	Amount Discharged for 250 days (kg/day)	250 Day Stream Conc. (µg/L)	Days Chronic COC[b] Exceeded (PDM)	RQ for Amphibian Chronic COC (3 µg/L)	RQ for Algae COC (7 µg/L)
TX0021458	Fort Bend County WCID2	N/A	N/A	N/A	N/A	N/A	0.10	1.0E+01	0	**3.4E+00**	**1.5E+00**
AL0001961	AKZO Chemicals, Inc.	5.7	3.1E-01	0	3.4E-03	4.4E-02	0.46	2.5E-02	0	8.3E-03	3.5E-03
LA0000329	Honeywell, Baton Rouge	0.20	8.1E-04	0	9.0E-06	1.2E-04	0.02	6.5E-05	0	2.2E-05	9.3E-06
LA0005401	ExxonMobil, Baton Rouge	0.01	4.0E-04	0	4.5E-06	5.7E-05	0.01	3.2E-05	0	1.1E-05	4.6E-06
OH0029149	Gabriel Performance	0.19	45	0	5.0E-01	**6.4E+00**	0.02	3.6	2	**1.2E+00**	5.1E-01
WV0004359	Natrium Plant	0.29	3.4E-02	0	3.8E-04	4.9E-03	0.02	2.9E-03	0	9.5E-04	4.1E-04
CA0107336	Sea World, San Diego[c]										
OH0007269	Dover Chemical Corp	1.8	1.3E+2	0	**1.4E+00[d]**	**1.8E+01**	0.14	10	15	**3.3E+00**	**1.4E+00**
LA0006181	Honeywell, Geismar	0.18	7.3E-04	0	8.1E-06	1.0E-04	0.02	6.1E-05	0	2.0E-05	8.7E-06
LA0038245	Clean Harbors, Baton Rouge	0.33	1.3E-03	0	1.5E-05	1.9E-04	0.03	1.0E-04	0	3.5E-05	1.5E-05
TX0119792	Equistar Chemicals LP	0.68	4.4	0	4.9E-02	6.3E-01	0.05	3.5E-01	0	1.2E-01	5.0E-02

NPDES	Facility Name	Amount Discharged for 20 days (kg/day)	20 Day Stream Conc. (µg/L)	Days Acute COC[a] Exceeded (PDM)	RQ for Amphibian Acute COC (90 µg/L)	RQ for Algae COC (7 µg/L)	Amount Discharged for 250 days (kg/day)	250 Day Stream Conc. (µg/L)	Days Chronic COC[b] Exceeded (PDM)	RQ for Amphibian Chronic COC (3 µg/L)	RQ for Algae COC (7 µg/L)
WV0001279	Chemours Chemicals LLC	0.11	1.1E0-02	0	1.2E-04	1.6E-03	0.01	8.0E-04	0	2.7E-04	1.2E-04
TX0007072	Eco Services Operations	0.26	49	0	5.4E-01	**7.0E+00**	0.02	3.9	2	**1.3E+00**	5.6E-01
KY0024082	Barbourville STP	N/A	N/A	N/A	N/A	N/A	0.01	3.5E-01	0	1.2E-01	5.0E-02
WA0030520	Central Kitsap WWTP	0.06	7.0E+01	N/A	7.76E-01	**10.0E+00**	0.01	5.8E-01	0	1.9E-01	8.3E-02
MO0002526	Bayer Crop Science	0.05	5.9E-01	0	6.56E-03	8.4E-02	0.0	4.7E-02	0	1.6E-02	6.7E-03
KY0027979	Eddyville STP	N/A	N/A	N/A	N/A	N/A	0.01	1.0	1	3.4E-01	1.5E-01
KY0103357	Richmond Silver Creek STP	N/A	N/A	N/A	N/A	N/A	0.0	3.1E-01	0	1.0E-01	4.4E-02
KY0003603	Arkema Inc.	0.02	9.5E-04	0	1.1E-05	1.4E-04	0.0	8.7E-05	0	2.9E-05	1.2E-05
KY009161	Caveland Environmental Auth	0.03	8.4E-02	0	9.3E-04	1.2E-02	0.0	5.6E-03	0	1.9E-03	8.0E-04
LA0002933	Occidental Chem Corp, Geismar	0.01	4.9E-05	0	5.4E-07	6.9E-06	0.0	4.0E-06	0	1.4E-06	5.8E-07

[a]Acute COC = 90 µg/L; acute RQs for POTW facilities were N/A because the days of the releases were assumed to be over 20 days.
[b]Chronic COC = 3 µg/L
[c]San Diego Sea World facility (CA0107336) was not included in the analysis since the reported level is above permit discharge limits; noncompliance and spills are not in the scope of this risk evaluation.
[d]Although the acute RQ = 1.4, the days of exceedances is zero because of the 20-day averaging period for acute exposures.

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).

All facilities assessed in this risk evaluation were modeled in E-FAST. The RQs and days of exceedance that indicate risk for aquatic organisms (facilities with an RQ ≥ 1 for the acute COC, or an RQ ≥ 1 and 20 days or more of exceedance for the chronic and algal COCs) for all facilities analyzed in this risk evaluation are presented in Table 4-2.

Using conservative scenarios, EPA concluded that the surface water concentrations did not exceed the acute COC (i.e., acute RQs < 1) for aquatic species for all sites except one site at Dover Chemical Corp (i.e., worst-case scenario; RQ = 1.4), as summarized in Table 4-2. EPA determined there is not an acute aquatic concern for carbon tetrachloride after further review of the Dover Chemical Corp site (see Section 2).

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 7Appendix 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. Although the chronic COC was exceeded by four facilities ranging from 1.2 to 3.4 (i.e., worst-case scenario; RQ = 3.4) and the algae COC was exceeded by four facilities ranging from 6.4 to 18 based on the 20-day stream concentration and by two facilities ranging from 1.4 to 1.5 based on the 250-day stream concentration, these carbon tetrachloride releases are not continuously released over time (i.e., chronic exposure). Frequency and duration of exposure also affects potential for adverse effects in aquatic organisms, especially for chronic exposures. Therefore, the number of days that a COC was exceeded was also calculated using E-FAST. The days of exceedance modeled in E-FAST are not necessarily consecutive and could occur sporadically throughout the year. For carbon tetrachloride, continuous aquatic exposures are more likely for the longer exposure scenarios (i.e., 100-365 days/yr of exceedance of a COC), and more of an interval or pulse exposure for shorter exposure scenarios (i.e., 1-99 days/yr of exceedances of a COC). Due to the volatile properties of carbon tetrachloride, it is more likely that a chronic exposure duration will occur when there are long-term consecutive days of release versus an interval or pulse exposure which would more likely result in an acute exposure duration. For all the sites analyzed in this risk evaluation of carbon tetrachloride, all of the release sites had < 20 days of exceedance of the chronic COC. Consequently, EPA determined there is not an acute, chronic, algal concern of carbon tetrachloride from the conditions of use for aquatic organisms.

4.1.3 Risk Estimation for Sediment

EPA did not quantitatively estimate sediment-bound carbon tetrachloride exposure to sediment-dwelling aquatic organisms. On-topic hazard studies for sediment exposures are not available in the scientific literature (and would not be expected due to the physical, chemical, and fate

properties of the chemical). 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 (793 mg/L) and low partitioning to organic matter (log K_{OC} = 0.79 – 1.93 (aquifer sediments) and 1.67 (marine and estuary sediments)) (see section 2.1). According to this reasonably available information, carbon tetrachloride is likely to be in pore water and not adsorbed to the sediment organic matter because the chemical has low partitioning to organic matter. Thus, qualitatively, sediment-bound carbon tetrachloride exposure concentrations are expected to be low. Consequently, EPA determined there is not an acute or chronic sediment-bound concern of carbon tetrachloride from the COUs and did not further analyze exposure pathways to ecological sediment-dwelling species in the risk evaluation.

4.1.4 Risk Estimation for Terrestrial

During problem formulation, EPA made refinements to the conceptual models resulting in the elimination of the terrestrial exposure pathway. As explained in section 2.5.3.2 of the problem formulation (U.S. EPA, 2018d), exposure to terrestrial organisms was removed from the scope of the evaluation. This exposure pathway is under programs of other environmental statutes, administered by EPA, which adequately assess and effectively manage exposures and for which long-standing regulatory and analytical processes already exist.

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 Hazard values or Point of Departures (PODs)*: 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.

Populations and Toxicological Approach	Occupational Use Scenarios of Carbon Tetrachloride
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
Notes: 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 **1.** Non-cancer health effects: Fatty changes in the liver **2.** Non-Cancer Hazard values or 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, EPA IRIS Assessment (U.S. EPA, 2010) Cancer **1.** Cancer health effects: carbon tetrachloride is classified as "likely to be carcinogenic to humans" **2.** Cancer Inhalation Unit Risk (IUR): 6×10^{-6} per µg/m^3 for lifetime continuous exposure
Uncertainty Factors (UF) Used in Non-Cancer Margin of Exposure (MOE) calculations	(UF_H = 10) × (UF_A = 3) = 30 Total UF=Benchmark MOE=30
Cancer Benchmark	1 in 10^4 cancer risk for worker populations
Notes: Adult workers (>16 years old) include both healthy female and male workers. UF_H=intraspecies UF; UF_A=interspecies 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: CNS **1.** *Non-Cancer Hazard values or Point of Departures (PODs)*: 2,750 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	($UF_H = 10$) × ($UF_A = 10$) = 100 Total UF=Benchmark MOE=100
Notes: 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 **1.** Non-cancer health effects: Fatty changes in the liver **2.** Non-Cancer POD: 245 mg/kg-d based on route to route extrapolation from $BMCL_{10[HEC]}$: 14.3 mg/m^3 for continuous exposures. Cancer **1.** Cancer health effects: carbon tetrachloride is classified as "likely to be carcinogenic to humans" **2.** Cancer Slope factor derived from Inhalation Unit Risk (IUR) of 6×10^{-6} per $\mu g/m^3$ for lifetime continuous exposure
Uncertainty Factors (UF) Used in Non-Cancer Margin of Exposure (MOE) calculations	($UF_H = 10$) × ($UF_A = 3$) = 30 Total UF=Benchmark MOE=30
Cancer Benchmark	1 in 10^4 cancer risk for worker populations
Notes: 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 3.2.3.1) UF_H=intraspecies UF; UF_A=interspecies. UF_H=intraspecies UF; UF_A=interspecies 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 dose, 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[19] 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 hr and 12 hr TWAs was 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 3.2.3.

[19] 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.

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 noncancer 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. 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).

Equation 4-2. Equation to Calculate Cancer Risks

$$\textit{Inhalation Cancer Risk} = \textit{Human Exposure} \times \textit{IUR}$$

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 $\mu g/m^3$ for continuous exposures)
CSF	= Inhalation unit risk adjusted for 0.8% dermal absorption

For carbon tetrachloride, EPA, consistent with OSHA (878 F.2d 389, 392 (D.C. Cir. 1989) and 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. It is 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 50th percentile (central tendency). 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 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 (Worker and ONU)		Calculated MOE with Respirator (Worker)*					
	ADC (mg/m^3)				APF =10		APF =25		APF =50	
	High-End (Worker)	Central Tendency (Worker and ONU)	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	4.0	0.76	90	474	900	4,740	2,250	11,850	4,500	23,700
Manufacturing - 12-hr TWA	4.8	0.50	65	620	650	6,200	1,625	15,500	3,250	31,000
Import/ Repackaging	0.30	0.057	1,200	6,316	12,000	63,160	30,000	157,900	60,000	315,800
Processing as Reactant/Intermediate – 8-hr TWA	4.0	0.76	90	474	900	4,740	2,250	11,850	4,500	23,700
Processing as Reactant/Intermediate – 12-hr TWA	4.8	0.50	65	620	650	6,200	1,625	15,500	3,250	31,000
Industrial Processing Aid	0.30	0.057	1,200	6,316	12,000	63,160	30,000	157,900	60,000	315,800
Additive	0.30	0.057	1,200	6,316	12,000	63,160	30,000	157,900	60,000	315,800
Disposal: Waste Handling	0.30	0.057	1,200	6,316	12,000	63,160	30,000	157,900	60,000	315,800
Specialty Uses-DoD Data	0.367	0.183	981	1,967	9,810	19,670	24,525	49,175	49,050	98,350
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. 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.

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.[20] Non-cancer risk estimates for chronic exposures for each occupational use scenario are presented in Table 4-8 below.

The calculated MOEs are greater than the benchmark MOEs of 30 for the high-end and central tendency exposures for most conditions of use without respirator use, except for the high-end exposures for manufacturing and processing as reactant/intermediate (8 hr and 12 hr TWA) COUs. 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.

[20] 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 POD of 31.1mg/m^3- 8 hrs (= 26.4 mg/m^3-12 hrs) and Benchmark MOE of 30

Condition of Use	EXPOSURE		Calculated MOE without Respirator (Worker and ONU)		Calculated MOE with Respirator (Worker)*					
	ADC (mg/m^3)				APF =10		APF =25		APF =50	
	High-End (Worker)	Central Tendency (Worker and ONU)	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	4.0	0.76	**8**	41	80	410	200	1,025	400	2,050
Manufacturing - 12-hr TWA	4.8	0.50	**6**	53	60	530	150	1,325	300	2,650
Import/ Repackaging	0.30	0.057	104	546	1.040	5,460	2,600	13,650	5,200	27,300
Processing as Reactant/Intermediate – 8-hr TWA	4.0	0.76	**8**	41	80	410	200	1,025	400	2,050
Processing as Reactant/Intermediate – 12-hr TWA	4.8	0.50	**6**	53	60	530	150	1,325	300	2,650
Industrial Processing Aid	0.30	0.057	104	546	1,040	5,460	2,600	13,650	5,200	27,300
Additive	0.30	0.057	104	546	1,040	5,460	2,600	13,650	5,200	27,300
Disposal: Waste Handling	0.30	0.057	104	546	1,040	5,460	2,600	13,650	5,200	27,300
Specialty Uses-DoD Data	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: 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.

4.2.4 Risk Estimation for Non-Cancer Effects Following Acute Dermal Exposures

Results from dermal studies with guinea pigs (Kronevi et al., 1979; Wahlberg and Boman, 1979) were used in conjunction with dermal absorption information for carbon tetrachloride to derive a POD for acute dermal exposures of 2,750 mg/kg (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-day)	Exposure Level	Acute Retained Dose (mg/kg-day)	Benchmark MOE (= Total UF)	Worker MOE, No Gloves	Worker MOE with Gloves: 5
Manufacture	**Liver** Liver toxicity for non to light alcohol users - Histopathological changes in the liver (guinea pigs) (Kronevi et al., 1979; Wahlberg and Boman, 1979)	2750	High End	1.1	100	2,500	12,500
Import and repackaging							
Additive							
Processing as a Reactant							
Processing Agent/Aid							
Recycling							
Waste disposal							
Laboratory Chemicals			Central Tendency	0.37	100	7,432	37,160
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 245 mg/kg-d for non-occluded exposures was extrapolated from the chronic inhalation $BMCL_{10[HEC]}$: 14.3 mg/m^3 for continuous exposures, which was derived in the EPA IRIS assessment (U.S. EPA, 2010) using 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.

4806 **Table 4-10. Risk Estimates from Chronic Dermal Exposures**

Condition of Use	Health Effect, Endpoint and Study	HED (mg/kg-day)	Exposure Level	Chronic Retained Dose (mg/kg-day)	Benchmark MOE (= Total UF)	Worker MOE, No Gloves	Worker MOE with Gloves: 5
Manufacture Import and repackaging Additive Processing as a Reactant Processing Agent/Aid Recycling Waste disposal Laboratory Chemicals Specialty Uses – Department of Defense Data	**Liver** Liver toxicity for non to light alcohol users - Histopathological changes in the liver (guinea pigs) (Kronevi et al., 1979; Wahlberg and Boman, 1979)	245	High End	1.1	30	223	1,115
			Central Tendency	0.37	30	662	3,310
Reactive Ion Etching	Negligible - Highly controlled work areas with small quantities applied						

4807 ### 4.2.6 Risk Estimation for Cancer Effects Following Chronic Inhalation
4808 ### Exposures

4809 EPA estimated the added cancer risks associated with chronic exposures to carbon tetrachloride
4810 in the workplace. The added cancer risk estimation for carbon tetrachloride was calculated by
4811 multiplying the occupational scenario-specific estimates (i.e., LADC) for both workers and
4812 occupational non-users by EPA's inhalation unit risk (IUR) to estimate the added cancer risk.
4813 Added cancer risks were expressed as number of cancer cases per million. Table 4-11 outlines
4814 the cancer risk estimates to workers from inhalation exposures for the conditions of use for
4815 carbon tetrachloride.
4816
4817 In general terms, the exposure frequency (i.e., the amount of days per year for workers or
4818 occupational non-users exposed to carbon tetrachloride) was considered to be 250 days per year
4819 and the occupational exposure duration was 40 years over a 70-year lifespan. It is recognized that
4820 these exposure assumptions are likely yielding conservative cancer risk estimates, but EPA does
4821 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 $\mu g/m^3$ and Benchmark Risk = 1 in 10^4

Condition of Use	Chronic, Cancer Exposures		Calculated Cancer Risk without Respirator (Worker and ONU)		Calculated Cancer Risk with Respirator (Worker)*					
	LADC (mg/m^3)				APF =10		APF =25		APF =50	
	High-End (Worker)	Central Tendency (Worker and ONU)	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency
Manufacturing - 8-hr TWA	0.47	0.07	**3E-03**	**4E-04**	**3E-04**	4E-05	1E-04	2E-05	6E-05	8E-06
Manufacturing - 12-hr TWA	0.83	0.07	**5E-03**	**4E-04**	**5E-04**	4E-05	**2E-04**	2E-05	1E-04	8E-06
Import/Repackaging	0.035	0.005	**2E-04**	3E-05	2E-05	3E-06	8E-06	1E-06	4E-06	6E-07
Processing as Reactant/Intermediate – 8-hr TWA	0.47	0.07	**3E-03**	**4E-04**	**3E-04**	4E-05	1E-04	2E-05	6E-05	8E-06
Processing as Reactant/Intermediate – 12-hr TWA	0.83	0.07	**5E-03**	**4E-04**	**5E-04**	4E-05	**2E-04**	2E-05	1E-04	8E-06
Industrial Processing Aid	0.035	0.005	**2E-04**	3E-05	2E-05	3E-06	8E-06	1E-06	4E-06	6E-07
Additive	0.035	0.005	**2E-04**	3E-05	2E-05	3E-06	8E-06	1E-06	4E-06	6E-07
Disposal: Waste Handling	0.035	0.005	**2E-04**	3E-05	2E-05	3E-06	8E-06	1E-06	4E-06	6E-07
Specialty Uses-DoD Data	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: Calculated extra-cancer risk are greater than the benchmark cancer risk or MOEs are below the benchmark MOE. Extra cancer risk was calculated as follows: "Central Tendency LADC ($\mu g/m^3$)" or "High-end LADC ($\mu g/m^3$)" × IUR (i.e., 6×10^{-6} per $\mu g/m^3$)

*Cancer risks with respirator use were calculated by dividing the cancer risk without a respirator by the respirator APF; 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.

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.

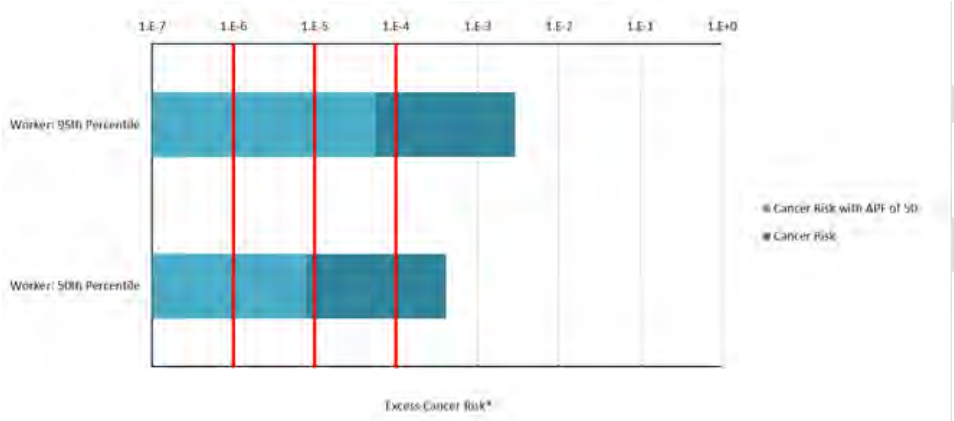

Figure 4-1. Cancer Risk Estimates for Occupational Use of Carbon Tetrachloride in Manufacturing and Processing as Reactant/Intermediate Based on Monitoring or Surrogate Monitoring Data 8 hr TWA

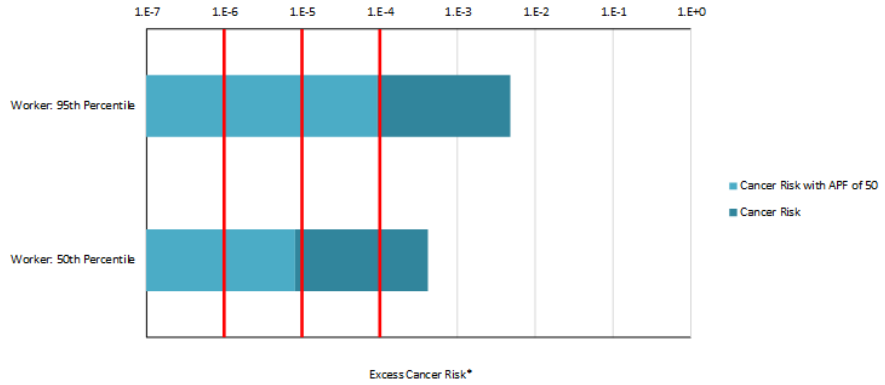

Figure 4-2. Cancer Risk Estimates for Occupational Use of Carbon Tetrachloride in Manufacturing and Processing as Reactant/Intermediate Based on Monitoring or Surrogate Monitoring Data 12 hr TWA

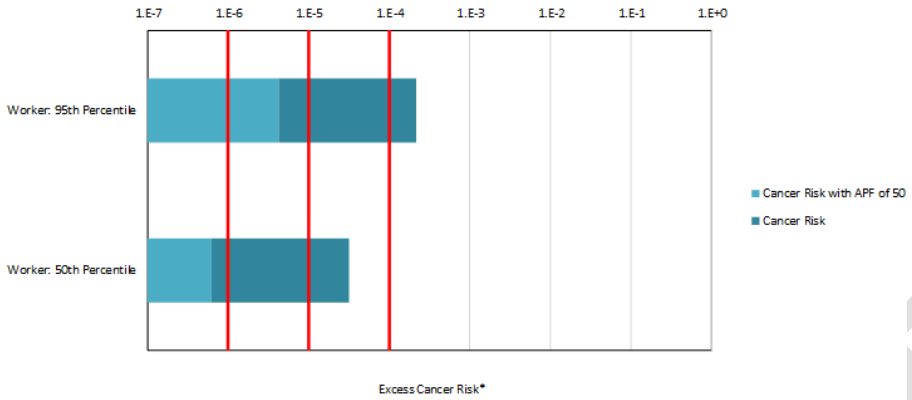

Figure 4-3. Cancer Risk Estimates for Occupational Use of Carbon Tetrachloride in Import, Processing Agent, Additive and Disposal/Recycling Based on Modeling

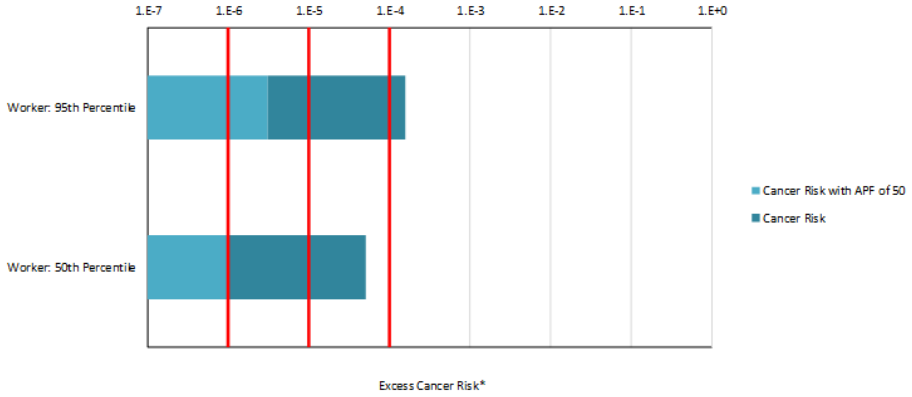

Figure 4-4. Cancer Risk Estimates for Occupational Use of Carbon Tetrachloride in Specialty Uses-DoD Based on Monitoring Data

4.2.7 Risk Estimations for Cancer Effects Following Chronic Dermal Exposures

EPA estimated the added cancer risks 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^{-4} per mg/kg for non-occluded exposures (see section 3.2.5.2.4). Table 4-12 outlines the non-cancer dermal risk estimates to workers for endpoints with and without gloves.

Table 4-12. 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: 5
Manufacture	High End	3E-4	6E-5
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-5	2E-5
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		

4.2.8 Summary of Non-cancer and Cancer Estimates for Inhalation and Dermal Exposures

Table 4-13 presents a summary of the MOEs and estimated cancer risks for the inhalation exposures from the conditions of use for carbon tetrachloride. The high-end chronic inhalation exposures for manufacturing and processing (8hr and 12hr TWA) COUs have MOEs below the benchmark MOE and cancer risks greater than the benchmark cancer risk. The central tendency chronic inhalation exposures for the same COUs have cancer risks greater than the benchmark. However, all those inhalation exposures are reduced with respirator use (APF 10, 25 or 50) resulting in MOEs greater than benchmark MOEs and cancer risks below the benchmark cancer risk.

There are cancer risks above the cancer risk benchmark for the high-end exposures for the additive, processing agent/aid, import and repackaging, specialty uses-DoD and

disposal/recycling COUs. Those high-end exposures are reduced with respirator use (APF 10) resulting in cancer risks below the benchmark.

The calculated MOEs for all the occupational dermal exposures without gloves are greater than the benchmark MOEs. The calculated cancer risks are lower than the benchmark cancer risk for the central tendency dermal exposures from all the COUs for carbon tetrachloride. The calculated cancer risks for the high-end dermal exposures for all COUs is higher than the benchmark cancer risk without the use of gloves. Those dermal high-end exposures are reduced with the use of gloves (PF =5) resulting in cancer risks below the benchmark.

4893 **Table 4-13. Summary of Estimated Non-cancer and Cancer Risks from Inhalation and Dermal Exposures[1]**

Life Cycle Stage	Category	Assessed Condition of Use	Population	Exposure Type	Exposure Levels	Risk estimates for No-PPE			Risk estimates with PPE**		
						Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE=100)	Chronic Non-cancer (inhalation /dermal benchmark MOE = 30)	Cancer Risk (cancer risk benchmark 1 in 10^4)	Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE=100)	Chronic Non-cancer (inhalation/ dermal benchmark MOE = 30)	Cancer Risk of 1 in 10^4
Manufacture	Domestic Manufacture	Domestic Manufacture	Worker (high-end and central tendency exposures) ONU (central tendency inhalation exposures)	8-hr TWA	Central Tendency	474	41	**4E-04**	N/A	N/A	4E-05 (APF =10)
					High -End	90	**8**	**3E-03**	N/A	80 (APF =10)	1E-04 (APF =25)
				12-hr TWA	Central Tendency	620	53	**4E-04**	N/A	N/A	4E-05 (APF =10)
					High -End	65	**6**	**5E-03**	N/A	60 (APF = 10)	1E-04 (APF =50)
				Dermal	Central Tendency	7,432	662	8E-05	N/A	N/A	N/A
					High -End	2,500	223	**3E-04**	N/A	N/A	6E-05 (PF =5)
	Import	Import and Repackaging	Worker (high-end and central tendency exposures) ONU (central tendency inhalation exposures)	8 hr-TWA	Central Tendency	6,316	546	3E-05	N/A	N/A	N/A
					High -End	1,200	104	**2E-04**	N/A	N/A	2E-05 (APF =10)
				Dermal	Central Tendency	7,432	662	8E-05	N/A	N/A	N/A
					High -End	2,500	223	**3E-04**	N/A	N/A	6E-05 (PF =5)
Process-ing	Processing as a reactant/ intermediate for manufacturing of HCFCs, HFCs , HFOs and PCE	Processing as Reactant/ Intermediate*	Worker (high-end and central tendency exposures)	8-hr TWA	Central Tendency	474	41	**4E-04**	N/A	N/A	4E-05 (APF =10)
					High -End	90	**8**	**3E-03**	N/A	80 (APF =10)	1E-04 (APF =25)
				12-hr TWA	Central Tendency	620	53	**4E-04**	N/A	N/A	4E-05 (APF =10)

Life Cycle Stage	Category	Assessed Condition of Use	Population	Exposure Type	Exposure Levels	Risk estimates for No-PPE			Risk estimates with PPE**		
						Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE=100)	Chronic Non-cancer (inhalation /dermal benchmark MOE = 30)	Cancer Risk (cancer risk benchmark 1 in 10^4)	Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE=100)	Chronic Non-cancer (inhalation/ dermal benchmark MOE = 30)	Cancer Risk of 1 in 10^4
			ONU (central tendency inhalation exposures)		High -End	65	**6**	**5E-03**	N/A	60 (APF = 10)	1E-04 (APF =50)
				Dermal	Central Tendency	7,432	662	8E-05	N/A	N/A	N/A
					High -End	2,500	223	**3E-04**	N/A	N/A	6E-05 (PF =5)
	Reactive ion etching (i.e., semi-conductor manufacturing)	Reactive ion etching (i.e., semi-conductor manufacturing)	Negligible - Highly controlled work areas with small quantities applied								
Distribution in commerce	Distribution	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								
Industrial/commercial use	Manufacturing of Petrochemicals-derived products and agricultural products	Industrial Processing Agent/ Aid)*	Worker (high-end and central tendency exposures)	8 hr TWA	Central Tendency	6,316	546	3E-05	N/A	N/A	N/A
					High -End	1,200	104	**2E-04**	N/A	N/A	2E-05 (APF =10)
			ONU (central tendency inhalation exposures)	Dermal	Central Tendency	7,432	662	8E-05	N/A	N/A	N/A
					High -End	2,500	223	**3E-04**	N/A	N/A	6E-05 (PF =5)
		Additive	Worker (high-end and central tendency exposures)	8 hr TWA	Central Tendency	6,316	546	3E-05	N/A	N/A	N/A
					High -End	1,200	104	**2E-04**	N/A	N/A	2E-05 (APF =10)
				Dermal	Central Tendency	7,432	662	8E-05	N/A	N/A	N/A

Life Cycle Stage	Category	Assessed Condition of Use	Population	Exposure Type	Exposure Levels	Risk estimates for No-PPE			Risk estimates with PPE**		
						Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE=100)	Chronic Non-cancer (inhalation /dermal benchmark MOE = 30)	Cancer Risk (cancer risk benchmark 1 in 10^4)	Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE=100)	Chronic Non-cancer (inhalation/ dermal benchmark MOE = 30)	Cancer Risk of 1 in 10^4
			ONU (central tendency inhalation exposures)		High -End	2,500	223	**3E-04**	N/A	N/A	6E-05 (PF =5)
	Other Basic Organic and Inorganic Chemical Manufacturing (i.e., chlorinated products used in solvents for cleaning and degreasing, adhesives, sealants, paints, coatings, asphalt)	Processing as a Reactant or Intermediate	Worker (high-end and central tendency exposures) ONU (central tendency inhalation exposures)	8-hr TWA	Central Tendency	474	41	**4E-04**	N/A	N/A	4E-05 (APF =10)
					High -End	90	**8**	**3E-03**	N/A	80 (APF =10)	1E-04 (APF =25)
				12-hr TWA	Central Tendency	620	53	**4E-04**	N/A	N/A	4E-05 (APF =10)
					High -End	65	**6**	**5E-03**	N/A	60 (APF = 10)	1E-04 (APF =50)
				Dermal	Central Tendency	7,432	662	8E-05	N/A	N/A	N/A
					High -End	2,500	223	**3E-04**	N/A	N/A	6E-05 (PF =5)
		Specialty Uses-DoD Data	Worker (high-end and central tendency exposures) ONU (central tendency inhalation exposures)	8 hr TWA	Central Tendency	1,967	346	5E-05	N/A	N/A	N/A
					High -End	981	141	**2E-04**	N/A	N/A	2E-05 (APF =10)
				Dermal	Central Tendency	7,432	662	8E-05	N/A	N/A	N/A
					High -End	2,500	223	**3E-04**	N/A	N/A	6E-05 (PF =5)
	Laboratory chemicals	Laboratory Chemicals	No data – exposure is low as laboratory typically uses small quantities inside a fume hood.								

Life Cycle Stage	Category	Assessed Condition of Use	Population	Exposure Type	Exposure Levels	Risk estimates for No-PPE			Risk estimates with PPE**		
						Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE=100)	Chronic Non-cancer (inhalation /dermal benchmark MOE = 30)	Cancer Risk (cancer risk benchmark 1 in 10^4)	Acute Non-cancer (inhalation benchmark MOE = 10; dermal benchmark MOE=100)	Chronic Non-cancer (inhalation/ dermal benchmark MOE = 30)	Cancer Risk of 1 in 10^4
Disposal	Disposal	Disposal/Recycling	Worker (high-end and central tendency exposures)	8 hr TWA	Central Tendency	6,316	546	3E-05	N/A	N/A	N/A
					High -End	1,200	104	**2E-04**	N/A	N/A	2E-05 (APF =10)
			ONU (central tendency inhalation exposures)	Dermal	Central Tendency	7,432	662	8E-05	N/A	N/A	N/A
					High -End	2,500	223	**3E-04**	N/A	N/A	6E-05 (PF =5)

[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 4-11 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.

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. Differences in the metabolism due to alcohol consumption, 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).

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.

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' 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' 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.

Occupational non-users (ONUs)

EPA evaluated inhalation risks for acute and chronic exposures for ONUs. However, EPA did not separately calculate inhalation risk estimates for ONUs and workers. 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 chemical 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 highly uncertain, and EPA has low confidence in these exposure estimates for ONUs.

Analysis of Exposure Monitoring Data

This draft 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.

In cases where there was no exposure monitoring data, EPA used monitoring data from similar conditions of use as surrogate (i.e., monitoring data from manufacturing were used as surrogate monitoring data for the processing COUs). While these conditions of use have similar worker activities contributing to exposures, it is unknown whether the results will be fully representative of worker exposure across different conditions of use.

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.

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 work day. 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 *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b).

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 Enforcement and Compliance.

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 of 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 G, 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). Some uncertainty may be associated with the use of the specific AFs used in the hazard assessment. There is no way of knowing exactly how much uncertainty to account for in the AFs. 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 influences 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 3.2.4.1.1). 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 mode of action (MOA) for carcinogenesis of carbon tetrachloride at low dose levels. Therefore, a low dose linear cancer risk model for carbon tetrachloride was used to calculate cancer risk, which is EPA's baseline approach to risk assessment when the MOA is unknown or not sufficiently supported by the evidence.

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 chronic exposures based on an equation in Jongeneel (2012). 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 bioactivation 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 (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, (2002) (see section 3.2.5.2.2).

4.5 Risk Characterization Confidence Levels

4.5.1 Environmental Risk

EPA has high confidence that there are no identified ecological risks from the TSCA conditions of use and exposure pathways within the scope of the risk evaluation for carbon tetrachloride. This is based on EPA using conservative, high end exposures and modeled surface water concentrations and the most conservative (highest toxicity)/environmentally-protective acute and chronic COC.

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* that estimates 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 work-day. 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 work day).

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 a skin irritant and sensitizer, which suggests that workers are persuaded on their own (in addition to the workplace industrial hygiene program and OSHA regulations) to wear 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. Aggregate exposures including dermal exposures with gloves are expected to be greatly influenced by the higher inhalation exposures (see retained absorbed doses from dermal exposures with gloves in Table 2-20). This greater influence by the inhalation route of exposure is also suggested by the high inhalation absorption for carbon tetrachloride and the number of activities that may generate fugitive emissions in the COUs (see section 2.4.1.7).

The EPA defines sentinel exposure as "*the exposure to 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 draft risk evaluation (see Table 2-18, Table 4-7 and Table 4-8).

5 Risk Determination

5.1 Unreasonable Risk

5.1.1 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 and 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).[21]

Under TSCA, conditions of use are defined as the circumstances, as determined by the Administrator, under which the substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of. TSCA §3(4).

An unreasonable risk may be indicated when health risks under the conditions of use are identified by comparing the estimated risks with the risk benchmarks and where the risks affect the general population or PESS, identified as relevant. For workers (which are one example of PESS), an unreasonable risk may be indicated when risks are not adequately addressed through expected use of workplace practices and exposure controls, including engineering controls or use of personal protective equipment (PPE). An unreasonable risk may also be indicated when environmental risks under the conditions of use are greater than environmental risk benchmarks. The risk estimates contribute to the evidence EPA uses to determine unreasonable risk.

EPA uses the term "indicates unreasonable risk" to indicate EPA concern for potential unreasonable risk. For non-cancer endpoints, "less than MOE benchmark" is used to indicate potential unreasonable risk; this occurs if an MOE value is less than the benchmark MOE (e.g., MOE 0.3 < benchmark MOE 30). For cancer endpoints, EPA uses the term "greater than risk benchmark" to indicate potential unreasonable risk; this occurs, for example, if the lifetime

[21] 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.

cancer risk value is greater than 1 in 10,000 (e.g., cancer risk value is 5×10^{-2} which is greater than the standard range of acceptable cancer risk benchmarks of 1×10^{-4} to 1×10^{-6}). For environmental endpoints, to indicate potential unreasonable risk EPA uses a risk quotient (RQ) value "greater than 1" (i.e., RQ >1). Conversely, EPA uses the term "does not indicate unreasonable risk" to indicate that it is unlikely that EPA has a concern for potential unreasonable risk. More details are described below.

The degree of uncertainty surrounding the MOEs, cancer risk or RQs is a factor in determining whether or not unreasonable risk is present. Where uncertainty is low, and EPA has high confidence in the hazard and exposure characterizations (for example, the basis for the characterizations is measured or monitoring data or a robust model and the hazards identified for risk estimation are relevant for conditions of use), the Agency has a higher degree of confidence in its risk determination. EPA may also consider other risk factors, such as severity of endpoint, reversibility of effect, or exposure-related considerations, such as magnitude or number of exposures, in determining that the risks are unreasonable under the conditions of use. Where EPA has made assumptions in the scientific evaluation, whether or not those assumptions are protective will also be a consideration. Additionally, EPA considers the central tendency and high-end scenarios when determining the unreasonable risk. High-end risk estimates (i.e., 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 no unreasonable risk determination for conditions of use where the substance's hazard and exposure potential, or where the risk-related factors described previously, lead EPA to determine that the risks are not unreasonable.

EPA's general approach to determining unreasonable risks to health or the environment is described in more detail in sections 5.1.2 and 5.1.3; these are not chemical-specific considerations and the examples listed may not necessarily be evaluated or considered for this chemical substance.

5.1.2 Risks to Human Health

5.1.2.1 Determining Non-Cancer Risks

Margins of exposure (MOEs) are used in EPA's risk evaluations as a starting point to estimate non-cancer risks for acute and chronic exposures. The non-cancer evaluation refers to potential 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. The benchmark for the MOE that is used 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. MOEs can provide a non-cancer risk profile by presenting a range of estimates for different non-cancer health effects for different exposure scenarios and are a widely recognized point estimate method for evaluating a range of potential non-cancer health risks from exposure to a chemical.

A calculated MOE that is less than the benchmark MOE indicates the possibility of risk to human health. Whether those risks are unreasonable will depend upon other risk-related factors, such as severity of endpoint, reversibility of effect, exposure-related considerations (e.g., duration, magnitude, frequency of exposure, population exposed), and the confidence in the information used to inform the hazard and exposure values. If the calculated MOE is greater than the benchmark MOE, generally it is less likely that there is risk.

Uncertainty factors (UFs) also play an important role in the risk estimation approach and in determining unreasonable risk. 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 in risk estimation and extrapolation for the MOE for specific endpoints and scenarios. However, these are often not the only uncertainties in a risk evaluation.

5.1.2.2 Determining Cancer Risks

EPA estimates cancer risks by determining 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 under specified use scenarios. 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., 1×10^{-6} to 1×10^{-4}) depending on the subpopulation exposed. Generally, EPA considers 1×10^{-6} to 1×10^{-4} as the appropriate benchmark for the general population, consumer users, and non-occupational PESS.[22]

For the subject chemical substance, the EPA, consistent with case law and 2017 NIOSH guidance,[23] 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 make risk determinations based on other benchmarks as appropriate. It is

[22] 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. 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).

[23] International Union, UAW v. Pendergrass, 878 F.2d 389 (D.C. Cir. 1989), citing Industrial Union Department, AFL-CIO v. American Petroleum Institute, 448 U.S. 607 (1980) ("Benzene decision"), in which it was found that a lifetime cancer risk of 1 in 1,000 was found to be clearly significant; and NIOSH (2016). Current intelligence bulletin 68: NIOSH chemical carcinogen policy, available at https://www.cdc.gov/niosh/docs/2017-100/pdf/2017-100.pdf.

important to note that exposure-related considerations (duration, magnitude, population exposed) can affect EPA's estimates of the excess lifetime cancer risk.

5.1.3 Determining Environmental Risk

To assess environmental risk, EPA generally identifies and evaluates environmental hazard data for aquatic, sediment-dwelling, and terrestrial organisms exposed under acute and chronic exposure conditions. The environmental risk includes any risks that exceed benchmark values to the aquatic and terrestrial environment from levels of the evaluated chemical found in the environment (e.g., surface water, sediment, soil, biota) based on the fate properties, relatively high potential for release, and the availability of environmental monitoring data and hazard data.

Environmental risks are estimated by calculating a RQ. The RQ is defined as:

RQ = Environmental Concentration / Effect Level

An RQ equal to 1 indicates that the exposures are the same as the concentration that causes effects. If the RQ is greater than 1, the exposure is greater than the effect concentration and there is potential for risk presumed. If the RQ is less than 1, the exposure is less than the effect concentration and unreasonable risk is not likely. The Concentrations of Concern (COC) or hazard value for certain aquatic organisms are used to calculate RQs for acute and chronic exposures. For environmental risk, EPA is more likely to determine that there is unreasonable risk if the RQ exceeds 1 for the conditions of use being evaluated. Consistent with EPA's human health evaluations, the RQ is not treated as a bright line and other risk-based factors may be considered (e.g., exposure scenario, uncertainty, severity of effect) for purposes of making a risk determination.

5.2 Risk Determination for Carbon Tetrachloride

EPA's preliminary determinations of unreasonable risk for specific conditions of use of carbon tetrachloride listed below are based on health risks to occupational non-users (ONUs) during occupational exposures.

As described in section 4, significant risks associated with more than one adverse effect (*e.g.* liver toxicity and cancer) were identified for particular conditions of use. In Table 5-1 and section 5.3 below, EPA identifies cancer as the driver endpoint for the conditions of use that EPA has determined present unreasonable risks. This is the effect that is most sensitive, and it is expected that addressing risks for this effect would address other identified risks.

- **Occupational non-users (ONUs):** EPA evaluated inhalation risks for acute and chronic exposures for occupational non-users (ONUs). However, EPA did not separately calculate inhalation risk estimates for ONUs and workers. 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 chemical 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 highly uncertain, and EPA has low confidence in these exposure estimates for ONUs. Recognizing the significant uncertainty surrounding EPA's inhalation exposure estimates for ONUs, EPA will continue to seek data on ONU inhalation exposures during the public comment period on the draft risk evaluation. In addition, because EPA is preliminarily making a finding that four COUs present an unreasonable risk for ONUs based on an increased cancer risk estimate of 4×10^{-4}, EPA will further analyze this information to determine whether this four-fold difference from the cancer risk benchmark falls within the range of uncertainty for these estimates. Dermal exposures are not expected because ONUs do not typically directly handle the carbon tetrachloride, nor they are in the immediate proximity of carbon tetrachloride. Estimated numbers of occupational non-users are in section 2.4.1.

As described below, risks to workers, general population, consumers, bystanders to consumer use, and the environment either were not relevant for these conditions of use or were evaluated and not found to be unreasonable. For the conditions of use where EPA found no unreasonable risk, EPA describes the estimated risks in section 4.2 (Table 4-7, Table 4-8, and Table 4-11)

- **Workers:** EPA evaluated workers' acute and chronic inhalation and dermal occupational exposures for cancer and non-cancer risks and determined whether any risks indicated are unreasonable. For all applicable conditions of use, acute and chronic inhalation and dermal exposure scenarios resulted in calculated MOEs and cancer risk levels that did not indicate risk (Table 4-7, Table 4-8, Table 4-9, Table 4-10, Table 4-11,Table 4-12) with expected PPE. As a result, EPA does not find unreasonable risks of injury to health of workers from acute and chronic inhalation and dermal exposures to carbon tetrachloride. EPA expects there is compliance with federal and state laws, such as 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 consistent with the applicable SDSs in a manner adequate to protect employees. Estimated numbers of workers are in section 2.4.1.

- **General population:** The Office of Chemical Safety and Pollution Prevention works closely with the offices within EPA that administer and implement the regulatory programs under these statutes. EPA believes that the TSCA risk evaluation should focus on those exposure pathways associated with TSCA uses that are not subject to the regulatory regimes discussed above because these pathways are likely to represent the greatest areas of concern to EPA. Examples of exposure pathways covered by other statutes for carbon tetrachloride such as: the ambient air pathway (i.e., carbon tetrachloride is listed as a Hazardous Air Pollutant in the Clean Air Act (CAA)), the drinking water pathway (i.e., National Primary Drinking Water Regulations (NPDWRs) are promulgated for carbon tetrachloride under the Safe Drinking Water Act), ambient water pathways (i.e., carbon tetrachloride is a priority pollutant with recommended water quality criteria for protection of human health under the CWA), the biosolids pathway (i.e., the biosolids pathway for carbon tetrachloride is currently being addressed in the CWA regulatory analytical process), and disposal pathways (i.e., carbon tetrachloride disposal is managed and prevented from further environmental release by RCRA and SDWA regulations). In addition, the Montreal Protocol and Title VI of the

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.

- **Consumers and bystanders to consumer use:** EPA did not include any consumer uses among the conditions of use within the scope of the risk evaluation for carbon tetrachloride. The CPSC banned the use of carbon tetrachloride in consumer products (excluding unavoidable residues not exceeding 10 ppm atmospheric concentration) in 1970. Therefore, EPA did not evaluate hazards or exposures to consumers or bystanders to consumer use in this risk evaluation, and there are no risk determinations for these populations.

- **Environmental risks:** EPA concluded that the surface water concentrations did not exceed the acute COC (i.e., acute RQs < 1) for aquatic species for all but one of the sites assessed (see Table 4-2). EPA determined there is not an acute aquatic concern for carbon tetrachloride after further review indicated that the one site had a one-time increased environmental release of carbon tetrachloride in 2014 due to an unexpected chemical spill. With respect to the chronic COC, due to the volatile properties of carbon tetrachloride, EPA determined that it is more likely that a chronic exposure duration will occur when there are long-term consecutive days of release versus an interval or pulse exposure, which would more likely result in an acute exposure duration. For all sites analyzed, none had more than 20 days where the chronic COC was exceeded (see Table 4-2). Consequently, EPA determined there is not an acute or chronic aquatic concern for carbon tetrachloride from the conditions of use. With respect to algae, no sites had more than 20 days where the algal COC was exceeded (see Table 4-2). Due to the quick regeneration time of many algae species, impacts to algae populations would be most likely to over long-term consecutive days of release (i.e., > 20) versus an interval or pulse exposure. Consequently, EPA determined there is not a concern for carbon tetrachloride exposure to algae from the 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, so EPA did not further evaluate exposure to sediment-dwelling organisms. Therefore, EPA does not find unreasonable environmental risks to aquatic species from the conditions of use for carbon tetrachloride (see section 4.1). Also, as explained in section 2.5.3.2 of the problem formulation (U.S. EPA, 2018d), exposure to terrestrial organisms was removed from the scope of the evaluation. This exposure pathway is considered to be covered under programs of other environmental statutes administered by EPA (e.g., CWA, RCRA, and CAA) which adequately assess and effectively manage exposures and for which long-standing regulatory and analytical processes already exist. Therefore, EPA did not evaluate hazards and exposures to terrestrial organisms in this risk evaluation, and there is no risk determination for terrestrial organisms.

Table 5-1 below presents an overview of risk determinations by condition of use. An in-depth explanation of each determination follows the table, in section 5.3.

5461 **Table 5-1. Summary of Unreasonable Risk Determinations by Condition of Use**

Condition of Use	Unreasonable Risk Determination
Domestic manufacture	**Presents an unreasonable risk of injury to health (occupational non-users)**
Import (including loading/unloading and repackaging)	Does not present an unreasonable risk of injury to health or the environment
Processing as a reactant in the production of hydrochlorofluorocarbons, hydrofluorocarbon, hydrofluoroolefin, and perchloroethylene	**Presents an unreasonable risk of injury to health (occupational non-users)**
Processing as a reactant/intermediate in reactive ion etching (i.e., semiconductor manufacturing)	Does not present an unreasonable risk of injury to health or the environment
Processing for incorporation into formulation, mixtures or reaction products (petrochemicals-derived manufacturing; agricultural products manufacturing; other basic organic and inorganic chemical manufacturing)	**Presents an unreasonable risk of injury to health (occupational non-users)** (other basic organic and inorganic chemical manufacturing).
	Does not present an unreasonable risk of injury to health or the environment (petrochemicals-derived manufacturing; agricultural products manufacturing)
Repackaging for use in laboratory chemicals	Does not present an unreasonable risk of injury to health or the environment
Recycling	Does not present an unreasonable risk of injury to health or the environment
Distribution in commerce	Does not present an unreasonable risk of injury to health or the environment
Industrial/commercial use as an industrial processing aid in the manufacture of petrochemicals-derived products and agricultural products.	Does not present an unreasonable risk of injury to health or the environment
Industrial/commercial use in the manufacture of other basic chemicals (including chlorinated compounds used in solvents, adhesives, asphalt, and paints and coatings)	**Presents an unreasonable risk of injury to health (occupational non-users)**
Industrial/commercial use in metal recovery	Does not present an unreasonable risk of injury to health or the environment
Industrial/commercial use as an additive	Does not present an unreasonable risk of injury to health or the environment
Specialty uses by the Department of Defense	Does not present an unreasonable risk of injury to health or the environment
Industrial/commercial use as a laboratory chemical	Does not present an unreasonable risk of injury to health or the environment
Disposal	Does not present an unreasonable risk of injury to health or the environment

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5.3 Detailed Risk Determinations by Conditions of Use

5.3.1 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 (occupational non-users (ONUs)).**
- Does not present an unreasonable risk of injury to health (workers).
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment dwelling and terrestrial organisms).

Unreasonable risk driver – ONUs:

- Cancer from chronic inhalation exposure.

Driver benchmark – ONUs:

- Cancer: Benchmark = 1×10^{-4}

Risk estimate – ONUs:

Cancer: Chronic inhalation risk estimate 4×10^{-4} and 5×10^{-3} (12-hr TWA) (central tendency and high end) (Table 4-11)

Risk Considerations: EPA assessed inhalation exposures using submitted monitoring data containing information on 8-hour and 12-hour shifts for this and other conditions of use for which this occupational exposure scenario is relevant. The unreasonable risk determination was based on the submitted monitoring data for 12-hour shifts. The submitted data cover two companies and are summarized in Table 2-6. There is uncertainty in the ONU risk estimate since the data did not distinguish between worker and ONU inhalation exposure estimates. To account for this uncertainty, EPA considered the central tendency estimate when determining ONU risk. As noted previously, EPA has low confidence in the exposure estimates for ONUs. For the purpose of making a risk determination for workers, EPA considered the high-end estimates. While those risk estimates for this condition of use indicate risk in the absence of PPE, the risk estimates for these pathways do not indicate risk for workers when expected use of PPE, a respirator with an APF of 50, was considered (Table 4-8 and Table 4-11). EPA's unreasonable risk determination for ONUs reflects the hazards associated with chronic exposure to carbon tetrachloride and is based on an expected absence of PPE for ONUs.

Life Cycle Stage	Category	Subcategory
Manufacture	Domestic Manufacture	Domestic manufacture

5.3.2 Manufacture- Import (includes repackaging and loading/unloading)

Section 6(b)(4)(A) unreasonable risk determination for import of carbon tetrachloride:

- Does not present an unreasonable risk of injury to health (workers and ONUs).
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment dwelling and terrestrial organisms).

Exposure scenario with highest risk estimate – workers and ONUs:

- Liver toxicity from chronic inhalation exposure and cancer from chronic dermal exposure.

Benchmarks – workers and ONUs:

- Liver toxicity: Benchmark MOE = 30.
- Cancer: Benchmark = 1×10^{-4}.

Risk estimates – workers:

- Liver toxicity: Chronic inhalation MOE 104 (high end) (Table 4-8).
- Cancer: Dermal risk estimate 6×10^{-5} (high end) with PPE (gloves PF 5) (Table 4-12).

Risk estimates – ONUs:

- Liver toxicity: Chronic inhalation MOEs 546 and 104 (central tendency and high end) (Table 4-8).
- Cancer: Chronic inhalation risk estimates 3×10^{-5} and 2×10^{-4} (central tendency and high end) (Table 4-11).

Risk Considerations: Risk estimates for workers and ONUs for acute and chronic inhalation and forworkers, chronic dermal do not indicate risk. While high-end risk estimates for this condition of use indicate risk in the absence of PPE, risk estimates for these pathways do not indicate risk for workers when expected use of PPE, a respirator with an APF of 10 and gloves with a PF of 5, was considered (Table 4-8, Table 4-11 and Table 4-12). EPA did not separately calculate risk estimates for ONUs and workers. ONU inhalation exposures are expected to be lower than inhalation exposures for workers directly handling the chemical substance; however, the relative exposure of ONUs to workers in these cases cannot be quantified. To account for this uncertainty, EPA considered the central tendency estimate when determining ONU risk. EPA's risk determination for ONUs is based on an expected absence of PPE. Dermal exposures are not expected for ONUs.

Life Cycle Stage	Category	Subcategory
Manufacture	Import	Import

5.3.3 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 (ONUs).**
- Does not present an unreasonable risk of injury to health (workers).
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment dwelling and terrestrial organisms).

Unreasonable risk driver – ONUs:

- Cancer from chronic inhalation exposure.

Driver benchmark – ONUs:

- Cancer: Benchmark = 1×10^{-4}

Risk estimate – ONUs:

- Cancer: Chronic inhalation risk estimates 4×10^{-4} and 5×10^{-3} (12-hr TWA) (central tendency and high end) (Table 4-11)

Risk Considerations: EPA assessed inhalation exposures using submitted monitoring data containing information on 8-hour and 12-hour shifts for this and other conditions of use for which this occupational exposure scenario is relevant. The unreasonable risk determination was based on the submitted monitoring data for 12-hour shifts. The submitted data cover two companies and are summarized in Table 2-6. There is uncertainty in the ONU risk estimate since the data did not distinguish between worker and ONU inhalation exposure estimates. To account for this uncertainty, EPA considered the central tendency estimate when determining ONU risk. As noted previously, EPA has low confidence in the exposure estimates for ONUs. For the purpose of making a risk determination for workers, EPA considered the high-end estimates. While those risk estimates for this condition of use indicate risk in the absence of PPE, the risk estimates for these pathways do not indicate risk for workers when expected use of PPE, a respirator with an APF of 50, was considered (Table 4-8 and Table 4-11). EPA's unreasonable risk determination for ONUs reflects the hazards associated with chronic exposure to carbon tetrachloride and is based on an expected absence of PPE for ONUs.

Life Cycle Stage	Category	Subcategory
Processing	Processing as a Reactant/ Intermediate	Hydrochlorofluorocarbons (HCFCs), Hydrofluorocarbon (HFCs) and Hydrofluoroolefin (HFOs)

Life Cycle Stage	Category	Subcategory
		Perchloroethylene (PCE)

5.3.4 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).
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment dwelling and terrestrial organisms).

Risk Considerations: 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).

Life Cycle Stage	Category	Subcategory
Processing	Processing as a Reactant/ Intermediate	Reactive ion etching (i.e., semiconductor manufacturing)

5.3.5 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 to incorporate into a formulation, mixture or reaction product (other basic organic and inorganic chemical manufacturing):

- **Presents an unreasonable risk of injury to health (ONUs).**
- Does not present an unreasonable risk of injury to health (workers).
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment dwelling and terrestrial organisms).

Unreasonable risk driver – ONUs:

- Cancer from chronic inhalation exposure

Driver benchmark – ONUs:

- Cancer: Benchmark = 1×10^{-4}

Risk estimate – ONUs:

- Cancer: Chronic inhalation risk estimates 4×10^{-4} and 5×10^{-3} (central tendency and high end) (Table 4-11)

Risk Considerations: EPA assessed inhalation exposures using submitted monitoring data containing information on 8-hour and 12-hour shifts for this and other conditions of use for which this occupational exposure scenario is relevant. The unreasonable risk determination was based on the submitted monitoring data for 12-hour shifts. The submitted data cover two companies and are summarized in Table 2-6. There is uncertainty in the ONU risk estimate since the data did not distinguish between worker and ONU inhalation exposure estimates. To account for this uncertainty, EPA considered the central tendency estimate when determining ONU risk. As noted previously, EPA has low confidence in the exposure estimates for ONUs. For the purpose of making a risk determination for workers, EPA considered the high-end estimates. While those risk estimates for this condition of use indicate risk in the absence of PPE, the risk estimates for these pathways do not indicate risk for workers when expected use of PPE, a respirator with an APF of 50, was considered (Table 4-8, Table 4-11). EPA's unreasonable risk determination for ONUs reflects the hazards associated with chronic exposure to carbon tetrachloride and is based on an expected absence of PPE for ONUs.

Section 6(b)(4)(A) unreasonable risk determination for processing carbon tetrachloride to incorporate into a formulation, mixture or reaction product (petrochemicals-derived manufacturing, agricultural products manufacturing):

- Does not present an unreasonable risk of injury to health (workers, ONUs).
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment dwelling and terrestrial organisms).

Exposure scenario with highest risk estimate – workers and ONUs:

- Liver toxicity from chronic inhalation exposure and cancer from chronic dermal exposure.

Benchmarks – workers and ONUs:

- Liver toxicity: Benchmark MOE = 30.
- Cancer: Benchmark = 1×10^{-4}.

Risk estimates – workers:

- Liver toxicity: Chronic inhalation MOE 104 (high end) (Table 4-8).
- Cancer: Chronic dermal risk estimate 6×10^{-5} (high end) with PPE (gloves PF 5) (Table 4-12).

Risk estimates – ONUs:

- Liver toxicity: Chronic inhalation MOEs 546 and 104 (central tendency and high end) (Table 4-8).
- Cancer: Chronic inhalation risk estimates 3×10^{-5} and 2×10^{-4} (central tendency and high end) (Table 4-11).

Risk Considerations: Risk estimates for workers and ONUs for acute and chronic inhalation and for workers, chronic dermal do not indicate risk. While high-end risk estimates for this condition of use indicate risk in the absence of PPE, risk estimates for these pathways do not indicate risk for workers when expected use of PPE, a respirator with an APF of 10 and gloves with PF of 5, was considered (Table 4-8, Table 4-11 and Table 4-12). EPA did not separately calculate risk estimates for ONUs and workers. ONU inhalation exposures are expected to be lower than inhalation exposures for workers directly handling the chemical substance; however, the relative exposure of ONUs to workers in these cases cannot be quantified. To account for this uncertainty, EPA considered the central tendency estimate when determining ONU risk. EPA's risk determination for ONUs is based on an expected absence of PPE. Dermal exposures are not expected for ONUs.

Life Cycle Stage	Category	Subcategory
Processing	Incorporation into Formulation, Mixture or Reaction Products	Petrochemicals-derived manufacturing; Agricultural products manufacturing; Other basic organic and inorganic chemical manufacturing.

5.3.6 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:

- Does not present an unreasonable risk of injury to health (workers and ONUs).
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment dwelling and terrestrial organisms).

Exposure scenario with highest risk estimate – workers and ONUs:

- Liver toxicity from chronic inhalation exposure and cancer from chronic dermal exposure.

Benchmarks – workers and ONUs:

- Liver toxicity: Benchmark MOE = 30.
- Cancer: Benchmark = 1×10^{-4}.

Risk estimates – workers:

- Liver toxicity: Chronic inhalation MOE 104 (high end) (Table 4-8).
- Cancer: Chronic dermal risk estimate 6×10^{-5} (high end) with PPE (gloves PF 5) (Table 4-12).

Risk estimates – ONUs:

- Liver toxicity: Chronic inhalation MOEs 546 and 104 (central tendency and high end) (Table 4-8).
- Cancer: Chronic inhalation risk estimates 3×10^{-5} and 2×10^{-4} (central tendency and high end) (Table 4-11).

Risk Considerations: Risk estimates for workers and ONUs for acute and chronic inhalation and for workers, chronic dermal do not indicate risk. While high-end risk estimates for this condition of use indicate risk in the absence of PPE, risk estimates for these pathways do not indicate risk for workers when expected use of PPE, a respirator with an APF of 10 and gloves with PF of 5, was considered (Table 4-8, Table 4-11 and Table 4-12). EPA did not separately calculate risk estimates for ONUs and workers. ONU inhalation exposures are expected to be lower than inhalation exposures for workers directly handling the chemical substance; however, the relative exposure of ONUs to workers in these cases cannot be quantified. To account for this uncertainty, EPA considered the central tendency estimate when determining ONU risk. EPA's risk determination for ONUs is based on an expected absence of PPE. Dermal exposures are not expected for ONUs.

Life Cycle Stage	Category	Subcategory
Processing	Processing - repackaging	Laboratory Chemicals

5.3.7 Processing-Recycling

Section 6(b)(4)(A) unreasonable risk determination for recycling of carbon tetrachloride:

- Does not present an unreasonable risk of injury to health (workers and ONUs).
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment dwelling and terrestrial organisms).

Exposure scenario with highest risk estimate – workers and ONUs:

- Liver toxicity from chronic inhalation exposure and cancer from chronic dermal exposure.

Benchmarks – workers and ONUs:

- Liver toxicity: Benchmark MOE = 30.
- Cancer: Benchmark = 1×10^{-4}.

Risk estimates – workers:

- Liver toxicity: Chronic inhalation MOE 104 (high end) (Table 4-8).
- Cancer: Chronic dermal risk estimate 6×10^{-5} (high end) with PPE (gloves PF 5) (Table 4-12).

Risk estimates – ONUs:

- Liver toxicity: Chronic inhalation MOEs 546 and 104 (central tendency and high end) (Table 4-8).
- Cancer: Chronic inhalation risk estimates 3×10^{-5} and 2×10^{-4} (central tendency and high end) (Table 4-11).

Risk Considerations: Risk estimates for workers and ONUs for acute and chronic inhalation and for workers, chronic dermal do not indicate risk. While high-end risk estimates for this condition of use indicate risk in the absence of PPE, risk estimates for these pathways do not indicate risk for workers when expected use of PPE, a respirator with an APF of 10 and gloves with PF of 5, was considered (Table 4-8, Table 4-11 and Table 4-12). EPA did not separately calculate risk estimates for ONUs and workers. ONU inhalation exposures are expected to be lower than inhalation exposures for workers directly handling the chemical substance; however, the relative exposure of ONUs to workers in these cases cannot be quantified. To account for this uncertainty, EPA considered the central tendency estimate when determining ONU risk. EPA's risk determination for ONUs is based on an expected absence of PPE. Dermal exposures are not expected for ONUs.

Life Cycle Stage	Category	Subcategory
Processing	Recycling	Recycling

5.3.8 Distribution in Commerce

Section 6(b)(4)(A) unreasonable risk determination for distribution of carbon tetrachloride:

- Does not present an unreasonable risk of injury to health (workers and ONUs).
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment dwelling and terrestrial organisms).

Risk Considerations: A quantitative evaluation of the distribution of carbon tetrachloride was not included in the risk evaluation because exposures and releases from distribution were considered within each condition of use.

Life Cycle Stage	Category	Subcategory
Distribution in commerce	Distribution	Distribution in commerce

5.3.9 Industrial/ Commercial Use - Industrial Processing Aid – Manufacturing of petrochemical-derived products and agricultural products

Section 6(b)(4)(A) unreasonable risk determination for use of carbon tetrachloride as an industrial processing aid in the manufacture of petrochemicals-derived products and agricultural products:

- Does not present an unreasonable risk of injury to health (workers and ONUs).
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment dwelling and terrestrial organisms).

Exposure scenario with highest risk estimate – workers and ONUs:

- Liver toxicity from chronic inhalation exposure and cancer from chronic dermal exposure.

Benchmarks – workers and ONUs:

- Liver toxicity: Benchmark MOE = 30.
- Cancer: Benchmark = 1×10^{-4}.

Risk estimates – workers:

- Liver toxicity: Chronic inhalation MOE 104 (high end) (Table 4-8).
- Cancer: Chronic dermal risk estimate 6×10^{-5} (high end) with PPE (gloves PF 5) (Table 4-12).

Risk estimates – ONUs:

- Liver toxicity: Chronic inhalation MOEs 546 and 104 (central tendency and high end) (Table 4-8).
- Cancer: Chronic inhalation risk estimates 3×10^{-5} and 2×10^{-4} (central tendency and high end) (Table 4-11).

Risk Considerations: Risk estimates for workers and ONUs for acute and chronic inhalation and for workers, chronic dermal do not indicate risk. While high-end risk estimates for this condition of use indicate risk in the absence of PPE, risk estimates for these pathways do not indicate risk for workers when expected use of PPE, a respirator with an APF of 10 and gloves with a PF of 5, was considered (Table 4-8, Table 4-11 and Table 4-12). EPA did not separately calculate risk estimates for ONUs and workers. ONU inhalation exposures are expected to be lower than inhalation exposures for workers directly handling the chemical substance; however, the relative exposure of ONUs to workers in these cases cannot be quantified. To account for this uncertainty, EPA considered the central tendency estimate when determining ONU risk. EPA's risk determination for ONUs is based on an expected absence of PPE. Dermal exposures are not expected for ONUs.

Life Cycle Stage	Category	Subcategory
Industrial/commercial use	Petrochemicals-derived Products Manufacturing	Processing aid
	Agricultural Products Manufacturing	
	Other Basic Organic and Inorganic Chemical Manufacturing	

5.3.10 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 use of carbon tetrachloride in the manufacture of other basic chemicals:

- **Presents an unreasonable risk of injury to health (ONUs).**
- Does not present an unreasonable risk of injury to health (workers).
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment dwelling and terrestrial organisms).

Unreasonable risk driver – ONUs:

- Cancer from chronic inhalation exposure.

Driver benchmark – ONUs:

- Cancer: Benchmark = 1×10^{-4}

Risk estimate – ONUs:

- Cancer: Chronic inhalation risk estimates 4×10^{-4} and 5×10^{-3} (12-hr TWA) (central tendency and high end) (Table 4-11)

Risk Considerations: EPA assessed inhalation exposures using submitted monitoring data containing information on 8-hour and 12-hour shifts for this and other conditions of use for which this occupational exposure scenario is relevant. The unreasonable risk determination was based on the submitted monitoring data for 12-hour shifts. The submitted data cover two companies and are summarized in Table 2-6. There is uncertainty in the ONU risk estimate since the data did not distinguish between worker and ONU inhalation exposure estimates. To account for this uncertainty, EPA considered the central tendency estimate when determining ONU risk. As noted previously, EPA has low confidence in the exposure estimates for ONUs. For the purpose of making a risk determination for workers, EPA considered the high-end estimates. While those risk estimates for this condition of use indicate risk in the absence of PPE, the risk estimates for these pathways do not indicate risk for workers when expected use of PPE, a

respirator with an APF of 50, was considered (Table 4-8 and Table 4-11). EPA's unreasonable risk determination for ONUs reflects the hazards associated with chronic exposure to carbon tetrachloride and is based on an expected absence of PPE for ONUs.

Life Cycle Stage	Category	Subcategory
Industrial/commercial use	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 of chlorinated compounds used in paints and coatings
		Manufacturing of inorganic chlorinated compounds (i.e., elimination of nitrogen trichloride in the production of chlorine and caustic)
		Manufacturing of chlorinated compounds used in asphalt

5.3.11 Industrial/Commercial Use – Metal recovery

Section 6(b)(4)(A) unreasonable risk determination for use of carbon tetrachloride in metal recovery:

- Does not present an unreasonable risk of injury to health (workers and ONUs).
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment dwelling and terrestrial organisms).

Exposure scenario with highest risk estimate – workers and ONUs:

- Liver toxicity from chronic inhalation exposure and cancer from chronic dermal exposure.

Benchmarks – workers and ONUs:

- Liver toxicity: Benchmark MOE = 30.
- Cancer: Benchmark = 1×10^{-4}.

Risk estimates – workers:

- Liver toxicity: Chronic inhalation MOE 104 (high end) (Table 4-8).
- Cancer: Chronic dermal risk estimate 6×10^{-5} (high end) with PPE (gloves PF 5) (Table 4-12).

Risk estimates – ONUs:

- Liver toxicity: Chronic inhalation MOEs 546 and 104 (central tendency and high end) (Table 4-8).
- Cancer: Chronic inhalation risk estimates 3×10^{-5} and 2×10^{-4} (central tendency and high end) (Table 4-11).

Risk Considerations: Risk estimates for workers and ONUs for acute and chronic inhalation and for workers, chronic dermal do not indicate risk. While high-end risk estimates for this condition of use indicate risk in the absence of PPE, risk estimates for these pathways do not indicate risk for workers when expected use of PPE, a respirator with an APF of 10 and gloves with a PF of 5, was considered (Table 4-8, Table 4-11 and Table 4-12). EPA did not separately calculate risk estimates for ONUs and workers. ONU inhalation exposures are expected to be lower than inhalation exposures for workers directly handling the chemical substance; however, the relative exposure of ONUs to workers in these cases cannot be quantified. To account for this uncertainty, EPA considered the central tendency estimate when determining ONU risk. EPA's risk determination for ONUs is based on an expected absence of PPE. Dermal exposures are not expected for ONUs.

Life Cycle Stage	Category	Subcategory
Industrial/commercial use	Other Uses	Processing aid (i.e., metal recovery).

5.3.12 Industrial/Commercial Use – Use an additive

Section 6(b)(4)(A) unreasonable risk determination for the use of carbon tetrachloride as an additive:

- Does not present an unreasonable risk of injury to health (workers and ONUs).
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment dwelling and terrestrial organisms).

Exposure scenario with highest risk estimate – workers and ONUs:

- Liver toxicity from chronic inhalation exposure and cancer from chronic dermal exposure.

Benchmarks – workers and ONUs:

- Liver toxicity: Benchmark MOE = 30.
- Cancer: Benchmark = 1×10^{-4}.

Risk estimates – workers:

- Liver toxicity: Chronic inhalation MOE 104 (high end) (Table 4-8)
- Cancer: Chronic dermal risk estimate 6×10^{-5} (high end) with PPE (gloves PF 5) (Table 4-12).

Risk estimates – ONUs:

- Liver toxicity: Chronic inhalation MOEs 546 and 104 (central tendency and high end) (Table 4-8).
- Cancer: Chronic inhalation risk estimates 3×10^{-5} and 2×10^{-4} (central tendency and high end) (Table 4-11).

Risk Considerations: Risk estimates for workers and ONUs for acute and chronic inhalation and for workers, chronic dermal do not indicate risk. While high-end risk estimates for this condition of use indicate risk in the absence of PPE, risk estimates for these pathways do not indicate risk for workers when expected use of PPE, a respirator with an APF of 10 and gloves with a PF of 5, was considered (Table 4-8, Table 4-11 and Table 4-12). EPA did not separately calculate risk estimates for ONUs and workers. ONU inhalation exposures are expected to be lower than inhalation exposures for workers directly handling the chemical substance; however, the relative exposure of ONUs to workers in these cases cannot be quantified. To account for this uncertainty, EPA considered the central tendency estimate when determining ONU risk. EPA's risk determination for ONUs is based on an expected absence of PPE. Dermal exposures are not expected for ONUs.

Life Cycle Stage	Category	Subcategory
Industrial/commercial use	Petrochemicals-derived Products Manufacturing	Additive

5.3.13 Industrial/Commercial Use – Specialty Uses – Department of Defense

Section 6(b)(4)(A) unreasonable risk determination for the specialty uses of carbon tetrachloride by the Department of Defense:

- Does not present an unreasonable risk of injury to health (workers and ONUs).
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment dwelling and terrestrial organisms).

Exposure scenario with highest risk estimate – workers and ONUs:

- Liver toxicity from chronic inhalation exposure and cancer from chronic dermal exposure.

Benchmarks – workers and ONUs:

- Liver toxicity: Benchmark MOE = 30.
- Cancer: Benchmark = 1×10^{-4}.

Risk estimates – workers:

- Liver toxicity: Chronic inhalation MOE 141 (high end) (Table 4-8).
- Cancer: Chronic dermal risk estimate 6×10^{-5} (high end) with PPE (gloves PF 5) (Table 4-12).

Risk estimates – ONUs:

- Liver toxicity: Chronic inhalation MOEs 346 and 141 (central tendency and high end) (Table 4-8).
- Cancer: Chronic inhalation risk estimates 3×10^{-5} and 2×10^{-4} (central tendency and high end) (Table 4-11).

Systematic Review confidence rating (hazard): High.

Systematic Review confidence rating (inhalation exposure): High.

Risk Considerations: Risk estimates for workers and ONUs for acute and chronic inhalation and for workers, chronic dermal do not indicate risk. While high-end risk estimates for this condition of use indicate risk in the absence of PPE, risk estimates for these pathways do not indicate risk for workers when expected use of PPE, a respirator with an APF of 10 and gloves with a PF of 5, was considered (Table 4-8, Table 4-11 and Table 4-12). EPA did not separately calculate risk estimates for ONUs and workers. ONU inhalation exposures are expected to be lower than inhalation exposures for workers directly handling the chemical substance; however, the relative exposure of ONUs to workers in these cases cannot be quantified. To account for this uncertainty, EPA considered the central tendency estimate when determining ONU risk. EPA's risk determination for ONUs is based on an expected absence of PPE. Dermal exposures are not expected for ONUs.

Life Cycle Stage	Category	Subcategory
Industrial/commercial use	Other Uses	Specialty uses (i.e., Department of Defense Data

5.3.14 Industrial/Commercial Use – Laboratory Chemical

Section 6(b)(4)(A) unreasonable risk determination for the use of carbon tetrachloride as a laboratory chemical:

- Does not present an unreasonable risk of injury to health (workers and ONUs).
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment dwelling and terrestrial organisms).

Risk Considerations: As discussed in section 2.4.1.7.8, EPA does not have data to assess worker exposures to carbon tetrachloride during laboratory use. However, due to the expected safety practices when using this chemical in a laboratory setting, carbon tetrachloride is applied in small quantities under a fume hood, thus reducing the potential for inhalation exposures.

Life Cycle Stage	Category	Subcategory
Industrial/commercial use	Laboratory chemicals	Laboratory chemical

5.3.15 Disposal

Section 6(b)(4)(A) unreasonable risk determination for disposal of carbon tetrachloride:

- Does not present an unreasonable risk of injury to health (workers and ONUs).
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment dwelling and terrestrial organisms).

Exposure scenario with highest risk estimate – workers and ONUs:

- Liver toxicity from chronic inhalation exposure and cancer from chronic dermal exposure.

Benchmarks – workers and ONUs:

- Liver toxicity: Benchmark MOE = 30.
- Cancer: Benchmark = 1×10^{-4}.

Risk estimates – workers:

- Liver toxicity: Chronic inhalation MOE 104 (high end) (Table 4-8).
- Cancer: Chronic dermal risk estimate 6×10^{-5} (high end) with PPE (gloves PF 5) (Table 4-12).

Risk estimates – ONUs:

- Liver toxicity: Chronic inhalation MOEs 546 and 104 (central tendency and high end) (Table 4-8).
- Cancer: Chronic inhalation risk estimates 3×10^{-5} and 2×10^{-4} (central tendency and high end) (Table 4-11).

Risk Considerations: Risk estimates for workers and ONUs for acute and chronic inhalation and for workers, chronic dermal do not indicate risk. While high-end risk estimates for this condition of use indicate risk in the absence of PPE, risk estimates for these pathways do not indicate risk for workers when expected use of PPE, a respirator with an APF of 10 and gloves with a PF of 5, was considered (Table 4-8, Table 4-11 and Table 4-12). EPA did not separately calculate risk estimates for ONUs and workers. ONU inhalation exposures are expected to be lower than

inhalation exposures for workers directly handling the chemical substance; however, the relative exposure of ONUs to workers in these cases cannot be quantified. To account for this uncertainty, EPA considered the central tendency estimate when determining ONU risk. EPA's risk determination for ONUs is based on an expected absence of PPE. Dermal exposures are not expected for ONUs.

Life Cycle Stage	Category	Subcategory
Disposal	Disposal	Industrial pre-treatment
		Industrial wastewater treatment
		Publicly owned treatment works (POTW)
		Underground injection
		Municipal landfill
		Hazardous landfill
		Other land disposal

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7 APPENDICES

Appendix A REGULATORY HISTORY

A.1 Federal Laws and Regulations

Table_Apx A-1. Federal Laws and Regulations

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

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.
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 contaminants which 1. may have an adverse effect on the health of persons; 2. are known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and 3. in the sole judgment of the Administrator, regulation of the	Carbon tetrachloride is subject to National Primary Drinking Water Regulations (NPDWR) under SDWA and EPA has set a MCLG of zero and an enforceable MCL of 0.005 mg/L (56 FR 3526 January 30, 1991).

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
	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.	
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 261.31(a)), and spent degreasing solvent (F001) (40 CFR 261.33(f)) (45 FR 33084 May 19, 1980). RCRA solid waste that leaches 0.5 mg/L or more carbon

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
		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). Carbon tetrachloride is also listed as an “Inactive Ingredient for approved Drug Products” by FDA (FDA

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

A.2 State Laws and Regulations

Table_Apx A-2. State Laws and Regulations

State Actions	Description of Action
State agencies of interest	
State permissible exposure limits	California PEL: 12.6 mg/L (Cal Code Regs. Title 8, section 5155), Hawaii PEL: 2 ppm (Hawaii Administrative Rules section 12-60-50).
State 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 Actions	Description of Action
State agencies of interest	
State air regulations	Allowable Ambient Levels (AAL): Rhode Island (12 R.I. Code R. 031-022), New Hampshire (RSA 125-I:6, ENV-A Chap. 1400).
State drinking water standards and guidelines	Arizona (14 Ariz. Admin. Register 2978, August 1, 2008), California (Cal Code Regs. Title 26, section 22-64444), Delaware (Del. Admin. Code Title 16, section 4462), Connecticut (Conn. Agencies Regs. section 19-13-B102), Florida (Fla. Admin. Code R. Chap. 62-550), Maine (10 144 Me. Code R. Chap. 231), Massachusetts (310 Code Mass. Regs. section 22.00), Minnesota (Minn R. Chap. 4720), New Jersey (7:10 N.J Admin. Code section 5.2), Pennsylvania (25 Pa. Code section 109.202), Rhode Island (14 R.I. Code R. section 180-003), Texas (30 Tex. Admin. Code section 290.104).
Other	In California, carbon tetrachloride was added to the Proposition 65 list in 1987 (Cal. Code Regs. Title 27, section 27001). Carbon tetrachloride is on the MA Toxic Use Reduction Act (TURA) list of 1989 (301 Code Mass. Regs. section 41.03).

A.3 International Laws and Regulations

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

Country/Organization	Requirements and Restrictions
Regulatory Actions by other Governments and Tribes	
Montreal Protocol	Carbon tetrachloride is considered an ozone depleting substance (ODS) and its production and use are controlled under the 1987 Montreal Protocol on Substances That Deplete the Ozone Layer and its amendments (Montreal Protocol Annex B – Group II).
Canada	Carbon tetrachloride is on the Canadian List of Toxic Substances (CEPA 1999 Schedule 1). Other regulations include: Federal Halocarbon Regulations, 2003 (SOR/2003-289). ODS Regulations, 1998 (SOR/99-7).
European Union (EU)	Carbon tetrachloride was evaluated under the 2012 Community rolling action plan (CoRAP) under regulation (European Commission [EC]) No 1907/2006 - REACH (Registration, Evaluation,

Country/Organization	Requirements and Restrictions
	Authorisation and Restriction of Chemicals) ECHA database. Accessed April 18, 2017). Carbon tetrachloride is restricted by regulation (EC) No 2037/2000 on substances that deplete the ozone layer.
Australia	Carbon tetrachloride was assessed under Environment Tier II of the Inventory Multi-Tiered Assessment and Prioritisation (IMAP), and there have been no reported imports of the chemical as a feedstock in the last 10 years (National Industrial Chemicals Notification and Assessment Scheme, NICNAS, 2017, *Environment Tier II Assessment for Methane, Tetrachloro-*. Accessed April, 18 2017).
Japan	Carbon tetrachloride is regulated in Japan under the following legislation: • Industrial Safety and Health Act (ISHA) • Act on the Evaluation of Chemical Substances and Regulation of Their Manufacture, etc. (Chemical Substances Control Law (CSCL)) • Act on Confirmation, etc. of Release Amounts of Specific Chemical Substances in the Environment and Promotion of Improvements to the Management Thereof • Poisonous and Deleterious Substances Control Act • Act on the Protection of the Ozone Layer through the Control of Specified Substances and Other Measures • Air Pollution Control Law • Water Pollution Control Law • Soil Contamination Countermeasures Act (National Institute of Technology and Evaluation (NITE) Chemical Risk Information Platform (CHIRP). Accessed April 13, 2017).
Australia, Austria, Belgium, Canada, Denmark, EU, Finland, France, Germany, Ireland, Israel, Japan, Latvia, New Zealand, People's Republic of China, Poland, Singapore, South Korea, Spain, Sweden, Switzerland, United Kingdom	Occupational exposure limits (OELs) for carbon tetrachloride. (GESTIS International limit values for chemical agents (Occupational exposure limits, OELs) database. Accessed April 18, 2017).
Basel Convention	Halogenated organic solvents (Y41) are listed as a category of waste under the Basel Convention-Annex I. Although the United States is

Country/Organization	Requirements and Restrictions
	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.

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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. *Draft 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, 2019c*).*

    b. *Draft 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, 2019i).

    c. *Draft 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, 2019f).

    d. *Draft Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Ecological Hazard Studies. Docket EPA-HQ-OPPT-2019-0499* (U.S. EPA, 2019e).

    e. *Draft 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, 2019h).

    f. *Draft Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Epidemiological Studies. Docket EPA-HQ-OPPT-2019-0499* (U.S. EPA, 2019g).

    g. *Draft 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, 2019d).

2. *Draft Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment Docket. EPA-HQ-OPPT-2019-0499* (U.S. EPA, 2019b)- 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. *Draft Risk Evaluation for Carbon Tetrachloride, Supplemental Excel File on Occupational Risk Calculations. Docket EPA-HQ-OPPT-2019-0499 (*U.S. EPA, 2019a*).*

Appendix C FATE AND TRANSPORT

Table_Apx 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 ug/L, liquid retention: 2 days): <0.1 ug/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

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Table_Apx 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_Apx 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

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6829 **Table_Apx 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. Adsorption/desorption: Carbon tetrachloride. 2017.)	(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	1.49±0.06%, pH 4.97±0.08		Sorption parameter: Koc: 143.6 +/-32.11; Sorption parameter: Kp:	The reviewer agreed with this study's overall quality level. Study	(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
	dried and sieved to 2 mm			2.140 +/-0.478	reported in ECHA (ECHA. Adsorption/desorption: Carbon tetrachloride. 2017.)		
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,		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
		5.3±0.6 Buried A, 1.4±0.5 Loess C					
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	Carbon content: extracted peat 64.0%, peat 57.1%, muck 53.1%, cellulose 44.4%; oxygen content: extracted peat		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
	reference peat soil; muck soil from Michigan State University Research Farm Lainsburg, MI; cellulose from Aldrich	28.9%, peat 33.9%, muck 37.5%, 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 CT conc 26 ug/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,	OC 0.8%; sand 56.4% clay		Sorption parameter: Monolayer adsorption capacity Xm:	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
	Inc.) sieved to 210-250 um analyzed by Soil Testing Laboratory of Texas A&M University	28.9%, silt 14.7%		7.3; 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 CT 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	boreal forest soil in Alberta, Canada; sub-	Not reported		Sorption parameter: τ-soil (partial lifetime of	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
and soil gas for determination of soil flux	tropical forest soil in South Florida, tropical forest soil in Puerto Rico			atmospheric CT 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/equi-librium 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,		Sorption parameter: Henry's isotherm constant K:	The reviewer downgraded this study's overall quality rating.	(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
		6.3% silt, 2.0% clay, pH 4.7		1.123 Sorption parameter: normalized isotherm constant Ki: 0.375	They noted: No controls 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	Organic carbon: 0.38-2.87%		Sorption parameter: Koc: 49-89	The reviewer downgraded this study's overall quality rating. They noted: Limited	(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
	Illinois River IL, Mississippi River MO, and Yellow River China				data was reported; no 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 CT 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)	The reviewer downgraded this study's overall quality rating. They noted: Study details were not	(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
				adsorptions on the 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	provided, and results 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

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6833 **Table_Apx 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

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Appendix D RELEASES TO THE ENVIRONMENT

Table_Apx D-1. Summary of Carbon Tetrachloride TRI Releases to the Environment for from 2018 (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, 2018f).
[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.

Table E-1. 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	280	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[b]	0	0	0	--	--
OH0007269	Dover Chemical Corp	320[c]	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

NPDES	Facility Name	Total Pounds Discharged Per Year (lbs/yr)						
		2014	2015	2016	2017	2018	5yr Mean	5yr Median
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 Cropscience	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]San Diego Sea World facility (CA0107336) was not included in the analysis since the reported level is above permit discharge limits; noncompliance and spills are not in the scope of this risk evaluation.

[c]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)

6862 **Table E-2. Surface Water Carbon Tetrachloride Concentrations for Acute (20 day) and Chronic (250 day) Scenarios and**
6863 **Amphibian Concentration of Concern Comparisons**

NPDES	Facility Name	Amount Discharged for 20 days (kg/day)	20 Day Stream Conc. (µg/L)	Days Acute COC[a] Exceeded (PDM)	Amount Discharged for 250 days (kg/day)	250 Day Stream Conc. (µg/L)	Days Chronic 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	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[c]						
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

NPDES	Facility Name	Amount Discharged for 20 days (kg/day)	20 Day Stream Conc. (µg/L)	Days Acute COC[a] Exceeded (PDM)	Amount Discharged for 250 days (kg/day)	250 Day Stream Conc. (µg/L)	Days Chronic COC[b] Exceeded (PDM)
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 Cropscience	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
LA0002933	Occidental Chem Corp, Geismar	0.01	4.9E-05	0	0.0	4.0E-06	0

[a]Acute COC = 90 µg/L
[b]Chronic COC = 3 µg/L
[c]San Diego Sea World facility (CA0107336) was not included in the analysis since the reported level is above permit discharge limits; noncompliance and spills are not in the scope of this risk evaluation.

6872 **Table E-3. Surface Water Carbon Tetrachloride Concentrations for Acute (20 day) and Chronic (250 day) Scenarios and Algal**
6873 **Concentration of Concern Comparisons**

NPDES	Facility Name	Amount Discharged for 20 days (kg/day)	20 Day Stream Conc. (µg/L)	Days Algal COC[a] Exceeded (PDM)	Amount Discharged for 250 days (kg/day)	250 Day Stream Conc. (µg/L)	Days Algal COC[a] 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]						
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

NPDES	Facility Name	Amount Discharged for 20 days (kg/day)	20 Day Stream Conc. (µg/L)	Days Algal COC[a] Exceeded (PDM)	Amount Discharged for 250 days (kg/day)	250 Day Stream Conc. (µg/L)	Days Algal COC[a] Exceeded (PDM)
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 Cropscience	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
LA0002933	Occidental Chem Corp, Geismar	0.01	4.9E-05	0	0.0	4.0E-06	0

[a]Algal COC = 7 µg/L
[b]San Diego Sea World facility (CA0107336) was not included in the analysis since the reported level is above permit discharge limits; noncompliance and spills are not in the scope of this risk evaluation.

6878 **Table E-3. Surface Water Carbon Tetrachloride Concentrations for Acute (20 day) and Chronic (250 day) Scenarios and Algal**
6879 **Concentration of Concern Comparison**

NPDES	Facility Name	Amount Discharged for 20 days (kg/day)	20 Day Stream Conc. (µg/L)	Days Algae COC[a] Exceeded (PDM)	Amount Discharged for 250 days (kg/day)	250 Day Stream Conc. (µg/L)	Days Algae 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	3.5	0
WV0004359	Natrium Plant	0.29	3.4E-02	0	0.02	2.9E-03	0
CA0107336	Sea World, San Diego[c]						
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

NPDES	Facility Name	Amount Discharged for 20 days (kg/day)	20 Day Stream Conc. (µg/L)	Days Algae COC[a] Exceeded (PDM)	Amount Discharged for 250 days (kg/day)	250 Day Stream Conc. (µg/L)	Days Algae COC[b] Exceeded (PDM)
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 Cropscience	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
LA0002933	Occidental Chem Corp, Geismar	0.01	4.9E-5	0	0.0	4.0E-06	0

[a,b]Algal COC = 7 µg/L

[c]San Diego Sea World facility (CA0107336) was not included in the analysis since the reported level is above permit discharge limits; noncompliance and spills are not in the scope of this risk evaluation

Appendix F OCCUPATIONAL EXPOSURES

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 *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure Assessment* (U.S. EPA, 2019b).

Appendix G ENVIRONMENTAL HAZARDS

G.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 14 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, 2019e). The data quality extraction results for carbon tetrachloride environmental hazard are presented in Table_Apx G-1.

Table_Apx G-1. Aquatic toxicity studies that were 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, Nominal	Increased body weight gain	(Weber et al., 1979)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Rainbow trout (*Oncorhynchus mykiss*)	Fresh	24-hour	NOAEL = 2 mL/kg body weight	0, 2.0 mL/kg	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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
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)	Intra-peritoneal, 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)	Intra-peritoneal, Nominal, Solvent: DMSO	Hepatic lesions	(Kotsanis and Metcalfe, 1988)	High

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
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)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Intra-peritoneal, Nominal, Solvent: Arachis oil	Serum albumin	(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)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Intra-peritoneal, Nominal, Solvent: Arachis oil	Glutathione peroxidase 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	3-day	LOAEL = 0.5 mL/kg body weight (30% v/v solution)	0, 0.5 mL/kg body weight (30% v/v solution)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Intra-peritoneal, Nominal, Solvent: Arachis oil	Glutamic-oxaloacetic transaminase activity	(Jia et al., 2013)	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)	Intra-peritoneal, Nominal, Solvent: Arachis oil	Total antioxidant capacity	(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)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Intra-peritoneal, Nominal, Solvent: Arachis oil	Toll-like receptor 4 protein level in liver	(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)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Intra-peritoneal, Nominal, Solvent: Arachis oil	Liver histopathology	(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)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Intra-peritoneal, Nominal, Solvent: Arachis oil	Interleukin 1 beta gene expression	(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)	Intra-peritoneal, 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)	Intra-peritoneal, 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

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	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
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

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	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)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Intra-peritoneal, Nominal, Solvent: Olive oil	Malondialdehyde content in liver	(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)	Intra-peritoneal, 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)	Intra-peritoneal, Nominal, Solvent: Olive oil	Glutamic-oxaloacetic 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	72-hour	LOAEL = 5 mL/kg body weight (30% v/v solution)	0, 5 mL/kg body weight (30% v/v solution)	Intra-peritoneal, 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)	Intra-peritoneal, 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)	Medium
Bluegill (*Lepomis macrochirus*)	Fresh	96-hour	LC_{50} = 27 mg/L	Not reported	Static, Nominal, Solvent: Not specified	Mortality	(Buccafusco et al., 1981)	Medium
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
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

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	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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, Nominal	Sodium/potassium ratio 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	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intra-peritoneal, 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	Intra-peritoneal, Nominal	Histological changes in the gill, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, Nominal	Histological changes in the trunk 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, Nominal	Magnesium 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, Nominal	Anion gap	(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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, Nominal	Histological changes in the liver, 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	Intra-peritoneal, Nominal	Histological changes in the liver, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, Nominal	Histological changes in the trunk kidney, regenerative	(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	Intra-peritoneal, Nominal	Histological changes in the head 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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	Intra-peritoneal, 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

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
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
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

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
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
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)	High
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)	High
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)	High
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

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
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								
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
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

Test Species	Fresh/ Salt Water	Duration	End-point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
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

G.2 Hazard Identification- Aquatic

Relevant data from the screened literature are summarized below (Table_Apx G-2) as ranges (min-max). Studies with data quality evaluation results of 'medium' to 'high' were used to characterize the environmental hazards of carbon tetrachloride. Table_Apx G-2 provides the species, media, duration, endpoint, effects, etc. for the acceptable acute 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) (medium); 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 - 181 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 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}). 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).

Table_Apx G-2. Aquatic toxicity studies that were 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) (medium); (Dawson et al., 1977) (medium)
	Aquatic invertebrates	L/EC_{50}	11.10 – 224.0	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)
	Amphibians	LC_{50}	**0.900** – 22.42	mg/L	Teratogenesis Leading to Mortality[c]	(Birge et al., 1980) (high); (Black et al., 1982) (high)
	Acute COC	0.09		mg/L		

Exposure Duration	Test organism	Endpoint	Hazard value[a]	Units	Effect Endpoint	References[b]
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)
	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)
		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]The study authors defined embryo-larval teratogenesis as the percent of survivors with gross and debilitating abnormalities likely to result in eventual mortality.

Toxicity to Sediment and Terrestrial Organisms

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. No relevant (on-topic) toxicity data were available for carbon tetrachloride to birds. Hazard studies for sediment and terrestrial organisms are not likely to be conducted because exposure to carbon tetrachloride by these organisms is not expected due to the physical, chemical, and fate properties of the chemical.

G.3 Weight of Evidence

During the data integration stage of systematic review, EPA analyzed, synthesized, and integrated the data/information. This involved weighing scientific evidence for quality and relevance, using a Weight of 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 H.2) and develop COCs as described in Appendix H.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 H-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); (Lee et al., 2006)) are contained within the on-topic data evaluation section of Appendix H.2, 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 Appendix Table G-2 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 0.010 – 92.5 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 0.09 mg/L and LC_{10} to 0.03 mg/L, respectively, from two high quality 9-days 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 0.09 mg/L and LC_{10} of 0.03 mg/L were used to derive an acute COC in Appendix Section G.5 and chronic COC in Appendix Section G.6. These values were from two scientific articles that EPA assigned an overall quality level of high and represents three species of amphibians.

The 72-hour algal EC_{10} of 0.0717 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 7G.7. This value is from one algal study that EPA assigned an overall quality of high.

G.4 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, 2013b). While there was data representing amphibians, fish, aquatic invertebrates, and aquatic plants, the data were not robust enough to conduct a more detailed species sensitivity distribution analysis. 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, 2013b), 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 is used (U.S. EPA, 2013b, 2012b).

G.5 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 experimental amphibian endpoint, is used as the conservative (screening-level) hazard level in this risk evaluation for carbon tetrachloride.

G.6 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.

G.7 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 experimental algal endpoint, is used as the lower bound hazard level for algal toxicity in this risk evaluation for carbon tetrachloride.

G.8 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, 2019e).

Appendix H 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_Apx H-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/m3	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/ cm3)	Once; contact for 5 days	LOAEL= 260 mg/ cm3 [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

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, 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
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= 125 ppm	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

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, 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
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

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	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
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/ cm2	15 minutes to 16 hours	LOAEL= 513 mg/ cm2 (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/ cm2	15 minutes to 16 hours	LOAEL= 513 mg/ cm2	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	NOAEL= 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

7139 **Table_Apx H-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)	Unnacceptable
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 2 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).

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Appendix I GENOTOXICITY

The *in vitro* and *in vivo* genotoxicity databases for carbon tetrachloride, including their limitations are described below.

I.1 In vitro Genotoxicity and Mutation

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

Bacterial mutagenicity with reference to strains more capable to detect oxidative damage.
Many experiments have tested carbon tetrachloride for mutagenesis in standard salmonella revers 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 twofold 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 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_Apx I-1. Bacterial mutagenesis data in systems believed relevant to detection of oxidative damage to DNA – excerpted from 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)
EE. coli WP2/pKM101	Reverse mutation	Gas phase exposure in a gas sampling bag for 24 hrs	+	+[e]	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; T: Toxicity; ND: No Data

[e] 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_Apx I-2. Chromosomal changes in *in vitro* studies mammalian cells from liver, kidney or lung; or cells with CYP2E1 genetic capability added – excerpted from 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[d]	(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	+[e] (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 fourfold) 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 town 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	+[e] (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

[e] 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.

[d] Results for the individual donors are presented.

I.2 In vivo Genotoxicity

Assessment of potential genotoxic effects of carbon tetrachloride should focus first on effects in the *in vivo* liver - CYP2E1 activity largely resides in the liver. Data from other tissues (lung and kidney) may supplement the liver data to a degree as these tissues have lesser but maybe relevant CYP2E1 capability.[24] It is not apparent that data for other tissues will reflect the CYP2E1 metabolism of CT.

The carbon tetrachloride database is sparse for *in vivo* tests studies of mutation and chromosomal changes in liver tissue (and such tests appear unavailable for the kidney and lung). Available studies as cited in EPA IRIS Assessment (U.S. EPA, 2010).

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 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…"

UDS

A number of rodent experiments assessed unscheduled DNA synthesis (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 dose not on balance demonstrate carbon tetrachloride genotoxicity, neither does is represent a fully sensitive body of studies to test for such effects.

[24] 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.

7292 **Table_Apx I-3.** *In vivo* mutation and chromosomal change studies for carbon tetrachloride in liver tissue – excerpted from EPA IRIS
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Test system	Endpoint	Test conditions	DNA adducts IRIS (2010) descriptor[a]	Dose[b]	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 CT (a much lower dose than used in many shorter term in vivo experiments. The sensitivity of this experiment could have been strengthened if CT 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. CT mutation frequesncy exceeded controls by 60% which was not indicated as significant. se 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 (DC-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)
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)

Test system	Endpoint	Test conditions	DNA adducts IRIS (2010) descriptor[a]	Dose[b]	Reference
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) [g]	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)

[a] + = positive, ± = equivocal or weakly positive, – = negative, (T) = toxicity
[b] i.m. = intramuscular, i.p. intraperitoneal, i.g. = intragastric gavage, s.c. = subcutaneous.

Appendix J 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_Apx J-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
40	251.6	3.482	72.26	-10.09	39.11	6.434	41.50

Appendix K 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, we believe there is direct potential for this compound to contribute to both of these processes.
- Other processes not evaluated in the process 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 CCl3•, 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.
(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) CT administration increases cell replication in liver tissue. A 1x administration of 40 mg/kg carbon tetrachloride increased BrdU uptake by cells in the peri-portal zone at 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 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 also 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, Ferroptosis: Death by Lipid Peroxidation. Trends Cell Biol. 26(3):165-176). 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 CT 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 deferrioxamine before carbon tetrachloride administration reduced both the liver toxicity (indicated by plasma GPT and SDH activity levels) and reduced lipid peroxidation (as indicated by exhaled ethane levels) (Siegers et al., 1988). The CT 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 deferrooxamine treatment. This suggests that the response observed was specifically relevant to carbon tetrachloride's toxic mode of action.

(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]

(8) Data on carbon tetrachloride increased GST-P liver foci in male rate 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

[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 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.

these foci thus 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 over states the available evidence. In the case of the 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 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.

[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.

The submitted example case scored dose response concordance as providing "moderate" support most of the proposed key events in the cytotoxicity MOA. In my 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., (2000) 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 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 (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 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_Apx K-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)	Unnaceptable
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 2 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).