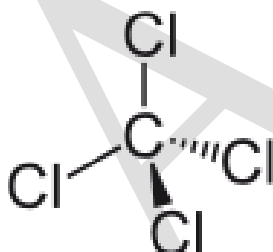


**Draft Risk Evaluation for  
Carbon Tetrachloride  
(Methane, Tetrachloro-)  
CASRN: 56-23-5**



*January 2020 DRAFT*

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318  
319 **Docket**

320 Supporting information can be found in public docket: [EPA-HQ-OPPT-2016-0733](https://www.epa.gov/epaospr/oppt-2016-0733).

321  
322 **Disclaimer**

323 Reference herein to any specific commercial products, process or service by trade name, trademark,  
324 manufacturer or otherwise does not constitute or imply its endorsement, recommendation or favoring by  
325 the United States Government.

326 **ABBREVIATIONS**

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327	°C	Degrees Celsius
328	AAL	Allowable Ambient Levels
329	ACGIH	American Conference of Government Industrial Hygienists
330	ADC	Average Daily Concentration
331	AEC	Acute Exposure Concentration
332	AIA	Aerospace Industries Association
333	AIHA	American Industrial Hygiene Association
334	APF	Assigned Protection Factor
335	atm	Atmosphere(s)
336	ATSDR	Agency for Toxic Substances and Disease Registries
337	AWQC	Ambient Water Quality Criteria
338	BCF	Bioconcentration Factor
339	BLS	Bureau of Labor Statistics
340	BUN	Blood Urea Nitrogen
341	CAA	Clean Air Act
342	CASRN	Chemical Abstract Service Registry Number
343	CBI	Confidential Business Information
344	CCl <sub>4</sub>	Carbon tetrachloride
345	CDR	Chemical Data Reporting
346	CEHD	Chemical Exposure Health Data
347	CERCLA	Comprehensive Environmental Response, Compensation and Liability Act
348	CFC	Chlorofluorocarbon
349	cm <sup>2</sup>	Square Centimeter(s)
350	cm <sup>3</sup>	Cubic Centimeter(s)
351	CPN	Chronic progressive nephropathy
352	CNS	Central Nervous System
353	COC	Concentration of Concern
354	CoRAP	Community Rolling Action Plan
355	CPSC	Consumer Product Safety Commission
356	CS <sub>2</sub>	Carbon Disulfide
357	CSATAM	Community-Scale Air Toxics Ambient Monitoring
358	CSCL	Chemical Substances Control Law
359	CSF	Cancer Slope Factor
360	CSM	Chlorosulphonated polyolefin
361	CYP450	Cytochrome P450
362	CWA	Clean Water Act
363	DMR	Discharge Monitoring Report
364	DNA	Deoxyribonucleic Acid
365	DoD	Department of Defense
366	DT50	Dissipation Time for 50% of the compound to dissipate
367	EC	European Commission
368	ECHA	European Chemicals Agency
369	EDC	Ethylene Dichloride
370	ELCR	Excess Lifetime Cancer Risk
371	EPA	Environmental Protection Agency
372	EPCRA	Emergency Planning and Community Right-to-Know Act

373	ESD	Emission Scenario Document
374	EU	European Union
375	FDA	Food and Drug Administration
376	FFDCA	Federal Food, Drug and Cosmetic Act
377	FHSA	Federal Hazardous Substance Act
378	FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
379	g	Gram(s)
380	GS	Generic scenario
381	HAP	Hazardous Air Pollutant
382	HCFC	Hydrochlorofluorocarbons
383	HCl	Hydrochloric Acid
384	HFC	Hydrofluorocarbon
385	HFO	Hydrofluoroolefin
386	HSIA	Halogenated Solvents Industry Alliance
387	HVLP	High Volume, Low Pressure
388	IBC	Intermediate Bulk Containers
389	IDLH	Immediately Dangerous to Life and Health
390	IMAP	Inventory Multi-Tiered Assessment and Prioritisation
391	IRIS	Integrated Risk Information System
392	ISHA	Industrial Safety and Health Act
393	kg	Kilogram(s)
394	km	Kilometer(s)
395	L	Liter(s)
396	LADC	Lifetime Average Daily Concentration
397	lb	Pound
398	LOD	Limit of Detection
399	log K <sub>oc</sub>	Logarithmic Soil Organic Carbon:Water Partitioning Coefficient
400	log K <sub>ow</sub>	Logarithmic Octanol:Water Partition Coefficient
401	m <sup>3</sup>	Cubic Meter(s)
402	MACT	Maximum Achievable Control Technology
403	MCL	Maximum Contaminant Level
404	MCLG	Maximum Contaminant Level Goal
405	MEMA	Motor and Equipment Manufacturer Association
406	mg	Milligram(s)
407	mmHg	Millimeter(s) of Mercury
408	MP	Montreal Protocol
409	mPa·s	Millipascal(s)-Second
410	NAC/AEGL	National Advisory Committee for Acute Exposure Guideline Levels
411	NAICS	North American Industrial Classification System
412	NATA	National Air Toxics Assessment
413	NATTS	National Air Toxics Trends Stations
414	NEI	National Emissions Inventory
415	NESHAP	National Emission Standards
416	NHANES	National Health and Nutrition Examination Survey
417	NIOSH	National Institute for Occupational Safety and Health
418	NPDES	National Pollutant Discharge Elimination System
419	NPDWR	National Primary Drinking Water Regulations
420	NTP	National Toxicology Program

421	NWQMC	National Water Quality Monitoring Council
422	OARS	Occupational Alliance for Risk Science
423	OBOD	Open Burn/Open Detection
424	OCSPP	Office of Chemical Safety and Pollution Prevention
425	ODS	Ozone Depleting Substance
426	OECD	Organisation for Economic Co-operation and Development
427	OELs	Occupational Exposure Limits/Levels
428	ONU	Occupational Non-Users
429	OPPT	Office of Pollution Prevention and Toxics
430	OSHA	Occupational Safety and Health Administration
431	OW	Office of Water
432	PCE	Perchloroethylene
433	PDM	Probabilistic Dilution Model
434	PEL	Permissible Exposure Limit
435	PESS	Potentially Exposed or Susceptible Subpopulations
436	PF	Protection Factor
437	POD	Point of Departure
438	POTW	Publicly Owned Treatment Works
439	ppm	Part(s) per Million
440	PPE	Personal Protective Equipment
441	QC	Quality Control
442	REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
443	RCRA	Resource Conservation and Recovery Act
444	REL	Recommended Exposure Limit
445	RFI	Reporting Forms and Instructions
446	RIE	Reactive Ion Etching
447	SDS	Safety Data Sheet
448	SDWA	Safe Drinking Water Act
449	SIAP	Screening Information Dataset Initial Assessment Profile
450	SIDS	Screening Information Dataset
451	SOC	Standard Occupational Classification
452	STEL	Short-term Exposure Limit
453	STORET	STORAge and RETrieval
454	SUSB	Statistics of US Businesses
455	SYR	Six-year Review
456	TCCR	Transparent, Clear, Consistent and Reasonable
457	TCLP	Toxicity Characteristic Leaching Procedure
458	TLV	Threshold Limit Value
459	TRI	Toxics Release Inventory
460	TSCA	Toxic Substances Control Act
461	TSDF	Treatment, Storage and Disposal Facilities
462	TURA	Toxic Use Reduction Act
463	TWA	Time-Weighted Average
464	UATMP	Urban Air Toxics Monitoring Program
465	UNEP	United Nations Environment Programme
466	U.S.	United States
467	USGS	United States Geological Survey
468	VOC	Volatile Organic Compounds

469	WEEL	Workplace Environmental Exposure Limit
470	WHO	World Health Organization
471	WQP	Water Quality Portal
472	$Y_{\text{derm}}$	Weight fraction of the chemical of interest in the liquid phase
473		

DRAFT

474 **EXECUTIVE SUMMARY**

475 This draft risk evaluation for carbon tetrachloride was performed in accordance with the Frank R.  
476 Lautenberg Chemical Safety for the 21st Century Act and is being disseminated for public comment and  
477 peer review. The Frank R. Lautenberg Chemical Safety for the 21st Century Act amended the Toxic  
478 Substances Control Act (TSCA), the Nation's primary chemicals management law, in June 2016. As per  
479 EPA's final rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances*  
480 *Control Act* (82 FR 33726), EPA is taking comment on this draft, and will also obtain peer review on  
481 this draft risk evaluation for carbon tetrachloride. All conclusions, findings, and determinations in this  
482 document are preliminary and subject to comment. The final risk evaluation may change in response to  
483 public comments received on the draft risk evaluation and/or in response to peer review, which itself  
484 may be informed by the public comments. The preliminary conclusions, findings, and determinations in  
485 this draft risk evaluation are for the purpose of identifying whether the chemical substance presents  
486 unreasonable risk or no unreasonable risk under the conditions of use, in accordance with TSCA section  
487 6, and are not intended to represent any findings under TSCA section 7.

488  
489 TSCA § 26(h) and (i) require EPA to use scientific information, technical procedures, measures,  
490 methods, protocols, methodologies and models consistent with the best available science and to base its  
491 decisions on the weight of the scientific evidence. To meet these TSCA § 26 science standards, EPA  
492 used the TSCA systematic review process described in the Application of Systematic Review in TSCA  
493 Risk Evaluations document ([U.S. EPA, 2018a](#)). The data collection, evaluation, and integration stages of  
494 the systematic review process are used to develop the exposure, fate, and hazard assessments for risk  
495 evaluations.

496  
497 Carbon tetrachloride [CASRN: 56-23-5] is a high production volume solvent. Previously, carbon  
498 tetrachloride was a high production solvent in consumer and fumigant products, including as a solvent to  
499 make refrigerants and propellants for aerosol cans, as a solvent for oils, fats, lacquers, varnishes, rubber  
500 waxes, and resins, and as a grain fumigant and dry-cleaning agent. The Montreal Protocol and Title VI  
501 of the Clean Air Act (CAA) Amendments of 1990 led to a phase-out of carbon tetrachloride production  
502 in the United States for most non-feedstock domestic uses in 1996 and the Consumer Product Safety  
503 Commission (CPSC) banned the use of carbon tetrachloride in consumer products (excluding  
504 unavoidable residues not exceeding 10 ppm atmospheric concentration) in 1970. As a result of this  
505 phase-out and ban, it is highly unlikely that there are any ongoing uses of carbon tetrachloride that could  
506 be considered legacy uses, and no such uses have been evaluated. Currently, carbon tetrachloride is used  
507 as a feedstock in the production of hydrochloro fluorocarbons (HCFCs), hydrofluorocarbons (HFCs) and  
508 hydrofluoroolefins (HFOs). EPA has identified information on the regulated use of carbon tetrachloride  
509 as a process agent in the manufacturing of petrochemicals-derived and agricultural products and other  
510 chlorinated compounds such as chlorinated paraffins, chlorinated rubber and others that may be used  
511 downstream in the formulation of solvents for degreasing and cleaning, adhesives, sealants, paints,  
512 coatings, rubber, cement and asphalt formulations. The use of carbon tetrachloride for non-feedstock  
513 uses (i.e., process agent, laboratory chemical) is regulated in accordance with the Montreal Protocol.

514  
515 Carbon tetrachloride has been reportable to the Toxics Release Inventory (TRI) chemical under Section  
516 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA) since 1987. It is  
517 designated a Hazardous Air Pollutant (HAP) under the Clean Air Act (CAA), and is a hazardous  
518 substance under the Comprehensive Environmental Response, Compensation and Liability Act  
519 (CERCLA). It is subject to National Primary Drinking Water Regulations (NPDWR) under the Safe

520 Drinking Water Act (SDWA) and designated as a toxic pollutant under the Clean Water Act (CWA) and  
521 as such is subject to effluent limitations.

522

### 523 ***Approach***

524 EPA used reasonably available information (defined in 40 CFR 702.33 as “information that EPA  
525 possesses or can reasonably generate, obtain, and synthesize for use in risk evaluations, considering  
526 the deadlines . . . for completing such evaluation”) in a “fit-for-purpose” approach, to develop a risk  
527 evaluation that relies on the best available science and is based on the weight of the scientific evidence.  
528 EPA used previous analyses as a starting point for identifying key and supporting studies to inform the  
529 exposure, fate, and hazard assessments. EPA also evaluated other studies that were published since these  
530 reviews. EPA reviewed the information and evaluated the quality of the methods and reporting of results  
531 of the individual studies using the evaluation strategies described in *Application of Systematic Review in*  
532 *TSCA Risk Evaluations* ([U.S. EPA, 2018a](#)).

533

534 In the problem formulation document ([U.S. EPA, 2018d](#)), EPA identified the carbon  
535 tetrachloride conditions of use and presented two conceptual models and an analysis plan for  
536 this current draft risk evaluation. These have been updated in the draft risk evaluation to remove two  
537 activities that are no longer considered conditions of use because they consist of outdated  
538 industrial/commercial processes (see section 1.4.2). EPA has quantitatively evaluated the risk to the  
539 environment and human health, using both monitoring data and modeling approaches, for the conditions  
540 of use identified in section 1.4.1 of this draft risk evaluation. EPA quantitatively evaluated the risk to  
541 aquatic species from exposure to surface water from water releases due to disposals of carbon  
542 tetrachloride associated with its manufacturing, processing, use, or disposal carbon tetrachloride. EPA  
543 also quantitatively evaluated the risk to workers, from inhalation and dermal exposures, and  
544 occupational non-users (ONUs)<sup>1</sup>, from inhalation exposures, by comparing the estimated exposures to  
545 acute and chronic human health hazards.

546

### 547 ***Exposures***

548 EPA used environmental monitoring data to assess ambient water exposure to aquatic organisms. While  
549 carbon tetrachloride is present in various environmental media, such as groundwater, surface water, and  
550 air, EPA stated in the problem formulation that EPA did not expect to include in the risk evaluation  
551 certain exposure pathways that are under the jurisdiction of other EPA-administered statutes, and stated  
552 that EPA expected to conduct no further analysis beyond what was presented in the problem formulation  
553 document for the environmental exposure pathways that remained in the scope of this draft risk  
554 evaluation. Further analysis was not conducted for exposure to aquatic organisms from the suspended  
555 soils or sediment pathway based on a qualitative assessment of the physical chemical properties and fate  
556 of carbon tetrachloride in the environment. However, exposures to aquatic organisms from ambient  
557 surface water were further analyzed in this draft risk evaluation to address a slight change in the  
558 environmental hazard chronic COC and the calculation of a distinct algal COC during the data quality  
559 evaluation process after the problem formulation phase. This assessment is used to inform the risk  
560 determination. These analyses are described in sections 2.1, 2.3 and 4.1 and Appendix E.

561

562 EPA evaluated exposures to carbon tetrachloride in occupational settings for the conditions of use  
563 included in the scope of the risk evaluation, listed in section 1.4 (Scope of the Evaluation). In  
564 occupational settings, EPA evaluated acute and chronic inhalation exposures to workers and ONUs, and

---

<sup>1</sup> ONUs are workers who do not directly handle carbon tetrachloride but perform work in an area where carbon tetrachloride is present.



565 acute and chronic dermal exposures to workers. EPA used inhalation monitoring data, where reasonably  
566 available and that met data evaluation criteria, as well as, modeling approaches, where reasonably  
567 available, to estimate potential inhalation exposures. There is uncertainty in the ONU inhalation risk  
568 estimate since the data did not distinguish between worker and ONU inhalation exposure estimates.  
569 While the difference between the exposures of ONUs and the exposures of workers directly handling the  
570 carbon tetrachloride generally cannot be quantified, ONU inhalation exposures are expected to be lower  
571 than inhalation exposures for workers directly handling the chemical. EPA considered the ONU  
572 exposures to be equal to the central tendency risk estimates for workers when determining ONU risk  
573 attributable to inhalation. While this is likely health protective as it assumes ONU exposure is greater  
574 than that of 50% of the workers, this is highly uncertain, and EPA has low confidence in these exposure  
575 estimates for ONUs. Dermal exposures are not expected because ONUs do not typically directly handle  
576 the carbon tetrachloride, nor they are in the immediate proximity of carbon tetrachloride. Dermal doses  
577 for workers were estimated in these scenarios because dermal monitoring data was not reasonably  
578 available. These analyses are described in section 2.4 of this draft risk evaluation.

579

### 580 ***Hazards***

581 EPA reviewed the environmental hazard data using the data quality review evaluation metrics and the  
582 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  
583 amphibians being the most sensitive taxa for acute and chronic exposures. Algal endpoints are  
584 considered separately from the other taxa and not incorporated into acute or chronic concentrations of  
585 concern (COCs) because durations normally considered acute for other species (e.g., 48, 72, or 96 hours)  
586 can encompass several generations of algae. A distinct COC is calculated for algal toxicity. The results  
587 of the environmental hazard assessment are in section 3.1.

588

589  
590 EPA evaluated reasonably available information for human health hazards and identified hazard  
591 endpoints including acute and chronic toxicity for non-cancer effects and cancer. EPA used the  
592 *Framework for Human Health Risk Assessment to Inform Decision Making* ([U.S. EPA, 2014](#)) to  
593 interpret, extract, and integrate carbon tetrachloride's human health hazard and dose-response  
594 information. EPA reviewed key and supporting information from previous hazard assessments [EPA  
595 IRIS Toxicologic Review ([U.S. EPA, 2010](#)), an ATSDR Toxicological Profile ([ATSDR, 2005](#)) and  
596 NAC Acute Exposure Guideline Levels (AEGL) ([NRC, 2014](#)) and other international assessments listed  
597 in Table 1-3. EPA also screened and evaluated new studies that were published since these reviews (i.e.,  
598 from 2010 – 2018).

599

600 EPA developed a hazard and dose-response analysis using endpoints observed in inhalation and oral  
601 hazard studies, evaluated the weight of the scientific evidence considering EPA and National Research  
602 Council (NRC) risk assessment guidance and selected the points of departure (POD) for acute and  
603 chronic, non-cancer endpoints, and inhalation unit risk and cancer slope factors for cancer risk estimates.  
604 Potential health effects of carbon tetrachloride exposure described in the literature include: effects on the  
605 central nervous system (CNS), liver, kidney, as well as skin irritation, and cancer. EPA identified acute  
606 PODs for inhalation and dermal exposures based on acute CNS effects observed in humans ([Davis, 1934](#)).  
607 The chronic POD for inhalation exposures are based on a study observing increased fatty changes  
608 in rodent livers ([Nagano et al., 2007a](#)). EPA identified a limited number of toxicity studies by the dermal  
609 route that were adequate for dose-response assessment. Therefore, most of the dermal candidate values  
610 were derived by route-to-route extrapolation from the inhalation PODs mentioned above. In accordance  
611 with U.S. EPA ([2005a](#)) *Guidelines for Carcinogen Risk Assessment*, carbon tetrachloride is classified  
612 “likely to be carcinogenic to humans” based on sufficient evidence in animals and limited supporting

613 evidence in humans. EPA calculated cancer risk with a linear model using cancer slope factors for low  
614 dose exposures of carbon tetrachloride, which is EPA's baseline approach to risk assessment when the  
615 MOA is unknown. A general correspondence has been observed between hepatocellular cytotoxicity and  
616 regenerative hyperplasia and the induction of liver tumors as a potential MOA. As indicated in ([U.S.  
617 EPA, 2010](#)), this MOA appears to play a significant role at relatively high exposures above the POD,  
618 driving the steep increase in liver tumors in this exposure range. Data to characterize MOA key events at  
619 low-exposure levels, however, are limited, hence the use of the baseline linear approach. EPA  
620 considered a nonlinear approach with exposures exceeding the POD (18 mg/m<sup>3</sup>) for continuous  
621 exposure, because above this level, the fitted dose-response model better characterizes what is known  
622 about the MOA of carcinogenicity of carbon tetrachloride at higher doses ([U.S. EPA, 2010](#)). The results  
623 of these analyses are described in section 3.2.

#### 624 ***Human Populations Considered in This Risk Evaluation***

625 EPA assumed those who use carbon tetrachloride would be adults of either sex (>16 years old),  
626 including pregnant women, and evaluated risks to individuals who do not use carbon tetrachloride but  
627 may be indirectly exposed due to their proximity to the user who is directly handling carbon  
628 tetrachloride.  
629

630  
631 The risk evaluation is based on potential central nervous system depression which can lead to workplace  
632 accidents and which is a precursor to more severe central nervous system effects such as incapacitation,  
633 loss of consciousness, and death, as well as liver toxicity and cancer as sensitive endpoints. The risk  
634 evaluation also assesses the risk to other potentially exposed or susceptible subpopulations, including  
635 people with pre-existing conditions and people with genetic variations that make them more susceptible.  
636 Exposures that do not present risks based on sensitive toxicity endpoints are not expected to present  
637 risks for other potential health effects of carbon tetrachloride because other health effects occur at higher  
638 levels of exposure.

#### 639 ***Risk Characterization***

640 This draft risk evaluation characterizes the environmental and human health risks from carbon  
641 tetrachloride under the conditions of use, including manufacture, processing, distribution, use and  
642 disposal. This risk characterization identifies potential risks that are used in the identification of  
643 unreasonable risks in the risk determination.  
644

645  
646 *Environmental Risk:* For environmental risk, EPA utilized a risk quotient (RQ) to compare the  
647 environmental concentration to the effect level to characterize the risk to aquatic organisms. EPA  
648 included a qualitative assessment describing carbon tetrachloride exposure from sediments and land-  
649 applied biosolids. Carbon tetrachloride is not expected to accumulate in sediments, and could be mobile  
650 in soil, and migrate to water or volatilize to air. The results of the risk characterization are in section 4.1,  
651 including a table that summarizes the RQs for acute and chronic risks.  
652

653 EPA determined that there are no acute or chronic environmental risks from the TSCA conditions of use  
654 of carbon tetrachloride. Using conservative scenarios, EPA demonstrated that the surface water  
655 concentrations did not exceed the acute or chronic COCs (i.e., RQs < 1) for aquatic species for all sites  
656 except one site (i.e., acute RQ = 1.4). EPA determined there is not an acute aquatic concern for carbon  
657 tetrachloride after further review of the site, which indicated that there was a one-  
658 time elevated environmental release of carbon tetrachloride in 2014 due to an unexpected chemical  
659 spill. Details of these estimates are in section 4.1.2.  
660

661 *Human Health Risks:* For human health risks to workers, EPA identified potential cancer and non-  
662 cancer human health risks from chronic inhalation exposures. EPA did not identify risks from acute  
663 exposures for central nervous system depression. For dermal exposures, EPA did not identify potential  
664 risks for non-cancer liver effects but identified potential cancer risks for high-end chronic exposures.  
665

666 For workers and ONUs, EPA estimated potential cancer risk from chronic exposures to carbon  
667 tetrachloride using an inhalation unit risk value or dermal cancer slope factor multiplied by the chronic  
668 exposure for each COU. For workers and ONUs, EPA also estimated potential non-cancer (liver) risks  
669 resulting from acute or chronic inhalation or dermal exposures and used a Margin of Exposure (MOE)  
670 approach. For workers, EPA estimated risks using several occupational exposure scenarios, which  
671 varied assumptions regarding the expected use of personal protective equipment (PPE) for respiratory  
672 and dermal exposures for workers directly handling carbon tetrachloride. More information on  
673 respiratory and dermal protection, including EPA's approach regarding the occupational exposure  
674 scenarios for carbon tetrachloride, is in section 2.4.1.1.  
675

676 For workers, chronic non-cancer risks were indicated for high-end exposures and cancer risks were  
677 indicated for both high-end and central tendency exposures for the manufacturing and processing  
678 conditions if PPE was not used. For most industrial/commercial conditions of use, cancer risks were also  
679 identified for high-end inhalation exposure scenarios if PPE was not used. With use of expected PPE  
680 during relevant conditions of use (COUs), worker exposures were estimated to be reduced with MOEs  
681 greater than benchmark MOEs and cancer risks below the benchmark cancer risk. EPA's estimates for  
682 worker risks for each occupational exposure scenario are presented in section 4.2 and summarized in  
683 Table 4-13. Cancer risks for workers were identified for high-end dermal exposures for all COUs (see  
684 section 4.2.7). The dermal high-end exposures are reduced with the use of gloves (PF =5) resulting in  
685 cancer risks below the benchmark. Risks were not identified for non-cancer liver effects for workers  
686 from dermal exposures (see sections 4.2.4, 4.2.5)  
687

688 For ONUs, cancer risks were indicated for inhalation occupational exposure scenarios for manufacturing  
689 and processing carbon tetrachloride conditions of use. ONUs are not expected to be using PPE to reduce  
690 exposures to carbon tetrachloride used in their vicinity. ONUs are not dermally exposed to carbon  
691 tetrachloride and dermal risks to ONUs were not identified. EPA's estimates for ONU risks for each  
692 occupational exposure scenario are presented in section 4.2 and summarized in Table 4-13  
693

#### 694 *Strengths, Limitations and Uncertainties in the Risk Characterization*

695 Key assumptions and uncertainties in the environmental risk estimation include the uncertainty around  
696 modeled releases that have surface water concentrations greater than the highest concentration of  
697 concern for aquatic organisms.  
698

699 For the human health risk estimation, key assumptions and uncertainties are related to the estimates for  
700 ONU inhalation exposures, because monitoring data were not readily available for many of the  
701 conditions of use evaluated. Therefore, there is low confidence in the ONU inhalation exposure  
702 estimates used in the risk calculations. An additional source of uncertainty in the dermal risk assessment  
703 is the inhalation to dermal route-to-route extrapolations and use of the limited available dermal data in a  
704 weight of evidence approach. Another source of uncertainty for the human health hazard is the evidence  
705 in support of a mode of action (MOA) for carcinogenesis of carbon tetrachloride at low dose levels.  
706 Therefore, a low dose linear cancer risk model for carbon tetrachloride was used to calculate cancer risk.  
707 Assumptions and key sources of uncertainty are detailed in section 4.4.  
708

709

***Potentially Exposed and Susceptible Subpopulations (PESS)***

710 TSCA § 6(b)(4) requires that EPA evaluate risk to relevant PESS. In developing the risk evaluation,  
711 EPA analyzed the reasonably available information to ascertain whether some human receptor groups  
712 may have greater exposure or greater susceptibility than the general population to the hazard posed by  
713 carbon tetrachloride. EPA considered carbon tetrachloride exposures to be higher among workers using  
714 carbon tetrachloride and ONUs in the vicinity of carbon tetrachloride use than the exposures  
715 experienced by the general population. Additionally, variability of susceptibility to carbon tetrachloride  
716 may be correlated with genetic polymorphism in its metabolizing enzymes. Factors other than  
717 polymorphisms that regulate CYP2E1 induction may have greater influence on the formation of the  
718 toxic metabolic product of carbon tetrachloride exposure. The CYP2E1 enzyme is easily induced by  
719 many substances, resulting in increased metabolism. For example, moderate to heavy alcohol drinkers  
720 may have increased susceptibility to carbon tetrachloride ([NRC, 2014](#)). To account for variation in  
721 sensitivity within human populations intraspecies uncertainty factors (UFs) were applied for non-cancer  
722 effects. The UF values selected are described in section 3.2.5.2.  
723

724

***Aggregate and Sentinel Exposures***

725 Exposures to carbon tetrachloride were evaluated by inhalation and dermal routes separately. Inhalation  
726 and dermal exposures are assumed to occur simultaneously for workers. EPA chose not to employ  
727 additivity of exposure pathways at this time within a condition of use because of the uncertainties  
728 present in the current exposure estimation procedures that may lead to an underestimate of aggregate  
729 exposure. Other identified uncertainties for performing an aggregate exposure assessment of carbon  
730 tetrachloride are discussed in section 4.6. Those uncertainties were also considered by EPA for  
731 determining not to employ additivity of exposure pathways. In this risk evaluation, EPA considered  
732 sentinel exposure the highest exposure given the details of the conditions of use and the potential  
733 exposure scenarios.  
734

735

***Risk Determination***

736 In each risk evaluation under TSCA section 6(b), EPA determines whether a chemical substance  
737 presents an unreasonable risk of injury to health or the environment, under the conditions of use. The  
738 determination does not consider costs or other non-risk factors. In making this determination, EPA  
739 considers relevant risk-related factors including, but not limited to: the effects of the chemical substance  
740 on health and human exposure to such substance under the conditions of use (including cancer and non-  
741 cancer risks); the effects of the chemical substance on the environment and environmental exposure  
742 under the conditions of use; the population exposed (including any potentially exposed or susceptible  
743 subpopulations); the severity of hazard (including the nature of the hazard, the irreversibility of the  
744 hazard); and uncertainties. EPA also takes into consideration the Agency's confidence in the data used  
745 in the risk estimate. This includes an evaluation of the strengths, limitations, and uncertainties associated  
746 with the information used to inform the risk estimate and the risk characterization. The rationale for the  
747 preliminary risk determination is discussed in section 5.1.  
748

749

750 ***Environmental Risks:*** EPA modeled industrial discharges of carbon tetrachloride to surface water to  
751 estimate surface water concentrations. The estimated surface water concentrations did not exceed the  
752 acute COC for aquatic species for all but one of the sites assessed, and the exceedance at that site was  
753 due to an unexpected chemical spill. None of the sites analyzed had more than 20 days where the  
754 chronic and algal COCs were exceeded. With respect to sediment-dwelling aquatic species, carbon  
755 tetrachloride is not expected to partition to or be retained in sediment and is expected to remain in  
756 aqueous phase due to its water solubility and low partitioning to organic matter. Consequently, EPA did

757 not further assess exposure to sediment-dwelling aquatic organisms. Therefore, in this draft risk  
758 evaluation, EPA does not find unreasonable environmental risk to aquatic species from the conditions of  
759 use for carbon tetrachloride. As explained in section 2.5.3.2 of the problem formulation ([U.S. EPA,  
760 2018d](#)), exposure to terrestrial organisms was removed from the scope of the evaluation. This exposure  
761 pathway is considered to be covered under programs of other environmental statutes, administered by  
762 EPA, which adequately assess and effectively manage exposures and for which long-standing regulatory  
763 and analytical processes already exist. Therefore, EPA did not evaluate hazards and exposures to  
764 terrestrial organisms in this draft risk evaluation, and there is no risk determination for terrestrial  
765 organisms.

766  
767 Risks of Injury to Health: EPA's preliminary determination of unreasonable risk for specific conditions  
768 of use of carbon tetrachloride listed below are based on health risks to occupational non-users. As  
769 described below, risks to workers, general population, consumers, and bystanders to consumer use either  
770 were not relevant for these conditions of use or were evaluated and not found to be unreasonable.

771  
772 Risks from acute exposures include central nervous system effects that are temporarily disabling, such  
773 as dizziness. Risks from chronic exposures include liver toxicity and cancer.

774  
775 Risk to Workers: EPA evaluated workers' acute and chronic inhalation and dermal occupational  
776 exposures for cancer and non-cancer risks and preliminarily determined that these risks are not  
777 unreasonable. This determination incorporates consideration of expected PPE (frequently estimated to  
778 be a respirator of APF 10, 25 or 50). A full description of EPA's preliminary determination for each  
779 condition of use is in section 5.3.

780  
781 Risk to the General Population: EPA is not including in this draft risk evaluation exposure pathways  
782 under programs of other environmental statutes, administered by EPA, which adequately assess and  
783 effectively manage exposures and for which long-standing regulatory and analytical processes already  
784 exist. The Office of Chemical Safety and Pollution Prevention works closely with EPA offices that  
785 administer and implement the regulatory programs under these statutes. EPA believes this TSCA risk  
786 evaluation should focus on those exposure pathways associated with TSCA uses that are not covered  
787 under other environmental regulatory regimes administered by EPA because these pathways are likely to  
788 represent the greatest areas of concern to EPA. As described in section 2.4.3 of this draft risk evaluation,  
789 exposure pathways for carbon tetrachloride for human receptors (i.e., general population) already  
790 addressed by these other statutory programs include ambient air, drinking water, ambient water,  
791 biosolids, and disposal. Because there are no other exposure pathways impacting the general population,  
792 EPA did not evaluate hazards or exposures to the general population in this risk evaluation, and there is  
793 no risk determination for the general population.

794  
795 Risks to Occupational Non-Users (ONUs): EPA evaluated ONU acute and chronic inhalation  
796 occupational exposures for cancer and non-cancer risks and preliminarily determined whether any risks  
797 indicated are unreasonable. Generally, risks identified for ONUs are linked to acute and chronic  
798 inhalation exposures. The determinations reflect the hazards associated with the occupational exposures  
799 to carbon tetrachloride and the expected absence of PPE for ONUs. The driver for EPA's determinations  
800 of unreasonable risk for ONUs is cancer from chronic inhalation exposure. The determinations reflect  
801 the severity of the hazards associated with the occupational exposures to carbon tetrachloride and the  
802 expected absence of PPE for ONUs. For dermal exposures, because ONUs are not expected to be  
803 dermally exposed to carbon tetrachloride, dermal risks to ONUs generally were not identified. ONU  
804 inhalation exposures are expected to be lower than inhalation exposures for workers directly handling

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

815  
816 For ONUs, EPA preliminarily determined that the conditions of use that present unreasonable risks  
817 include the domestic manufacture of carbon tetrachloride; the processing of carbon tetrachloride as a  
818 reactant or intermediate in the production of hydrochlorofluorocarbons (HCFCs), hydrofluorocarbon  
819 (HFC), hydrofluoroolefin (HFO), and perchloroethylene (PCE); processing for incorporation into  
820 formulation, mixtures or reaction products (other basic organic and inorganic chemical manufacturing);  
821 and industrial/commercial use in the manufacture of other basic chemicals (including chlorinated  
822 compounds used in solvents, adhesives, asphalt, and paints and coatings). A full description of EPA's  
823 preliminary determination for each condition of use is in section 5.3.

824  
825 Risk to Consumers and Bystanders to Consumer Use: EPA did not include any consumer uses among  
826 the conditions of use within the scope of the risk evaluation for carbon tetrachloride. The Consumer  
827 Product Safety Commission (CPSC) banned the use of carbon tetrachloride in consumer products  
828 (excluding unavoidable residues not exceeding 10 ppm atmospheric concentration) in 1970. While  
829 carbon tetrachloride is used in the manufacturing of other chlorinated compounds that may be  
830 subsequently added to commercially available products, EPA expects that consumer use of such  
831 products would present only de minimis exposure to, or otherwise insignificant risk from, carbon  
832 tetrachloride given the high volatility of carbon tetrachloride and the extent of reaction and efficacy of  
833 the separation/purification process for purifying final products. Therefore, EPA did not evaluate hazards  
834 or exposures to consumers or bystanders to consumer use in this risk evaluation, and there are no risk  
835 determinations for these populations.

836  
837 Summary of Risk Determinations:

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

841

Conditions of Use that Do Not Present an Unreasonable Risk
<ul style="list-style-type: none"><li>• Import (including loading/unloading and repackaging)</li><li>• Processing as a reactant/intermediate in reactive ion etching (i.e., semiconductor manufacturing)</li><li>• Processing for incorporation into formulation, mixtures or reaction products (petrochemicals-derived manufacturing; agricultural products manufacturing)</li><li>• Repackaging for use in laboratory chemicals</li><li>• Recycling</li><li>• Distribution in commerce</li></ul>

**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

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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

847

**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)

848

**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)

849

**1 INTRODUCTION**

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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.

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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.

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

876  
877 EPA used reasonably available information consistent with the best available science for physical  
878 chemical and fate properties, potential exposures, and relevant hazards according to the systematic  
879 review process. For the human exposure pathways, EPA evaluated inhalation exposures to vapors and  
880 mists for workers and occupational non-users, and dermal exposures via skin contact with liquids for  
881 workers. EPA characterized risks to ecological receptors from exposures via surface water in the risk  
882 characterization section of this draft risk evaluation based on the analyses briefly described above.

883  
884 This document is structured such that the Introduction (Section 1) presents the basic physical-chemical  
885 properties of carbon tetrachloride, and background information on its regulatory history, conditions of  
886 use and conceptual models, with emphasis on any changes since the publication of the problem  
887 formulation. This section also includes a discussion of the systematic review process utilized in this draft  
888 risk evaluation. Exposures (Section 2) provides a discussion and analysis of both human and  
889 environmental exposures that can be expected based on the conditions of use for carbon tetrachloride.  
890 Hazards (Section 3) discusses environmental and human health hazards of carbon tetrachloride. The  
891 Risk characterization (Section 4) integrates and assesses reasonably available information on human  
892 health and environmental hazards and exposures, as required by TSCA (15 U.S.C 2605(b)(4)(F)). This  
893 section also includes a discussion of any uncertainties and how they impact the draft risk evaluation. As  
894 required under TSCA 15 U.S.C. 2605(b)(4), a determination of whether the risk posed by this chemical  
895 substance is unreasonable is presented in the Risk Determination (Section 0).

896  
897 As per EPA's final rule, [Procedures for Chemical Risk Evaluation Under the Amended Toxic](#)  
898 [Substances Control Act](#) (82 Fed. Reg. 33726) (hereinafter "Risk Evaluation Rule"), this draft risk  
899 evaluation is subject to both public comment and peer review, which are distinct but related processes.  
900 EPA is providing 60 days for public comment, which will inform the EPA Science Advisory Committee  
901 on Chemicals (SACC) peer review process. EPA seeks public comment on all aspects of this draft risk  
902 evaluation, including all conclusions, findings, and determinations.

903  
904 Peer review will be conducted in accordance with EPA's regulatory procedures for chemical risk  
905 evaluations, including using the [EPA Peer Review Handbook](#) and other methods consistent with section  
906 26 of TSCA (*See* 40 CFR 702.45). As explained in the Risk Evaluation Rule, the purpose of peer review  
907 is for the independent review of the science underlying the risk assessment. Peer review will therefore  
908 address aspects of the underlying science as outlined in the charge to the peer review panel such as  
909 hazard assessment, assessment of dose-response, exposure assessment, and risk characterization.



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

914 EPA solicited input on the first 10 chemicals as it developed use dossiers, scope documents, and  
 915 problem formulations. At each step, EPA has received information and comments specific to individual  
 916 chemicals and of a more general nature relating to various aspects of the risk evaluation process,  
 917 technical issues, and the regulatory and statutory requirements. EPA has considered comments and  
 918 information received at each step in the process and factored in the information and comments as the  
 919 Agency deemed appropriate and relevant including comments on the published problem formulation of  
 920 carbon tetrachloride. Thus, in addition to any new comments on the draft risk evaluation, the public  
 921 should re-submit or clearly identify at this point any previously filed comments, modified as appropriate,  
 922 that are relevant to this risk evaluation and that the submitter feels have not been addressed. EPA does  
 923 not intend to further respond to comments submitted prior to the publication of this draft risk evaluation  
 924 unless they are clearly identified in comments on this draft risk evaluation.

## 925 **1.1 Physical and Chemical Properties**

926 Carbon tetrachloride is a colorless liquid at room temperature with a sweet, aromatic and ethereal odor  
 927 resembling chloroform ([Merck, 1996](#)); ([U.S. Coast Guard, 1985](#)). Carbon tetrachloride is expected to  
 928 volatilize based on its high vapor pressure (115 mm Hg at 25°C) ([Lide, 1999](#)). Carbon tetrachloride has  
 929 a log  $K_{ow}$  value of 2.83 ([Hansch et al., 1995](#)), indicating that this chemical is moderately miscible in  
 930 water. A summary of the physical and chemical properties of carbon tetrachloride are listed in Table 1-1.  
 931  
 932

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

Property	Value <sup>a</sup>	References
Molecular formula	CCl <sub>4</sub>	
Molecular weight	153.82	
Physical form	Colorless liquid with sweet odor	( <a href="#">Merck, 1996</a> ); ( <a href="#">U.S. Coast Guard, 1985</a> )
Melting point	-23°C	( <a href="#">Lide, 1999</a> )
Boiling point	76.8°C	( <a href="#">Lide, 1999</a> )
Density	1.4601 g/cm <sup>3</sup> at 20°C	( <a href="#">Lide, 1999</a> )
Vapor pressure	115 mm Hg at 25°C	( <a href="#">Boublík et al., 1984</a> )
Vapor density	5.3 (relative to air)	( <a href="#">Boublík et al., 1984</a> )
Water solubility	793 mg/L at 25°C	( <a href="#">Horvath, 1982</a> )
Octanol:water partition coefficient (log $K_{ow}$ )	2.83	( <a href="#">Hansch et al., 1995</a> )
Henry's Law constant	0.0276 atm m <sup>3</sup> /mole	( <a href="#">Leighton and Calo, 1981</a> )
Flash point	None	( <a href="#">U.S. Coast Guard, 1985</a> )

Property	Value <sup>a</sup>	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)

<sup>a</sup> Measured unless otherwise noted.

933

## 934 1.2 Uses and Production Volume

935 Carbon tetrachloride is a high production volume solvent. Over one hundred forty two million pounds of  
 936 carbon tetrachloride were produced or imported in the U.S. in 2015 according to the EPA's [Chemical](#)  
 937 [Data Reporting](#) (CDR) database. The Montreal Protocol and Title VI of the Clean Air Act (CAA)  
 938 Amendments of 1990 led to a phase-out of carbon tetrachloride production in the United States for most  
 939 non-feedstock domestic uses in 1996 and the Consumer Product Safety Commission (CPSC) banned the  
 940 use of carbon tetrachloride in consumer products (excluding unavoidable residues not exceeding 10 ppm  
 941 atmospheric concentration) in 1970. Currently, carbon tetrachloride is used as a feedstock in the  
 942 production of hydrochlorofluorocarbons (HCFCs), hydrofluorocarbons (HFCs) and hydrofluoroolefins  
 943 (HFOs). As explained in the problem formulation ([U.S. EPA, 2018d](#)), EPA identified additional  
 944 information on the regulated use of carbon tetrachloride as a process agent (non-feedstock uses) in the  
 945 manufacturing of petrochemicals-derived and agricultural products and other chlorinated compounds  
 946 such as chlorinated paraffins, chlorinated rubber and others that may be used downstream in the  
 947 formulation of solvents for degreasing and cleaning, adhesives, sealants, paints, coatings, rubber, cement  
 948 and asphalt formulations. The use of carbon tetrachloride for non-feedstock uses (i.e., process agent,  
 949 laboratory chemical) is regulated in accordance with the Montreal Protocol.

950

951 The 2016 CDR (reporting period 2012 to 2015) reporting data for carbon tetrachloride are provided in  
 952 Table 1-2 for carbon tetrachloride from EPA's CDR database ([U.S. EPA, 2017b](#)).

953

954 **Table 1-2. Production Volume of Carbon Tetrachloride in Chemical Data Reporting (CDR)**  
 955 **Reporting Period (2012 to 2015)<sup>a</sup>**

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

<sup>a</sup> ([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](#)).

956

## 957 1.3 Regulatory and Assessment History

### 958 1.3.1 Regulatory History

959 EPA conducted a search of existing domestic and international laws, regulations and assessments  
 960 pertaining to carbon tetrachloride. EPA compiled this summary from data available from federal, state,  
 961 international and other government sources, as cited in Appendix A. EPA evaluated and considered the

962 impact of existing laws and regulations (e.g., regulations on landfill disposal, design, and operations) in  
 963 the problem formulation step to determine what, if any, further analysis might be necessary as part of the  
 964 risk evaluation (see section 2.5.3.2 in ([U.S. EPA, 2018d](#))).

965

966 ***Federal Laws and Regulations***

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

970

971 ***State Laws and Regulations***

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

975

976 ***Laws and Regulations in Other Countries and International Treaties or Agreements***

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

980

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

987

988 **Table 1-3. Assessment History of Carbon Tetrachloride**

Authoring Organization	Assessment
<b>EPA assessments</b>	
U.S. EPA, Office of Water (OW)	<a href="#">Update of Human Health Ambient Water Quality Criteria: Carbon Tetrachloride 56-23-5, EPA-HQ-OW-2014-0135-0182 (2015)</a>
U.S. EPA, Integrated Risk Information System (IRIS)	<a href="#">Toxicological Review of Carbon Tetrachloride In Support of Summary Information on IRIS (2010)</a>
U.S. EPA, Office of Water	<a href="#">Carbon Tetrachloride Health Advisory, Office of Drinking Water US Environmental Protection Agency (1987)</a>
National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee)	<a href="#">Carbon Tetrachloride – Final AEGL Document (2014)</a>
<b>Other U.S.-based organizations</b>	
Agency for Toxic Substances and Disease Registry (ATSDR)	<a href="#">Toxicological Profile for Carbon Tetrachloride (2005)</a>

Authoring Organization	Assessment
California Environment Protection Agency, Office of Environmental Health Hazard Assessment	<a href="#">Public Health Goal for Carbon Tetrachloride (2000)</a>
<b>International</b>	
Health Canada	<a href="#">Guidelines for Canadian Drinking Water Quality, Guideline Technical Document, Carbon Tetrachloride (2010)</a>
Organisation for Economic Co-operation and Development's Screening Information Dataset (OECD SIDS), Co-CAM, 10-12	<a href="#">SIDS SIAP for Carbon Tetrachloride (2011)</a>
World Health Organization (WHO)	<a href="#">Carbon Tetrachloride in Drinking Water, Background document for development of WHO Guidelines for Drinking -water Quality (2004)</a>
National Industrial Chemicals Notification and Assessment Scheme (Australia)	<a href="#">Environment Tier II Assessment for Methane, Tetrachloro- (2017, last update) (2017)</a>

989

## 1.4 Scope of the Evaluation

990

### 1.4.1 Conditions of Use Included in the Risk Evaluation

991

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.

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

997

998

999

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

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### 1.4.2 Subcategories Determined Not To Be Conditions of Use

1011

#### 1.4.2.1 Specialty Uses – Aerospace Industry

1012

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

1013

1014 concerning activities associated with carbon tetrachloride. As a result of that review, EPA has  
1015 determined uses of carbon tetrachloride that were previously thought to be a condition of use are no  
1016 longer used in current practices and are not reasonably foreseen to be resumed. Consequently, EPA will  
1017 not consider or evaluate these activities or associated hazards or exposures in the risk evaluation for  
1018 carbon tetrachloride. Specialty uses of carbon tetrachloride, specifically adhesives and cleaning  
1019 operations, were identified in the aerospace industry based on information provided by the Aerospace  
1020 Industries Association (AIA) ([Riegle, 2017](#)). However, upon reaching out to AIA for specific use  
1021 details, AIA replied with the following statement:

1022  
1023 *After additional investigation, usage identified by AIA companies were based upon products that*  
1024 *have been discontinued. There appear to be products that contain trace amounts of carbon*  
1025 *tetrachloride (<1%) that might be a reaction by-product, contaminant or imperfect distillation of*  
1026 *perchloroethylene. Therefore, carbon tetrachloride is no longer an AIA concern. ([AIA, 2019](#))*  
1027

1028 Based on all present information, EPA did not evaluate the use of carbon tetrachloride in cleaning  
1029 operations (vapor degreasing, etc.) or use as an adhesive in the aerospace industry as there are no data  
1030 supporting its use in the industry and there is no significant human exposure from products used in the  
1031 aerospace industry. Additionally, there are current regulatory actions (The Montreal Protocol and CAA  
1032 Title VI) that prohibit the direct use of carbon tetrachloride in the formulation of commercially available  
1033 products for industrial/commercial/consumer uses (including aerosol and non-aerosol  
1034 adhesives/sealants, paints/coatings, and cleaning/degreasing solvent products), except as a laboratory  
1035 chemical (Problem Formulation section 2.2.2.1) ([U.S. EPA, 2018d](#)).

#### 1036 **1.4.2.2 Manufacturing of Pharmaceuticals**

1037 EPA had identified uses of carbon tetrachloride as a process agent in the manufacturing of  
1038 pharmaceuticals (i.e., ibuprofen) in the problem formulation ([U.S. EPA, 2018d](#)). In 1983, EPA presented  
1039 a report entitled *Preliminary Study of Sources of Carbon Tetrachloride: Final Report*. This report stated  
1040 that carbon tetrachloride was used as a solvent to dissolve solid reactants during the pharmaceutical  
1041 manufacturing process, which included ibuprofen ([U.S. EPA, 1983](#)). However, the Science History  
1042 Institute published an article titled, *The Greening of Chemistry*, which explains that ibuprofen was once  
1043 manufactured with the use of multiple solvents, one of which was carbon tetrachloride. It continues to  
1044 explain, "...in the early 1990s ibuprofen got a makeover. Using catalysts rather than excess reagents to  
1045 drive the reactions, chemists halved the number of stages in the ibuprofen manufacturing process and  
1046 eliminated carbon tetrachloride, a toxic solvent, from the process" ([Hoag, 2016](#)). EPA found no  
1047 evidence to suggest that the manufacturing of ibuprofen, or any other pharmaceuticals, still utilizes  
1048 carbon tetrachloride or that such use is reasonably foreseen to resume. Accordingly, EPA no longer  
1049 considers use as a process agent in the manufacturing of pharmaceuticals to be a condition of use of  
1050 carbon tetrachloride and does not evaluate it in this draft risk evaluation.  
1051

#### 1052 **1.4.2.3 Exclusions During Problem Formulation**

1053 In problem formulation, EPA removed from the risk evaluation any activities and exposure pathways  
1054 that EPA concluded do not warrant inclusion in the risk evaluation. Consequently, EPA did not evaluate  
1055 these activities and conditions of use or associated hazards or exposures in the risk evaluation for carbon  
1056 tetrachloride. For example, for one activity that was listed as a "condition of use" in the scope document,  
1057 incorporation of carbon tetrachloride into an article, EPA had insufficient information following the  
1058 further investigations during problem formulation to find that it is a circumstance under which the

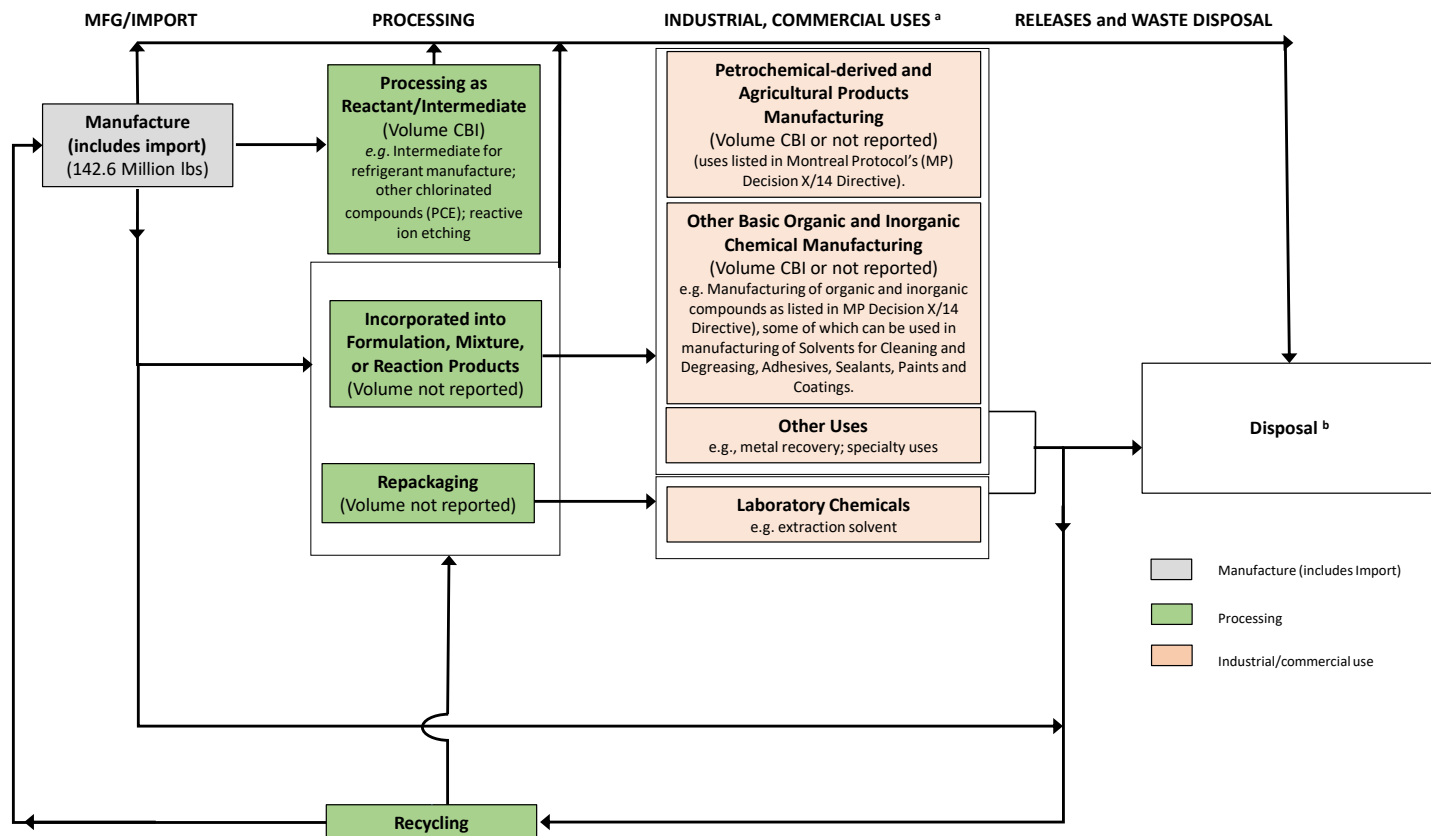
1059 chemical is actually "intended, known, or reasonably foreseen to be manufactured, processed,  
1060 distributed in commerce, used, or disposed of" ([U.S. EPA, 2018d](#)).

1061  
1062 In addition, there are conditions of use for which EPA had sufficient basis to conclude during problem  
1063 formulation would present only de minimis exposures or otherwise insignificant risks and that did not  
1064 warrant further evaluation or inclusion in the risk evaluation. These activities and conditions of use  
1065 consist of industrial/commercial/consumer uses of carbon tetrachloride in commercially available  
1066 aerosol and non-aerosol adhesives/sealants, paints/coatings, and cleaning/degreasing solvent products.

1067  
1068 Based on information obtained by EPA, there are no approved consumer uses for carbon tetrachloride.  
1069 There are current regulatory actions that prohibit the direct use of carbon tetrachloride as a reactant or  
1070 additive in the formulation of commercially available products for industrial/commercial/consumer uses  
1071 (including aerosol and non-aerosol adhesives/sealants, paints/coatings, and cleaning/degreasing solvent  
1072 products), except as a laboratory chemical. The use of carbon tetrachloride (and mixtures containing it)  
1073 in household products has also been banned by CPSC since 1970, with the exception of "unavoidable  
1074 manufacturing residues of carbon tetrachloride in other chemicals that under reasonably foreseen  
1075 conditions of use do not result in an atmospheric concentration of carbon tetrachloride greater than 10  
1076 parts per million." 16 CFR 1500.17(a)(2).

1077  
1078 The domestic and international use of carbon tetrachloride as a process agent is addressed under the  
1079 Montreal Protocol (MP) side agreement, Decision X/14: Process Agents ([UNEP/Ozone Secretariat,  
1080 1998](#)). This decision lists a limited number of specific manufacturing uses of carbon tetrachloride as a  
1081 process agent (non-feedstock use) in which carbon tetrachloride may not be destroyed in the production  
1082 process. Based on the process agent applications, carbon tetrachloride is used in the manufacturing of  
1083 other chlorinated compounds that may be subsequently added to commercially available products (i.e.,  
1084 solvents for cleaning/degreasing, adhesives/sealants, and paints/coatings). Given the high volatility of  
1085 carbon tetrachloride and the extent of reaction and efficacy of the separation/purification process for  
1086 purifying final products, EPA expects insignificant or unmeasurable concentrations of carbon  
1087 tetrachloride as a manufacturing residue in the chlorinated substances in the commercially available  
1088 products. In its regulations on the protection of stratospheric ozone at 40 CFR part 82, EPA excludes  
1089 from the definition of controlled substance the inadvertent or coincidental creation of insignificant  
1090 quantities of a listed substance (including carbon tetrachloride) resulting from the substance's use as a  
1091 process agent (40 CFR 82.3). These expectations and current regulations are consistent with public  
1092 comments received by EPA, [EPA-HQ-OPPT-2016-0733-0005](#) and [EPA-HQ-OPPT-2016-0733-0017](#),  
1093 stating that carbon tetrachloride may be present in a limited number of industrial products with  
1094 chlorinated ingredients at a concentration of less than 0.003% by weight.

1095  
1096 Based on the information identified by EPA, carbon tetrachloride is not a direct reactant or additive in  
1097 the formulation of solvents for cleaning and degreasing, adhesives and sealants or paints and coatings.  
1098 Because industrial, commercial, and consumer use of such products (solvents for cleaning/degreasing,  
1099 adhesives/sealants, and paints/coatings) would present only de minimis exposure to or otherwise  
1100 insignificant risk from manufacturing residues of carbon tetrachloride in chlorinated compounds, EPA  
1101 determined during problem formulation that these conditions of use did not warrant evaluation, and EPA  
1102 has not considered or evaluated these conditions of use or associated hazards or exposures in the risk  
1103 evaluation for carbon tetrachloride.



1104  
1105 **Figure 1-1. Carbon Tetrachloride Life Cycle Diagram**

1106 The life cycle diagram depicts the conditions of use that are within the scope of the risk evaluation during various life cycle stages including  
1107 manufacturing, processing, use (industrial/commercial), distribution and disposal. The production volumes shown are for reporting year 2015  
1108 from the 2016 CDR reporting period (U.S. EPA, 2016d). Activities related to distribution (e.g., loading, unloading) will be considered  
1109 throughout the carbon tetrachloride life cycle, rather than using a single distribution scenario.

1110 <sup>a</sup> See Table 1-4 for additional uses not mentioned specifically in this diagram.

1111 <sup>b</sup> Disposal refers to the following activities - Industrial pre-treatment, Industrial wastewater treatment, publicly owned treatment works (POTW), Underground injection,  
1112 Municipal landfill, Hazardous landfill, Other land disposal, Municipal waste incinerator, Hazardous waste incinerator, Off-site waste transfer

1113

1114 **Table 1-4. Categories and Subcategories of Conditions of Use Included in the Scope of the**  
 1115 **Risk Evaluation**

Life Cycle Stage	Category <sup>a</sup>	Subcategory <sup>b</sup>	References
Manufacture	Domestic Manufacture	Domestic manufacture	( <a href="#">U.S. EPA, 2016d</a> )
	Import	Import	( <a href="#">U.S. EPA, 2016d</a> )
Processing	Processing as a Reactant/ Intermediate	Hydrochlorofluorocarbons (HCFCs), Hydrofluorocarbon (HFCs) and Hydrofluoroolefin (HFOs)	Use document, <a href="#">EPA-HQ-OPPT-2016-0733-0003</a> ; Public comments, <a href="#">EPA-HQ-OPPT-2016-0733-0007</a> , <a href="#">EPA-HQ-OPPT-2016-0733-0008</a> , <a href="#">EPA-HQ-OPPT-2016-0733-0016</a> and <a href="#">EPA-HQ-OPPT-2016-0733-0064</a> ; ( <a href="#">U.S. EPA, 2016d</a> )
		Perchloroethylene (PCE)	Use document, <a href="#">EPA-HQ-OPPT-2016-0733-0003</a> ; Public comments, <a href="#">EPA-HQ-OPPT-2016-0733-0007</a> and <a href="#">EPA-HQ-OPPT-2016-0733-0008</a> ; ( <a href="#">U.S. EPA, 2016d</a> )
		Reactive ion etching (i.e., semiconductor manufacturing)	Use document, <a href="#">EPA-HQ-OPPT-2016-0733-0003</a> ; Public comment, <a href="#">EPA-HQ-OPPT-2016-0733-0063</a>
	Incorporation into Formulation, Mixture or Reaction Products	Petrochemicals-derived manufacturing; Agricultural products manufacturing; Other basic organic and inorganic chemical manufacturing.	( <a href="#">U.S. EPA, 2016d</a> ); Use document, <a href="#">EPA-HQ-OPPT-2016-0733-0003</a> ; ( <a href="#">U.S. EPA, 2016b</a> ); ( <a href="#">UNEP/Ozone Secretariat, 1998</a> ); Public comment, <a href="#">EPA-HQ-OPPT-2016-0733-0064</a>
	Processing - repackaging	Laboratory Chemicals	( <a href="#">U.S. EPA, 2016b</a> )



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	Recycling	Recycling	( <a href="#">U.S. EPA, 2016d</a> ), ( <a href="#">U.S. EPA, 2016b</a> )
Distribution in commerce	Distribution	Distribution in commerce	( <a href="#">U.S. EPA, 2016b</a> ); Use document, <a href="#">EPA-HQ-OPPT-2016-0733-0003</a> .
Industrial/commercial use	Petrochemicals-derived Products Manufacturing	Processing aid	Use document, <a href="#">EPA-HQ-OPPT-2016-0733-0003</a> ; ( <a href="#">U.S. EPA, 2016d</a> ); ( <a href="#">UNEP/Ozone Secretariat, 1998</a> )
		Additive	Use document, <a href="#">EPA-HQ-OPPT-2016-0733-0003</a> ; Public comment, <a href="#">EPA-HQ-OPPT-2016-0733-0012</a> ; ( <a href="#">U.S. EPA, 2016b</a> ); ( <a href="#">UNEP/Ozone Secretariat, 1998</a> )
	Agricultural Products Manufacturing	Processing aid	( <a href="#">U.S. EPA, 2016d</a> ), Use document, <a href="#">EPA-HQ-OPPT-2016-0733-0003</a> ; Public comments, <a href="#">EPA-HQ-OPPT-2016-0733-0007</a> and <a href="#">EPA-HQ-OPPT-2016-0733-0008</a> ; ( <a href="#">UNEP/Ozone Secretariat, 1998</a> )
	Other Basic Organic and Inorganic Chemical Manufacturing	Manufacturing of chlorinated compounds used in solvents for cleaning and degreasing	Use document, <a href="#">EPA-HQ-OPPT-2016-0733-0003</a> ; Public comments, <a href="#">EPA-HQ-OPPT-2016-0733-0011</a> , <a href="#">EPA-HQ-OPPT-2016-0733-0012</a> and <a href="#">EPA-HQ-OPPT-2016-0733-0015</a> ; ( <a href="#">UNEP/Ozone Secretariat, 1998</a> )
		Manufacturing of chlorinated compounds used in adhesives and sealants	Use document, <a href="#">EPA-HQ-OPPT-2016-0733-0003</a> ; Public comments, <a href="#">EPA-HQ-OPPT-2016-0733-0011</a> , <a href="#">EPA-HQ-OPPT-2016-0733-0024</a> ,

			<a href="#">EPA-HQ-OPPT-2016-0733-0012</a> , and <a href="#">EPA-HQ-OPPT-2016-0733-0015</a> ; ( <a href="#">UNEP/Ozone Secretariat, 1998</a> )
		Manufacturing of chlorinated compounds used in paints and coatings	Use document, <a href="#">EPA-HQ-OPPT-2016-0733-0003</a> Public comment, <a href="#">EPA-HQ-OPPT-2016-0733-0024</a> ; ( <a href="#">UNEP/Ozone Secretariat, 1998</a> )
		Manufacturing of inorganic chlorinated compounds (i.e., elimination of nitrogen trichloride in the production of chlorine and caustic)	Public comment, <a href="#">EPA-HQ-OPPT-2016-0733-0027</a> ; ( <a href="#">UNEP/Ozone Secretariat, 1998</a> )
		Manufacturing of chlorinated compounds used in asphalt	Use document, <a href="#">EPA-HQ-OPPT-2016-0733-0003</a> ; ( <a href="#">UNEP/Ozone Secretariat, 1998</a> )
	Other Uses (i.e., Specialty Uses)	Processing aid (i.e., metal recovery, DoD uses).	Use document, <a href="#">EPA-HQ-OPPT-2016-0733-0003</a>
	Laboratory Chemicals	Laboratory chemical	Use document, <a href="#">EPA-HQ-OPPT-2016-0733-0003</a> ; ( <a href="#">U.S. EPA, 2016d</a> ), Public comments, <a href="#">EPA-HQ-OPPT-2016-0733-0007</a> ; <a href="#">EPA-HQ-OPPT-2016-0733-0013</a> and <a href="#">EPA-HQ-OPPT-2016-0733-0063</a>
Disposal	Disposal <sup>c</sup>	Industrial pre-treatment	( <a href="#">U.S. EPA, 2017g</a> )
		Industrial wastewater treatment	( <a href="#">U.S. EPA, 2017g</a> )

	Publicly owned treatment works (POTW)	( <a href="#">U.S. EPA, 2017g</a> )
	Underground injection	( <a href="#">U.S. EPA, 2017g</a> )
	Municipal landfill	( <a href="#">U.S. EPA, 2017g</a> )
	Hazardous landfill	( <a href="#">U.S. EPA, 2017g</a> )
	Other land disposal	( <a href="#">U.S. EPA, 2017g</a> )
	Municipal waste incinerator	( <a href="#">U.S. EPA, 2017g</a> )
	Hazardous waste incinerator	( <a href="#">U.S. EPA, 2017g</a> )
	Off-site waste transfer	( <a href="#">U.S. EPA, 2017g</a> )
<p><sup>a</sup>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.</p> <p><sup>b</sup>These subcategories reflect more specific uses of carbon tetrachloride.</p> <p><sup>c</sup>Disposal subcategories were evaluated for workplace exposures.</p>		

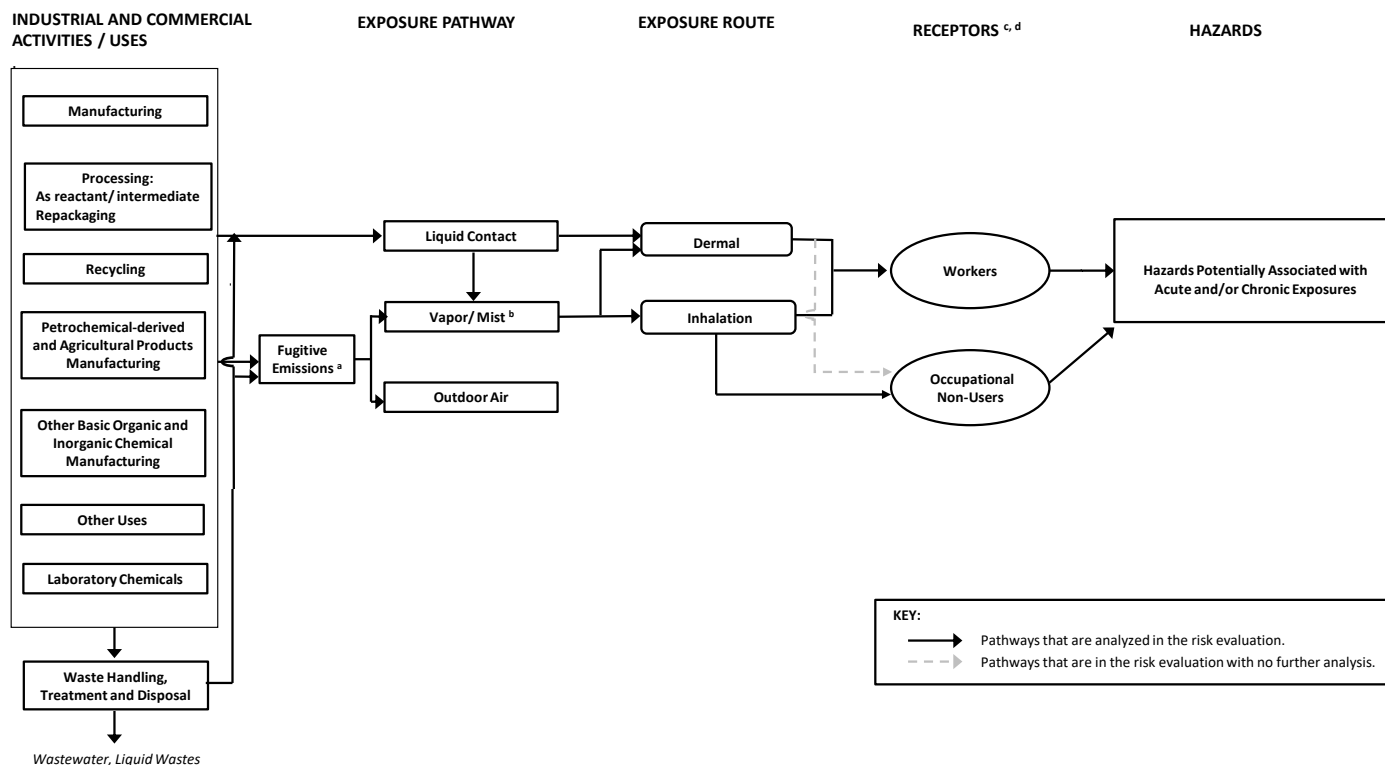
1116

1117 **1.4.3 Conceptual Models**

1118 EPA considered the potential for hazards to human health and the environment resulting from  
 1119 exposure pathways outlined in the preliminary conceptual models of the carbon tetrachloride  
 1120 scope document ([U.S. EPA, 2017e](#)). The preliminary conceptual models were refined in the  
 1121 problem formulation document ([U.S. EPA, 2018d](#)). Based on review and evaluation of  
 1122 reasonably available data for carbon tetrachloride, EPA determined in the problem formulation  
 1123 that no further analysis of the environmental release pathways outlined in the conceptual models  
 1124 was necessary due to a qualitative assessment of the physical chemical properties and fate of  
 1125 carbon tetrachloride in the environment, and a quantitative comparison of hazards and exposures  
 1126 for aquatic organisms.

1127  
 1128 Upon further evaluation of the reasonably available hazard data of carbon tetrachloride after the  
 1129 problem formulation phase, EPA decreased the environmental hazard chronic COC from 7 µg/L  
 1130 to 3 µg/L and conducted further analysis of the aquatic pathway to evaluate potential risk to  
 1131 aquatic organisms from carbon tetrachloride. The conceptual models for this risk evaluation are  
 1132 shown below in Figure 1-2 and Figure 1-3.

1133



1134  
 1135 **Figure 1-2. Carbon Tetrachloride Conceptual Model for Industrial/Commercial Activities and Uses: Potential Exposures and**  
 1136 **Hazards**

1137 The conceptual model presents the exposure pathways, exposure routes and hazards to human receptors from industrial/commercial  
 1138 activities and uses of carbon tetrachloride.

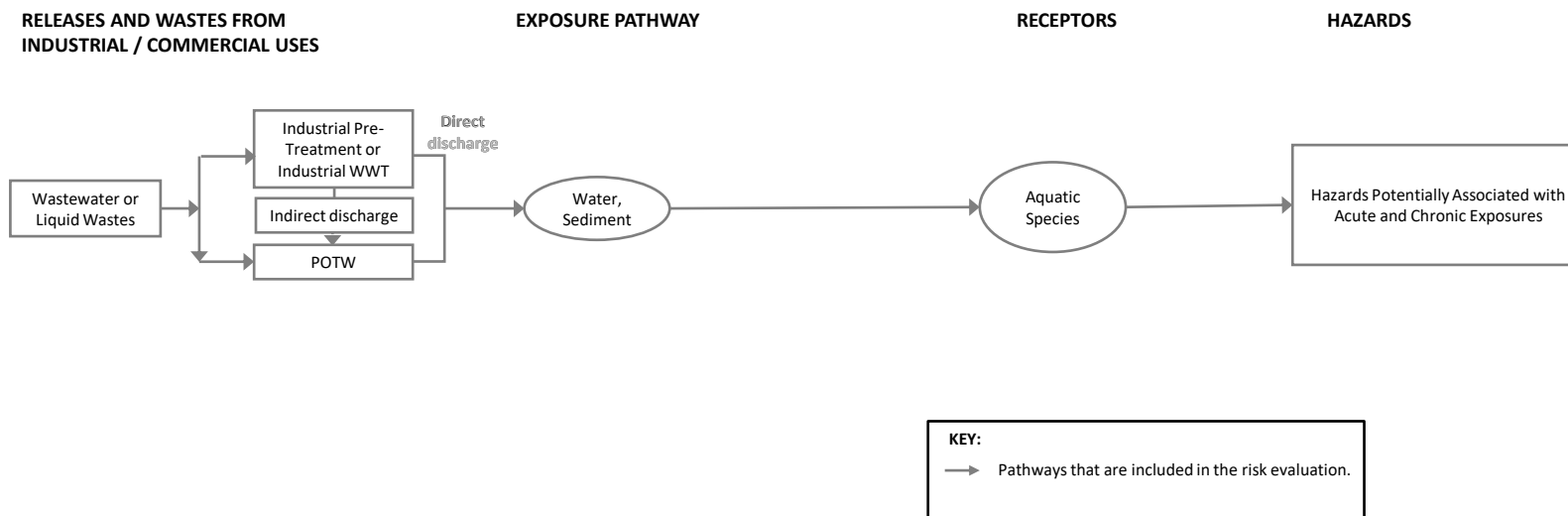
1139 <sup>a</sup>Fugitive air emissions include fugitive equipment leaks from valves, pump seals, flanges, compressors, sampling connections, open-ended lines; evaporative  
 1140 losses from surface impoundment and spills; and releases from building ventilation systems.

1141 <sup>b</sup>Includes possible vapor intrusion into industrial/commercial facility from carbon tetrachloride ground water; exposure to mists is not expected for ONU.

1142 <sup>c</sup>Receptors include PESS.

1143 <sup>d</sup>When data and information are available to support the analysis, EPA also considers the effect that engineering controls and/or personal protective equipment  
 1144 have on occupational exposure levels.

1145



1146

1147

1148 **Figure 1-3. Carbon Tetrachloride Conceptual Model for Environmental Releases and Wastes: Potential Exposures and**  
1149 **Hazards**

1150 The conceptual model presents the exposure pathways, exposure routes and hazards to environmental receptors from environmental  
1151 water releases of carbon tetrachloride.

## 1152 **1.5 Systematic Review**

---

1153 TSCA requires EPA to use scientific information, technical procedures, measures, methods,  
1154 protocols, methodologies and models consistent with the best available science and base  
1155 decisions under TSCA section 6 on the weight of scientific evidence. Within the TSCA risk  
1156 evaluation context, the weight of the scientific evidence is defined as “*a systematic review*  
1157 *method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-*  
1158 *established protocol to comprehensively, objectively, transparently, and consistently identify and*  
1159 *evaluate each stream of evidence, including strengths, limitations, and relevance of each study*  
1160 *and to integrate evidence as necessary and appropriate based upon strengths, limitations, and*  
1161 *relevance” (40 C.F.R. 702.33).*

1162  
1163 To meet the TSCA science standards, EPA will be guided by the systematic review process  
1164 described in the *Application of Systematic Review in TSCA Risk Evaluations* document ([U.S.](#)  
1165 [EPA, 2018a](#)). The process complements the risk evaluation process in that the data collection,  
1166 data evaluation and data integration stages of the systematic review process are used to develop  
1167 the exposure and hazard assessments based on reasonably available information. EPA defines  
1168 “reasonably available information” to mean information that EPA possesses, or can reasonably  
1169 generate, obtain and synthesize for use in risk evaluations, considering the deadlines for  
1170 completing the evaluation (40 C.F.R. 702.33).

1171  
1172 EPA is implementing systematic review methods and approaches within the regulatory context  
1173 of the amended TSCA. Although EPA will make an effort to adopt as many best practices as  
1174 practicable from the systematic review community, EPA expects modifications to the process to  
1175 ensure that the identification, screening, evaluation and integration of data and information can  
1176 support timely regulatory decision making under the aggressive timelines of the statute.  
1177

### 1178 **1.5.1 Data and Information Collection**

---

1179 EPA planned and conducted a comprehensive literature search based on key words related to the  
1180 different discipline-specific evidence supporting the risk evaluation (e.g., environmental fate and  
1181 transport; engineering releases and occupational exposure; environmental exposure; and  
1182 environmental and human health hazard). EPA then developed and applied inclusion and  
1183 exclusion criteria during the title and abstract screening to identify information potentially  
1184 relevant for the risk evaluation process. The literature and screening strategy as specifically  
1185 applied to carbon tetrachloride is described in the *Application of Systematic Review in TSCA Risk*  
1186 *Evaluations* ([U.S. EPA, 2018a](#)) and results of screening were published in *Carbon tetrachloride*  
1187 *(CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document* ([U.S. EPA,](#)  
1188 [2017a](#)).

1189  
1190 For studies determined to be on-topic (or relevant) after title and abstract screening, EPA  
1191 conducted a full text screening to further exclude references that were not relevant to the risk  
1192 evaluation. Screening decisions were made based on eligibility criteria documented in the form  
1193 of the populations, exposures, comparators, and outcomes (PECO) framework or a modified

1194 framework.<sup>2</sup> Data sources that met the criteria were carried forward to the data evaluation stage.  
1195 The inclusion and exclusion criteria for full text screening for carbon tetrachloride are available  
1196 in Appendix F of the *Problem Formulation of the Risk Evaluation for Carbon Tetrachloride*  
1197 ([U.S. EPA, 2018d](#)).  
1198

1199 In addition to the comprehensive literature search and screening process described above, EPA  
1200 leverage the information presented in previous assessments,<sup>3</sup> when identifying relevant key and  
1201 supporting data,<sup>4</sup> and information for developing the carbon tetrachloride risk evaluation. This is  
1202 discussed in the *Strategy for Conducting Literature Searches for Carbon Tetrachloride:*  
1203 *Supplemental Document to the TSCA Scope Document* ([EPA-HQ-OPPT-2016-0733-0050](#)). In  
1204 general, many of the key and supporting data sources were identified in the comprehensive  
1205 *Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope*  
1206 *Document* ([U.S. EPA, 2017a](#)). However, there were instances that EPA missed relevant  
1207 references that were not captured in the initial categorization of the on-topic references. EPA  
1208 found additional relevant data and information using backward reference searching, which was a  
1209 technique that will be included in future search strategies. This issue was discussed in section 4  
1210 of the *Application of Systematic Review for TSCA Risk Evaluations* ([U.S. EPA, 2018a](#)). Other  
1211 relevant key and supporting references were identified through targeted supplemental searches to  
1212 support the analytical approaches and methods in the carbon tetrachloride risk evaluation (e.g., to  
1213 locate specific information for exposure modeling) or to identify new data and information  
1214 published after the date limits of the initial search.  
1215

1216 EPA used previous chemical assessments to quickly identify relevant key and supporting  
1217 information as a pragmatic approach to expedite the quality evaluation of the data sources, but  
1218 many of those data sources were already captured in the comprehensive literature search as  
1219 explained above. EPA also considered newer information not taken into account by previous  
1220 chemical assessments as described in the *Strategy for Conducting Literature Searches for*  
1221 *Carbon Tetrachloride: Supplemental Document to the TSCA Scope Document* ([EPA-HQ-OPPT-](#)  
1222 [2016-0733-0050](#)). EPA then evaluated the confidence of this information rather than evaluating  
1223 the confidence of all the underlying evidence ever published on carbon tetrachloride's fate and  
1224 transport, environmental releases, and environmental and human exposure and hazard potential.  
1225 Such a comprehensive evaluation of all of the data and information ever published for a chemical  
1226 substance would be extremely labor intensive and could not be achieved under the TSCA  
1227 statutory deadlines for most chemical substances, especially those that have a data rich database.  
1228 EPA also considered how this approach to data gathering would change the conclusions  
1229 presented in the previous assessments.  
1230

---

<sup>2</sup> 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.

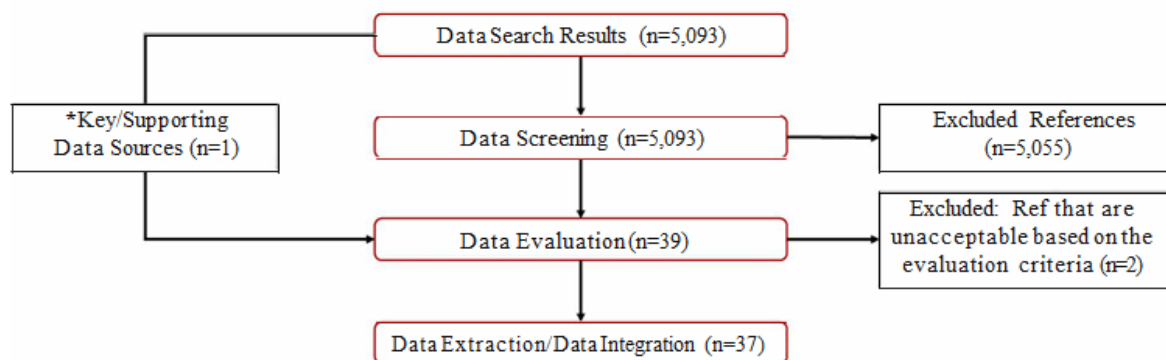
<sup>3</sup> Examples of existing assessments are EPA's chemical assessments (e.g. previous work plan risk assessments, problem formulation documents), ATSDR's Toxicological Profiles, EPA's IRIS assessments and ECHA's dossiers. This is described in more detail in the *Strategy for Conducting Literature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

<sup>4</sup> Key and supporting data and information are those that support key analyses, arguments, and/or conclusions in the risk evaluation.

1231 Using this pragmatic approach, EPA maximized the scientific and analytical efforts of other  
 1232 regulatory and non-regulatory agencies by accepting for the most part, the relevant scientific  
 1233 knowledge gathered and analyzed by others, except for influential information sources that may  
 1234 impact the weight of the scientific evidence underlying EPA’s findings. This influential  
 1235 information (i.e., key/supporting studies) came from a smaller pool of information sources  
 1236 subjected to the rigor of the TSCA systematic review process to ensure that the best available  
 1237 science is incorporated into the weight of the scientific evidence used to support the carbon  
 1238 tetrachloride draft risk evaluation.

1239 The literature flow diagrams shown in Figure 1-4, Figure 1-5, Figure 1-6, Figure 1-7 and Figure  
 1240 1-8 highlight the results obtained for each scientific discipline based on this approach. Each  
 1241 diagram provides the total number of references considered at the start of each systematic review  
 1242 stage (i.e., data search, data screening, data evaluation, data extraction/data integration) and those  
 1243 excluded based on criteria guiding EPA’s screening and data quality evaluation decisions.  
 1244

1245 EPA made the decision to bypass the data screening step for data sources that were highly  
 1246 relevant to the draft risk evaluation as described above. These data sources are depicted as  
 1247 “key/supporting data sources” in the literature flow diagrams. Note that the number of  
 1248 “key/supporting data sources” were excluded from the total count during the data screening stage  
 1249 and added, for the most part, to the data evaluation stage depending on the discipline-specific  
 1250 evidence. The exception was the engineering releases and occupational exposure data sources  
 1251 that were subject to a combined data extraction and evaluation step (Figure 1-5).  
 1252



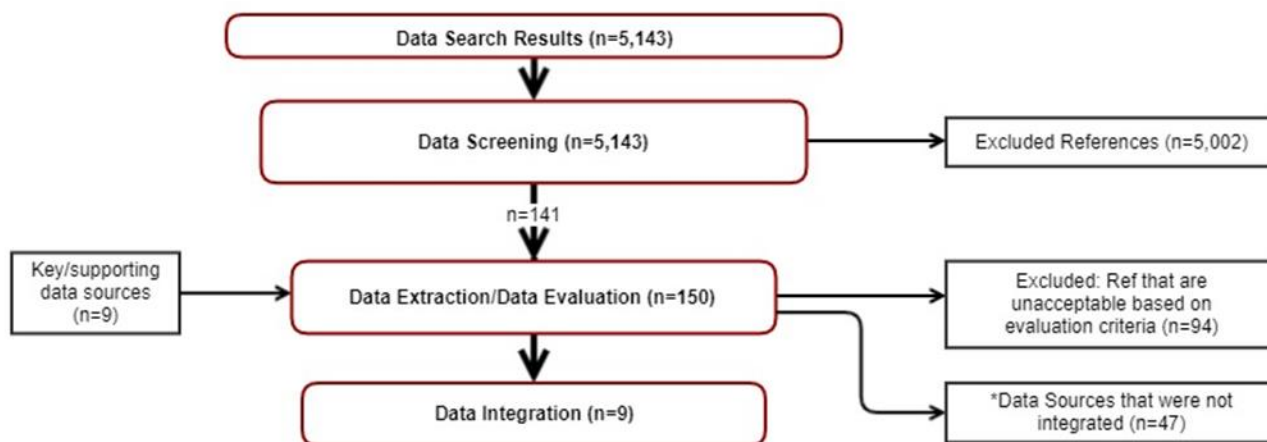
\*These are key and supporting studies from existing assessments (e.g., EPA IRIS assessments, ATSDR assessments, ECHA dossiers) that were highly relevant for the TSCA risk evaluation. These studies bypassed the data screening step and moved directly to the data evaluation step. Data sources identified 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.

1253  
 1254 **Figure 1-4. Key/Supporting Data Sources for Environmental Fate and Transport**  
 1255

1256 The number of publications considered in each step of the systematic review of the carbon  
 1257 tetrachloride’s fate and transport literature is summarized in Figure 1-4. Literature on the  
 1258 environmental fate and transport of carbon tetrachloride were gathered and screened as described  
 1259 in *Appendix C of the Application of Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018a](#)).  
 1260 Additional information regarding the literature search and screening strategy for carbon  
 1261 tetrachloride is provided in EPA’s *Strategy for Conducting Literature Searches for Carbon*



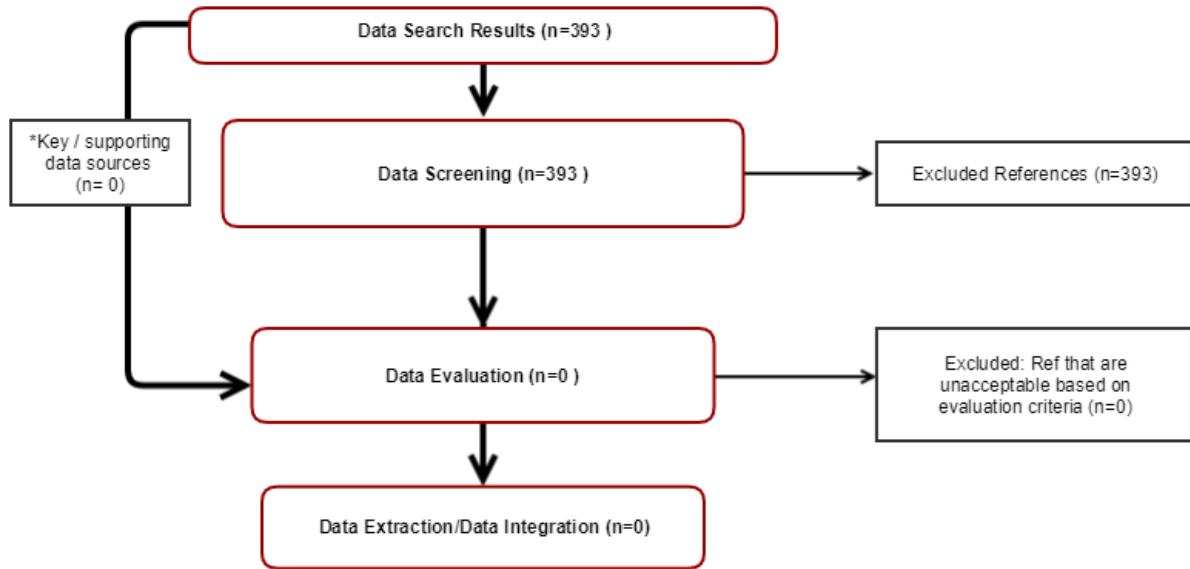
1262 *Tetrachloride: Supplemental File for the TSCA Scope Document* ([EPA-HQ-OPPT-2016-0733-](#)  
 1263 [0050](#)). The results of this screening are published in the *Carbon tetrachloride (CASRN 56-23-5)*  
 1264 *Bibliography: Supplemental File for the TSCA Scope Document* ([U.S. EPA, 2017a](#)).  
 1265



\*The quality of data in these sources (n=47) were acceptable for risk assessment purposes, but they were ultimately excluded from further consideration based on EPA's integration approach for environmental release and occupational exposure data/information. EPA's approach uses a hierarchy of preferences that guide decisions about what types of data/information are included for further analysis, synthesis and integration into the environmental release and occupational exposure assessments. EPA prefers using data with the highest rated quality among those in the higher level of the hierarchy of preferences (i.e., data > modeling > occupational exposure limits or release limits). If warranted, EPA may use data/information of lower rated quality as supportive evidence in the environmental release and occupational exposure assessments.

1266  
 1267 **Figure 1-5. Key/Supporting Data Sources for Releases and Occupational Exposures**  
 1268

1269 As shown in Figure 1-5, the literature search strategy for carbon tetrachloride's environmental  
 1270 releases and occupational exposures yielded 5,143 data sources. Of these data sources, 141 were  
 1271 determined to be relevant to the risk evaluation through the data screening process. These  
 1272 relevant data sources were entered to the data extraction/evaluation phase. After data  
 1273 extraction/evaluation, EPA identified several data gaps and performed a supplemental targeted  
 1274 search to address these gaps (e.g. to locate information needed for exposure modeling). The  
 1275 supplemental search yielded 9 relevant data sources that bypassed the data screening step and  
 1276 were evaluated and extracted in accordance with Appendix D of Data Quality Criteria for  
 1277 Occupational Exposure and Release Data of the *Application of Systematic Review in TSCA Risk*  
 1278 *Evaluations* ([U.S. EPA, 2018a](#)). Of the 150 sources from which data were extracted and  
 1279 evaluated, 94 sources only contained data that were rated as unacceptable based on flaws  
 1280 detected during the evaluation. Of the 56 sources forwarded for data integration, data from 9  
 1281 sources were integrated, and 47 sources contained data that were not integrated (e.g., lower  
 1282 quality data that were not needed due to the existence of higher quality data, data for release  
 1283 media that were removed from scope after data collection).  
 1284

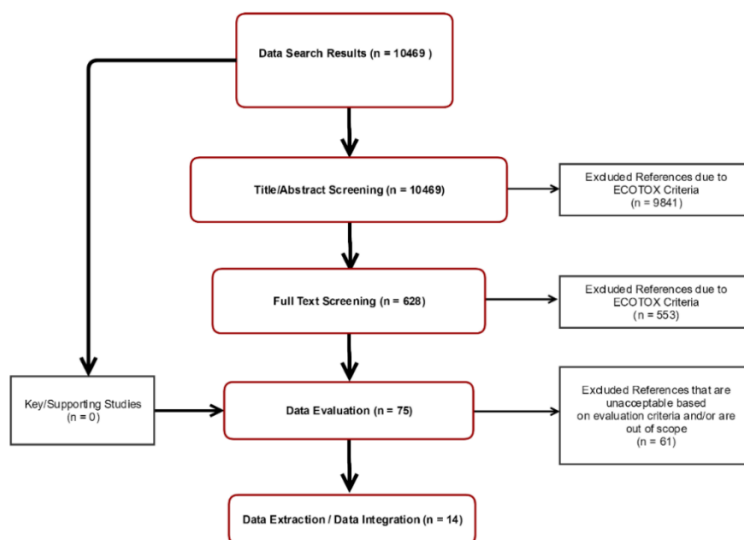


\*These are key and supporting data sources from existing assessments (e.g., EPA IRIS assessments, ATSDR assessments, ECHA dossiers) that were highly relevant for the TSCA risk evaluation. These studies bypassed the data screening step and moved directly to the data evaluation step.

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1294

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

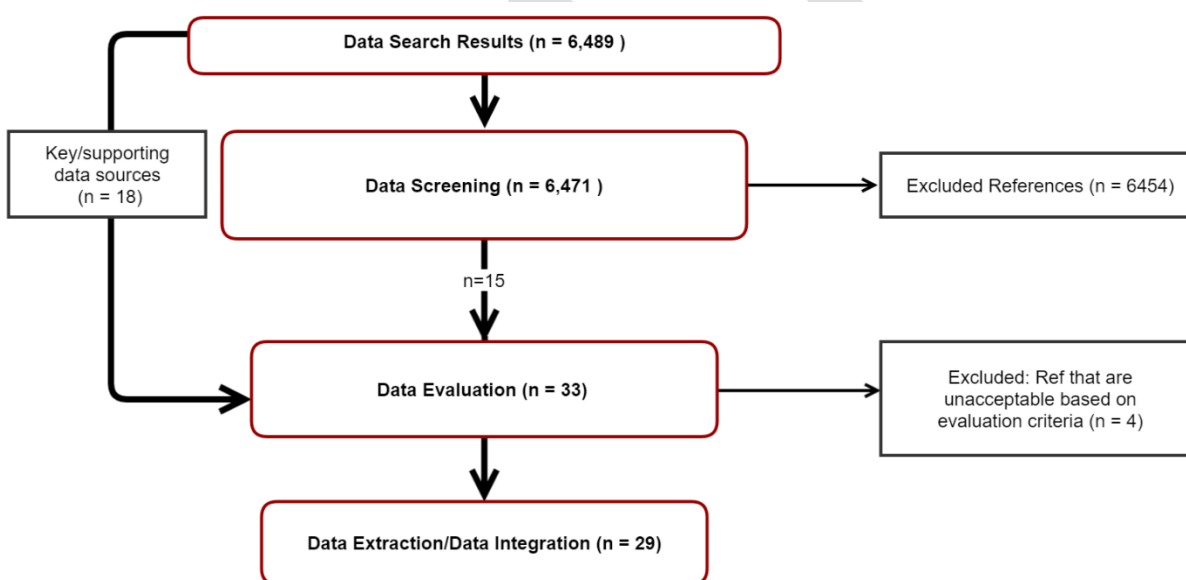
The number of data and information sources considered in each step of the systematic review of carbon tetrachloride literature on environmental exposure is summarized in Figure 1-6. The literature search results for environmental exposures yielded 393 data sources. Of these data sources, none were determined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



1295  
1296  
1297

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

1298 The environmental hazard data sources were identified through literature searches and screening  
 1299 strategies using the ECOTOX Standing Operating Procedures. For studies determined to be on-  
 1300 topic after title and abstract screening, EPA conducted a full text screening to further exclude  
 1301 references that were not relevant to the risk evaluation. Screening decisions were made based on  
 1302 eligibility criteria as documented in the ECOTOX User Guide ([U.S. EPA, 2018c](#)). Additional  
 1303 details can be found in the *Strategy for Conducting Literature Searches for Carbon*  
 1304 *Tetrachloride*: Supplemental Document to the TSCA Scope Document, [EPA-HQ-OPPT-2016-](#)  
 1305 [0733-0050](#). During problem formulation, EPA made refinements to the conceptual models  
 1306 resulting in the exclusion of the terrestrial species exposure pathways and studies that are not  
 1307 biologically relevant from the scope of the risk evaluation. The terrestrial species exposure  
 1308 pathways were considered to be covered under programs of other environmental statutes  
 1309 administered by EPA, which adequately assess and effectively manage such exposures  
 1310 (e.g., RCRA, CAA). Therefore, environmental hazard data sources on terrestrial organisms and  
 1311 on metabolic endpoints were excluded from data quality evaluation. The “Key/Supporting  
 1312 Studies” box represents data sources typically cited in existing assessments and considered  
 1313 highly relevant for the TSCA risk evaluation because they were used as key and supporting  
 1314 information by regulatory and non-regulatory organizations to support their chemical hazard and  
 1315 risk assessments. These citations were found independently from the ECOTOX process. These  
 1316 studies bypassed the data screening step and moved directly to the data evaluation step.  
 1317



1318  
 1319 **Figure 1-8. Key/Supporting Data Sources for Human Health Hazards**

1320  
 1321 The literature search strategy used to gather human health hazard information for carbon  
 1322 tetrachloride yielded 6,489 studies. This included 18 key and supporting studies (identified from  
 1323 previous regulatory assessments) that skipped the initial screening process and proceeded  
 1324 directly to the data evaluation phase. Of the 6,489 studies identified for carbon tetrachloride  
 1325 6,454 were excluded as off topic during the title and abstract screening phase. The remaining 15  
 1326 human health hazard studies advanced to full text screening; a total of 29 studies were  
 1327 determined to be relevant to the draft risk evaluation. These relevant data sources were evaluated  
 1328 and extracted in accordance with the process described in Appendix G of the *Application of*

1329 *Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018a](#)). Additional details can be found  
1330 in EPA's Strategy for *Strategy for Conducting Literature Searches for Carbon Tetrachloride:*  
1331 *Supplemental Document to the TSCA Scope Document* ([EPA-HQ-OPPT-2016-0733-0050](#)). The  
1332 results of this screening process are published in the *Carbon tetrachloride (CASRN 56-23-5)*  
1333 *Bibliography: Supplemental File for the TSCA Scope Document* ([U.S. EPA, 2017a](#)).  
1334

### 1335 **1.5.2 Data Evaluation**

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1336 During the data evaluation stage, EPA typically assesses the quality of the data sources using the  
1337 evaluation strategies and criteria described in *Application of Systematic Review in TSCA Risk*  
1338 *Evaluations* ([U.S. EPA, 2018a](#)). EPA evaluated the quality of the all data sources that passed  
1339 full-text screening. Each data source received an overall confidence rating of high, medium, low  
1340 or unacceptable.

1341  
1342 The results of these data quality evaluations are provided in sections 1.1 (Physical and Chemical  
1343 Properties), 2.1 (Fate and Transport) and 2.5.2 (Hazards). Supplemental files 1A - 1H (see list of  
1344 supplemental files in Appendix B) also provide details of the data evaluations including  
1345 individual metric scores and the overall study score for each data source.  
1346

### 1347 **1.5.3 Data Integration**

---

1348 During data integration and analysis, EPA considers quality, consistency, relevancy, coherence  
1349 and biological plausibility to make final conclusions regarding the weight of the scientific  
1350 evidence. As stated in *Application of Systematic Review in TSCA Risk Evaluations* ([U.S. EPA,](#)  
1351 [2018a](#)), data integration involves transparently discussing the significant issues, strengths, and  
1352 limitations as well as the uncertainties of the reasonably available information and the major  
1353 points of interpretation ([U.S. EPA, 2018e](#)).  
1354

1355 EPA used previous assessments to identify key and supporting information and then analyzed  
1356 and synthesized available evidence regarding carbon tetrachloride's chemical properties,  
1357 environmental fate and transport properties and its potential for exposure and hazard. EPA's  
1358 analysis also considered recent data sources that were not considered in the previous assessments  
1359 (section 1.5.1) as well as reasonably available information on potentially exposed or susceptible  
1360 subpopulations.

1361  
1362 The exposures and hazards sections describe EPA's analysis of the relevant lines of evidence that  
1363 were found acceptable for the risk evaluation based on the data quality reviews provided in the  
1364 supplemental files.

## 1365 **2 EXPOSURES**

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1366 This section describes EPA's approach to assessing environmental and human exposures. First,  
1367 the fate and transport of carbon tetrachloride in the environment is characterized. Then, carbon  
1368 tetrachloride's environmental releases are assessed. This information is then integrated into an  
1369 assessment of environmental exposures. Last, occupational exposures (including potentially  
1370 exposed or susceptible subpopulations) are assessed. For all exposure-related disciplines, EPA

1371 screened, evaluated, extracted and integrated reasonably available empirical data. In addition,  
1372 EPA used models to estimate exposures. Both empirical data and modeled estimates were  
1373 considered when selecting values for use in the exposure assessment.

## 1374 **2.1 Fate and Transport**

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### 1375 **2.1.1 Fate and Transport Approach and Methodology**

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1376 EPA gathered and evaluated environmental fate information according to the process described  
1377 in the *Application of Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018a](#)).  
1378 Reasonably available environmental fate data were selected for use in the current evaluation.  
1379 Furthermore, EPA used previous regulatory and non-regulatory chemical assessments to inform  
1380 the environmental fate and transport information discussed in this section and Appendix C. EPA  
1381 had confidence in the information used in the previous assessments to describe the  
1382 environmental fate and transport of carbon tetrachloride and thus used it to make scoping  
1383 decisions.

1384  
1385 EPA conducted a comprehensive search and screening process as described in section 1.5. Using  
1386 this pragmatic approach, EPA evaluated the confidence of the key and supporting data sources of  
1387 previous assessments as well as newer information instead of evaluating the confidence of all the  
1388 underlying evidence ever published on environmental fate and transport for carbon tetrachloride.  
1389 This allowed EPA to maximize the scientific and analytical efforts of other regulatory and non-  
1390 regulatory agencies by accepting for the most part the scientific knowledge gathered and  
1391 analyzed by others except for influential information sources. Those exceptions would constitute  
1392 a smaller pool of sources subject to the rigor of the TSCA systematic review process to ensure  
1393 that the risk evaluation uses the best available science and the weight of the scientific evidence.  
1394 Other fate estimates were based on modeling results from EPI Suite™ ([U.S. EPA, 2012a](#)), a  
1395 predictive tool for physical/chemical and environmental fate properties. The data evaluation  
1396 tables describing their review can be found in the supplemental document, *Risk Evaluation for*  
1397 *Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of*  
1398 *Environmental Fate and Transport Studies* ([U.S. EPA, 2019c](#)).

1399  
1400 The carbon tetrachloride environmental fate characteristics and physical-chemical properties  
1401 used in fate assessment are presented in Table 2-1. EPA used EPI Suite™ estimations and  
1402 reasonably available fate data to characterize the environmental fate and transport of carbon  
1403 tetrachloride. Please note that this section and Appendix C may also cite other data sources as  
1404 part of the reasonably available evidence on the fate and transport properties of carbon  
1405 tetrachloride. EPA did not subject these other data sources to the later phases of the systematic  
1406 review process (i.e., data evaluation and integration) based on the approach explained above.

### 1407 **2.1.2 Fate and Transport**

---

1408 Environmental fate includes both transport and transformation processes. Environmental  
1409 transport is the movement of the chemical within and between environmental media.  
1410 Transformation occurs through the degradation or reaction of the chemical with other species in  
1411 the environment. Hence, knowledge of the environmental fate of the chemical informs the  
1412 determination of the specific exposure pathways and potential human and environmental  
1413 receptors EPA considered in the risk evaluation. Table 2-1 provides environmental fate data that  
1414 EPA identified and considered in developing the scope for carbon tetrachloride. This information

1415 has not changed from that provided in the scope and problem formulation documents ([U.S. EPA,](#)  
1416 [2018d](#)).

1417  
1418 During problem formulation, EPA considered volatilization during wastewater treatment,  
1419 volatilization from lakes and rivers followed by upward diffusion in the troposphere,  
1420 biodegradation rates, and soil organic carbon:water partition coefficient (log  $K_{OC}$ ) when making  
1421 changes to the conceptual models, as described in section 2.5.3.1 of the problem formulation  
1422 document ([U.S. EPA, 2018d](#)).

1423  
1424 EPI Suite™ ([U.S. EPA, 2012a](#)) modules were used to predict volatilization of carbon  
1425 tetrachloride from wastewater treatment plants, lakes, and rivers. The EPI Suite™ module that  
1426 estimates chemical removal in sewage treatment plants (“STP” module) was run using default  
1427 settings to evaluate the potential for carbon tetrachloride to volatilize to air or adsorb to sludge  
1428 during wastewater treatment. The STP module estimates that about 90% of carbon tetrachloride  
1429 in wastewater will be removed by volatilization and 2% by adsorption. This estimation can be  
1430 confirmed with a wastewater treatment removal study showing that carbon tetrachloride  
1431 partitioned to the water column for greater than 99% and the range of <10 to 0.1% was  
1432 distributed in sludge ([Chen et al., 2014](#)).

1433  
1434 The EPI Suite™ module that estimates volatilization from lakes and rivers (“Volatilization”  
1435 module) was run using default settings to evaluate the volatilization half-life of carbon  
1436 tetrachloride in surface water. The volatilization module estimates that the half-life of carbon  
1437 tetrachloride in a model river will be about 1.3 hours and the half-life in a model lake will be  
1438 about 5 days.

1439  
1440 The EPI Suite™ module that predicts biodegradation rates (“BIOWIN” module) was run using  
1441 default settings to estimate biodegradation rates of carbon tetrachloride under aerobic conditions.  
1442 Three of the models built into the BIOWIN module (BIOWIN 1, 2 and 6) estimate that carbon  
1443 tetrachloride will not rapidly biodegrade in aerobic environments. However, BIOWIN 5 shows  
1444 moderate biodegradation under aerobic conditions. On the other hand, the model that estimates  
1445 anaerobic biodegradation (BIOWIN 7) predicts that carbon tetrachloride will biodegrade  
1446 moderately under anaerobic conditions.

1447  
1448 In water, under aerobic conditions, a negative result has been reported for a ready  
1449 biodegradability test according to OECD TG 301C MITI (I) (Ministry of International Trade and  
1450 Industry, Japan) test method. This test method, however, uses high concentrations of the test  
1451 substance so that toxicity to aerobic bacteria may have occurred, which may have prevented or  
1452 limited biodegradation ([ECHA, 2012](#)). The overwhelming evidence suggests that aerobic  
1453 biodegradation is very slow and anaerobic biodegradation is moderate to rapid ([ECHA, 2012](#);  
1454 [OECD, 2011](#); [ATSDR, 2005](#); [CalEPA, 2000](#)).

1455  
1456 Based on the available environmental fate data, carbon tetrachloride is likely to biodegrade  
1457 slowly under aerobic conditions with pathways that are environment- and microbial population-  
1458 dependent. Anaerobic degradation has been observed to be faster than aerobic degradation under  
1459 some conditions with acclimated microbial populations. Anaerobic biodegradation could be a  
1460 significant degradation mechanism in soil and ground water.

1461  
1462 The log  $K_{OC}$  reported in the carbon tetrachloride scoping document were measured values in the  
1463 range of 1.69 – 2.16, while the estimated value range using EPI Suite™ is 1.6 – 2.5. These  
1464 values are supported by the basic principle of environmental chemistry which states that the  $K_{OC}$   
1465 is typically within one order of magnitude (one log unit) of the octanol:water partition coefficient  
1466 ( $K_{OW}$ ). Indeed, the log  $K_{OW}$  reported for carbon tetrachloride in Table 2-1 is a measured value of  
1467 2.83, which is within the expected range. Further, the  $K_{OC}$  could be approximately one order of  
1468 magnitude larger than predicted by EPI Suite™ before sorption would be expected to  
1469 significantly impact the mobility of carbon tetrachloride in groundwater. The log  $K_{OC}$  and log  
1470  $K_{OW}$  reported in previous assessments of carbon tetrachloride were in the range of 1.69 – 2.16  
1471 and 2.64 – 2.83, respectively ([ECHA, 2012](#); [OECD, 2011](#); [ATSDR, 2005](#)), while measured  
1472 values found in studies via the process of systematic review of highly rated literatures are in the  
1473 range of 1.11 – 2.43 for various surface soil types; 0.79 – 1.93 for aquifer sediments; 1.67 for  
1474 marine and estuary sediments ([Riley et al., 2010](#); [Roose et al., 2001](#); [Zhao et al., 1999](#); [Duffy et](#)  
1475 [al., 1997](#); [Rogers and McFarlane, 1981](#)), and these values are associated with low sorption to soil  
1476 and sediment.  
1477

1478 **Table 2-1. Environmental Fate Characteristics of Carbon Tetrachloride**

Property or Endpoint	Value <sup>a</sup>	References
Direct photodegradation	Minutes (atmospheric-stratospheric)	( <a href="#">OECD, 2011</a> )
Indirect photodegradation	>330 years (atmospheric)	( <a href="#">OECD, 2011</a> ); ( <a href="#">Cox et al., 1976</a> )
Hydrolysis half-life	7000 years at 1 ppm	( <a href="#">OECD, 2011</a> ); ( <a href="#">Mabey and Mill, 1978</a> )
Abiotic soil degradation	5 days (autoclaved soils)	( <a href="#">Anderson et al., 1991</a> )
Biodegradation	6 to 12 months (soil - estimated) <sup>b</sup>  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)	( <a href="#">OECD, 2011</a> ); ( <a href="#">ECHA, 2012</a> ); ( <a href="#">ATSDR, 2005</a> ); ( <a href="#">HSDB, 2005</a> ); ( <a href="#">Van Eekert et al., 1998</a> ); ( <a href="#">Bouwer and McCarty, 1983</a> ); ( <a href="#">Doong and Wu, 1992</a> ); ( <a href="#">Tabak et al., 1981</a> ); ( <a href="#">de Best et al., 1997</a> )
Wastewater Treatment	Mass distribution/partition: Water – >99% Sludge – >10 – 0.1%	( <a href="#">Chen et al., 2014</a> )
Bioconcentration factor (BCF)	30 bluegill sunfish 40 rainbow trout	( <a href="#">OECD, 2011</a> )
Bioaccumulation factor (BAF)	19 (estimated)	( <a href="#">U.S. EPA, 2012a</a> )
Soil organic carbon:water partition coefficient (log K <sub>oc</sub> )	1.11 – 2.43 (from various soil types) 0.79 – 1.93 (aquifer sediments) 1.67 (marine and estuary sediments)	( <a href="#">ECHA, 2012</a> ); ( <a href="#">OECD, 2011</a> ); ( <a href="#">Duffy et al., 1997</a> ); ( <a href="#">Rogers and McFarlane, 1981</a> ) ( <a href="#">Roose et al., 2001</a> ); ( <a href="#">Zhao et al., 1999</a> ); ( <a href="#">Riley et al., 2010</a> )
<sup>a</sup> Measured unless otherwise noted.		
<sup>b</sup> This figure (6 to 12 months) represents a half-life estimate based on the estimated aqueous aerobic biodegradation half-life of carbon tetrachloride.		

1479  
1480 Carbon tetrachloride shows minimal susceptibility to indirect photolysis by hydroxyl radicals in  
1481 the troposphere, where its estimated tropospheric half-life exceeds 330 years. Ultimately, carbon  
1482 tetrachloride diffuses upward into the stratosphere where it is photodegraded to form the  
1483 trichloromethyl radical and chlorine atoms ([OECD, 2011](#)). Carbon tetrachloride is efficiently



1484 degraded by direct photolysis under stratospheric conditions and the DT<sub>50</sub> (Dissipation Time for  
1485 50% of the compound to dissipate) value is in the order of minutes. However, the troposphere to  
1486 the stratosphere migration of carbon tetrachloride is very long and this migration time limits the  
1487 dissipation. The rate of photodegradation increases at altitudes >20 km and beyond.

1488  
1489 Carbon tetrachloride dissolved in water does not photodegrade or oxidize in any measurable  
1490 amounts, with a calculated hydrolysis half-life of 7,000 years based on experimental data at a  
1491 concentration of 1 ppm (OECD, 2011). Removal mechanisms from water could include  
1492 volatilization due to the Henry's Law constant and anaerobic degradation in subsurface  
1493 environment.

1494  
1495 Estimated and measured BCF and BAF values ranging from 19 – 40 indicate that carbon  
1496 tetrachloride has low bioaccumulation potential in fish (U.S. EPA, 2012a; OECD, 2011).

## 1497 **2.2 Environmental Releases**

1498 Releases to the environment from the conditions of use (e.g., industrial/commercial processes or  
1499 commercial uses resulting in down-the-drain releases) are one component of potential exposure  
1500 and may be derived from reported data that are obtained through direct measurement,  
1501 calculations based on empirical data and/or assumptions, and models.

1502  
1503 Under the Emergency Planning and Community Right-to-Know Act (EPCRA) section 313 rule,  
1504 carbon tetrachloride is a Toxics Release Inventory (TRI)-reportable substance effective January  
1505 1, 1987. The TRI database includes information on disposal and other releases of carbon  
1506 tetrachloride to air, water, and land, in addition to how it is being managed through recycling,  
1507 treatment, and burning for energy recovery. Facilities are required to report if they manufacture  
1508 (including import) or process more than 25,000 pounds of carbon tetrachloride, or if they  
1509 otherwise use more than 10,000 pounds of carbon tetrachloride.

1510  
1511 TRI reporting by subject facilities is required by law to provide information on releases and other  
1512 waste management activities of Emergency Planning and Community Right-to-Know Act  
1513 (EPCRA) Section 313 chemicals (i.e., TRI chemicals) to the public for informed decision  
1514 making and to assist the EPA in determining the need for future regulations. Section 313 of  
1515 EPCRA and Section 6607 of the Pollution Prevention Act (PPA) require certain industrial  
1516 facilities to report release and other waste management quantities of TRI-listed chemicals  
1517 annually when a reporting threshold is triggered, but these statutes do not impose any monitoring  
1518 burden for determining the quantities.

1519 TRI data are self-reported by the subject facility where some facilities are required to measure or  
1520 monitor emission or other waste management quantities due to regulations unrelated to the TRI  
1521 Program, or due to company policies. These existing, readily available data are often used by  
1522 facilities for TRI reporting purposes. When measured (e.g., monitoring) data are not “readily  
1523 available,” or are known to be non-representative for TRI reporting purposes, the TRI  
1524 regulations require that facilities determine release and other waste management quantities of  
1525 TRI-listed chemicals by making “reasonable estimates.” Such reasonable estimates include a  
1526 variety of different approaches ranging from published or site-specific emission factors (e.g.,

1527 AP-42), mass balance calculations, or other engineering estimation methods or best engineering  
1528 judgement. TRI reports are then submitted directly to EPA on an annual basis and must be  
1529 certified by a facility's senior management official that the quantities reported to TRI are  
1530 reasonable estimates as required by law.

1531 Based on 2018 TRI ([U.S. EPA, 2018f](#)), 49 facilities reported almost 252 thousand pounds of  
1532 carbon tetrachloride released into the environment. Of these environmental releases, the largest  
1533 releases of over 176 thousand pounds were to air (fugitive and point source air emissions), less  
1534 than 2 thousand pounds were released to water (surface water discharges), over 73 thousand  
1535 pounds were released to land (of which disposal to Resource Conservation and Recovery Act  
1536 (RCRA) Subtitle C landfills is the primary disposal method), and under 146 pounds were  
1537 released in other forms such as indefinite storage. Carbon tetrachloride migration to groundwater  
1538 from RCRA Subtitle C landfills regulated by the state/local jurisdictions will likely be mitigated  
1539 by landfill design (double liner, leachate capture) and requirements to adsorb liquids onto solid  
1540 absorbant and containerize prior to disposal. See Appendix D for a TRI summary table on the  
1541 2018 releases of carbon tetrachloride to various media.

## 1542 **2.3 Environmental Exposures**

---

1543 In the problem formulation ([U.S. EPA, 2018d](#)), EPA presented an analysis and preliminary  
1544 conclusions on environmental exposures to aquatic species based on releases to surface water,  
1545 and from sediments and suspended biosolids. No additional information regarding environmental  
1546 exposures was received or identified by the EPA following the publication of the problem  
1547 formulation that would alter the preliminary conclusions about environmental exposures  
1548 presented in the problem formulation ([U.S. EPA, 2018d](#)). As reviewed during problem  
1549 formulation, carbon tetrachloride is present in environmental media such as groundwater, surface  
1550 water, and air. EPA conducted analysis of the environmental release pathways to aquatic  
1551 receptors based on a qualitative assessment of the fate and transport properties of carbon  
1552 tetrachloride in the environment (described in section 2.1), and a quantitative comparison of  
1553 hazards and exposures for aquatic organisms as described in section 2.5.3.2 of the problem  
1554 formulation ([U.S. EPA, 2018d](#)), which has been updated in section 4.1.2 below.

### 1555 **2.3.1 Environmental Exposures – Aquatic Pathway**

---

1556 As explained in section 2.5.3.1 of the Problem Formulation document ([U.S. EPA, 2018d](#)), EPA  
1557 conducted a qualitative assessment of carbon tetrachloride exposures to aquatic species from  
1558 sediments and suspended solids and determined that it was not necessary to further analyze these  
1559 exposures quantitatively. The qualitative assessment explains that due to the log  $K_{oc}$  (1.7 – 2.16)  
1560 and high solubility of 793 mg/L at 25°C, sorption of carbon tetrachloride to sediments and  
1561 suspended solids is unlikely. The fate information on carbon tetrachloride identified in the  
1562 systematic review confirmed the validity of the fate values used for concluding that risk to  
1563 aquatic species from sediments and solid do not need further analysis.

1564  
1565 After publication of the problem formulation, EPA identified additional data on ecological  
1566 hazards requiring an update of the analysis of carbon tetrachloride releases and surface water  
1567 concentrations. In order to update this analysis, EPA modeled industrial discharges to surface  
1568 water to estimate surface water concentration using five years (2014 through 2018) EPA NPDES  
1569 permit Discharge Monitoring Report (DMR) data on the top highest carbon tetrachloride  
1570 releasing facilities based on the reported annual loadings (lbs/year). EPA used the Probabilistic

1571 Dilution Model (PDM) within EPA's Exposure and Fate Assessment Screening Tool, version  
1572 2014 (E-FAST 2014) to estimate surface water concentrations resulting from facilities' reported  
1573 annual release/loading amounts. Further information on the releases of carbon tetrachloride to  
1574 surface water and the estimated surface water carbon tetrachloride concentrations for acute and  
1575 chronic scenarios based on E-FAST can be found in Table 4-2 and Appendix E.

### 1576 **2.3.1.1 Methodology for Modeling Surface water Concentrations from** 1577 **Facilities releases (E-FAST 2014)**

---

1578 Surface water concentrations resulting from wastewater releases of carbon tetrachloride from  
1579 facilities that use, manufacture, or process the chemical were modeled using EPA's E-FAST,  
1580 Version 2014 (U.S. EPA, 2007). As appropriate, two scenarios were modeled per release: release  
1581 of the annual load over an estimated maximum number of operating days (250 days/year) to  
1582 model a chronic aquatic exposure scenario and over 20 days/year to model acute aquatic  
1583 exposure. E-FAST 2014 is a model that estimates chemical concentrations in water to which  
1584 aquatic life may be exposed using upper percentile and/or mean exposure parametric values,  
1585 resulting in possible conservative exposure estimates. Advantages to this model are that it  
1586 requires minimal input parameters and it has undergone extensive peer review by experts outside  
1587 of EPA. To obtain more detailed information on the E-FAST 2014 tool from the user  
1588 guide/background document, visit this web address: [https://www.epa.gov/tsca-screening-tools/e-  
1589 fast-exposure-and-fate-assessment-screening-tool-version-2014](https://www.epa.gov/tsca-screening-tools/e-fast-exposure-and-fate-assessment-screening-tool-version-2014).

1590  
1591 In some ways, the E-FAST estimates are overestimating aquatic exposure, because carbon  
1592 tetrachloride is a volatile chemical and E-FAST does not take volatilization into consideration;  
1593 and for static water bodies, E-FAST does not take dilution into consideration.

### 1594 Overall Confidence in Estimated Water Surface Concentrations

1595 EPA has medium confidence in the estimated water surface concentrations because the modeled  
1596 estimates are based on conservative assumptions and parameters explained above (i.e., top  
1597 discharging facilities), which could result in overestimation of the water concentrations, in  
1598 addition to the uncertainties associated with the E-FAST model and DMR dataset (see section  
1599 4.4.2).  
1600

### 1601 **2.3.2 Terrestrial Environmental Exposure**

---

1602 Terrestrial species populations living near industrial/commercial facilities using carbon  
1603 tetrachloride may be exposed to the chemical through environmental media. Terrestrial species  
1604 populations living near industrial/commercial facilities using carbon tetrachloride may be  
1605 exposed via multiple routes such as ingestion of surface waters and inhalation of outdoor air. As  
1606 described above, carbon tetrachloride is present and measurable through monitoring in a variety  
1607 of environmental media including ambient air, surface water and ground water.  
1608

1609 During problem formulation EPA determined that carbon tetrachloride present in various media  
1610 pathways (i.e., air, water, land) fall under the jurisdiction of existing regulatory programs and  
1611 associated analytical processes carried out under other EPA-administered statutes and that these  
1612 existing programs and processes adequately assess and effectively manage the exposures (see  
1613 section 2.5.3.2 of the problem formulation document) (U.S. EPA, 2018d). Therefore, these  
1614 exposure pathways were excluded from the scope of this risk evaluation, and terrestrial  
1615 environmental exposure data were not analyzed as part of this risk evaluation.

1616

## 2.4 Human Exposures

---

1617

### 2.4.1 Occupational Exposures

---

1618 Occupational exposures could be direct or indirect and the magnitude of exposure for an  
1619 occupational worker could be a function of duration, proximity and intensity of exposures. The  
1620 duration of exposure, which partially depends on worker mobility, could vary for different  
1621 employee groups. EPA considers workers at the facility who neither directly perform activities  
1622 near the carbon tetrachloride source area nor regularly handle carbon tetrachloride to be  
1623 occupational non-users (ONU). Workers that are directly handling carbon tetrachloride and/or  
1624 perform activities near sources of carbon tetrachloride are in the near field and are called workers  
1625 throughout this report. The near-field is reported to be conceptualized as a volume of air within  
1626 one-meter in any direction of the worker's head and the far-field comprised the remainder of the  
1627 room ([Tielemans et al., 2008](#)). The source area/exposure zone could be judged by several factors  
1628 such as the chemical inventory, ventilation of the facility, vapor pressure and emission potential  
1629 of the chemical, process temperature, size of the room, job tasks, and modes of chemical  
1630 dispersal from activities ([Leblanc et al., 2018](#)). Corn and Esmen ([1979](#)) indicated that the  
1631 assignment of zones is a professional judgment and not a scientific exercise.

1632

1633 The job classifications for ONUs could be dependent on the conditions of use. For example,  
1634 ONUs for manufacturing include supervisors, managers, and tradesmen that may be in the  
1635 manufacturing area, but do not perform tasks that result in the same level of exposures as  
1636 production workers. It could be challenging to characterize direct and indirect exposures for  
1637 some conditions of use since it is not uncommon for employees at a facility to perform multiple  
1638 types of tasks throughout the work day. Workers could perform activities that bring them into  
1639 direct contact with carbon tetrachloride and also perform additional tasks as ONUs. The  
1640 groupings of employees are not necessarily distinct as workers perform a variety of tasks over  
1641 the course of the day that could result in direct exposure and indirect exposure. Indirect  
1642 exposures of employees working near contaminants could be difficult to separate due to  
1643 overlapping tasks that makes it difficult to delineate exposures of workers and ONUs.

1644

1645 EPA assessed occupational exposures following the analysis plan published in section 2.6.1.2 of  
1646 the problem formulation document ([U.S. EPA, 2018d](#)). EPA evaluated acute and chronic  
1647 inhalation exposures to workers and ONUs in association with carbon tetrachloride  
1648 manufacturing, import and repackaging, its use in industrial applications as a reactant/  
1649 intermediate and process agent, laboratory chemicals and disposal. Appendix F of the problem  
1650 formulation document ([U.S. EPA, 2018d](#)) provides additional detail on the mapping of the  
1651 conditions of use to the Occupational Exposure Scenario (OES) groups used in this risk  
1652 evaluation. EPA used inhalation monitoring data when available and that met data evaluation  
1653 criteria (see section 1.5); and modeling approaches to estimate potential inhalation exposures  
1654 when inhalation monitoring data were not reasonably available. Specific inhalation assessment  
1655 methodology is described in further detail below for each type of assessment.

1656

1657 EPA also estimated dermal doses for workers in these scenarios since dermal monitoring data  
1658 was not reasonably available. EPA modeled dermal doses using the *EPA Dermal Exposure to*  
1659 *Volatile Liquids Model* which improves upon the existing *EPA 2-Hand Dermal Exposure* model  
1660 by accounting for the effect of evaporation on dermal absorption for volatile chemicals and the

1661 potential exposure reduction due to glove use. More information about this model and how it was  
1662 used may be found in section 2.4.1.4 and Appendix F. EPA does not expect dermal exposures for  
1663 occupational non-users due to no direct contact with the chemical.

1664  
1665 ***Components of the Occupational Exposure Assessment***

1666 The occupational exposure assessment of each condition of use comprises the following  
1667 components:

- 1668
- 1669 • **Process Description:** A description of the condition of use, including the role of the  
1670 chemical in the use; process vessels, equipment, and tools used during the condition of  
1671 use.
  - 1672 • **Number of Sites:** The sites that use the chemical for the given condition of use.
  - 1673 • **Worker Activities:** Descriptions of the worker activities, including an assessment for  
1674 potential points of worker exposure and environmental releases.
  - 1675 • **Number of Workers and Occupational Non-Users:** An estimate of the number of sites,  
1676 number of workers and occupational non-users potentially exposed to the chemical for  
1677 the given condition of use. Unless mentioned otherwise in this report, the total number of  
1678 workers and ONUs are number of personnel per site per day. See Appendix A of the  
1679 supplemental document *Risk Evaluation for Carbon Tetrachloride, Supplemental*  
1680 *Information on Releases and Occupational Exposure Assessment* ([U.S. EPA, 2019b](#)) for a  
1681 discussion of EPA’s approach for determining an estimation for the number of affected  
1682 workers.
  - 1683 • **Inhalation Exposure:** Central tendency and high-end estimates of inhalation exposure to  
1684 workers and occupational non-users. See Appendix B and Appendix C of the  
1685 supplemental document *Risk Evaluation for Carbon Tetrachloride, Supplemental*  
1686 *Information on Releases and Occupational Exposure Assessment* ([U.S. EPA, 2019b](#)).
  - 1687 • **Dermal Exposure:** It estimates for multiple scenarios, accounting for simultaneous  
1688 absorption and evaporation, and different protection factors of glove use. A separate  
1689 dermal exposure section (2.4.1.8) is included that provides estimates of the dermal  
1690 exposures for all the assessed conditions of use. EPA assessed dermal exposure to  
1691 workers using the *Dermal Exposure to Volatile Liquids Model*. The dermal exposure  
1692 scenarios consider impact of glove use. Dermal exposure assessment is described in more  
1693 detail Appendix E of the document *Risk Evaluation for Carbon Tetrachloride,*  
1694 *Supplemental Information on Releases and Occupational Exposure Assessment* ([U.S.](#)  
1695 [EPA, 2019b](#)).

1696 The OSHA Personal Protective Equipment (PPE) Standard, 29 CFR § 1910.132, requires that  
1697 employers conduct a hazard assessment of the workplace to identify all the hazards that exist and  
1698 determine what methods to use to protect workers from these identified hazards. PPE is one of  
1699 the options that may be utilized to protect employees from hazardous exposures based on the  
1700 findings of the hazard assessment. The OSHA determines the technological and economic  
1701 feasibility of implementing engineering controls to meet different concentration benchmarks. If  
1702 the employer determines that exposures are not hazardous, OSHA does not require controls such  
1703 as PPE. Conversely if the employer identifies a hazardous exposure, OSHA requires control  
1704 measures.

1705

1706 The OSHA respirator protection standard, 29 CFR § 1910.134(a)(1), recommends employers  
1707 utilize the hierarchy of controls for reducing or removing chemical hazards. Based on the  
1708 hierarchy of controls, the most effective controls are elimination, substitution, or engineering  
1709 controls. These are followed by administrative controls and finally the use of PPE. The  
1710 respiratory protection standard requires the use of feasible engineering controls as the primary  
1711 means to control air contaminants. Respirators are required when effective engineering controls  
1712 are not feasible. They are the last means of worker protection in the hierarchy of controls. When  
1713 effective engineering and administrative controls are not feasible to adequately protect workers  
1714 and maintain compliance with other OSHA statutory and regulatory requirements under 29 CFR  
1715 § 1910.1000, employers should utilize respirator protective equipment. (29 CFR §  
1716 1910.134(a)(1)).

1717  
1718 If information and data indicate that use or handling of a chemical cannot, under worst-case  
1719 conditions, release concentrations of a respiratory hazard above a level that would trigger the  
1720 need for a respirator or require use of a more protective respirator employees would not be  
1721 assumed to wear them. Employers also use engineering or administrative controls to bring  
1722 employee exposures below permissible exposure limits for airborne contaminants. respirators  
1723 would be used to supplement engineering and administrative controls only when these controls  
1724 cannot be feasibly implemented to reduce employee exposure to permissible levels.

1725  
1726 ***Occupational Exposures Approach and Methodology***  
1727 To assess inhalation exposure, EPA reviewed workplace inhalation monitoring data collected by  
1728 government agencies such as OSHA and NIOSH, monitoring data submitted by industry  
1729 organizations through public comments, and monitoring data found in published literature (i.e.,  
1730 personal exposure monitoring data and area monitoring data). Studies were evaluated using the  
1731 evaluation strategies laid out in the *Application of Systematic Review in TSCA Risk Evaluations*  
1732 ([U.S. EPA, 2018a](#)).

1733  
1734 For several conditions of use, the EPA modeled exposure in occupational settings. The models  
1735 were used to either supplement existing exposure monitoring data or to provide exposure  
1736 estimates where data are insufficient. For example, the EPA developed the *Tank Truck and*  
1737 *Railcar Loading and Unloading Release and Inhalation Exposure Model* to estimate worker  
1738 exposure during container and truck unloading activities that occur at industrial facilities.

1739  
1740 • Using the time-weighted average (TWA) exposure concentrations obtained from  
1741 monitoring data or modeling, EPA calculated the Acute Concentration (AC), Average  
1742 Daily Concentrations (ADC) and Lifetime Average Daily Concentration (LADC) to  
1743 assess risk. The AC, ADC, and LADC equations are described in *Risk Evaluation for*  
1744 *Carbon Tetrachloride, Supplemental Information on Releases and Occupational*  
1745 *Exposure Assessment* ([U.S. EPA, 2019b](#)).

1746  
1747 See Appendix E of the supplemental document *Risk Evaluation for Carbon Tetrachloride,*  
1748 *Supplemental Information on Releases and Occupational Exposure Assessment* ([U.S. EPA,](#)  
1749 [2019b](#)) for a discussion of EPA's statistical analysis approach for assessing dermal exposure.

#### 1750 **2.4.1.1 Process Description**

1751 EPA performed a literature search to find descriptions of processes involved in each condition of

1752 use to identify worker activities that could potentially result in occupational exposures. Where  
1753 process descriptions were unclear or not available, EPA referenced relevant Emission Scenario  
1754 Documents (ESD's) or Generic Scenarios (GS's). Process descriptions for each condition of use  
1755 can be found in section 2.4.1.3.

#### 1756 **2.4.1.2 Number of Workers and ONUs**

1757 Where available, EPA used CDR data to provide a basis to estimate the number of workers and  
1758 ONUs. EPA supplemented the available CDR data with U.S. economic data using the following  
1759 method:

- 1760
- 1761 1. Identify the North American Industry Classification System (NAICS) codes for the  
1762 industry sectors associated with these uses by reviewing Chemical Data Reporting (CDR)  
1763 data, Toxics Release Inventory (TRI) data, and EPA Generic Scenarios (GS's) and  
1764 Organisation for Economic Co-operation and Development (OECD) Emission Scenario  
1765 Documents (ESDs) for the chemical.
- 1766 2. Estimate total employment by industry/occupation combination using the Bureau of  
1767 Labor Statistics' Occupational Employment Statistics data (BLS Data).
- 1768 3. Refine the Occupational Exposure Scenarios (OES) estimates where they are not  
1769 sufficiently granular by using the U.S. Census' Statistics of US Businesses (SUSB) data  
1770 (SUSB Data) on total employment by 6-digit NAICS.
- 1771 4. Use market penetration data to estimate the percentage of employees likely to be using  
1772 carbon tetrachloride instead of other chemicals. If no market penetration data were  
1773 available, estimate of the number of sites using carbon tetrachloride from given NAICS  
1774 code and multiply by the estimated workers and ONUs/site provided in BLS data.
- 1775 5. Combine the data generated in Steps 1 through 5 to produce an estimate of the number of  
1776 employees using carbon tetrachloride in each industry/occupation combination, and sum  
1777 these to arrive at a total estimate of the number of employees with exposure.
- 1778

1779 There are a few uncertainties surrounding the estimated number of workers potentially exposed  
1780 to carbon tetrachloride, as outlined below. Most are unlikely to result in a systematic  
1781 underestimate or overestimate and could result in an inaccurate estimate. There are inherent  
1782 limitations to the use of CDR data as they are reported by manufacturers and importers of carbon  
1783 tetrachloride. CDR may not capture all sites and workers associated with any given chemical.  
1784 There are also uncertainties with BLS data. First, BLS' OES employment data for each  
1785 industry/occupation combination are only available at the 3-, 4-, or 5-digit NAICS level, rather  
1786 than the full 6-digit NAICS level. This lack of granularity could result in an overestimate of the  
1787 number of exposed workers if some 6-digit NAICS are included in the less granular BLS  
1788 estimates but are not likely to use carbon tetrachloride for the assessed applications. EPA  
1789 addressed this issue by refining the OES estimates using total employment data from the U.S.  
1790 Census' SUSB. However, this approach assumes that the distribution of occupation types (SOC  
1791 codes) in each 6-digit NAICS is equal to the distribution of occupation types at the parent 5-digit  
1792 NAICS level. If the distribution of workers in occupations with carbon tetrachloride exposure  
1793 differs from the overall distribution of workers in each NAICS, then this approach could result in  
1794 inaccuracy. The judgments about which industries (represented by NAICS codes) and  
1795 occupations (represented by SOC codes) are associated with the uses assessed in this report are  
1796 based on EPA's understanding of how carbon tetrachloride is used in each industry. Designations  
1797 of which industries and occupations have potential exposures is nevertheless subjective, and

1798 some industries/occupations with few exposures might erroneously be included, or some  
1799 industries/occupations with exposures might erroneously be excluded. This would result in  
1800 inaccuracy but would be unlikely to systematically either overestimate or underestimate the  
1801 count of exposed workers.

### 1802 **2.4.1.3 General Inhalation Exposure Assessment Approach and Methodology**

1803 EPA provided occupational exposure results representative of *central tendency* conditions and  
1804 *high-end* conditions. A central tendency could be representative of occupational exposures in the  
1805 center of the distribution for a given condition of use. For risk evaluation, EPA may use the 50<sup>th</sup>  
1806 percentile (median), mean (arithmetic or geometric), mode, or midpoint values of a distribution  
1807 as representative of the central tendency scenario. EPA's preference is to provide the 50<sup>th</sup>  
1808 percentile of the distribution. However, if the full distribution is not known, the mean, mode, or  
1809 midpoint of the distribution represents the central tendency depending on the statistics available  
1810 for the distribution.

1811  
1812 A high-end could be representative of occupational exposures that occur at probabilities above  
1813 the 90<sup>th</sup> percentile but below the exposure of the individual with the highest exposure ([U.S. EPA,](#)  
1814 [1992a](#)). For risk evaluation, EPA provided high-end results at the 95<sup>th</sup> percentile. If the 95<sup>th</sup>  
1815 percentile is not available, EPA may use a different percentile greater than or equal to the 90<sup>th</sup>  
1816 percentile but less than or equal to the 99.9<sup>th</sup> percentile, depending on the statistics available for  
1817 the distribution. If the full distribution is not known and the preferred statistics are not available,  
1818 EPA may estimate a maximum or bounding estimate in lieu of the high-end.

1819  
1820 For occupational exposures, EPA may use measured or estimated air concentrations to calculate  
1821 exposure concentration metrics required for risk assessment, such as average daily concentration  
1822 and lifetime average daily concentration. These calculations require additional parameter inputs,  
1823 such as years of exposure, exposure duration and frequency, and lifetime years. EPA may  
1824 estimate exposure concentrations from monitoring data, modeling, or occupational exposure  
1825 limits.

1826  
1827 For the final exposure result metrics, each of the input parameters (e.g., air concentrations,  
1828 working years, exposure frequency, lifetime years) may be a *point estimate* (i.e., a single  
1829 descriptor or statistic, such as central tendency or high-end) or a *full distribution*. EPA will  
1830 consider three general approaches for estimating the final exposure result metrics:

- 1831
- 1832 • Deterministic calculations: EPA will use combinations of point estimates of each  
1833 parameter to estimate a central tendency and high-end for each final exposure metric  
1834 result. EPA will document the method and rationale for selecting parametric  
1835 combinations to be representative of central tendency and high-end.
  
  - 1836 • Probabilistic (stochastic) calculations: EPA will pursue Monte Carlo simulations using  
1837 the full distribution of each parameter to calculate a full distribution of the final exposure  
1838 metric results and selecting the 50<sup>th</sup> and 95<sup>th</sup> percentiles of this resulting distribution as  
1839 the central tendency and high-end, respectively.
  
  - 1840 • Combination of deterministic and probabilistic calculations: EPA may have full  
1841 distributions for some parameters but point estimates of the remaining parameters. For



1842 example, EPA may pursue Monte Carlo modeling to estimate exposure concentrations,  
1843 but only have point estimates of working years of exposure, exposure duration and  
1844 frequency, and lifetime years. In this case, EPA will document the approach and rationale  
1845 for combining point estimates with distribution results for estimating central tendency  
1846 and high-end results.

1847 EPA follows the following hierarchy in selecting data and approaches for assessing inhalation  
1848 exposures:

- 1849
- 1850 1. Monitoring data:
    - 1851 a. Personal and directly applicable
    - 1852 b. Area and directly applicable
    - 1853 c. Personal and potentially applicable or similar
    - 1854 d. Area and potentially applicable or similar
  - 1855 2. Modeling approaches:
    - 1856 a. Surrogate monitoring data
    - 1857 b. Fundamental modeling approaches
    - 1858 c. Statistical regression modeling approaches
  - 1859 3. Occupational exposure limits:
    - 1860 a. OSHA PEL
    - 1861 b. Company-specific OELs (for site-specific exposure assessments, e.g., there is only one  
1862 manufacturer who provides to EPA their internal OEL but does not provide monitoring  
1863 data)
    - 1864 c. Voluntary limits (ACGIH TLV, NIOSH REL, Occupational Alliance for Risk Science  
1865 (OARS) workplace environmental exposure level (WEEL) [formerly by AIHA])
- 1866

1867 Exposures are calculated from the datasets provided in the sources depending on the size of the  
1868 dataset. For datasets with six or more data points, central tendency and high-end exposures were  
1869 estimated using the 50<sup>th</sup> percentile and 95<sup>th</sup> percentile. For datasets with three to five data points,  
1870 central tendency exposure was calculated using the 50<sup>th</sup> percentile and the maximum was  
1871 presented as the high-end exposure estimate. For datasets with two data points, the midpoint was  
1872 presented as a midpoint value and the higher of the two values was presented as a higher value.  
1873 Finally, data sets with only one data point presented the value as a what-if exposure. EPA cannot  
1874 determine the statistical representativeness of the values for the small sample size. For datasets  
1875 including exposure data that were reported as below the limit of detection (LOD), EPA estimated  
1876 the exposure concentrations for these data, following EPA's *Guidelines for Statistical Analysis of*  
1877 *Occupational Exposure Data* ([U.S. EPA, 1994](#)) which recommends using the  $\frac{LOD}{\sqrt{2}}$  if the  
1878 geometric standard deviation of the data is less than 3.0 and  $\frac{LOD}{2}$  if the geometric standard  
1879 deviation is 3.0 or greater. Specific details related to each condition of use can be found in  
1880 section 2.4.1.7. For each condition of use, these values were used to calculate chronic (non-  
1881 cancer and cancer) exposures. Equations and sample calculations for chronic exposures can be  
1882 found in the supplemental document *Risk Evaluation for Carbon Tetrachloride, Supplemental*  
1883 *Information on Releases and Occupational Exposure Assessment* ([U.S. EPA, 2019b](#)).  
1884

1885 EPA used exposure monitoring data and exposure models to estimate inhalation exposures for all  
 1886 conditions of use. Specific details related to the use of monitoring data for each condition of use  
 1887 can be found in section 2.4.1.7.

1888  
 1889 A summary of the key occupational acute and chronic inhalation exposure concentration models  
 1890 for carbon tetrachloride are presented below. The supplemental document *Risk Evaluation for*  
 1891 *Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure*  
 1892 *Assessment* ([U.S. EPA, 2019b](#)) provides detailed discussion on the values of the exposure  
 1893 parameters and air concentrations input into these models.

1894  
 1895 *Acute and Chronic Inhalation Exposure Concentrations Models*

1896 A key input to the acute and chronic models for occupational assessment is 8-hr time-weighted  
 1897 average air concentration (TWA). The 8-hr TWA air concentrations are time averaged to  
 1898 calculate acute exposure, average daily concentration (ADC) for chronic, non-cancer risks, and  
 1899 lifetime average daily concentration (LADC) for chronic, cancer risks.

1900  
 1901 Acute workplace exposures are assumed to be equal to the contaminant concentration in air (8-hr  
 1902 TWA), per Equation A-1.

1903  
 1904 **Equation 2-1**

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

1905  
 1906 Where:

- 1907 **AEC** = acute exposure concentration [mg/m<sup>3</sup>]  
 1908 **C** = contaminant concentration in air (8-hour TWA) [mg/m<sup>3</sup>]  
 1909 **ED** = exposure duration [hr/day]  
 1910 **AT<sub>acute</sub>** = acute averaging time [hr/day]

1911  
 1912  
 1913 ADC and LADC are used to estimate workplace chronic exposures for non-cancer and cancer  
 1914 risks, respectively. These exposures are estimated as follows:

1915  
 1916 **Equation 2-2**

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

1917  
 1918  
 1919 Where:

- 1920 **ADC** = average daily concentration (8-hr TWA) used for chronic non-cancer risk  
 1921 calculations  
 1922 **LADC** = lifetime average daily concentration (8-hr TWA) used for chronic cancer risk  
 1923 calculations  
 1924 **C** = contaminant concentration in air (8-hr TWA)  
 1925 **ED** = exposure duration (8 hr/day)  
 1926 **EF** = exposure frequency (250 days/yr)  
 1927 **WY** = exposed working years per lifetime (tenure values used to represent: 50<sup>th</sup>  
 1928 percentile = 31; 95<sup>th</sup> percentile = 40)

1929  $AT$  = averaging time, non-cancer risks ( $WY \times 250$  days/yr  $\times$  8 hr/day)  
 1930  $AT_c$  = averaging time, cancer risks (lifetime ( $LT$ )  $\times$  365 days/year  $\times$  24 hr/day; where  
 1931  $LT = 78$  years)

1932 **2.4.1.4 General Dermal Exposure Assessment Approach and Methodology**

1933 Dermal exposure data were not readily available for the conditions of use in the assessment.  
 1934 Because carbon tetrachloride is a volatile liquid, the dermal absorption of carbon tetrachloride  
 1935 depends on the type and duration of exposure. Where exposure is without gloves, only a fraction  
 1936 of carbon tetrachloride that comes into contact with the skin will be absorbed as the chemical  
 1937 readily evaporates from the skin. Specific details used to calculate the dermal exposure to carbon  
 1938 tetrachloride can be found in section 2.4.1.8.

1939 A summary of the key occupational dermal dose models for carbon tetrachloride are presented  
 1940 below. The supplemental document *Risk Evaluation for Carbon Tetrachloride, Supplemental*  
 1941 *Information on Releases and Occupational Exposure Assessment* ([U.S. EPA, 2019b](#)) provides  
 1942 detailed discussion on the values of the exposure parameters input into these models.

1943 *Key Dermal Exposure Dose Models*

1944 Current EPA dermal models do not incorporate the evaporation of material from the dermis. The  
 1945 dermal potential dose rate,  $D_{exp}$  (mg/day), is calculated as ([U.S. EPA, 2013a](#)):

1946 **Equation 2-3**

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

1947  
 1948 Where:

1949  $S$  is the surface area of contact: 535 cm<sup>2</sup> (central tendency) and 1,070 cm<sup>2</sup> (high end),  
 1950 representing the total surface area of one and two hands, respectively (note that EPA has no  
 1951 data on actual surface area of contact for any OES).

1952  $Q_u$  is the quantity remaining on the skin: 1.4 mg/cm<sup>2</sup>-event (central tendency) and 2.1 mg/cm<sup>2</sup>-  
 1953 event (high end). These are the midpoint value and high end of range default value,  
 1954 respectively, used in the *EPA's dermal contact with liquids models*.

1955  $Y_{derm}$  is the weight fraction of the chemical of interest in the liquid: EPA will assess a unique  
 1956 value of this parameter for each occupational scenario or group of similar occupational  
 1957 scenarios ( $0 \leq Y_{derm} \leq 1$ ).

1958  $FT$  is the frequency of events (integer number per day; 1 event/day).  
 1959

1960 Here  $Q_u$  does not represent the quantity remaining after evaporation, but represents the quantity  
 1961 remaining after the bulk liquid has fallen from the hand that cannot be removed by wiping the  
 1962 skin (e.g., the film that remains on the skin).

1963 One way to account for evaporation of a volatile solvent would be to add a multiplicative factor  
 1964 to the EPA model to represent the proportion of chemical that remains on the skin after  
 1965 evaporation,  $f_{abs}$  ( $0 \leq f_{abs} \leq 1$ ):

1966

1967 **Equation 2-4**

1968 
$$D_{exp} = S \times (Q_u \times f_{abs}) \times Y_{derm} \times FT$$

1969 This approach simply removes the evaporated mass from the calculation of dermal uptake.  
 1970 Evaporation is not instantaneous, but the EPA model already has a simplified representation of  
 1971 the kinetics of dermal uptake. More information about this approach is presented in the  
 1972 supplemental document *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on*  
 1973 *Releases and Occupational Exposure Assessment* ([U.S. EPA, 2019b](#)).

1974  
 1975 Safety equipment manufacturers recommend Silver Shield®/4H®, Viton (synthetic rubber and  
 1976 fluoropolymer elastomer), Viton/Butyl and Nitrile for gloves and DuPont Tychem® BR and LV,  
 1977 Responder® and TK; ONESuit® TEC; and Kappler Zytron® 300, 400, and 500 as protective  
 1978 materials for clothing. Most nitrile gloves have a breakthrough time of only a few minutes and  
 1979 thus offer little protection when exposed to carbon tetrachloride. For operations involving the use  
 1980 of larger amounts of carbon tetrachloride, when transferring carbon tetrachloride from one  
 1981 container to another or for other potentially extended contact, the only gloves recommended are  
 1982 Viton. The gloves should not be assumed to provide full protection. Regarding glove use, data  
 1983 about the frequency of effective glove use – that is, the proper use of effective gloves – is very  
 1984 limited in industrial settings. Initial literature review suggests that there is unlikely to be  
 1985 sufficient data to justify a specific probability distribution for effective glove use for a chemical  
 1986 or industry. Instead, the impact of effective glove use should be explored by considering  
 1987 different percentages of effectiveness (e.g., 25% vs. 50% effectiveness).

1988  
 1989 EPA also made assumptions about glove use and associated protection factors. Where workers  
 1990 wear gloves, workers are exposed to carbon tetrachloride-based product that may penetrate the  
 1991 gloves, such as seepage through the cuff from improper donning of the gloves, and if the gloves  
 1992 occlude the evaporation of carbon tetrachloride from the skin. Where workers do not wear  
 1993 gloves, workers are exposed through direct contact with carbon tetrachloride.

1994  
 1995 Gloves only offer barrier protection until the chemical breaks through the glove material. Using a  
 1996 conceptual model, Cherrie (2004) proposed a glove workplace protection factor – the ratio of  
 1997 estimated uptake through the hands without gloves to the estimated uptake through the hands  
 1998 while wearing gloves: this protection factor is driven by flux, and thus varies with time. The  
 1999 European Centre For Ecotoxicology and Toxicology of Chemicals Targeted Risk Assessment  
 2000 (ECETOC TRA) model represents the protection factor of gloves as a fixed, assigned protection  
 2001 factor equal to 5, 10, or 20 ([Marquart et al., 2017](#)), where, similar to the APR for respiratory  
 2002 protection, the inverse of the protection factor is the fraction of the chemical that penetrates the  
 2003 glove. Dermal doses without and with glove use are estimated in the occupational exposure  
 2004 sections below and summarized in Table 2-20.

2005  
 2006 For most scenarios, EPA did not find enough data to determine statistical distributions of the  
 2007 actual exposure parameters and concentration inputs to the inhalation and dermal models  
 2008 described above. Within the distributions, central tendencies describe 50<sup>th</sup> percentile or the  
 2009 substitute that most closely represents the 50<sup>th</sup> percentile. The high-end of a distribution  
 2010 describes the range of the distribution above 90<sup>th</sup> percentile ([U.S. EPA, 1992b](#)). Ideally, EPA  
 2011 would use the 50<sup>th</sup> and 95<sup>th</sup> percentiles for each parameter. Where these statistics were unknown,  
 2012 the mean or median (mean is preferable to median) served as substitutes for 50<sup>th</sup> percentile and

2013 the high-end of ranges served as a substitute for 95<sup>th</sup> percentile. However, these substitutes were  
2014 highly uncertain and not ideal substitutes for the percentiles. EPA could not determine whether  
2015 these substitutes were suitable to represent statistical distributions of real-world scenarios.

2016 **2.4.1.5 Consideration of Engineering Controls and Personal Protective**

2017 **Equipment**

2018 OSHA and NIOSH recommend employers utilize the hierarchy of controls to address hazardous  
2019 exposures in the workplace. The hierarchy of controls strategy outlines, in descending order of  
2020 priority, the use of elimination, substitution, engineering controls, administrative controls, and lastly  
2021 PPE. The hierarchy of controls prioritizes the most effective measures first which is to eliminate  
2022 or substitute the harmful chemical (e.g., use a different process, substitute with a less hazardous  
2023 material), thereby preventing or reducing exposure potential. Following elimination and  
2024 substitution, the hierarchy recommends engineering controls to isolate employees from the  
2025 hazard, followed by administrative controls, or changes in work practices to reduce exposure  
2026 potential (e.g., source enclosure, local exhaust ventilation systems, temperature). Administrative  
2027 controls are policies and procedures instituted and overseen by the employer to protect worker  
2028 exposures. The respirators do not replace engineering controls and they are implemented in  
2029 addition to feasible engineering controls (29 CFR § 1910.134(a)(1). The PPE (e.g., respirators,  
2030 gloves) could be used as the last means of control, when the other control measures cannot  
2031 reduce workplace exposure to an acceptable level.

2032  
2033 ***Respiratory Protection***

2034 OSHA's Respiratory Protection Standard (29 CFR § 1910.134) requires employers in certain  
2035 industries to address workplace hazards by implementing engineering control measures and, if  
2036 these are not feasible, provide respirators that are applicable and suitable for the purpose  
2037 intended. Engineering and administrative controls must be implemented whenever employees are  
2038 exposed above the PEL. If engineering and administrative controls do not reduce exposures to  
2039 below the PEL, respirators must be worn. Respirator selection provisions are provided in §  
2040 1910.134(d) and require that appropriate respirators are selected based on the respiratory  
2041 hazard(s) to which the worker will be exposed and workplace and user factors that affect  
2042 respirator performance and reliability. Assigned protection factors (APFs) are provided in Table  
2043 1 under § 1910.134(d)(3)(i)(A) (see below in Table 2-2) and refer to the level of respiratory  
2044 protection that a respirator or class of respirators could be provided to employees when the  
2045 employer implements a continuing, effective respiratory protection program. Implementation of  
2046 a full respiratory protection program requires employers to provide training, appropriate  
2047 selection, fit testing, cleaning, and change-out schedules in order to have confidence in the  
2048 efficacy of the respiratory protection.

2049  
2050 The United States has several regulatory and non-regulatory exposure limits for carbon  
2051 tetrachloride. The OSHA Permissible Exposure Limit (PEL) is 10 ppm time-weighted average  
2052 (TWA) and the Ceiling limit is 200 ppm as a maximum peak. The short-term exposure limit  
2053 (STEL) is 25 ppm for five minutes once every four hours. The NIOSH Recommended Exposure  
2054 Limit (REL) is 2 ppm (12.6 mg/m<sup>3</sup>) for a 60-minute Short-term Exposure Limit (STEL) ([OSHA,](#)  
2055 [2017](#)). NIOSH indicates that carbon tetrachloride has an immediately dangerous to life and  
2056 health (IDLH) value of 200 ppm ([ATSDR, 2017](#)) based on acute inhalation toxicity data in  
2057 humans. OSHA's other occupational safety and health standards that would apply to carbon

2058 tetrachloride exposures that exceed these levels include hazard assessment, exposure monitoring,  
 2059 and control measures such as engineering controls and respiratory protection (29 CFR  
 2060 1910.1000).

2061  
 2062 Respirators should be used when effective engineering controls are not feasible as per OSHA’s  
 2063 29 CFR § 1910.134. Knowledge of the range of respirator APFs is intended to assist employers  
 2064 in selecting the appropriate type of respirator, based on exposure monitoring data, that could  
 2065 provide a level of protection needed for a specific exposure scenario. Table 2-2 lists the range of  
 2066 APFs for respirators. The APFs are not to be assumed to be interchangeable for any condition of  
 2067 use, workplace, worker or ONU. Employers should first consider elimination, substitution,  
 2068 engineering, and administrative controls to reduce exposure potential and, if exposures remain  
 2069 over a regulatory limit, employers are required to institute a respiratory protection program and  
 2070 provide employees with NIOSH-certified respirators. Where other hazardous agents could exist  
 2071 in addition to carbon tetrachloride, consideration of combination cartridges would be necessary.  
 2072 Table 2-2 can be used as a guide to show the protectiveness of each category of respirator; EPA  
 2073 took this information into consideration as discussed in section 4.2.1. Based on the APF,  
 2074 inhalation exposures may be reduced by a factor of 5 to 10,000 when employers implement an  
 2075 effective respiratory protection program.

2076  
 2077 **Table 2-2. Assigned Protection Factors for Respirators in OSHA Standard 29 CFR §**  
 2078 **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	<b>25</b>
• 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)					

2079  
 2080 The National Institute for Occupational Safety and Health (NIOSH) and the U.S. Department of  
 2081 Labor’s Bureau of Labor Statistics (BLS) conducted a voluntary survey of U.S. employers  
 2082 regarding the use of respiratory protective devices between August 2001 and January 2002. The  
 2083 survey had a 75.5% response rate ([NIOSH, 2003](#)). A voluntary survey may not be representative  
 2084 of all private industry respirator use patterns as some establishments with low or no respirator

2085 use could have chosen to not respond to the survey. Therefore, results of the survey could  
2086 potentially be biased towards higher respirator use. NIOSH and BLS estimated about 619,400  
2087 establishments used respirators for voluntary or required purposes (including emergency and  
2088 non-emergency uses). About 281,800 establishments (45%) were estimated to have had  
2089 respirator use for required purposes in the 12 months prior to the survey. The 281,800  
2090 establishments estimated to have had respirator use for required purposes were estimated to be  
2091 approximately 4.5% of all private industry establishments in the U.S. at the time ([NIOSH, 2003](#)).  
2092 The survey found that the establishments that required respirator use had the following respirator  
2093 program characteristics ([NIOSH, 2003](#)):  
2094

- 2095 • 59% provided training to workers on respirator use;
- 2096 • 34% had a written respiratory protection program;
- 2097 • 47% performed an assessment of the employees' medical fitness to wear respirators;
- 2098 • 24% included air sampling to determine respirator selection.
- 2099

2100 The survey report does not provide a result for respirator fit testing or identify if fit testing was  
2101 included in one of the other program characteristics. Of the establishments that had respirator use  
2102 for a required purpose within the 12 months prior to the survey, NIOSH and BLS found ([NIOSH,](#)  
2103 [2003](#)):  
2104

- 2105 • Non-powered air purifying respirators are most common, 94% overall and varying from  
2106 89% to 100% across industry sectors
  - 2107 ○ A high majority use dust masks, 76% overall and varying from 56% to 88% across  
2108 industry sectors of the establishments;
  - 2109 ○ A varying fraction use half-mask respirators, 52% overall and varying from 26% to  
2110 66% across industry sectors;
  - 2111 ○ A varying fraction use full-facepiece respirators, 23% overall and varying from 4% to  
2112 33% across industry sectors.
- 2113 • Powered air-purifying respirators represent a minority of respirator use, 15% overall and  
2114 varying from 7% to 22% across industry sectors;
- 2115 • Supplied air respirators represent a minority of respirator use, 17% overall and varying  
2116 from 4% to 37% across industry sectors.
- 2117

2118 In a more recent article, the University of Pittsburgh, CDC, and RAND Corporation used the  
2119 OSHA data base to examine all inspections in manufacturing in 47 states from 1999 through  
2120 2006 ([Mendeloff et al., 2013](#)); the examination starts with 1999 because an expanded OSHA  
2121 respiratory program standard became effective in late 1998. The article identified inspections and  
2122 establishments at which respiratory protection violations were cited, and it compares the  
2123 prevalence of violations by industry with the prevalence reported in the BLS survey of respirator  
2124 use. The pattern of noncompliance across industries mostly mirrored the survey findings about  
2125 the prevalence of requirements for respirator use. The probability of citing a respiratory  
2126 protection violation was similar across establishment size categories, except for a large drop for  
2127 establishments with over 200 workers. The presence of a worker accompanying the inspector  
2128 increased the probability that a respiratory program violation could be cited; the presence of a  
2129 union slightly decreased it. Thus, the likelihood of respirator use may not be widespread or  
2130 effective.

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**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		0	1
b. Gloves with available permeation data indicating that the material of construction offers good protection for the substance	Industrial/Commercial Uses	80	5
c. Chemically resistant gloves (i.e., as <i>b</i> 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

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**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



2163 tetrachloride as a reactant to produce large quantities of another chemical. Exposure from the use  
 2164 of carbon tetrachloride in reactive ion etching would be inaccurately captured if it was included  
 2165 in the assessment for the use of carbon tetrachloride as a reactant.

2166  
 2167 Similarly, the categories and subcategories originally listed in the problem formulation document  
 2168 ([U.S. EPA, 2018d](#)) for incorporation into formulation are regrouped to either the use of carbon  
 2169 tetrachloride as a reactant to manufacturing a chlorinated compound that is subsequently  
 2170 formulated into a product or as a processing aid/agent used to aid in the manufacture of  
 2171 formulated products (agricultural chemicals, petrochemicals-derived products, and any other  
 2172 basic organic and inorganic chemical manufacturing). The former case is evaluated in the  
 2173 reactant section and the latter in the processing aid section.

2174  
 2175 A crosswalk of all the conditions of use listed in Table 1-4 to the conditions of use assessed for  
 2176 occupational exposures is provided in Table 2-4 below.

2177  
 2178 **Table 2-4. Crosswalk of Subcategories of Use Listed in Table 1-4 and the Sections Assessed**  
 2179 **for Occupational Exposure**

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4 <sup>5</sup>	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)	

<sup>5</sup> These subcategories reflect more specific uses of carbon tetrachloride.

Life Cycle Stage	Category Reported in Table 1-4	Subcategory Reported in Table 1-4 <sup>5</sup>	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) <sup>6</sup>
	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/comm mercial 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)

<sup>6</sup> 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 <sup>5</sup>	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) <sup>7</sup>
		Industrial wastewater treatment	
		Publicly owned treatment works (POTW)	
		Underground injection	
		Municipal landfill	
		Hazardous landfill	
		Other land disposal	
		Municipal waste incinerator	

<sup>7</sup> 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 <sup>5</sup>	Category in Current Engineering Assessment
		Hazardous waste incinerator	
		Off-site waste transfer	

2180  
 2181 The following sections contain process descriptions and the specific details (worker activities,  
 2182 analysis for determining number of workers, and exposure assessment approach and results) for  
 2183 the assessment for the regrouped conditions of use. The following sections provide a summary of  
 2184 the engineering assessments focusing on results. Additional details on how EPA arrived at the  
 2185 results can be found in the supplemental *Risk Evaluation for Carbon Tetrachloride*,  
 2186 *Supplemental Information on Releases and Occupational Exposure Assessment* ([U.S. EPA,](#)  
 2187 [2019b](#)).

#### 2.4.1.7 Inhalation Exposure Assessment

2188  
 2189 The following sections present inhalation exposure estimates for each condition of use.

##### 2.4.1.7.1 Domestic Manufacturing

#### Process Description

2192 Currently, most carbon tetrachloride is manufactured using one of three methods:

- 2193 1. Chlorination of Hydrocarbons or Chlorinated Hydrocarbons
- 2194 2. Oxychlorination of Hydrocarbons
- 2195 3. CS<sub>2</sub> Chlorination ([Holbrook, 2000](#))

2196  
 2197  
 2198 EPA assessed the import of carbon tetrachloride separate from domestic manufacturing (see  
 2199 2.4.1.7.2) in order to account for differences in the expected industrial operations and the  
 2200 associated worker activities which would otherwise be inaccurately captured if included in  
 2201 this scenario.

#### Worker Activities

2202  
 2203  
 2204 Worker activities at manufacturing facilities may involve manually adding raw materials or  
 2205 connecting/disconnecting transfer lines used to unload containers into storage or reaction vessels,  
 2206 rinsing/cleaning containers and/or process equipment, collecting and analyzing quality control  
 2207 (QC) samples, manually loading carbon tetrachloride product, or connecting/disconnecting  
 2208 transfer lines used to load carbon tetrachloride product into containers.

2209  
 2210 ONUs for manufacturing include supervisors, managers, and tradesmen that may be in the same  
 2211 area as exposure sources but may not perform tasks that result in the same level of exposures as  
 2212 workers. The presence and motions of the worker or ONUs near/far away from the source or the  
 2213 performance of ventilation units could have a considerable influence on the flow field around the  
 2214 person and thus on the dispersion of the chemical from the source to the breathing zone.

2215

## 2216 **Number of Workers and Occupational Non-Users**

2217 The CDR Rule under TSCA (40 CFR Part 711) requires that U.S. manufacturers and importers  
 2218 provide EPA with information on chemicals they manufacture (including imports). For the 2016  
 2219 CDR cycle, data collected for each chemical include the company name, volume of each  
 2220 chemical manufactured/imported, the number of workers employed at each site, and information  
 2221 on whether the chemical is used in the commercial, industrial, and/or consumer sector. Based on  
 2222 activity information reported in the 2016 CDR and 2016 TRI, EPA identified seven sites that  
 2223 domestically manufacture CCl<sub>4</sub>.

2224  
 2225 To determine the total number of workers and ONUs, EPA used the average worker and ONUs  
 2226 estimates from the BLS analysis based on each site's reported NAICS code in TRI ([U.S. BLS,](#)  
 2227 [2016](#)). EPA used the average worker and ONUs estimates from the BLS analysis based on the  
 2228 reported NAICS codes (or 325199 when not available) in TRI. To determine the total number of  
 2229 workers and ONUs, EPA used the average worker and ONUs estimates from the BLS analysis  
 2230 based on each site's reported NAICS code in TRI ([U.S. BLS, 2016](#)). EPA used the average  
 2231 worker and ONUs estimates from the BLS analysis based on the reported NAICS codes (or  
 2232 325199 when not available) in TRI.

2233  
 2234 EPA used the seven sites reported as domestic manufacturers in the 2016 CDR and/or 2017 TRI  
 2235 and the average worker and ONUs estimates from the BLS analysis and TRI reported NAICS  
 2236 codes to determine the total number of workers and ONUs. This resulted in 5 sites being  
 2237 classified under 325199 and 2 sites under 325180. There is a total of 243 workers and 115 ONUs  
 2238 (see Table 2-5).

2239  
 2240 **Table 2-5. Estimated Number of Workers Potentially Exposed to Carbon Tetrachloride**  
 2241 **During Manufacturing**

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

2242  
 2243 **Inhalation Exposure**  
 2244 EPA assessed inhalation exposures during manufacturing using identified monitoring data. Table  
 2245 2-6 summarizes 8-hr and 12-hr TWA samples obtained from data submitted by the Halogenated  
 2246 Solvents Industry Alliance (HSIA) via public comment for two companies ([HSIA, 2019](#)). For  
 2247 additional details on the methodology and approach for data analysis that produced the following  
 2248 results, refer to *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on*  
 2249 *Releases and Occupational Exposure Assessment* ([U.S. EPA, 2019b](#))

2250  
 2251 HSIA ([2019](#)) provided monitoring data for carbon tetrachloride collected by two companies  
 2252 listed as "Company A" and "Company B". The data were collected between 2005 and 2018 with  
 2253 full-shift data collected over 8 to 12 hours during which workers engaged in a variety of  
 2254 activities including collecting catch samples; performing filter changes; line and equipment  
 2255 opening; loading and unloading; process sampling; and transferring of hazardous wastes ([HSIA,](#)  
 2256 [2019](#)). EPA assessed two exposure scenarios: 1) 8-hr TWA exposures; and 2) 12-hr TWA

2257 exposures. Both sets of manufacturing monitoring data were determined to have a “high”  
 2258 confidence rating through EPA’s systematic review process.

2259  
 2260 **Table 2-6. Summary of Worker Inhalation Exposure Monitoring Data for Manufacture of**  
 2261 **Carbon Tetrachloride**

Exposure Calculation	Number of Samples	Central Tendency (mg/m <sup>3</sup> )	High-End (mg/m <sup>3</sup> )	Confidence Rating of Associated Air Concentration Data
<b>8-hr TWA Results for Company A and B</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	
<b>12-hr TWA Results for Company A and B</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	

2262 Equations and parameters for calculation of the ADC and LADC are described in supplemental document *Risk*  
 2263 *Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure*  
 2264 *Assessment* ([U.S. EPA, 2019b](#)).

2265 **2.4.1.7.2 Import and Repackaging**

2266 Domestic production and importation of carbon tetrachloride is currently prohibited under  
 2267 regulations implementing the Montreal Protocol (MP) and CAA Title VI, except when  
 2268 transformed (used and entirely consumed, except for trace quantities, in the manufacture of other  
 2269 chemicals for commercial purposes), destroyed (including destruction after use as a catalyst or  
 2270 stabilizer), or used for essential laboratory and analytical uses. (40 CFR Part 82, 60 FR 24970,  
 2271 24971 (May 10, 1995)). Therefore, once imported or manufactured, carbon tetrachloride will be  
 2272 handled again either on-site or by another facility for the identified uses described in detail in the  
 2273 following sections.

2274  
 2275 The import and repackaging scenarios cover only those sites that purchase carbon tetrachloride  
 2276 from domestic and/or foreign suppliers and repackage the carbon tetrachloride from bulk  
 2277 containers into smaller containers for resale (i.e., laboratory chemicals). It does not include sites  
 2278 that import carbon tetrachloride and either: (1) store the chemical in a warehouse and resell  
 2279 directly without repackaging; (2) act as the importer of record for carbon tetrachloride but carbon  
 2280 tetrachloride is never present at the site<sup>8</sup>; or (3) import the chemical and process or use the  
 2281 chemical directly at the site. In case #1, there is little or negligible opportunity for exposures or  
 2282 releases as the containers are never opened. In case #2, the potential for exposure and release is  
 2283 at the site receiving carbon tetrachloride, not the “import” site and exposures/releases at the site

<sup>8</sup> 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.

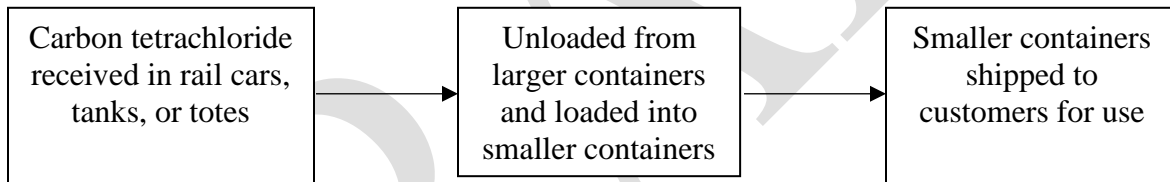
2284 receiving carbon tetrachloride are assessed in the relevant scenario based on the condition of use  
2285 for carbon tetrachloride at the site. Similarly, for case #3, the potential for exposure and release  
2286 at these sites are evaluated in the relevant scenario depending on the condition of use for carbon  
2287 tetrachloride at the site.

2288  
2289 **Process Description**

2290 EPA assessed the import and repackaging of carbon tetrachloride together because both uses  
2291 share similar operations and worker activities that are expected to result in similar exposures.

2292  
2293 In general, commodity chemicals are imported into the United States in bulk via water, air, land,  
2294 and intermodal shipments ([Tomer and Kane, 2015](#)). These shipments take the form of  
2295 oceangoing chemical tankers, railcars, tank trucks, and intermodal tank containers. Chemicals  
2296 shipped in bulk containers may be repackaged into smaller containers for resale, such as drums  
2297 or bottles. Domestically manufactured commodity chemicals may be shipped within the United  
2298 States in liquid cargo barges, railcars, tank trucks, tank containers, intermediate bulk containers  
2299 (IBCs)/totes, and drums. Both import and domestically manufactured commodity chemicals may  
2300 be repackaged by wholesalers for resale; for example, repackaging bulk packaging into drums or  
2301 bottles.

2302  
2303 For this risk evaluation, EPA assesses the repackaging of carbon tetrachloride from bulk  
2304 packaging to drums and bottles at wholesale repackaging sites (see Figure 2-1).



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2312 **Figure 2-1. General Process Flow Diagram for Import and Repackaging**

2313  
2314 **Worker Activities**

2315 Based on EPA's knowledge of the chemical industry, worker activities at import and  
2316 repackaging sites are potentially exposed while connecting and disconnecting hoses and transfer  
2317 lines to containers and packaging to be unloaded (e.g., railcars, tank trucks, totes), intermediate  
2318 storage vessels (e.g., storage tanks, pressure vessels), analyzing QC samples, and final packaging  
2319 containers (e.g., drums, bottles).

2320  
2321 ONUs for repackaging include supervisors, managers, and tradesmen that may be in the  
2322 repackaging area but do not perform tasks that result in the same level of exposures as  
2323 repackaging workers.

2324  
2325 **Number of Workers and Occupational Non-Users**

2326 Upon review of CDR data, EPA determined one import site. None of the CDR submissions  
2327 reported a repackaging activity in the industrial processing and use section. The number of  
2328 potentially exposed workers was estimated based on data from the BLS for NAICS code 424690  
2329 ([U.S. BLS, 2016](#); [U.S. Census Bureau, 2015](#)).

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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<sup>3</sup> 8-hr TWA and a high-end exposure of 0.30 mg/m<sup>3</sup> 8-hr TWA.



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2373

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

Exposure Calculation	Central Tendency (mg/m <sup>3</sup> )	High-End (mg/m <sup>3</sup> )	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	

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#### 2.4.1.7.3 Processing as a Reactant or Intermediate

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##### Process Description

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

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- 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](#)).

2404

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

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**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).

2448 **Table 2-9. Estimated Number of Workers Potentially Exposed to Carbon Tetrachloride**  
 2449 **During Processing as a Reactant**

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

2450

### 2451 **Inhalation Exposure**

2452 EPA identified one source for inhalation exposure monitoring data related to the use of carbon  
 2453 tetrachloride as a reactant; however, the discrete sample values as well as the number of samples  
 2454 taken were not available to estimate exposure concentrations. The manufacturing setting and  
 2455 associated worker activities are similar for both the manufacture and use as a reactant or  
 2456 intermediate of carbon tetrachloride. Therefore, the exposure sources, exposure routes, and  
 2457 exposure levels for the manufacture of carbon tetrachloride will be used to assess the inhalation  
 2458 exposure during the use of carbon tetrachloride as a reactant or intermediate.<sup>9</sup>

2459

2460 The manufacturing monitoring data were determined to have a “high” confidence rating through  
 2461 EPA’s systematic review process. Although these data are not directly applicable to processing  
 2462 of carbon tetrachloride as a reactant, EPA expects a high degree of overlap of worker tasks at  
 2463 both manufacturing sites and sites processing carbon tetrachloride as a reactant. Based on this  
 2464 expectation and the strength of the monitoring data, EPA has a medium to high level of  
 2465 confidence in the assessed exposures. See section 2.4.1.7.2 for the assessment of worker  
 2466 exposure from chemical manufacturing activities.

2467

#### **2.4.1.7.4 Specialty Uses - Department of Defense Data**

2468 EPA reached out to the Department of Defense (DoD) for monitoring data for the first 10  
 2469 chemical substances that are the subject of the Agency’s initial chemical risk evaluations. The  
 2470 DoD provided monitoring data from its Defense Occupational and Environmental Health  
 2471 Readiness System – Industrial Hygiene (DOEHRS-IH), which collects occupational and  
 2472 environmental health risk data from each service branch. The DoD provided inhalation  
 2473 monitoring data for three branches of the military: The Army, Air Force, and Navy ([Defense  
 2474 Occupational and Environmental Health Readiness System - Industrial Hygiene \(DOEHRS-IH\),  
 2475 2018](#)). These data are not distinguished among the three branches.

2476

2477 The following subsections provide an overview of the DoD data. EPA only used the Open  
 2478 Burn/Open detection (OBOD) clean-up data in this assessment as these were the only data EPA  
 2479 could use to assess 8-hr TWA exposures. The sampling results for the remaining six processes

<sup>9</sup> 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 tetrachloropyridine (Federal Register, Vol. 57, No. 252, December 31, 1992, 62765)

2480 were measured over a period less than 50 percent of the duration of the process (or an 8-hr shift  
 2481 if the process duration was not specified). No extrapolation of data was performed to estimate 8-  
 2482 hr TWA exposure using those data that were sampled only a fraction of the process time (or an  
 2483 8-hr shift).

2484  
 2485 **Data Overview**

2486 The data provided by DoD includes 105 data points for carbon tetrachloride from samples taken  
 2487 during seven processes:

- 2488
- 2489 1. OBOD Clean-Up
  - 2490 2. Detonation Chamber
  - 2491 3. Mobile Detonation Test Facility
  - 2492 4. Plastics/Modeling (Thermoforming)
  - 2493 5. Solvent Extraction of Explosive Samples
  - 2494 6. Glue Sound Dampening Material to Torpedo Body
  - 2495 7. Spray Painting – High Volume, Low Pressure (HVLP) Spray Gun

2496 The provided personal breathing zone samples for all of the DoD activities are summarized in  
 2497 Table 2-10. All sample results are indicated as less than a value, which is considered to be the  
 2498 limit of detection (LOD). The DoD data stated that all workers monitored worked an 8-hr shift.  
 2499 For some processes, the DoD data do not provide the process duration.

2500  
 2501

**Table 2-10. DoD Inhalation Monitoring Results**

Process	Worker Activity Description	Worker Activity Frequency	Process Duration (hours)	Min. Sample Result (mg/m <sup>3</sup> )	Max. Sample Result (mg/m <sup>3</sup> )	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 <sup>1</sup>	-	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 <sup>3</sup> )	Max. Sample Result (mg/m <sup>3</sup> )	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

2502 <sup>1</sup>All three samples provided were listed as < 0.2 ppm (1.26 mg/m<sup>3</sup>)

2503

2504 **OBOD Clean-Up Process Description**

2505 During the OBOD clean-up process, employees clean up residual metal and ash. Small metal  
 2506 pieces and ash are drummed and stored. Once drum(s) are full, personnel perform sampling to  
 2507 determine disposal requirements. Larger pieces of metal can be sold for recycling once deemed  
 2508 inert. Clean-up is performed in steel toe boots, coveralls, and respiratory protection (powered air-  
 2509 purifying respirator [PAPR] with tight-fitting facepiece and organic vapor and HEPA cartridge).  
 2510 A self-contained breathing apparatus (SCBA) is available for emergencies and as needed for  
 2511 clean-up ([Defense Occupational and Environmental Health Readiness System - Industrial](#)  
 2512 [Hygiene \(DOEHRS-IH\), 2018](#)).

2513

2514 **Inhalation Exposure**

2515 As the exposure values are reported to be below the LOD, EPA assessed the data as a range from  
 2516 0 to 1.26 mg/m<sup>3</sup> using the midpoint (0.68 mg/m<sup>3</sup>) to calculate the central tendency 8-hr TWA  
 2517 and the maximum value (1.26 mg/m<sup>3</sup>) to calculate the high end 8-hr TWA. Additionally, the  
 2518 DoD data indicates that OBOD clean-up has a duration of one to two hours. The sampling  
 2519 duration of the January 27, 2015 monitoring was 140 minutes (approximately 2.3 hours). The  
 2520 workers' exposures are zero for the remainder of an 8-hr shift. Therefore, EPA averaged the 140-  
 2521 minute midpoint and maximum sample results over eight hours to calculate the 8-hr TWA  
 2522 exposure.

2523

2524 DoD reported the process frequency for the OBOD cleaning as every 2-3 weeks. EPA  
 2525 incorporated this data and adjusted the exposure frequency to reflect the limited work exposure  
 2526 time when calculating the central tendency and high-end ADC and LADC. The central tendency  
 2527 ADC and LADC are calculated using the midpoint of the process frequency range, 2.5 weeks  
 2528 (125 days/year), and the high-end ADC and LADC are calculated using maximum of the process  
 2529 frequency range, 3 weeks (150 days/year). Results are displayed in Table 2-11.

2530

2531

2532 **Table 2-11. Summary of Worker Inhalation Exposure Monitoring Data for Specialty Use of**  
 2533 **Carbon Tetrachloride**

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

2534 Equations and parameters for calculation of the ADC and LADC are described in supplemental document *Risk*  
 2535 *Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational Exposure*  
 2536 *Assessment* ([U.S. EPA, 2019b](#)).

#### 2537 **2.4.1.7.5 Reactive Ion Etching**

##### 2538 **Process Description**

2539 Reactive ion etching (RIE) is a microfabrication technique used in miniature electronic  
 2540 component manufacture. Ion bombardment and a reactive gas, such as carbon tetrachloride, are  
 2541 used to selectively etch wafers ([U.S. EPA, 2017d](#)).

2542  
 2543 Typically, a clean environment is essential for manufacturing the miniature electronic  
 2544 components (primarily semiconductors) that require RIE. Flaws in the wafer surface or  
 2545 contamination of the materials used can result in “opens” or “shorts” in the transistor circuits,  
 2546 causing them to be unusable ([OECD, 2010](#)). Therefore, current semiconductor fabrication  
 2547 facilities (i.e., ‘fabs’) are built to Class-1 cleanroom specifications, which means there is no more  
 2548 than one particle larger than 0.5-micron in one cubic foot of air. In addition, cleaning operations  
 2549 precede and follow most of the manufacturing process steps. Wet processing, during which  
 2550 wafers are repeatedly immersed in or sprayed with solutions, is commonly used to minimize the  
 2551 risk of contamination. In addition, many processes operate within a positive pressure  
 2552 environment ([OECD, 2010](#)).

2553  
 2554 EPA assessed the use of carbon tetrachloride in reactive ion etching separately from processing  
 2555 as a reactant or intermediate to account for differences in the work environments, the industrial  
 2556 processes, and the quantities of carbon tetrachloride used which would otherwise be inaccurately  
 2557 captured if reactive ion etching was included in the reactant scenario.

##### 2558 **Worker Activities**

2560 Specific worker activities for RIE were not identified, but EPA utilized the worker activities  
 2561 listed in the *Emission Scenario Document (ESD) on Photoresist Use in Semiconductor*  
 2562 *Manufacturing* because worker activities will be similar for RIE as they are for using  
 2563 photoresists. According to the *ESD on Photoresist Use in Semiconductor Manufacturing*, there  
 2564 are two main worker activity groups at a facility that utilizes RIE that include: equipment  
 2565 operators and equipment maintenance/waste management technicians. Equipment operators’  
 2566 main role is to change-out the liquid etching containers containing carbon tetrachloride.

2567 Equipment maintenance/waste management technicians clean empty containers, clean/maintain  
2568 equipment, and change-out the excess solvent collection containers ([OECD, 2010](#)).  
2569

2570 When workers must enter the cleanroom environment to perform their duties, the worker is  
2571 required to wear full-body coveralls (i.e., “space suits”), respirators, face shields, and gloves.  
2572 Additionally, wafers are often manipulated robotically within the closed system, or transferred  
2573 within “micro” enclosures between process steps to limit worker exposure. However, some sites  
2574 have separate work areas outside the wafer processing area (e.g., “chemical kitchens”) in which  
2575 the photoresist and other chemical containers and supply lines are connected. If workers handle  
2576 the photoresist bottles and other chemical containers in a separate area, such as the chemical  
2577 kitchen, they will likely be wearing solvent-resistant gloves, aprons, goggles, and respirators  
2578 with organic vapor cartridges to minimize exposure ([OECD, 2010](#)).  
2579

#### 2580 **Number of Workers and Occupational Non-Users**

2581 Based on information in the *ESD on Photoresist Use in Semiconductor Manufacturing*, EPA  
2582 identified the NAICS code 334413, Semiconductor and Related Device Manufacturing, as the  
2583 NAICS code could include sites using carbon tetrachloride as a RIE ([OECD, 2010](#)). EPA  
2584 estimated the number of workers and ONUs for this NAICS code using Bureau of Labor  
2585 Statistics’ OES data and the U.S. Census’ SUSB ([U.S. BLS, 2016](#); [U.S. Census Bureau, 2015](#)).  
2586 This analysis resulted in an average of 50 workers and 45 ONU per site. EPA does not have data  
2587 to estimate the number of sites using carbon tetrachloride as a RIE; therefore, only the per site  
2588 data are presented in Table 2-12.  
2589

2590 **Table 2-12. Estimated Number of Workers Potentially Exposed to Carbon Tetrachloride**  
2591 **During Use as a RIE**

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

2592  
2593 **Inhalation Exposure**  
2594 The worker exposures to carbon tetrachloride during RIE are negligible. Due to the performance  
2595 requirements of products typically produced via RIE, carbon tetrachloride could be applied in  
2596 small amounts in a highly controlled work area, thus eliminating or significantly reducing the  
2597 potential for exposures. EPA anticipates that carbon tetrachloride is used in RIE applications in  
2598 limited quantities and among limited facilities. This is consistent with assumptions for similar  
2599 industry processes provided in the *ESD on Chemical Vapor Deposition in the Semiconductor*  
2600 *Industry* and *ESD on Photoresist Use in Semiconductor Manufacturing* ([OECD, 2015, 2010](#)).

#### 2601 **2.4.1.7.6 Industrial Processing Agent/Aid**

##### 2602 **Process Description**

2603 According to the *TRI Reporting Forms and Instructions (RFI) Guidance Document*, a processing  
2604 aid is a “chemical that is added to a reaction mixture to aid in the manufacture or synthesis of  
2605 another chemical substance but is not intended to remain in or become part of the product or  
2606 product mixture”. Examples of such chemicals include, but are not limited to, process solvents,  
2607 catalysts, inhibitors, initiators, reaction terminators, and solution buffers ([U.S. EPA, 2018g](#)).  
2608 Additionally, processing agents are intended to improve the processing characteristics or the

2609 operation of process equipment, but not intended to affect the function of a substance or article  
 2610 created ([U.S. EPA, 2016b](#)).

2611  
 2612 The domestic and international use of carbon tetrachloride as a process agent is addressed under  
 2613 the MP side agreement, Decision X/14: Process Agents ([UNEP/Ozone Secretariat, 1998](#)). This  
 2614 decision lists a limited number of specific manufacturing uses of carbon tetrachloride as a  
 2615 process agent (non-feedstock use) in which carbon tetrachloride may not be reacted or destroyed  
 2616 in the production process. Approved uses of carbon tetrachloride as a process agent are listed  
 2617 below in Table 2-13.

2618  
 2619 **Table 2-13. List of Approved Uses of Carbon Tetrachloride as a Process Agents in the MP**  
 2620 **Side Agreement, Decision X/14: Process Agents<sup>1</sup>**

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-terephthal-amide	17	Isosorbid mononitrate
9	Manufacture of styrene butadiene rubber	18	Omeprazol

2621 <sup>1</sup>EPA found no evidence to suggest that the manufacturing of ibuprofen, or any other pharmaceuticals, still utilizes carbon tetrachloride or that  
 2622 such use is reasonably foreseen to resume. Accordingly, EPA no longer considers use as a process agent in the manufacturing of pharmaceuticals  
 2623 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

2624  
 2625 EPA has identified uses of carbon tetrachloride as a process agent in the manufacturing of  
 2626 petrochemical-derived products, agricultural products, inorganic compounds (i.e., chlorine), and  
 2627 chlorinated compounds that are used in the formulation of solvents for cleaning and degreasing,  
 2628 adhesive and sealants, paints and coatings and asphalt ([U.S. EPA, 2017d](#)). A current example of  
 2629 using carbon tetrachloride as a process agent in petrochemicals-derived product manufacturing is  
 2630 the manufacture of chlorinated rubber resins. The resulting resins are thermoplastic, odorless,  
 2631 and non-toxic. Carbon tetrachloride is preferred in this process as it is the only solvent not  
 2632 attacked by chlorine ([U.S. EPA, 2017d](#)).

### 2633 **Worker Activities**

2634 During processing, workers are primarily exposed while connecting and disconnecting hoses and  
 2635 transfer lines to containers and packaging to be unloaded (e.g., railcars, tank trucks, totes, drums,  
 2636 bottles) and intermediate storage vessels (e.g., storage tanks, pressure vessels).

2637  
 2638  
 2639 ONUs for use of carbon tetrachloride used as a processing agent/aid include supervisors,



2640 managers, and tradesmen that may be in the same area as exposure sources but do not perform  
 2641 tasks that result in the same level of exposures as workers.

2642  
 2643 **Number of Workers and Occupational Non-Users**

2644 Using 2016 CDR data and 2017 TRI data, EPA confirmed three sites that use carbon  
 2645 tetrachloride as a processing agent/aid.

2646  
 2647 To determine the total number of workers and ONUs, EPA used the average worker and ONUs  
 2648 estimates from the BLS analysis based on their NAICS codes ([U.S. BLS, 2016](#)). This resulted in  
 2649 an estimated 67 workers and 32 ONUs (see Table 2-14).

2650  
 2651 **Table 2-14. Estimated Number of Workers Potentially Exposed to Carbon Tetrachloride**  
 2652 **During Use as a Processing Agent/Aid**

Number of Sites	Total Exposed Workers	Total Exposed Occupational Non-Users	Total Exposed
3	67	32	99

2653  
 2654 **Inhalation Exposure**

2655 EPA did not find any exposure monitoring data for use of carbon tetrachloride as a processing  
 2656 agent/aid; therefore, exposures were assessed with the Tank Truck and Railcar Loading and  
 2657 Unloading Release and Inhalation Exposure Model.

2658  
 2659 See section 2.4.1.7.2 for the assessment of worker exposure from chemical unloading activities.  
 2660 The exposure sources, routes, and exposure levels are similar to those at an import/repackaging  
 2661 facility, where unloading and handling are the key worker activities. Inhalation exposure  
 2662 assessment for processing carbon tetrachloride as a processing agent/aid is estimated by the Tank  
 2663 Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model used in the  
 2664 import/repackaging scenario.

2665 **2.4.1.7.7 Additive**

2666 **Process Description**

2667 Additives are chemicals combined with a chemical product to enhance the properties of the  
 2668 product. Additives typically stay mixed within the finished product and remain unreacted.

2669  
 2670 This section includes the assessment of the use of carbon tetrachloride as an additive for  
 2671 petrochemicals-derived products manufacturing and agricultural products manufacturing.  
 2672 Specific uses of carbon tetrachloride as an additive include both an additive used in plastic  
 2673 components used in the automotive industry ([HSIA, 2017](#)) and a fuel additive ([U.S. EPA, 2017d](#)).

2674  
 2675  
 2676 **Worker Activities**

2677 Similar to manufacturing facilities, worker activities use of carbon tetrachloride as an additive  
 2678 may involve manually adding raw materials or connecting/disconnecting transfer lines used to  
 2679 unload containers into storage or reaction vessels, rinsing/cleaning containers and/or process  
 2680 equipment, collecting and analyzing quality control (QC) samples, and packaging formulated

2681 products into containers and tank trucks. The exact activities and associated level of exposure  
 2682 will differ depending on the degree of automation, presence of engineering controls, and use of  
 2683 PPE at each facility.

2684  
 2685 ONUs for use of carbon tetrachloride as an additive include supervisors, managers, and  
 2686 tradesmen that may be in the same area as exposure sources but do not perform tasks that result  
 2687 in the same level of exposures as workers.

2688  
 2689 **Number of Workers and Occupational Non-Users**

2690 Upon review of the 2017 TRI data, EPA found that one site reported the use of carbon  
 2691 tetrachloride as a formulation component ([U.S. EPA, 2018f](#)). EPA determined the number of  
 2692 workers using the related SOC codes from BLS analysis that are associated with the primary  
 2693 NAICS code, 325211, listed in TRI. This resulted in an estimated 27 workers and 12 ONUs  
 2694 potentially exposed at sites using carbon tetrachloride as an additive (see Table 2-15).

2695  
 2696 **Table 2-15. Estimated Number of Workers Potentially Exposed to Carbon Tetrachloride**  
 2697 **when used as an Additive**

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

2698  
 2699 **Inhalation Exposure**

2700 EPA did not find any exposure monitoring data for use of carbon tetrachloride as an additive;  
 2701 therefore, exposures from use of carbon tetrachloride as an additive were assessed with the *Tank*  
 2702 *Truck and Railcar Loading and Unloading Release and Inhalation Exposure Model*.

2703  
 2704 See section 2.4.1.7.2 for the assessment of worker exposure from chemical unloading activities.  
 2705 The exposure sources, routes, and exposure levels are similar to those at an import/ repackaging  
 2706 facility, where unloading and handling are the key worker activities. Inhalation exposure  
 2707 assessment for the use of carbon tetrachloride as an additive is estimated by the Tank Truck and  
 2708 Railcar Loading and Unloading Release and Inhalation Exposure Model used in the  
 2709 import/repackaging scenario.

2710 **2.4.1.7.8 Laboratory Chemicals**

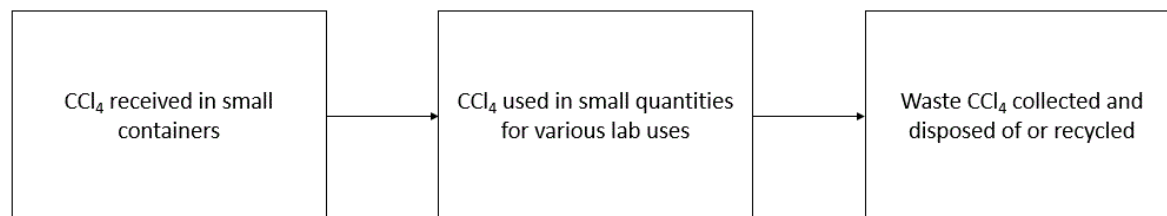
2711 **Process Description**

2712 Carbon tetrachloride is used in a variety of laboratory applications, which include, but are not  
 2713 limited to, the following:

- 2714
- 2715 • Chemical reagent;
  - 2716 • Extraction solvent; and
  - 2717 • Reference material or solvent in analytical procedures, such as spectroscopic  
 2718 measurements ([U.S. EPA, 2017d](#)).

2719

2720 Specific process descriptions for how carbon tetrachloride is used in each of these applications is  
 2721 not known. In general, carbon tetrachloride is typically received in small containers and used in  
 2722 small quantities on a lab bench in a fume cupboard or hood. After use, waste carbon tetrachloride  
 2723 is collected and disposed or recycled. Figure 2-2 depicts this general process.  
 2724



2725  
 2726 CCl<sub>4</sub> = carbon tetrachloride

2727  
 2728 **Figure 2-2. General Laboratory Use Process Flow Diagram**  
 2729

2730 EPA assessed the repackaging of carbon tetrachloride separately (see section 2.4.1.7.2) in order  
 2731 to account for differences in the industrial processing methods, processing quantities, and the  
 2732 associated worker interaction which would otherwise be inaccurately captured if included in this  
 2733 scenario.  
 2734

### 2735 **Worker Activities**

2736 Specific worker activities for using laboratory uses were not identified, but the workers could be  
 2737 potentially exposed to carbon tetrachloride in laboratories during multiple activities, including  
 2738 unloading of carbon tetrachloride from the containers in which they were received, transferring  
 2739 carbon tetrachloride into laboratory equipment (i.e., beakers, flasks, other intermediate storage  
 2740 containers), dissolving substances into carbon tetrachloride or otherwise preparing samples that  
 2741 contain carbon tetrachloride analyzing these samples, and discarding the samples.  
 2742

2743 ONUs include employees that work at the sites where carbon tetrachloride is used, but they do  
 2744 not directly handle the chemical and are therefore could have lower inhalation exposures and  
 2745 would not have dermal exposures. ONUs for this condition of use include supervisors, managers,  
 2746 and other employees that may be in the laboratory but do not perform tasks that result in the  
 2747 same level of exposures as those workers that engage in tasks related to the use of carbon  
 2748 tetrachloride.  
 2749

### 2750 **Number of Workers and Occupational Non-Users**

2751 Using 2016 CDR data and 2017 TRI data, EPA confirmed one industrial use of carbon  
 2752 tetrachloride as a laboratory chemical for fewer than ten sites ([U.S. EPA, 2018f](#), [2016a](#)). EPA  
 2753 determined the number of workers using the related SOC codes from BLS analysis that are  
 2754 associated with the primary NAICS code, 541380, Testing Laboratories.  
 2755

2756 To determine the high-end total number of workers and ONUs, EPA used the high-end number  
 2757 of sites from CDR (nine sites) and the BLS OES data to estimate number of workers per site.  
 2758 This resulted in a total of 87 exposed workers and ONUs (see Table 2-16).  
 2759

2760 To determine the low-end total number of workers and ONUs, EPA used the low-end number of  
 2761 sites from CDR (one site) and the BLS OES data to estimate workers per site listed for these  
 2762 industrial use sites. This resulted in a total of ten exposed workers and ONUs (see Table 2-16).  
 2763

2764 **Table 2-16. Estimated Number of Workers Potentially Exposed to Carbon Tetrachloride**  
 2765 **During Use as a Laboratory Chemical**

Number of Sites	Total Exposed Workers	Total Exposed Occupational Non-Users	Total Exposed
<b>High-End</b>			
9	9	78	87
<b>Low-End</b>			
1	1	9	10

2766  
 2767 **Inhalation Exposure**

2768 EPA does not have monitoring data to assess worker exposures to carbon tetrachloride during  
 2769 laboratory use. Following workplace safety protocols for the use of chemicals in laboratories,  
 2770 carbon tetrachloride is generally handled in small amounts as required for reactions or analyses.  
 2771 Carbon tetrachloride is handled under a fume hood as per good laboratory practices, thus  
 2772 reducing the potential for inhalation exposures

2773 **2.4.1.7.9 Disposal/Recycling**

2774 This scenario is meant to include sites like hazardous waste treatment sites (TSDFs), including  
 2775 incinerators, landfills, other forms of treatment, and solvent or other material reclamation or  
 2776 recycling. These are sites largely covered under RCRA (e.g., RCRA permitted TSDFs) but also  
 2777 include municipal waste combustors and landfills.  
 2778

2779 **Process Description**

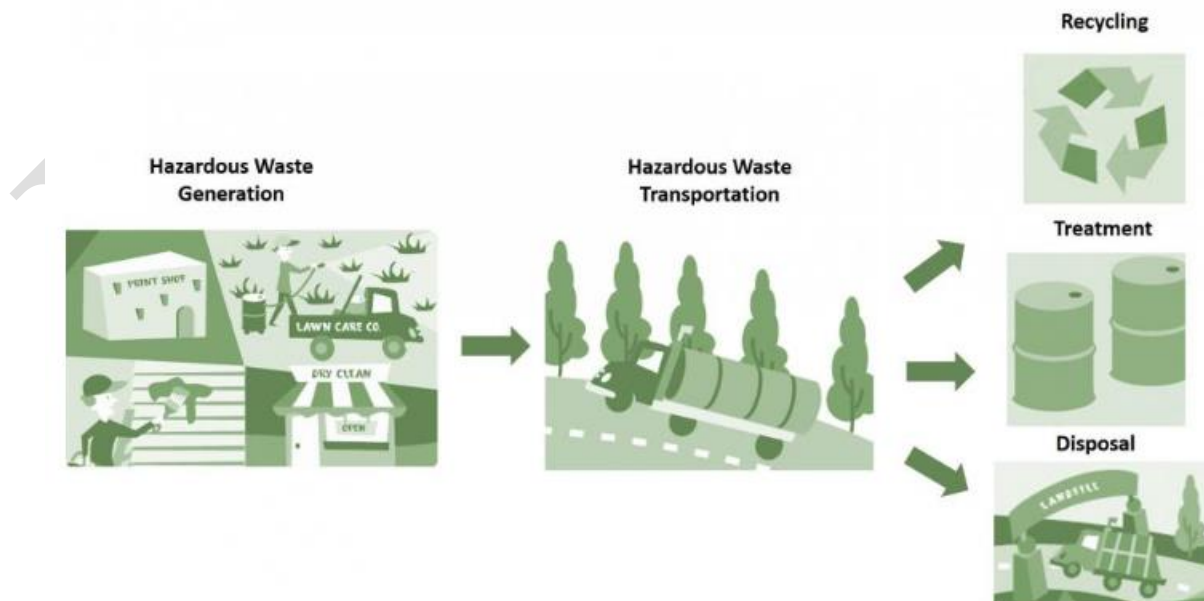
2780 Each of the conditions of use of carbon tetrachloride may generate waste streams of the chemical  
 2781 that are collected and transported to third-party sites for disposal, treatment, or recycling.  
 2782 Industrial sites that treat or dispose onsite wastes that they themselves generate are assessed in  
 2783 each condition of use assessment in sections 2.4.1.7.1 to 2.4.1.7.8. Wastes of carbon tetrachloride  
 2784 that are generated during a condition of use and sent to a third-party site for treatment, disposal,  
 2785 or recycling may include the following:  
 2786

- 2787 • Wastewater: carbon tetrachloride may be contained in wastewater discharged to POTW  
 2788 or other, non-public treatment works for treatment. Industrial wastewater containing  
 2789 carbon tetrachloride discharged to a POTW may be subject to EPA or authorized NPDES  
 2790 state pretreatment programs.
- 2791 • Solid Wastes: Solid wastes are defined under RCRA as any material that is discarded by  
 2792 being: abandoned; inherently waste-like; a discarded military munition; or recycled in  
 2793 certain ways (certain instances of the generation and legitimate reclamation of secondary  
 2794 materials are exempted as solid wastes under RCRA). Solid wastes may subsequently  
 2795 meet RCRA’s definition of hazardous waste by either being listed as a waste at 40 CFR  
 2796 §§ 261.30 to 261.35 or by meeting waste-like characteristics as defined at 40 CFR §§

2797 261.20 to 261.24. Solid wastes that are hazardous wastes are regulated under the more  
2798 stringent requirements of Subtitle C of RCRA, whereas non-hazardous solid wastes are  
2799 regulated under the less stringent requirements of Subtitle D of RCRA.  
2800

- 2801 ○ Carbon tetrachloride is both a listed and a characteristic hazardous waste. Carbon  
2802 tetrachloride is a non-specific-source listed hazardous waste under waste number  
2803 F001 (spent halogenated degreasing solvents) [40 CFR § 261.31] and a source-  
2804 specific listed hazardous waste under waste number K016 (heavy ends or  
2805 distillation residues from the production of carbon tetrachloride, which may  
2806 contain residual carbon tetrachloride) [40 CFR §261.32]. Discarded, commercial-  
2807 grade carbon tetrachloride is a listed hazardous waste under waste number U211  
2808 40 CFR § 261.33.
- 2809 ○ Carbon tetrachloride is a toxic contaminant under RCRA with waste number  
2810 D019. A solid waste can be a hazardous waste due to its toxicity characteristic if  
2811 its extract following the Toxicity Characteristic Leaching Procedure (TCLP) (or  
2812 the liquid waste itself if it contains less than 0.5% filterable solids) contains at  
2813 least 0.5 mg/L of carbon tetrachloride [40 CFR § 261.24].  
2814
- 2815 ● Wastes Exempted as Solid Wastes under RCRA: Certain conditions of use of carbon  
2816 tetrachloride may generate wastes of carbon tetrachloride that are exempted as solid  
2817 wastes under 40 CFR § 261.4(a). For example, the generation and legitimate reclamation  
2818 of hazardous secondary materials of carbon tetrachloride may be exempt as a solid waste.

2819  
2820 2016 TRI data lists off-site transfers of carbon tetrachloride to land disposal, wastewater  
2821 treatment, incineration, and recycling facilities ([U.S. EPA, 2017b, f](#)). See Figure 2-3 for a  
2822 general depiction of the waste disposal process.  
2823



2824  
2825  
2826

**Figure 2-3. Typical Waste Disposal Process**

Source: ([U.S. EPA, 2017c](#))

2827

2828 **Worker Activities**

2829 At waste disposal sites, workers are potentially exposed via dermal contact with waste containing  
 2830 carbon tetrachloride or via inhalation of carbon tetrachloride vapor. Depending on the  
 2831 concentration of carbon tetrachloride in the waste stream, the route and level of exposure may be  
 2832 similar to that associated with container unloading activities. At municipal waste incineration  
 2833 facilities, there may be one or more technicians present on the tipping floor to oversee  
 2834 operations, direct trucks, inspect incoming waste, or perform other tasks as warranted by  
 2835 individual facility practices. At landfills, typical worker activities may include operating refuse  
 2836 vehicles to weigh and unload the waste materials, operating bulldozers to spread and compact  
 2837 wastes, and monitoring, inspecting, and surveying a landfill site [California Department of  
 2838 Resources Recycling and Recovery ([CalRecycle, 2018](#))].

2839

2840 **Number of Workers and Occupational Non-Users**

2841 The 2016 CDR uses did not show any submissions for waste handling, so EPA reviewed the  
 2842 2017 TRI data and found twelve sites reported using carbon tetrachloride during waste handling  
 2843 ([U.S. EPA, 2018f](#), [2017b](#), [2016d](#)).

2844

2845 EPA determined the number of workers using the related SOC codes from BLS analysis that are  
 2846 associated with the primary NAICS codes listed in TRI ([U.S. BLS, 2016](#)). This analysis resulted  
 2847 in 125 workers and 63 ONUs potentially exposed at sites using carbon tetrachloride as a  
 2848 processing agent/aid (see Table 2-17).

2849

2850 **Table 2-17. Estimated Number of Workers Potentially Exposed to Carbon Tetrachloride**  
 2851 **During Waste Handling**

Number of Sites	Total Exposed Workers	Total Exposed Occupational Non-Users	Total Exposed
12	125	63	188

2852

2853 **Inhalation Exposure**

2854 EPA did not find any exposure monitoring data for waste handling of carbon tetrachloride;  
 2855 therefore, exposures from waste handling activities were assessed with the *Tank Truck and*  
 2856 *Railcar Loading and Unloading Release and Inhalation Exposure Model*. The following  
 2857 subsections detail the results of EPA's occupational exposure assessment for waste handling are  
 2858 based on modeling.

2859

2860 See section 2.4.1.7.2 for the assessment of worker exposure from chemical unloading activities.  
 2861 The exposure sources, routes, and exposure levels are similar to those at an import/repackaging  
 2862 facility, where unloading and handling are the key worker activities. Inhalation exposure  
 2863 assessment for the disposal of carbon tetrachloride is estimated by the Tank Truck and Railcar  
 2864 Loading and Unloading Release and Inhalation Exposure Model used in the import/repackaging  
 2865 scenario.

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**2.4.1.7.10 Summary of Occupational Inhalation Exposure Assessment**

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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 performed, 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 <sup>3</sup> )		AC TWA (mg/m <sup>3</sup> )		ADC TWA (mg/m <sup>3</sup> )		LADC TWA (mg/m <sup>3</sup> )			
	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 <sup>a</sup>		Overall Rating for Workers <sup>b</sup>
			Monitoring				Modeling			Worker	ONU	
			Data (#)	Surrogate	Worker	ONU	Worker	ONU				
Manufacturing	PBZ sampling	Data is provided from one source	✓ (373)	✗	✓	✗	✗	✗	Routine monitoring data available for work environment	✓	—	
	High data quality											
	Source of information available directly from manufacturer	Many data points were at or below the limit of detection										
	CDR provided employee counts for specific manufacturing site											
Data from multiple facilities												
Import and Repackaging	CDR provided employee counts for specific Import and Repackaging sites	No Monitoring Data	✗	✗	✗	✗	✓	✗	Assesses exposure based on loading and unloading only. Assumes controlled and closed systems for all other operations.	✓	—	
		EPA models are not specific to Import and Repackaging										
	Model uses published EPA emission factors	Relies on process and protection assumptions										
		May underestimate worker exposure										
Processing as a Reactant or Intermediate	PBZ sampling	No monitoring data for this CoU; Surrogate data from manufacturing	✗	✓ (373)	✓	✗	✓	✗	Routine monitoring data available for work environment	✓	—	
	415 data points											

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Occupational Exposure Scenario	Strength	Challenge	Inhalation Exposure						Representativeness	Dermal Exposure Modeling <sup>a</sup>		Overall Rating for Workers <sup>b</sup>
			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							Routine monitoring data available for work environment	✓	—	
		Only 3 data points	✓ (3)	✗	✓	✗	✗	✗				
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.	✓	—	
		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										

PEER REVIEW DRAFT, DO NOT CITE OR QUOTE

Occupational Exposure Scenario	Strength	Challenge	Inhalation Exposure						Representativeness	Dermal Exposure Modeling <sup>a</sup>		Overall Rating for Workers <sup>b</sup>
			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.	✓	—	
		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.	✓	—	
		EPA models are not specific to disposal/recycling	✗	✗	✗	✗	✓	✗				
	Model uses published EPA emission factors	Relies on process and protection assumptions										

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<sup>a</sup>Dermal exposure estimates, which are based on high-end/central tendency parameters and commercial/industrial settings, have medium level of confidence.

<sup>b</sup>ONU exposure estimates, which are based on central tendency parameters, have low levels of confidence.

#### 2884                    **2.4.1.8      Dermal Exposure Assessment**

2885      Because carbon tetrachloride is a volatile liquid, the dermal absorption of carbon tetrachloride  
2886      depends on the type and duration of exposure. Where exposure is without gloves, only a fraction  
2887      of carbon tetrachloride that comes into contact with the skin will be retained as the chemical  
2888      readily evaporates from the skin. However, dermal exposure may be significant in cases of  
2889      occluded exposure, repeated contacts, or dermal immersion. For example, work activities with a  
2890      high degree of splash potential may result in carbon tetrachloride liquids trapped inside the  
2891      gloves, inhibiting the evaporation of carbon tetrachloride and increasing the exposure duration.  
2892      Specific methodology for dermal exposure estimation is detailed in Appendix E of the document  
2893      *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and*  
2894      *Occupational Exposure Assessment* ([U.S. EPA, 2019b](#)).  
2895

2896      Table 2-20 presents the estimated dermal retained dose for *workers* in various exposure  
2897      scenarios, focusing on what-if scenarios for glove use. The dose estimates assume one exposure  
2898      event (applied dose) per work day and that approximately four percent of the applied dose is  
2899      absorbed through the skin during industrial settings. The conditions of use for carbon  
2900      tetrachloride are industrial uses that occur in closed systems where dermal exposure is likely  
2901      limited to chemical loading/unloading activities (e.g., connecting hoses) and taking quality  
2902      control samples. Across all types of uses, the maximum possible exposure concentration ( $Y_{\text{derm}}$ )  
2903      exists during industrial uses that generally occur in closed systems. Therefore, all conditions of  
2904      use for carbon tetrachloride are assessed at the maximum  $Y_{\text{derm}}$ , or 1. In addition to the what-if  
2905      scenarios for glove use, EPA considered the potential for occluded dermal exposures; however,  
2906      based on the worker activities for the condition of use for carbon tetrachloride, EPA determined  
2907      occluded exposures to be unlikely. Occluded scenarios are generally expected where workers are  
2908      expected to come into contact with bulk liquid carbon tetrachloride during use in open systems  
2909      (e.g., during solvent changeout in vapor degreasing and dry cleaning) and not expected in closed  
2910      systems (e.g., during connection/disconnection of hoses used in loading of bulk containers in  
2911      manufacturing). For further description of the applicable scenarios, see Appendix E of *Risk*  
2912      *Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational*  
2913      *Exposure Assessment* ([U.S. EPA, 2019b](#)). EPA assesses the following what-if glove use  
2914      scenarios for all conditions of use of carbon tetrachloride for workers:  
2915

2916      No gloves used: Operators in these industrial uses, while working around closed-system  
2917      equipment, may not wear gloves or may wear gloves for abrasion protection or gripping that are  
2918      not chemical resistant.  
2919

- 2920                    • Gloves used with a protection factor of 5, 10, and 20: Operators may wear  
2921                    chemical-resistant gloves when taking quality control samples or when  
2922                    connecting and disconnecting hoses during loading/unloading activities. The  
2923                    gloves could offer a range of protection, depending on the type of glove and  
2924                    employee training provided.
- 2925                    • Scenarios not assessed: EPA does not assess occlusion as workers in these  
2926                    industries are not likely to come into contact with bulk liquid carbon tetrachloride

2927 that could lead to chemical permeation under the cuff of the glove or excessive  
2928 liquid contact time leading to chemical permeation through the glove.

2929 The skin is a very complex and dynamic human organ composed of an outer epidermis and inner  
2930 dermis with functions well beyond that of just a barrier to the external environment. Dermal  
2931 absorption depends largely on the barrier function of the stratum corneum, the outermost  
2932 superficial layer of the epidermis, and is modulated by factors such as skin integrity, hydration,  
2933 density of hair follicles and sebaceous glands, thickness at the site of exposure assessment,  
2934 physiochemical properties of the substance, chemical exposure concentration, and duration of  
2935 exposure. The workplace protection factor for gloves is based on the ratio of uptake through the  
2936 unprotected skin to the corresponding uptake through the hands when protective gloves are worn.

2937 The exposure assessments were conducted considering vapor pressure and other physical-  
2938 chemical properties of carbon tetrachloride. The key barrier of the skin is located in the  
2939 outermost layer of the skin, the stratum corneum, which consists of corneocytes surrounded by  
2940 lipid regions. Due to increased area of contact and reduced skin barrier properties, repeated skin  
2941 contact with chemicals could have even higher than expected exposure if evaporation of the  
2942 chemical occurs and the concentration of chemical in contact with the skin increases. In the  
2943 workplace the wearing of gloves could have important consequences for dermal uptake. If the  
2944 worker is handling a chemical without any gloves, a splash of the liquid or immersion of the  
2945 hand in the chemical may overwhelm the skin contamination layer so that the liquid chemical  
2946 essentially comprises the skin contamination layer. If the material is undiluted, then uptake could  
2947 proceed rapidly as there will be a large concentration difference between the skin contamination  
2948 layer and the peripheral blood supply. Conversely, if the contaminant material is in a dilute form,  
2949 there will be relatively slow uptake. If the worker is wearing a glove the situation will be  
2950 different. In case the chemical comes into contact with the outer glove surface, there will be no  
2951 flux into the inner glove contamination layer until the chemical breaks through. The chemical  
2952 could partition into the glove and then diffuse towards the inner glove surface; then it could  
2953 partition into the skin contamination layer. Diffusion through the stratum corneum is dependent  
2954 on the concentration. The glove protection factor is unlikely to be constant for a glove type but  
2955 could be influenced by the work situation and the duration of the exposure as glove performance  
2956 and pass/fail criteria are also dependent on cut, puncture and abrasion resistance; chemical  
2957 permeation and degradation; holes; heat and flame resistance; vibration, and dexterity of  
2958 operation and operator.

2959 As shown in Table 2-20 the calculated retained dose is low for all dermal exposure scenarios as  
2960 carbon tetrachloride evaporates quickly after exposure. Dermal exposure to liquid is not expected  
2961 for occupational non-users, as they do not directly handle carbon tetrachloride.

2962 **Table 2-20. Estimated Dermal Acute and Chronic Retained Doses for Workers for All**  
 2963 **Conditions of Use<sup>10</sup>**

Category	Exposure Level	Acute Potential Dose Rate	Acute Retained Dose	Chronic Retained Dose, Non-Cancer	Chronic Retained Dose, Cancer
		APDR <sub>exp</sub> (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

#### 2964 **2.4.2 Consumer Exposures**

2965 As explained in section 1.4.1, there are no consumer uses of carbon tetrachloride within the  
 2966 scope of the risk evaluation. No additional information was received by EPA following the  
 2967 publication of the problem formulation that would update the problem formulation conclusion  
 2968 that carbon tetrachloride is expected to be present in consumer products at trace levels resulting  
 2969 in de minimis exposures or otherwise insignificant risks and therefore that consumer uses do not  
 2970 warrant inclusion in the risk evaluation. Accordingly, EPA did not analyze consumer exposures  
 2971 in the risk evaluation for carbon tetrachloride.

#### 2972 **2.4.3 General Population Exposures**

2973 As explained in sections 1 and 2.5 of the problem formulation document ([U.S. EPA, 2018d](#)),  
 2974 EPA is not including in this draft risk evaluation exposure pathways under programs of other  
 2975 environmental statutes, administered by EPA, which adequately assess and effectively manage  
 2976 exposures and for which long-standing regulatory and analytical processes already exist.  
 2977 Therefore, based on information obtained by EPA and presented in section 2.5.3.2 of the  
 2978 problem formulation document ([U.S. EPA, 2018d](#)), EPA is not evaluating any exposure  
 2979 pathways to human receptors (i.e., general population) from environmental releases and waste  
 2980 streams associated with industrial/commercial activities for carbon tetrachloride which result in  
 2981 releases to the following pathways: ambient air pathway (carbon tetrachloride is listed as a  
 2982 Hazardous Air Pollutant (HAP) in the Clean Air Act (CAA)), drinking water pathway (National  
 2983 Primary Drinking Water Regulations (NPDWRs) are promulgated for carbon tetrachloride under  
 2984 the Safe Drinking Water Act (SDWA)), ambient water pathways (carbon tetrachloride is a  
 2985 priority pollutant with recommended water quality criteria for protection of human health under  
 2986 the Clean Water Act (CWA)), biosolids pathways (carbon tetrachloride in biosolids is currently  
 2987 being addressed in the CWA regulatory analytical process), and disposal pathways (carbon  
 2988 tetrachloride disposal pathways are subject to regulation under the RCRA, SDWA, and CAA).

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

2989 Because there are no other exposure pathways impacting the general population, EPA did not  
2990 analyze general population exposures in the risk evaluation for carbon tetrachloride.

## 2991 **2.5 Other Exposure Considerations**

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### 2992 **2.5.1 Potentially Exposed or Susceptible Subpopulations**

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2993 TSCA § 6(b)(4)(A) requires that a risk evaluation “determine whether at chemical substance  
2994 presents an unreasonable risk of injury to health or the environment, without consideration of  
2995 cost or other non risk factors, including an unreasonable risk to a potentially exposed or  
2996 susceptible subpopulation identified as relevant to the risk evaluation by the Administrator,  
2997 under the conditions of use.” TSCA § 3(12) states that “the term ‘potentially exposed or  
2998 susceptible subpopulation’ means a group of individuals within the general population identified  
2999 by the Administrator who, due to either greater susceptibility or greater exposure, may be at  
3000 greater risk than the general population of adverse health effects from exposure to a chemical  
3001 substance or mixture, such as infants, children, pregnant women, workers, or the elderly.”  
3002

3003 In developing the draft risk evaluation, the EPA analyzed the reasonably available information to  
3004 ascertain whether some human receptor groups may have greater exposure or susceptibility than  
3005 the general population to the hazard posed by a chemical. During problem formulation, the EPA  
3006 identified the following potentially exposed or susceptible subpopulations based on their greater  
3007 exposure to carbon tetrachloride: workers and occupational non-users. Accordingly, EPA has  
3008 assessed potential risks to these two subpopulations in this draft risk evaluation. Section 3.2.5.2  
3009 describes the hazard information identifying susceptibility to the toxic effects of carbon  
3010 tetrachloride in individuals with histories of alcohol usage.

### 3011 **2.5.2 Aggregate and Sentinel Exposures**

---

3012 As a part of risk evaluation, Section 2605(b)(4)(F)(ii) of TSCA requires EPA to describe whether  
3013 aggregate or sentinel exposures were considered under the identified conditions of use and the  
3014 basis for their consideration. EPA has defined aggregate exposure as “the combined exposures to  
3015 an individual from a single chemical substance across multiple routes and across multiple  
3016 pathways.” (40 C.F.R. 702.33). EPA defines sentinel exposure as “exposure to a single chemical  
3017 substance that represents the plausible upper bound relative to all other exposures within a broad  
3018 category of similar or related exposures.” (40 C.F.R. 702.33). EPA considered sentinel exposure  
3019 in the form of high-end estimates for occupational exposure scenarios which incorporate dermal  
3020 and inhalation exposure, as these routes are expected to present the highest exposure potential  
3021 based on details provided for the manufacturing, processing and use scenarios discussed in the  
3022 previous section. The exposure calculation used to estimate dermal exposure to liquid is  
3023 conservative for high-end occupational scenarios where it assumes full contact of both hands and  
3024 no glove use. See further information on aggregate and sentinel exposures in section 4.6.

## 3025 **3 HAZARDS**

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### 3026 **3.1 Environmental Hazards**

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3027 EPA conducted comprehensive searches for data on the environmental hazards of carbon  
3028 tetrachloride, as described in the *Strategy for Conducting Literature Searches for Carbon*

3029 *Tetrachloride: Supplemental File for the TSCA Scope Document* ([EPA-HQ-OPPT-2016-0733-](#)  
3030 [0050](#)). Based on an initial screening, EPA analyzed the hazards of carbon tetrachloride identified  
3031 in this risk evaluation document. The relevance of each hazard endpoint within the context of a  
3032 specific exposure scenario was judged for appropriateness. For example, hazards that occur only  
3033 as a result of chronic exposures may not be applicable for acute exposure scenarios. This means  
3034 that it is unlikely that every identified hazard was analyzed for every exposure scenario.

3035  
3036 Further, EPA focused in the risk evaluation process on conducting timely, relevant, high-quality,  
3037 and scientifically credible risk evaluations. See 82 FR 33726, 33728 (July 20, 2017). Each risk  
3038 evaluation is "fit-for-purpose," meaning the level of refinement will vary as necessary to  
3039 determine whether the chemical substance presents an unreasonable risk. Given the nature of the  
3040 evidence, for the conditions of use of the specific chemical substance, and when information and  
3041 analysis are sufficient to make a risk determination using assumptions, uncertainty factors, and  
3042 models or screening methodologies, EPA may decide not to refine its analysis further (40 CFR  
3043 702.41(a)(6), (7); see also 82 FR at 33739-40).

### 3044 **3.1.1 Approach and Methodology**

3045 As part of the problem formulation, EPA reviewed and characterized the environmental hazards  
3046 associated with carbon tetrachloride (see section 2.5.3.1. of the problem formulation document)  
3047 ([U.S. EPA, 2018d](#)). EPA identified the following sources of environmental hazard data for  
3048 carbon tetrachloride: ECHA ([2017](#)), OECD SIDS Initial Assessment Profile (SIAP) ([2011](#)), and  
3049 [Australia's 2017 National Industrial Chemicals Notification and Assessment Scheme \(NICNAS\)](#).  
3050 In addition, scientific studies were identified in a literature search for carbon tetrachloride  
3051 (*Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope*  
3052 *Document*, [EPA-HQ-OPPT-2016-0733](#)) and were evaluated based on data quality evaluation  
3053 metrics and rating criteria described in the *Application of Systematic Review in TSCA Risk*  
3054 *Evaluations* ([U.S. EPA, 2018a](#)) and *Strategy for Assessing Data Quality in TSCA Risk*  
3055 *Evaluation* ([U.S. EPA, 2018e](#)). Since only studies with data quality evaluation results of 'high'  
3056 and 'medium' quality ratings were available to characterize the environmental hazards, no  
3057 studies with 'low' ratings were used. The Agency attempted but was not able to obtain the full  
3058 scientific publications listed in ECHA, SIAP, and NICNAS. As a result, these data could not be  
3059 systematically reviewed and were not used in the risk evaluation. Even if the Agency had  
3060 obtained the full studies and considered them acceptable, EPA determined that the ecotoxicity  
3061 values presented in ECHA, SIAP, and NICNAS would not have resulted in a more conservative  
3062 environmental hazard assessment. The robust summary endpoints from these sources align with  
3063 the dataset EPA used to assess the hazards of carbon tetrachloride. Furthermore, the acute and  
3064 chronic COCs for carbon tetrachloride were based on the lowest toxicity value in the dataset.

3065  
3066 Of the 75 on-topic environmental hazard sources identified by the ECOTOX process, 61  
3067 citations were considered out of scope and/or unacceptable in data quality based on the data  
3068 quality evaluation metrics and the rating criteria described in the *Application of Systematic*  
3069 *Review in TSCA Risk Evaluations* ([U.S. EPA, 2018a](#)). The data quality evaluation results for the  
3070 remaining 14 on-topic studies for carbon tetrachloride environmental hazard are presented in the  
3071 document *Risk Evaluation for Carbon Tetrachloride, Systematic Review Supplemental File:*  
3072 *Data Quality Evaluation of Environmental Hazard Studies* ([U.S. EPA, 2019e](#)). Relevant test data  
3073 from the screened literature are summarized in 7Appendix G as ranges (min-max).

3074



### 3.1.2 Hazard Identification-Toxicity to Aquatic Organisms

---

3075  
3076 EPA identified and evaluated carbon tetrachloride environmental hazard data for fish, aquatic  
3077 invertebrates, amphibians, and algae across acute and chronic exposure durations. During  
3078 problem formulation, terrestrial species exposure pathways were considered to be covered under  
3079 programs of other environmental statutes administered by EPA, which adequately assess and  
3080 effectively manage such exposures (e.g., RCRA and CAA). Thus, environmental hazard data  
3081 sources on terrestrial organisms and on metabolic endpoints were considered out of scope and  
3082 excluded from data quality evaluation.

3083  
3084 As a result of a screening-level comparison of the reasonably available environmental hazard  
3085 data with exposure concentrations, it was determined that no further hazard analyses were  
3086 necessary (see section 2.5.3.1. of the problem formulation document) ([U.S. EPA, 2018d](#)). Upon  
3087 further evaluation of the reasonably available hazard data of carbon tetrachloride after the  
3088 problem formulation phase, EPA decreased the environmental hazard chronic COC from 7 µg/L  
3089 to 3 µg/L. Consequently, EPA assessed the risk of aquatic organisms in this draft risk evaluation.  
3090 The derived acute COC (62 µg/L) and chronic COC (3 µg/L) are based on environmental  
3091 toxicity endpoint values (e.g., EC<sub>50</sub>) from Brack and Rottler ([1994](#)) and ([Black et al., 1982](#); [Birge  
3092 et al., 1980](#)), respectively. The data represent the lowest bound of all carbon tetrachloride data  
3093 available in the public domain and provide the most conservative hazard values. Further details  
3094 about the environmental hazards of carbon tetrachloride are available in Appendix G.

3095  
3096 Previously, algal endpoints were considered together with data from other taxa in the acute and  
3097 chronic COC calculations. Now, algal endpoints are considered separately from the other taxa  
3098 and not incorporated into acute or chronic COCs because durations normally considered acute  
3099 for other species (e.g., 48, 72, or 96 hours) can encompass several generations of algae. A  
3100 distinct COC is calculated for algal toxicity.

#### Overall Confidence in COCs

3101  
3102 After evaluating all available carbon tetrachloride test data, EPA has high confidence in the  
3103 environmental hazard data for carbon tetrachloride and high confidence that the data incorporates  
3104 the most conservative (highest toxicity)/environmentally-protective acute and chronic  
3105 concentrations of concern (as described above).  
3106

## 3.2 Human Health Hazards

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### 3.2.1 Approach and Methodology

---

3108  
3109 EPA used the approach described in section 1.5 to evaluate, extract and integrate carbon  
3110 tetrachloride's human health hazard and dose-response information. Figure 3-1 presents the steps  
3111 for the hazard identification and dose response process used by EPA in this risk evaluation draft.  
3112

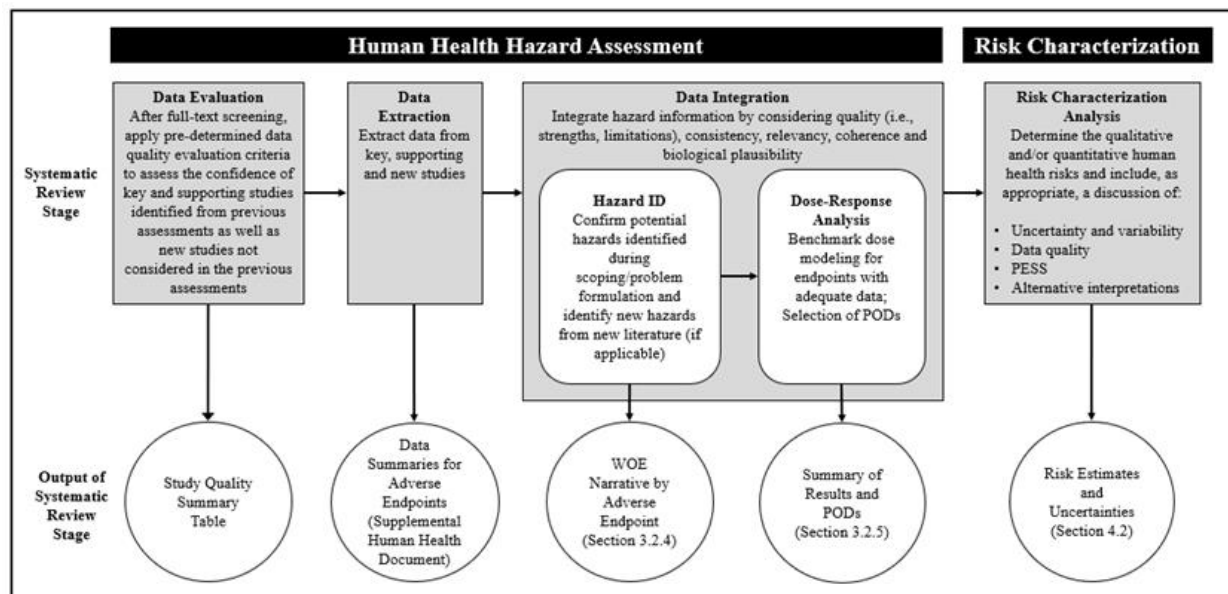


Figure 3-1. Hazard Identification and Dose-Response Process

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

3144 (e.g., toxicokinetics data). Therefore, EPA is using these data to support the risk evaluation.  
3145 Information that was rated unacceptable was considered in the risk evaluation under a weight of  
3146 evidence approach, when necessary to fulfill data gaps. Information on human health hazard  
3147 endpoints for all acceptable studies (with high, medium or low scores) evaluated is presented in  
3148 Appendix H.

3149  
3150 Adverse health effects associated with exposure to carbon tetrachloride were identified by  
3151 considering the quality and weight of the scientific evidence to identify the most sensitive  
3152 hazards or key endpoints. Based on the systematic review of the reasonably available data, EPA  
3153 narrowed the focus of the carbon tetrachloride hazard characterization to liver toxicity,  
3154 neurotoxicity, kidney toxicity, reproductive/ developmental toxicity, and cancer. In addition, a  
3155 summary of key studies and endpoints carried forward in the draft risk evaluation can be found  
3156 in Appendix H, including the no-observed- or lowest-observed-adverse-effect levels (NOAEL  
3157 and LOAEL) for health endpoints by target organ/system, the corresponding benchmark dose  
3158 lower confidence limits (BMDLs), when available, and the corresponding human equivalent  
3159 concentrations (HECs), and uncertainty factors (UFs).

3160  
3161 These key studies provided the dose-response information necessary for selection of points of  
3162 departure (PODs). The EPA defines a POD as the dose-response point that marks the beginning  
3163 of a low-dose extrapolation. This point can be the lower bound on the dose for an estimated  
3164 incidence, or a change in response level from a dose-response model (e.g., benchmark dose or  
3165 BMD), a NOAEL value, or a lowest-observed-adverse-effect level (LOAEL) for an observed  
3166 incidence, or a change in the level (i.e., severity) of a given response. PODs were adjusted as  
3167 appropriate to conform to the specific exposure scenarios evaluated.

3168  
3169 The potential mode of action (MOA) for cancer was evaluated according to the framework for  
3170 MOA analysis described in the EPA [Guidelines for Carcinogen Risk Assessment \(U.S. EPA, 2005b\)](#).  
3171 The evidence for genotoxicity is summarized in Appendix I.

3172  
3173 The dose-response assessment used for selection of PODs for cancer and non-cancer endpoints  
3174 and the benchmark dose analysis used in the draft risk evaluation are found in section 3.2.5.  
3175 Development of the carbon tetrachloride hazard and dose-response assessments considered  
3176 principles set forth in various risk assessment guidances/guidelines issued by the National  
3177 Research Council and the EPA.

3178  
3179 Given that the inhalation and dermal routes of exposure are the routes of concern for this risk  
3180 evaluation, studies conducted via these routes of exposure were considered for POD derivation in  
3181 this assessment. Nevertheless, oral exposure data are presented herein below for weight of  
3182 evidence support in the selection of hazard endpoints and PODs. No acceptable toxicological  
3183 data are available by the dermal route and physiologically based pharmacokinetic/  
3184 pharmacodynamic (PBPK/PD) models that would facilitate route-to-route extrapolation to the  
3185 dermal route have not been identified for carbon tetrachloride. Therefore, inhalation PODs were  
3186 extrapolated for use via the dermal route using assumptions about absorption in this risk  
3187 evaluation.

3188

3189 The EPA consulted EPA's [Guidelines for Developmental Toxicity Risk Assessment \(U.S. EPA,](#)  
3190 [1991\)](#) when making the decision to use developmental toxicity studies to evaluate risks that may  
3191 be associated with acute exposure to carbon tetrachloride during occupational exposure  
3192 scenarios. This decision is based on the EPA's policy, which is based on the health-protective  
3193 assumption that a single exposure during a critical window of fetal development may produce  
3194 adverse developmental effects. The EPA guidelines state that for developmental toxic effects, a  
3195 primary assumption is that a single exposure at a critical time in development may produce an  
3196 adverse developmental effect, i.e., repeated exposures is not a necessary prerequisite for  
3197 developmental toxicity to be manifested ([U.S. EPA, 1991](#)). However limited evidence from  
3198 gestational exposure studies for carbon tetrachloride in rats suggest that developmental effects  
3199 are likely associated with the sustained lower maternal weight over gestation days 6-15 rather  
3200 than the result of exposure to carbon tetrachloride on a single day of the study ([NRC, 2014](#)) (see  
3201 sections 3.2.5.1 and 3.2.4.1.1).  
3202

3203 A summary table which includes all endpoints considered for this assessment, the no-observed-  
3204 or lowest-observed-adverse-effect levels (NOAEL and LOAEL) for health endpoints by target  
3205 organ/system and the results of the data evaluation is provided in Appendix H. The sections  
3206 below present the analysis, synthesis and integration of the hazard information resulting from  
3207 those data sources that have low, medium or high overall data quality.

### 3208 **3.2.2 Toxicokinetics**

---

3209 The toxicokinetics of carbon tetrachloride have been comprehensively described in previous  
3210 toxicological assessments (see Table 1-3). In summary, the IRIS assessment describes that  
3211 carbon tetrachloride is rapidly absorbed by any route of exposure. Once absorbed, carbon  
3212 tetrachloride is widely distributed among tissues, especially those with high lipid content,  
3213 reaching peak concentrations in <1–6 hours, depending on exposure concentration or dose.  
3214 Animal studies show that volatile metabolites are released in exhaled air, whereas nonvolatile  
3215 metabolites are excreted in feces and to a lesser degree, in urine.  
3216

3217 The metabolism of carbon tetrachloride has been extensively studied in *in vivo* and *in vitro*  
3218 mammalian systems. Carbon tetrachloride is metabolized in the body, primarily by the liver, but  
3219 also in the kidney, lung, and other tissues containing CYP450. Based on reasonably available  
3220 information, the initial step in biotransformation of carbon tetrachloride is reductive  
3221 dehalogenation: reductive cleavage of one carbon-chlorine bond to yield chloride ion and the  
3222 trichloromethyl radical. Biotransformation of carbon tetrachloride to reactive metabolites,  
3223 including the trichloromethyl radical, is hypothesized to be a key event in the toxicity of carbon  
3224 tetrachloride. The fate of the trichloromethyl radical depends on the availability of oxygen and  
3225 includes several alternative pathways for anaerobic or aerobic conditions (i.e., anaerobic  
3226 dimerization to form hexachloroethane, aerobic trapping by oxygen to form a trichloromethyl  
3227 peroxy radical).

### 3228 **3.2.3 Hazard Identification**

---

#### 3229 **3.2.3.1 Non-Cancer Hazards**

---

3230 For non-cancer hazard characterization, EPA reviewed the reasonably available information on  
3231 acute, subchronic, and chronic exposure to carbon tetrachloride via the inhalation, dermal and  
3232 oral routes and evaluated the identified hazard endpoints. Studies were evaluated according to

3233 the *Application of Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018a, b](#)). The  
3234 results of the data quality evaluation for the non-cancer studies are described here and included  
3235 in the data extraction summary table in Appendix H.  
3236

### 3237 ***Toxicity Following Acute Exposure***

3238 Overall, the database evaluating the acute toxicity of carbon tetrachloride is limited to numerous  
3239 case reports on acute inhalation exposure of humans to carbon tetrachloride, most without  
3240 adequate exposure characterization, in addition to a small number of animal studies. Human case  
3241 reports following acute exposures identify liver as a primary target organ of toxicity and the  
3242 kidney as an additional primary target organ of toxicity. Neurotoxicity indicated as central  
3243 nervous system (CNS) depression is another primary effect of carbon tetrachloride in humans  
3244 following acute exposures, with examples of neurotoxic effects including drowsiness, headache,  
3245 dizziness, weakness, coma and seizures. Gastrointestinal symptoms such as nausea and vomiting,  
3246 diarrhea and abdominal pain are considered another initial acute effect ([U.S. EPA, 2010](#);  
3247 [ATSDR, 2005](#)). Unmetabolized carbon tetrachloride is expected to depress the CNS, while most  
3248 other toxic effects of carbon tetrachloride are related to its biotransformation products catalyzed  
3249 by CYP-450 enzymes ([ATSDR, 2005](#)).  
3250

3251 The National Advisory Committee for Acute Exposure Guideline Levels for hazardous  
3252 substances (NAC/AEGL) ([NRC, 2014](#)) describe case reports of human fatalities resulting from  
3253 acute exposure to carbon tetrachloride, which provide a clinical picture of dizziness, nausea,  
3254 abdominal pain, oliguria, anuria, and death being attributed to renal failure and hepatotoxicity.  
3255 NAC/AEGL has concluded that although data on lethality in humans following acute exposures  
3256 to carbon tetrachloride are available, exposure concentration and duration information are  
3257 lacking.  
3258

### 3259 ***Hazard Effects from Acute Inhalation Exposures – Human Data***

3260 The EPA IRIS Assessment ([U.S. EPA, 2010](#)) concluded that the CNS depression is an  
3261 immediate effect in acute toxicity studies in animals exposed by inhalation to relatively high  
3262 concentrations of carbon tetrachloride.  
3263

3264 Similar conclusions were reached by NAC/AEGL ([NRC, 2014](#)) based on human data.  
3265 NAC/AEGL developed acute exposure guideline levels-2 (AEGL-2) ([NRC, 2014](#)) for carbon  
3266 tetrachloride based on CNS effects observed in humans. AEGL-2 values are defined as the  
3267 airborne concentrations of a substance above which it is predicted that the general population,  
3268 including susceptible individuals, could experience irreversible or other serious, long-lasting  
3269 adverse health effects or an impaired ability to escape.<sup>11</sup>  
3270

3271 NAC/AEGL evaluated a series of experiments conducted by Davis ([1934](#))(data quality rating =  
3272 low) to determine their suitability to derive AEGL-2 values for carbon tetrachloride. In one  
3273 study, three human subjects were exposed to carbon tetrachloride at 317 ppm (concentration

---

<sup>11</sup> 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<sub>01</sub> (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.

3274 calculated on the basis of room volume and amount of carbon tetrachloride) for 30 min. CNS  
3275 effects, including nausea, vomiting, dizziness, and headaches, were reported by the subjects but  
3276 clinical assessments (urinalysis, blood count, hemoglobin levels, blood pressure, and heart rate)  
3277 remained normal for up to 48 h post-exposure (Davis, 1934). Similar effects were reported by  
3278 subjects exposed at 1,191 ppm for 15 min, with the exception that one of the four subjects found  
3279 the exposure to be intolerable after 9 min (i.e., the subject experienced headache, nausea,  
3280 vomiting). Exposures at 2,382 ppm for 3-7 min produced these effects in addition to dizziness,  
3281 listlessness, and sleepiness. The observed CNS effects were apparently not long-lasting but were  
3282 considered severe enough to impair escape or normal function and, therefore, a conservative end  
3283 point (i.e., hazard effect) for deriving AEGL-2 values by NAC/AEGL.

3284  
3285 In the second experiment, four subjects (ages 35, 48, 22, and 30; gender not specified) were  
3286 exposed to a carbon tetrachloride at 76 ppm for 2.5 h. There were no symptoms or signs of  
3287 toxicity in any of the subjects. In a third experiment, the same subjects in the second experiment  
3288 were exposed 24 hours later to carbon tetrachloride at 76 ppm for 4 h and did not have signs or  
3289 symptoms. Davis (1934) also reported that renal effects were observed in a worker  
3290 experimentally exposed to carbon tetrachloride at 200 ppm for 8 h with renal function returning  
3291 to near normal 2 months after exposure.

3292  
3293 The AEGL-2 values were derived on the basis of the highest no-effect level of 76 ppm for CNS  
3294 effects in humans exposed carbon tetrachloride for 4 h (Davis, 1934). The AEGL-2 values are  
3295 derived using an interspecies uncertainty factor of 1 because the study was conducted in humans,  
3296 and an intraspecies uncertainty factor of 10 to account for individuals who may be more  
3297 susceptible to the toxic effects of carbon tetrachloride, including greater potential of carbon  
3298 tetrachloride-induced toxicity in individuals with histories of alcohol usage.

3299  
3300 *Hazard Effects from Acute Inhalation and Oral Exposures – Animal Data*  
3301 IRIS, ATSDR and AEGL have identified and evaluated a small number of available acute animal  
3302 studies for carbon tetrachloride. Systematic review for this risk evaluation found that two of the  
3303 main acute animal studies in those previous hazard assessments have unacceptable data quality:  
3304 Hayes et al., (1986) acute study, which has an ECHA reliability = 4 and Adams et al., (1952)  
3305 acute study (ECHA reliability score not available). Nevertheless, the EPA IRIS Assessment  
3306 (U.S. EPA, 2010) and ATSDR profile (ATSDR, 2005) provide a weight of evidence evaluation  
3307 on the effects observed in animal studies after acute oral and inhalation exposure to carbon  
3308 tetrachloride. In animals acutely exposed to carbon tetrachloride, the liver appears to be the  
3309 primary target organ; damage to the kidney occurs at slightly higher doses. Hepatic toxicity is  
3310 frequently demonstrated by significant increases in serum enzyme activities that peak between  
3311 24 and 48 hours after dosing (U.S. EPA, 2010). Similarly, ATSDR (2005) evaluated the acute  
3312 toxicity database for carbon tetrachloride and determined that hepatotoxicity appeared to be the  
3313 critical effect from acute duration exposure. However, ATSDR (2005) did not derive an MRL for  
3314 acute-duration inhalation exposure to carbon tetrachloride due in part to data limitations. A more  
3315 recent and comprehensive review of both acute epidemiological data and animal studies by  
3316 NAC/AEGL (NRC, 2014) concluded that animal inhalation toxicity data for carbon tetrachloride  
3317 affirm hepatotoxic and renal effects, as well as anesthetic-like effects, as primary end points; and  
3318 that findings from animal studies are consistent with those associated with human exposures.

3319 In addition to acute toxicity data evaluated by IRIS, AEGL and ATSDR, the systematic review  
 3320 identified an additional study evaluating liver toxicity of carbon tetrachloride after single dose  
 3321 administration with high overall quality based on the quality criteria in the *Application of*  
 3322 *Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018a](#)). In this additional study by Sun  
 3323 et al., ([2014](#)) (data quality rating = high), a total of 30 male Sprague-Dawley rats (5 rats/group)  
 3324 were given single oral gavage doses of carbon tetrachloride at 0, 50, or 2000 mg/kg. Rats were  
 3325 then sacrificed at either 6- or 24-hours post-dosing (5/group/time point). An additional group of  
 3326 male rats (5/group) were given oral doses of vehicle (corn oil) or carbon tetrachloride for 3-days  
 3327 at the same doses and sacrificed 24-hours after the third dose (72 hours). Rats lost weight 24-  
 3328 hours after a single exposure to 2,000 mg/kg (or after 3 daily doses at 2,000 mg/kg). Control and  
 3329 low-dose animals gained weight normally. Food consumption was also decreased in high-dose  
 3330 rats. Significant, dose-related increases in serum ALT (30-114%), AST (15-213%), and ALP  
 3331 (37-137%) were observed in both dose groups following exposure for 3 days. Twenty-four  
 3332 hours after exposure, ALT was significantly increased by 15% at 50 mg/kg, but not 2000 mg/kg.  
 3333 ALP was significantly increased by 78% at 2000 mg/kg after 24 hours. Other significant  
 3334 potentially exposure-related findings were limited to the high-dose group and included a 26-49%  
 3335 increase in BUN 6- or 24-hours after a single exposure, a 24-33% decrease in cholesterol, and a  
 3336 59-69% decrease in triglycerides 24-hours after one or three exposures, and a 12-23% decrease  
 3337 in glucose 6- or 24-hours after a single exposure. No other consistent clinical chemistry findings  
 3338 were observed. No significant changes were observed in liver triglyceride levels.  
 3339

3340 Centrilobular necrosis, centrilobular degeneration, and cytoplasmic vacuolization were observed  
 3341 at 6- and 24-hours post-dose in all animals given a single dose of 2,000 mg/kg. In animals given  
 3342 3 doses of 2,000 mg/kg carbon tetrachloride, 80% were observed with centrilobular  
 3343 degeneration, while 100% were observed with centrilobular necrosis and cytoplasmic  
 3344 vacuolization. Mean severity scores for centrilobular necrosis and degeneration were highest 24-  
 3345 hours after a single exposure, whereas severity scores for cytoplasmic vacuolization were highest  
 3346 after 3 exposures. Six hours after a single exposure to 50 mg/kg, 40% of animals (n=2) showed  
 3347 minimal centrilobular necrosis. Hepatic lesions were not observed at other time points following  
 3348 exposure to 50 mg/kg. No hepatic lesions were observed in control groups at any time point. No  
 3349 exposure-related kidney lesions were observed in any group ([Sun et al., 2014](#)).  
 3350

3351 Table 3-1 and Table 3-2 present a summary of acute toxicity studies in humans by the inhalation  
 3352 route and in rats by the oral route of exposure, which are either a critical study identified for  
 3353 establishing AEGL values or a study published after the completion of the IRIS assessment ([U.S.](#)  
 3354 [EPA, 2010](#)) and NAC/AEGL ([NRC, 2014](#)).  
 3355

3356 **Table 3-1. Acute Inhalation Toxicity Study in Humans (Critical Study for NAC/AEGL-2**  
 3357 **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	( <a href="#">Davis, 1934</a> )	low; basis for AEGL-2

3358 Note: information on associated human studies from ([Davis, 1934](#)) can be found in text.

3359

3360 **Table 3-2. Acute Toxicity Oral study in Sprague-Dawley Rats with Acceptable Data**  
 3361 **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	( <a href="#">Sun et al., 2014</a> )	High

3362

3363 *Hazard Effects from Oral and Inhalation Exposures During Gestation*

3364 Developmental effects from carbon tetrachloride exposures are more extensively studied by the  
 3365 oral route than any other route of exposure. The lowest adverse effect level for developmental  
 3366 hazards from oral exposures was identified in the EPA IRIS Assessment ([U.S. EPA, 2010](#)) in  
 3367 Narotsky ([1997](#)) (data quality rating = high). In this study, groups of 12–14 timed-pregnant F344  
 3368 rats received carbon tetrachloride at doses of 0, 25, 50, or 75 mg/kg-day in either corn oil or an  
 3369 aqueous emulsion (10% Emulphor) on GDs 6–15. Dose-related piloerection was observed in  
 3370 dams at  $\geq 50$  mg/kg-day for both vehicles but was seen in more animals and for longer periods in  
 3371 the corn oil groups. Dams exposed to 75 mg/kg-day in corn oil also exhibited kyphosis (rounded  
 3372 upper back) and statistically significant weight loss. Dams exposed to 50 and 75 mg/kg-day in  
 3373 aqueous emulsion showed only significantly reduced body weight gain. Full-litter resorption  
 3374 occurred with an incidence of 0/13, 0/13, 5/12 (42%), and 8/12 (67%) in the control through  
 3375 high-dose corn oil groups and 0/12, 0/12, 2/14 (14%), and 1/12 (8%) in the respective aqueous  
 3376 groups. The difference between vehicles was statistically significant at the highest dose. Among  
 3377 the surviving litters, there were no effects on gestation length, prenatal or postnatal survival, or  
 3378 pup weight or morphology. The 25 mg/kg-day dose was a NOAEL for developmental and  
 3379 maternal toxicity and the 50 mg/kg-day dose a LOAEL for full-litter resorption and maternal  
 3380 toxicity (i.e., reduced maternal weight gain, piloerection) with either corn oil or aqueous vehicle,  
 3381 although these effects were more pronounced with the corn oil vehicle. EPA ([2010](#)) noted that  
 3382 the NOAEL in this developmental study (25 mg/kg-day) exceeds the POD for the RfD based on  
 3383 liver effects by over 6-fold and the LOAEL (50 mg/kg-day) by 13-fold and is consistent with  
 3384 developmental toxicity endpoints as less sensitive than measures of hepatotoxicity.

3385

3386 The IRIS assessment identified Schwetz et al. ([1974](#)) (data quality rating = high) as the most  
 3387 detailed inhalation exposure developmental toxicity study available. In the Schwetz et al. ([1974](#))  
 3388 study, groups of pregnant Sprague-Dawley were exposed whole-body by inhalation to 0, 300, or  
 3389 1,000 ppm carbon tetrachloride vapor for 7 hours/day on days 6-15 of gestation. A significant  
 3390 increase in the serum glutamic-pyruvic transaminase activity was observed in rats exposed to  
 3391 300 and 1000 ppm by the end of the exposure period. This effect was no longer observed by day  
 3392 6 post exposure. The developmental effects at the LOAEC of 300 ppm consisted of decreased



3393 fetal body weight (7%) and decreased crown-rump length (3.5%). The same effects were  
 3394 observed at 1,000 ppm (i.e., 14% decreased fetal body weight, 4.5% decreased crown-rump  
 3395 length) in addition to increases in sternebral anomalies (13% at 1,000 ppm vs 2% in controls).  
 3396 Maternal toxicity was observed at 300 and 1,000 ppm. Food consumption and body weight were  
 3397 significantly reduced in treated dams compared with controls. Hepatotoxicity was indicated by  
 3398 significantly elevated serum ALT, gross changes in liver appearance (pale, mottled liver), and  
 3399 significantly increased liver weight (26% at 300 ppm and 44% at 1,000 ppm).

3400  
 3401 The systematic review process for this risk evaluation did not identify additional developmental  
 3402 toxicity data by the inhalation or oral routes for carbon tetrachloride. Table 3-3 presents the  
 3403 developmental toxicity studies with acceptable data quality.  
 3404

3405 **Table 3-3. Developmental Toxicity Studies in Fisher 344 and Sprague-Dawley Rats with**  
 3406 **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	( <a href="#">Narotsky et al., 1997</a> )	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	( <a href="#">Schwetz et al., 1974</a> )	high

3407  
 3408 ***Subchronic and Chronic Hazards from Inhalation and Oral Exposures***

3409 Consistent with human data, toxicity assays in animals exposed orally or by inhalation of sub-  
 3410 chronic or chronic duration identify the liver as the major target organ. While the liver appears to  
 3411 be the primary target organ from exposure to carbon tetrachloride by both the oral and inhalation  
 3412 routes, the kidney is also a target organ for carbon tetrachloride exposure.  
 3413

3414 All the key and supporting inhalation and oral studies in the EPA IRIS Assessment ([U.S. EPA,  
 3415 2010](#)) were rated acceptable with low, medium or high overall quality data using the quality  
 3416 criteria in the *Application of Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018a](#)).  
 3417 Those acceptable studies are briefly described in this section and Appendix H. The systematic  
 3418 review process for this risk evaluation did not identify additional subchronic and chronic toxicity  
 3419 data for carbon tetrachloride.  
 3420

3421 ***Inhalation***

3422 The IRIS assessment concluded that the liver and kidney are the most prominent targets of  
 3423 carbon tetrachloride in subchronic and chronic inhalation toxicity studies in animals. Renal

3424 damage was reported less frequently in these animal studies and generally at higher  
3425 concentrations than those causing liver damage. The key and supporting subchronic and chronic  
3426 inhalation studies in the IRIS assessment are summarized below.

3427  
3428 The IRIS RfC is based on the findings from bioassays conducted by Nagano ([2007a](#)) (data quality  
3429 rating = high). In one of the subchronic inhalation studies in rats, F344/DuCrj rats (10/sex/group)  
3430 were subjected to whole body exposure of carbon tetrachloride vapor (Purity: 99.8%)  
3431 concentrations of 0, 10, 30, 90, 270, or 810 ppm (0, 63, 189, 566, 1,700, or 5,094 mg/m<sup>3</sup>) for 6  
3432 hours/day, 5 days/week for 13 weeks. The lowest exposure concentration of 10 ppm was a  
3433 LOAEC for rats for hepatic effects including increased liver weight and histopathological effects  
3434 ranging from slight fatty change, cytological alteration, and granulation to ceroid deposits,  
3435 fibrosis, pleomorphism, proliferation of bile ducts and cirrhosis. While small fatty droplets were  
3436 not evident in male rats at any concentration, large droplets were significantly elevated at  $\geq 30$   
3437 ppm in both male and female rats. Different types of significantly altered cell foci (acidophilic,  
3438 basophilic, clear cell, and mixed cell foci) was evident at 810 ppm in male rats and 270 ppm in  
3439 female rats. A NOAEC was not identified.

3440  
3441 A similar whole body exposure to carbon tetrachloride (99.8%) vapor was conducted in mice  
3442 ([Nagano et al., 2007b](#)) (data quality rating = high) where groups of Crj: BDF1 mice  
3443 (10/sex/group) were exposed at concentrations of 0, 10, 30, 90, 270, or 810 ppm (0, 63, 189,  
3444 566, 1,700, or 5,094 mg/m<sup>3</sup>) for 6 hours/day, 5 days/week for 13 weeks. A similar set of end  
3445 points as that of the rat study were measured in mice. However, the incidence of altered cell foci  
3446 was not significantly elevated in male mice at  $< 270$  ppm and was not noted in female mice.  
3447 Additional liver lesions observed include: nuclear enlargement with atypia and altered cell foci  
3448 ( $\geq 270$  ppm) and collapse (possibly resulting from the necrotic loss of hepatocytes) at ( $\geq 30$  ppm).  
3449 The lowest exposure level of 10 ppm is a LOAEC for hepatic effects (slight cytological  
3450 alterations) in male mice. Hepatic effects (i.e., fatty change, fibrosis and cirrhosis) were observed  
3451 in female mice exposed to ( $\geq 30$  ppm).

3452  
3453 Significant increases were observed in liver weights ( $\geq 10$  ppm for males and  $\geq 30$  ppm for female  
3454 rats) and kidney weights ( $\geq 10$  ppm for male rats and  $\geq 90$  ppm for female rats). Statistically  
3455 significant, exposure-related decreases in hemoglobin and hematocrit were observed at  $\geq 90$  ppm in  
3456 both males and females. At 810 ppm, red blood cell count was also significantly decreased in both  
3457 sexes. Serum chemistry changes included large, statistically significant, and exposure-related  
3458 increases in ALT, AST, LDH, ALP, and LAP (leucine aminopeptidase) in males at  $\geq 270$  ppm and  
3459 females at  $\geq 90$  ppm. In general, female mice were less sensitive to hematological alterations than  
3460 male mice. Nephrotoxicity was observed at higher concentrations than toxicity to the liver,  
3461 although kidney weights were increased significantly at 10 ppm in male rats and  $\geq 90$  ppm in  
3462 female rats. Glomerulosclerosis was observed only at the highest concentration (810 ppm) of  
3463 exposure in rats. No histopathological changes were observed in the nasal cavity, larynx, trachea  
3464 or lungs of any carbon tetrachloride-exposed mouse or rat groups.

3465  
3466 Nagano et al., ([2007a](#)) (data quality rating = high) conducted studies with groups of F344/DuCrj  
3467 rats (50/sex/group) exposed whole body to 0, 5, 25, or 125 ppm (0, 31.5, 157, or 786 mg/m<sup>3</sup>) of  
3468 carbon tetrachloride (99.8% pure) vapor for 6 hours/day, 5 days/week for 104 weeks. An  
3469 increase in the severity of proteinuria in rats of both sexes was observed at the low exposure  
3470 concentration of 5 ppm; however, interpretation of the observed proteinuria and the renal lesions

3471 in the F344 rat is difficult because this strain has a high spontaneous incidence of renal lesions.  
3472 Increases in the incidence and severity of nonneoplastic liver lesions (fatty change, fibrosis,  
3473 cirrhosis) were seen at 25 and 125 ppm in both males and females. Therefore, 5 ppm was  
3474 considered a NOAEC based on liver toxicity at 25 and 125 ppm evidenced by serum chemistry  
3475 changes (including significant increases in ALT, AST, LDH, LAP, and GGT) and  
3476 histopathologic changes (fatty change, fibrosis, and cirrhosis). Kidney effects described above  
3477 were also considered for determining the NOAEC value, which is the basis of the EPA IRIS  
3478 RfC.

3479  
3480 A similar 2-year (104 week) study was conducted by the same group in Crj: BDF1 mice ([Nagano](#)  
3481 [et al., 2007a](#)) (data quality rating = high). Groups of 50/sex were exposed to 0, 5, 25, or 125 ppm  
3482 (0, 31.5, 157, or 786 mg/m<sup>3</sup>) of carbon tetrachloride (99% pure) vapor for 6 hours/day, 5  
3483 days/week for 104 weeks. The 25ppm concentration was a LOAEC in this study for effects on  
3484 the liver (increased weight, serum chemistry changes indicative of damage, and lesions), kidney  
3485 (serum chemistry changes and lesions), and spleen (lesions); decreased growth; and reduced  
3486 survival. The 5-ppm level was a NOAEC.

3487  
3488 Benson and Springer ([1999](#)) (data quality rating = high) exposed groups of F344/Crl rats, B6C3F1  
3489 mice, and Syrian hamsters (10 males/species) by nose only inhalation to 0, 5, 20 or 100 ppm of  
3490 carbon tetrachloride for 6 hours per day, 5 days per week for 1, 4 or 12 weeks. The chamber  
3491 concentrations were monitored throughout the exposure. According to study authors, the  
3492 objectives of the study were 3-fold. The first objective was to evaluate the metabolism of carbon  
3493 tetrachloride to get an estimate of species sensitivity. These studies were conducted as either  
3494 whole-body exposures (for *in vivo* metabolism) or nose only exposures (for toxicokinetic  
3495 studies). *In vitro* studies using human liver microsomes were also conducted. The second  
3496 objective was to assess the genotoxic or non-genotoxic mechanisms of liver tumors for carbon  
3497 tetrachloride exposure. The third objective is to compare *in vitro* and *in vivo* metabolism studies  
3498 to revise the model for uptake, fate and metabolism of carbon tetrachloride to provide an  
3499 estimate for a human metabolic rate constant. Cell proliferation was evaluated in these animals  
3500 by implanting a minipump containing BrdU (bromodeoxyuridine) in each animal prior to  
3501 necropsy. At sacrifice, blood was collected for ALT and SDH determinations, and liver sections  
3502 were collected for histopathological examination and BrdU detection. In summary, Benson and  
3503 Springer ([1999](#)) used *in vitro* data on metabolism of carbon tetrachloride by human liver  
3504 microsomes, together with *in vitro* and *in vivo* rodent data, to estimate the *in vivo* human  
3505 metabolic rate constants and generated experimental information that allowed expanding the rat  
3506 PBPK model of Paustenbach et al., ([1988](#)) to include parameters for the hamster.

3507  
3508 Following repeated carbon tetrachloride inhalation exposure in the Benson and Springer ([1999](#))  
3509 studies, hepatocellular proliferation was reported along with necrosis and regenerative cell  
3510 proliferation at 20 and 100 ppm in mice. In rats, liver microsomal protein levels were increased  
3511 by 45% and 63% following 5-day inhalation exposure at 5 ppm without any change in the 12-  
3512 week exposure group. In hamsters, following carbon tetrachloride inhalation exposure (100 ppm)  
3513 microsomal protein levels were decreased by 33% and 54% in both the 5-day and the 12-week  
3514 exposure groups. Mice did not exhibit any decrease in microsomal protein content at any  
3515 concentration of exposure. Significant increases in percent BrdU positive cells in the cell  
3516 proliferation assays were apparent at 20 and 100 ppm in mice and at 100 ppm in hamsters. Serum

3517 levels of ALT and SDH were significantly increased in mice at  $\geq 20$  ppm and in rats and hamsters at  
3518 100 ppm.

3519  
3520 Cytochromes CYP2E1 and CYP2B, which are the primary enzymes responsible for  
3521 biotransformation of carbon tetrachloride in rodents, were measured in all exposed and control  
3522 animals in the metabolic studies (Benson and Springer, 1999). In all species, microsomal  
3523 measurement of these enzymes indicated that while enzyme induction increased several fold as  
3524 dose increased, catalytic activity was not significantly altered.

3525  
3526 The rate of carbon tetrachloride metabolism was measured in rat, mouse and hamster species.  
3527 The metabolic rate of carbon tetrachloride did not vary more than 2-fold between the three  
3528 species. A NOAEC of 5ppm and a LOAEC of 20 ppm for hepatotoxicity was identified for mice.  
3529 Hamsters and rats were less sensitive than mice, with NOAEC of 20 ppm and LOAEC of 100  
3530 ppm, respectively.

3531  
3532 Adams et al., (1952) (data quality rating = low) conducted studies with Wistar-derived rats (15–  
3533 25/sex), outbred guinea pigs (5–9/sex), outbred rabbits (1–2/sex), and Rhesus monkeys (1–2 of  
3534 either sex) exposed to carbon tetrachloride vapor (>99% pure), 7 hours/day, 5 days/week for 6  
3535 months at concentrations of 5, 10, 25, 50, 100, 200, or 400 ppm (31, 63, 157, 315, 630, 1,260, or  
3536 2,520 mg/m<sup>3</sup>). Matched control groups included unexposed and air exposed. Animals were  
3537 observed frequently for appearance and general behavior and were weighed twice weekly.  
3538 Selected animals were used for hematological analyses periodically throughout the study.  
3539 Moribund animals and those surviving to scheduled sacrifice were necropsied. The lungs, heart,  
3540 liver, kidneys, spleen, and testes were weighed, and sections from these and 10 other tissues  
3541 were prepared for histopathological examination. Serum chemistry analyses were performed in  
3542 terminal blood samples and part of the liver was frozen and used for lipid analyses. In this study,  
3543 the primary target of carbon tetrachloride in all species was the liver. In guinea pigs, liver effects  
3544 progressed from a slight, statistically significant increase in relative liver weight in females at 5  
3545 ppm to slight-to-moderate fatty degeneration and increases in liver total lipid, neutral fat, and  
3546 esterified cholesterol at 10 ppm, and cirrhosis at 25 ppm. However, the effect at the 5-ppm dose  
3547 was not considered adverse, as there were no histopathological changes in the liver at 5 ppm. In  
3548 the kidney, slight tubular degeneration was observed at 200 ppm and increased kidney weight  
3549 was noted at 400 ppm. Mortality was increased at  $\geq 100$  ppm. A similar progression of effects  
3550 was seen in rats, (no effects at 5 ppm, mild liver changes at 10 ppm, cirrhosis at 50 ppm, and  
3551 liver necrosis, kidney effects, testicular atrophy, growth depression, and mortality at 200 ppm  
3552 and above). In rabbits, 10 ppm was without effect, 25 ppm produced increase in liver weight and  
3553 mild liver changes (mild fatty degeneration and(in) by histological examinations, 50 ppm  
3554 produced moderate liver changes, and 100 ppm produced growth depression. Monkeys were the  
3555 least sensitive species tested, with evidence of adverse effects (mild liver lesions and increased  
3556 liver lipid) only at 100 ppm, the highest concentration tested. This study identified NOAEL and  
3557 LOAEL values, respectively, of 5 and 10 ppm in rats and guinea pigs, 10 and 25 ppm in rabbits,  
3558 and 50 and 100 ppm in monkeys, all based on hepatotoxic effects.

3559  
3560 Table 3-4 presents a summary of subchronic and chronic inhalation studies in various  
3561 experimental animal species for carbon tetrachloride with acceptable data quality.

3562  
3563

3564  
3565  
3566**Table 3-4. Subchronic and Chronic Inhalation Studies in Various Experimental Animal 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 <sup>3</sup> (0, 5, 25 or 125 ppm)	6 hours/ day, 5 days/ week for 104 weeks	NOAEC= 31 mg/m <sup>3</sup> , LOAEC= 157 mg/m <sup>3</sup>	Increased AST, ALT, LDH, GPT, BUN, CPK; lesions in the liver (fatty changes, fibrosis)	( <a href="#">Nagano et al., 2007a</a> )	High
Mouse, Crj:BDF1 (SPF), M/F (n= 100/group)	Inhalation, vapor, whole body	0, 31, 157 or 786 mg/m <sup>3</sup> (0, 5, 25 or 125 ppm)	6 hours/ day, 5 days/ week for 104 weeks	NOAEC=31 mg/m <sup>3</sup> (M)	Reduced survival; increased ALT, AST, LDH, ALP, protein, total bilirubin, and BUN; decreased urinary pH; increased liver weight; spleen and liver lesions	( <a href="#">Nagano et al., 2007a</a> )	High
Mouse, BDF1, M/ F (n=20/ group)	Inhalation, vapor, whole body	0, 63, 189, 566, 1699, 5096 mg/m <sup>3</sup> (0, 10, 30, 90, 270, or 810 ppm)	6 hours/ day, 5 days/ week for 13 weeks	LOAEC= 63 mg/m <sup>3</sup>	Slight cytological alterations in the liver; Cytoplasmic globules	( <a href="#">Nagano et al., 2007b</a> )	High
Rat, F344, M/ F (n=20/ group)	Inhalation, vapor, whole body	0, 63, 189, 566, 1699, 5096 mg/m <sup>3</sup> (0, 10, 30, 90, 270, 810 ppm)	6 hours/ day, 5 days/ week for 13 weeks	NOAEC= 63 mg/m <sup>3</sup> (F), LOAEC=189 mg/m <sup>3</sup> (F)	Increased liver weight; Large droplet fatty change in liver	( <a href="#">Nagano et al., 2007b</a> )	High
Mouse, B6C3F1, M (n=10/ group)	Inhalation, whole body	0, 31, 126, or 629 mg/m <sup>3</sup> (0, 5, 20 or 100 ppm)	6 hours/ day, 5 days/ week for 12 weeks	NOAEC= 31 mg/m <sup>3</sup> (M), LOAEC= 126 mg/m <sup>3</sup> (M)	Increased ALT, SDH; necrosis and cell proliferation in liver	( <a href="#">Benson and Springer, 1999</a> )	Low
Hamster, Syrian, M (n=10/ group)	Inhalation, whole body	0, 31, 127 or 636 mg/m <sup>3</sup> (0, 5, 20 or 100 ppm)	6 hours/ day, 5 days/ week for 12 weeks	NOAEC= 126 mg/m <sup>3</sup> (M), LOAEC= 629 mg/m <sup>3</sup> (M)	Increased ALT, SDH; necrosis and cell proliferation in liver	( <a href="#">Benson and Springer, 1999</a> )	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 <sup>3</sup> (0, 5, 10, 25, 50, 100, 200 or 400 ppm)	7 hours/ day, 5 days/ week for 6 months	NOAEC= 31 mg/m <sup>3</sup> , LOAEC= 63 mg/m <sup>3</sup>	Increased liver weight; fatty degeneration in liver	( <a href="#">Adams et al., 1952</a> )	Low
Guinea pig, M/ F (n=10-18 group)	Inhalation, vapor, whole body	0, 31, 63, 157, 315, 629, 1258 or 2516 mg/m <sup>3</sup> (0, 5, 10, 25, 50, 100, 200 or 400 ppm)	7 hours/ day, 5 days/ week for 6 months	NOAEC= 31 mg/m <sup>3</sup> , LOAEC= 63 mg/m <sup>3</sup>	Increased liver weight; fatty degeneration in liver	( <a href="#">Adams et al., 1952</a> )	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 <sup>3</sup> (0, 5, 10, 25, 50, 100, 200 or 400 ppm)	7 hours/ day, 5 days/ week for 6 months	NOAEC= 63 mg/m <sup>3</sup> , LOAEC= 157 mg/m <sup>3</sup>	Increased liver weight; fatty degeneration and slight cirrhosis in liver	( <a href="#">Adams et al., 1952</a> )	Low
Monkey, rhesus, M/ F (n=2-4/ group)	Inhalation, vapor, whole body	0, 31, 63, 157, 315 or 630 mg/ m <sup>3</sup> (0, 5, 20, 25, 50 or 100 ppm)	7 hours/ day, 5 days/ week for 6 months	NOAEC= 315 mg/m <sup>3</sup> , LOAEC= 629 mg/m <sup>3</sup>	Slight fatty degeneration and increased lipid content in liver	( <a href="#">Adams et al., 1952</a> )	Low

3567  
3568 *Oral*  
3569 U.S. EPA (2010) identifies the following subchronic oral gavage studies  
3570 as supporting studies in the derivation of the RfD for carbon tetrachloride, Condie et al. (1986),  
3571 Allis et al. (1990) and Hayes et al. (1986). Bruckner et al. (1986) was the principal study.  
3572 Consistent with human data, toxicity assays in animals (i.e., rats, mice) exposed orally identify  
3573 the liver to be the major target organ, with oral NOAELs between 0.71 and 0.86 mg/kg.  
3574 Subchronic oral studies that also examined non-hepatic endpoints (Bruckner et al., 1986; Hayes  
3575 et al., 1986) did not observe effects in the kidneys or other organs. These studies are summarized  
3576 below as follows.

3577  
3578 In a subchronic study by Bruckner et al. (1986) (data quality rating = high) groups of 15–16 adult  
3579 male Sprague-Dawley rats were given doses of 0, 1, 10, or 33 mg/kg of analytical-grade carbon  
3580 tetrachloride by oral gavage in corn oil 5 days/week (time-weighted average doses of 0, 0.71,  
3581 7.1, or 23.6 mg/kg-day) for 12 weeks. Body weight gain in this group was significantly reduced  
3582 by 6% after 30 days and 17% after 90 days in the high dose group. In the high dose group (23.6  
3583 mg/kg-day) liver enzymes including ALT (up to 34 times control levels), SDH (up to 50 times  
3584 control levels), and OCT (up to 8 times control levels) were significantly elevated from week 2  
3585 through the end of exposure. In addition, significantly increased relative liver weight and  
3586 degenerative lesions were observed. Reported liver lesions included lipid vacuolization, nuclear  
3587 and cellular polymorphism, bile duct hyperplasia, and periportal fibrosis. Severe degenerative  
3588 changes, such as Councilman-like bodies (single-cell necrosis), deeply eosinophilic cytoplasm,  
3589 and pyknotic nuclei, were occasionally noted as well. No evidence of nephrotoxicity was  
3590 observed. At lower doses moderate effects were seen in animals. At 7.1 mg/kg-day only a  
3591 significant (two- to threefold) elevation of SDH during the second half of the exposure period  
3592 and the presence of mild centrilobular vacuolization in the liver was observed. Serum ALT and  
3593 SDH levels returned towards control levels in both mid- and high-dose rats following a 2-week  
3594 recovery period although hepatic lesions of less severity with the exception of fibrosis and bile  
3595 duct hyperplasia were still present in both groups. No effects were observed in rats exposed to  
3596 0.71 mg/kg-day. This study identified a NOAEL of 0.71 mg/kg-day and a LOAEL of 7.1 mg/kg-  
3597 day for carbon tetrachloride-induced liver toxicity.

3598  
3599 A subchronic study conducted by Condie (1986) (data quality rating = high) compared the  
3600 effects of two different gavage vehicles on the toxicity of carbon tetrachloride in mice. CD-1  
3601 mice (12/sex/group) were treated with 0, 1.2, 12, or 120 mg/kg of carbon tetrachloride by oral  
3602 gavage in either corn oil or 1% Tween-60 aqueous emulsion 5 days/week for 12 weeks (average

3603 daily doses of 0, 0.86, 8.6, or 86 mg/kg-day) (Condie et al., 1986). Fifteen deaths occurred  
3604 during the study (6 in male mice, 9 in female mice). Of the total deaths, 8 were attributed to  
3605 gavage (4 male and 4 female mice). These deaths did not appear to influence the study outcome.  
3606 In the high-dose group (86 mg/kg-day) relative liver weight was significantly elevated. In  
3607 addition, liver enzymes were significantly increased (ALT (77–89 times control levels in corn oil  
3608 and 10–19 times control levels in Tween-60), AST (14–15 times control levels in corn oil and 3–  
3609 4 times control levels in Tween-60), and LDH (12–15 times control levels in corn oil and 2–3  
3610 times control levels in Tween-60). Histopathological findings include increased incidence and  
3611 severity of hepatocellular vacuolization, inflammation, hepatocytomegaly, necrosis, and portal  
3612 bridging fibrosis. The only difference between oral gavage vehicles observed at 86 mg/kg-day  
3613 was a greater incidence and severity of necrosis in mice given carbon tetrachloride in corn oil.  
3614 The difference between vehicles was more apparent at the middle dose of 8.6 mg/kg-day. This  
3615 dose produced significantly elevated ALT and mild-to-moderate liver lesions in mice gavaged  
3616 with corn oil but was identified as a NOAEL for mice gavaged with Tween-60. The low dose of  
3617 0.86 mg/kg-day was identified as the NOAEL for mice gavaged with corn oil. In general, both  
3618 sexes responded similarly, with severity of histopathologic changes in males slightly greater than  
3619 females.

3620  
3621 A subchronic study in mice was conducted at higher doses by Hayes (1986) (data quality rating =  
3622 medium). CD-1 mice (20/sex/group) received daily oral gavage doses of 0, 12, 120, 540, or  
3623 1,200 mg/kg-day of carbon tetrachloride in corn oil for 90 days (Hayes et al., 1986). An  
3624 untreated control group of 20 male and 20 female mice was maintained as well. Dose-related  
3625 effects including increases in serum LDH, ALT, AST, ALP, and 5'-nucleotidase and a decrease  
3626 in serum glucose were observed in both sexes. Treatment-related lesions were observed in the  
3627 liver, including fatty change, hepatocytomegaly, karyomegaly, bile duct hyperplasia, necrosis,  
3628 and chronic hepatitis associated with increases in absolute and relative liver weight. Other  
3629 changes in organ weight include increases in spleen and thymus weights. No treatment-related  
3630 lesions were observed in the kidney. No changes were found in urinalysis or hematology  
3631 parameters. It should be noted that, compared with untreated controls, vehicle controls had  
3632 significantly elevated serum LDH and ALT, altered organ weights, and increased incidence of  
3633 liver lesions (e.g., necrosis in 5/19 in vehicle controls versus 0/20 in untreated controls and 20/20  
3634 in the 12 mg/kg-day group). This study failed to identify a NOAEL; the low dose of 12 mg/kg-  
3635 day was a LOAEL for hepatic effects.

3636  
3637 Allis (1990)(data quality rating = medium) conducted a study to investigate the ability of rats to  
3638 recover from toxicity induced by subchronic exposure to carbon tetrachloride. Groups of 48 60-  
3639 day-old male F344 rats were given 0, 20, or 40 mg/kg of carbon tetrachloride 5 days/week for 12  
3640 weeks (average daily doses of 0, 14.3, or 28.6 mg/kg-day) by oral gavage in corn oil. One day  
3641 after the end of exposure, significant dose-related changes were found for relative liver weight,  
3642 serum ALT, AST, and LDH (all increased), and liver CYP450 (decreased) in both dose groups.  
3643 In addition, serum ALP and cholesterol were increased in the high-dose group only. In the low-  
3644 dose group, histopathological examination of the liver revealed cirrhosis in 2/6 rats and vacuolar  
3645 degeneration and hepatocellular necrosis in 6/6 rats; in the high-dose group, histopathological  
3646 examination revealed cirrhosis (as well as degeneration and necrosis) in 6/6 rats. Serum enzyme  
3647 levels and CYP450 returned to control levels within 8 days of the end of exposure. Severity of  
3648 microscopic lesions declined during the postexposure period, but cirrhosis persisted in the high-

3649 dose group through the end of the experiment. Relative liver weight decreased during the  
 3650 postexposure period but did not reach control levels in the high-dose group even after 22 days.  
 3651 Neither of the radiolabeled tracer techniques detected a decreased functional capacity in cirrhotic  
 3652 livers, a finding that could not be explained by the investigators. The low dose of 14.3 mg/kg-  
 3653 day was a LOAEL for hepatic toxicity in this study. Table 3-5 presents the subchronic oral  
 3654 toxicity studies with acceptable data quality.  
 3655

3656 **Table 3-5. Subchronic Oral Toxicity Studies in Rats and Mice with Acceptable Quality**  
 3657 **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	( <a href="#">Hayes et al., 1986</a> )	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	( <a href="#">Bruckner et al., 1986</a> )	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	( <a href="#">Allis et al., 1990</a> )	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)	( <a href="#">Condie et al., 1986</a> )	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; hepatocytomegaly, vacuolation, inflammation, necrosis, and fibrosis in liver	( <a href="#">Condie et al., 1986</a> )	High

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### ***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](#)).

3667 The limited number of animal studies by the dermal route, which have been cited in the previous  
3668 assessments for carbon tetrachloride (see Table 1-3) were found to be acceptable with low,  
3669 medium or high overall quality data based on the quality criteria in the *Application of Systematic  
3670 Review in TSCA Risk Evaluations* ([U.S. EPA, 2018a](#)). Those acceptable studies are briefly  
3671 described in Appendix H. The systematic review process for this risk evaluation did not identify  
3672 additional dermal toxicity data for carbon tetrachloride.

3673  
3674 Among the few dermal studies, Kronevi ([1979](#)) (data quality rating = unacceptable due to lack of  
3675 negative controls and small number of animals) is the only available animal dermal study that  
3676 includes histopathological observations of the liver and kidney in addition to skin tissue. In this  
3677 study, guinea pigs weighing 440 and 570 g were dermally exposed to a single application of 1  
3678 mL of carbon tetrachloride in a 3.1 cm<sup>2</sup> skin depot (513 mg/cm<sup>2</sup>)<sup>12</sup> for 15 minutes, 1 hour, 4  
3679 hours, or 16 hours. Changes in liver morphology were observed from carbon tetrachloride  
3680 exposure only in the 16 hour exposure group. At 16 hours, the study authors reported marked  
3681 hydropic changes in the central two-thirds of each lobule of hepatocytes. These changes were  
3682 characterized by large clear cytoplasmic spaces. There also was a tendency to necrotic lesions  
3683 characterized by homogenous, slightly eosinophilic, and slightly PAS-positive structures within  
3684 the cytoplasm of most of these hepatocytes. The glycogen was absent all over the specimens and  
3685 the nuclei showed a tendency to degeneration. Animals exposed to the same dose levels of  
3686 carbon tetrachloride for 15 minutes, 1 hr or 4 hr did not show liver morphology alterations.<sup>13</sup>

<sup>12</sup> 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.

<sup>13</sup> 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.

3687 There were no reported kidney changes from dermal exposures to carbon tetrachloride in this  
 3688 study.

3689  
 3690 In Wahlberg and Boman (1979) (data quality rating = medium), guinea pigs (20 animals/dose)  
 3691 were exposed to carbon tetrachloride by a single application of 0.5 or 2.0 ml to a 3.1 cm<sup>2</sup> area of  
 3692 skin. Application area was occluded to prevent inhalation and ingestion. Dermal contact with  
 3693 carbon tetrachloride occurred for 5 consecutive days to the single applied dose under occluded  
 3694 exposure conditions. For animals exposed to 0.5 ml, mortality was observed from day 3 (1 out of  
 3695 20 animals died) to day 14. Five animals died by the end of the observation period. Among  
 3696 animals exposed to 2.0 mL, mortality was observed from day 1 (1 out of 20 animals died) to day  
 3697 21. A total of 13 animals died in the 2.0 mL dose group by the end of the observation period.

3698  
 3699 Besides the few animal studies with dermal exposures, information on the toxicity of carbon  
 3700 tetrachloride following dermal exposure is mostly based on anecdotal evidence. For instance, the  
 3701 IRIS assessment describes one case report of carbon tetrachloride- induced toxicity that can at  
 3702 least partially be attributed to absorption across the skin (Farrell and Senseman, 1944). The  
 3703 worker was exposed 8 hours/day by using a fine spray of carbon tetrachloride to saturate a cloth  
 3704 wrapped around the fingers. Although some exposure is likely to have occurred by inhalation,  
 3705 absorption through the skin of the hands was considered as the primary route of exposure. After  
 3706 an unspecified period of time at this job, the worker showed weakness, pain in the limbs, and  
 3707 loss or reduction of certain reflexes. The patient lost 8 pounds in the month between onset of  
 3708 illness and hospitalization. The signs and symptoms of neurotoxicity reversed after several  
 3709 months without exposure.

3710  
 3711 presents acute toxicity dermal studies in guinea pigs with experimental observations in liver  
 3712 toxicity and/or toxicity progression over time.

3713  
 3714 **Table 3-6. Acute Toxicity Dermal Studies in Guinea Pigs with Observations on Liver**  
 3715 **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 <sup>2</sup> (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 <sup>2</sup> (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

3716 \*As reported by study authors: mL of highly pure carbon tetrachloride solution.

3717 **3.2.3.2 Epidemiological Data on Non-Cancer Toxicity**

3718 Epidemiological data on non-cancer effects of carbon tetrachloride published prior to 2010 have  
 3719 been evaluated in previous assessments (see Table 1-3). For instance, the occupational study by

3720 Tomenson et al., (1995) (data quality = medium) was considered by EPA IRIS as the basis for  
 3721 the RfC derivation. The study was not selected as the basis for the RfC because exposures for  
 3722 almost two-thirds of the workers were estimated, so that there is some uncertainty in the study  
 3723 NOAEL and LOAEL values.

3724  
 3725 Tomenson et al., (1995) conducted a cross-sectional study of hepatic function in 135 carbon  
 3726 tetrachloride-exposed workers in three chemical plants in northwest England and in a control  
 3727 group of 276 unexposed workers. The exposure assessment was based on historical personal  
 3728 monitoring data for various jobs at the three plants. Subjects were placed into one of three  
 3729 exposure categories—low ( $\leq 1$  ppm), medium (1.1–3.9 ppm), or high ( $\geq 4$  ppm)—according to  
 3730 their current jobs. Overall, this study suggests an effect of occupational carbon tetrachloride  
 3731 exposure on the liver at exposures in the range of  $>1$ –3.9 ppm (6.3–24.5 mg/m<sup>3</sup>); this exposure  
 3732 range is considered a LOAEL. The low exposure category in this study ( $\leq 1$  ppm or  $\leq 6.3$  mg/m<sup>3</sup>)  
 3733 is a NOAEL.

3734  
 3735 Table 3-7 presents human epidemiological studies published on or after 2010 that have acceptable  
 3736 data quality according to the systematic review for this risk evaluation. As shown in the table, the  
 3737 studies do not suggest significant association between carbon tetrachloride exposure and  
 3738 Parkinson’s Disease or autism.

3739  
 3740 **Table 3-7. Acceptable Epidemiological Studies for Non-Cancer Toxicity of Carbon**  
 3741 **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

3742 **3.2.3.3 Genotoxicity and Cancer Hazards**

3743 **3.2.3.3.1 Genotoxicity**

3744 A substantial body of publications have studied genotoxic effects of carbon tetrachloride as  
 3745 documented in the EPA IRIS Toxicological Review of carbon tetrachloride (U.S. EPA, 2010).  
 3746 The results of this review, as further supported in data summaries provided in Appendix  
 3747 K Appendix I indicate:

- 3748
- 3749 • There is little direct evidence that carbon tetrachloride induces intragenic or point  
 3750 mutations in mammalian systems.
- 3751 • Multiple studies have characterized the formation of endogenously produced DNA  
 3752 adducts, chromosomal aberrations, and micronucleus formation. The presence of cellular  
 3753 toxicity in a number of studies, complicates the evaluation of the database.

- 3754
- 3755
- 3756
- 3757
- 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.

3758 The systematic review did not identify additional genetic toxicity studies with carbon  
3759 tetrachloride rated of medium or high overall quality based on the quality criteria in the  
3760 *Application of Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018a](#)).  
3761 The *in vitro* and *in vivo* genotoxicity databases for carbon tetrachloride, including their  
3762 limitations are described in Appendix I.  
3763

#### 3.2.3.3.2 Carcinogenicity

3764

3765 Under the *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005b](#)), EPA classifies carbon  
3766 tetrachloride as "likely to be carcinogenic to humans" based on: "(1) inadequate evidence of  
3767 carcinogenicity in humans and (2) sufficient evidence in animals by oral and inhalation exposure,  
3768 i.e., hepatic tumors in multiple species (rat, mouse, and hamster) and pheochromocytomas (adrenal  
3769 gland tumors) in mice."  
3770

#### Epidemiological Data on Carcinogenicity

3771

3772 The 2010 EPA IRIS assessment concluded that the evidence in humans was inadequate to show an  
3773 association between exposure to carbon tetrachloride and carcinogenicity. There was some limited  
3774 evidence for certain types of cancer in occupational populations thought to have had some  
3775 exposure to carbon tetrachloride, including non-Hodgkin's lymphoma, lymphosarcoma and  
3776 lymphatic leukemia, esophageal and cervical cancer, breast cancer, astrocytic brain cancer, and  
3777 rectal cancer ([U.S. EPA, 2010](#)).  
3778

3779 Table 3-8 presents epidemiological studies published after completion of the EPA IRIS  
3780 assessment that have been found to be of acceptable data quality in the systematic review for this  
3781 risk evaluation. Among the 11 studies, there was one study of breast cancer, one study of  
3782 head/neck cancer, one study of kidney cancer, two studies of lung cancer, two studies of  
3783 lymphohematopoietic cancers, and four studies of cancers of the nervous system.  
3784

3785 Combining these with the several studies noted in the IRIS assessment, there was little evidence  
3786 of an association between carbon tetrachloride exposure and the lymphohematopoietic cancers  
3787 (non-Hodgkin lymphoma, lymphosarcoma, lymphatic leukemia, multiple myeloma, and mycosis  
3788 fungoides – the most common form of cutaneous T-cell lymphoma), breast cancer, head/neck  
3789 cancer, kidney cancer, or lung cancer. However, four of these newer studies report results for  
3790 cancers of the nervous system – as did one study from the IRIS assessment ([Heineman et al.,  
3791 1994](#)). Three of these were specific to astrocytic brain tumors which include astrocytoma,  
3792 glioma, and glioblastoma and occur in adults. The fourth was a study of neuroblastoma – a  
3793 childhood cancer of the nervous system.  
3794

3795  
3796**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).	( <a href="#">Heck et al., 2013</a> )	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).	( <a href="#">Nelson et al., 2012</a> )	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).	( <a href="#">Neta et al., 2012</a> )	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).	( <a href="#">Ruder et al., 2013</a> )	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 5 <sup>th</sup> quintile carbon tetrachloride exposure compared to 1 <sup>st</sup> quintile exposure. Significant trend across quintiles.	( <a href="#">Garcia et al., 2015</a> )	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	<a href="#">(Carton et al., 2017)</a>	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.	<a href="#">(Purdue et al., 2016)</a>	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).	<a href="#">(Gold et al., 2010)</a>	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	<a href="#">(Morales-Suárez-Varela et al., 2013)</a>	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.	<a href="#">(Mattei et al., 2014)</a>	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	<a href="#">(Vizcaya et al., 2013)</a>	Medium

3797  
3798  
3799  
3800

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

3801 and inhalation exposure. Carbon tetrachloride has also been shown to induce  
 3802 pheochromocytomas in mice by oral and inhalation exposure. Information on the carcinogenic  
 3803 effects of carbon tetrachloride via the dermal route in humans and animals is limited or absent.  
 3804

3805 The IRIS assessment ([U.S. EPA, 2010](#)) identifies the ([Nagano et al., 2007a](#)) bioassay of carbon  
 3806 tetrachloride by the inhalation route described in section 3.2.3.1 (data quality = high) as a  
 3807 bioassay that provides data adequate for dose-response modeling. In this bioassay, carbon  
 3808 tetrachloride produced a statistically significant increase in hepatocellular adenomas and  
 3809 carcinomas in rats and mice of both sexes, and adrenal pheochromocytomas in mice of both  
 3810 sexes.

3811  
 3812 Tumor incidence data for rats in the 104-week inhalation study in F344/DCR rats described  
 3813 above are presented in Table 3-9 ([Nagano et al., 2007a](#)). The incidence of hepatocellular  
 3814 adenomas and carcinomas was statistically significantly increased in male and female rats at 125  
 3815 ppm. The incidence of hepatocellular carcinomas in female 25-ppm rats (6%) was not  
 3816 statistically elevated compared with the concurrent control but did exceed the historical control  
 3817 range for female rats (0–2%). The increase in liver carcinoma over historical control (2/1,797)  
 3818 was statistically significant (based on Fisher's exact test; two-tailed p-value = 0.0002). No other  
 3819 tumors occurred with an increased incidence in treated rats. Incidences of foci of cellular  
 3820 alteration (preneoplastic lesions of the liver), including clear, acidophilic, basophilic, and mixed  
 3821 cell foci, were significantly increased in the 25-ppm female rats; in males, only the incidence of  
 3822 basophilic cell foci was increased at 125 ppm.  
 3823

3824 Tumor incidence data in mice are presented in Table 3-10. The incidences of liver tumors in  
 3825 control mice (18% in males and 4% in females for hepatocellular adenomas and 34% in males  
 3826 and 4% in females for hepatocellular carcinomas) were similar to historical control data for liver  
 3827 tumors in Crj:BDF1 mice in 20 studies at JBRC. The gender differences in unexposed mice are  
 3828 thought to be related to inhibition of liver tumor formation by female estrogen levels. The  
 3829 incidences of hepatocellular adenomas and carcinomas were significantly elevated in both sexes  
 3830 at  $\geq 25$  ppm. At 5 ppm, the incidence of liver adenomas in female mice (8/49 or 16%) was  
 3831 statistically significantly elevated compared to the concurrent control group and exceeded the  
 3832 historical control range (2–10%). The incidence of benign adrenal pheochromocytomas was  
 3833 significantly increased in males at 25 or 125 ppm and females at 125 ppm.

3834 **Table 3-9. Incidence of liver tumors in F344 rats exposed to carbon tetrachloride vapor for**  
 3835 **104 weeks (6 hours/day, 5 days/week)<sup>a</sup>**

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

3836 <sup>a</sup>The exposure concentrations adjusted to continuous exposure (i.e., multiplied by  $5/7 \times 6/24 = 0.9, 4.5,$  and

3837 22.3 ppm.  
 3838 <sup>b</sup>Statistically significant trend for increased tumor incidence by Peto's test ( $p \leq 0.01$ ).  
 3839 <sup>c</sup>Tumor incidence significantly elevated compared with that in controls by Fisher's exact test ( $p \leq 0.01$ ).  
 3840 <sup>d</sup>Statistically significant ( $p \leq 0.001$  by Fisher's exact test) in comparison to the historical control  
 3841 incidence (2/1,797). Sources: ([Nagano et al., 2007a](#))

3842  
 3843  
 3844  
 3845  
 3846 **Table 3-10. Incidence of liver and adrenal tumors in BDF<sub>1</sub> mice exposed to carbon**  
 3847 **tetrachloride vapor for 104 weeks (6 hours/day, 5 days/week)<sup>a</sup>**  
 3848

Tumor	Male				Female			
	0 ppm	5 ppm	25 ppm	125 ppm	0 ppm	5 ppm	25 ppm	125 ppm
Hepatocellular adenoma	9/50 <sup>b</sup>	10/50	27/50 <sup>c</sup>	16/50	2/50 <sup>b</sup>	8/49 <sup>d</sup>	17/50 <sup>c</sup>	5/49
Hepatocellular carcinoma	17/50 <sup>b</sup>	12/50	44/50 <sup>c</sup>	47/50 <sup>c</sup>	2/50 <sup>b</sup>	1/49	33/50 <sup>c</sup>	48/49 <sup>c</sup>
Hepatocellular adenoma or carcinoma	24/50 <sup>b</sup>	20/50	49/50 <sup>c</sup>	49/50 <sup>c</sup>	4/50 <sup>b</sup>	9/49	44/50 <sup>c</sup>	48/49 <sup>c</sup>
Adrenal pheochromocytoma <sup>e</sup>	0/50 <sup>b</sup>	0/50	16/50 <sup>c</sup>	32/50 <sup>c</sup>	0/50 <sup>b</sup>	0/49	0/50	22/49 <sup>c</sup>

3849 <sup>a</sup>The exposure concentrations adjusted to continuous exposure (i.e., multiplied by  $5/7 \times 6/24 = 0.9, 4.5,$  and  
 3850 22.3 ppm.

3851 <sup>b</sup>Statistically significant trend for increased tumor incidence by Peto's test ( $p \leq 0.01$ ).

3852 <sup>c</sup>Tumor incidence was significantly elevated compared with controls by Fisher's exact test ( $p \leq 0.01$ ).

3853 <sup>d</sup>Tumor incidence was significantly elevated compared with controls by Fisher's exact test ( $p \leq 0.05$ ).

3854 <sup>e</sup>All pheochromocytomas in the mouse were benign with the exception of one malignant pheochromocytoma in  
 3855 the 125-ppm male mouse group. Sources: ([Nagano et al., 2007a](#))

3856  
 3857 The systematic review did not identify additional cancer studies with carbon tetrachloride with  
 3858 acceptable data quality based on the quality criteria in the *Application of Systematic Review in*  
 3859 *TSCA Risk Evaluations* ([U.S. EPA, 2018a](#)).

### 3860 **3.2.4 Weight of Scientific Evidence**

3861 The following sections describe the weight of the scientific evidence for both non-cancer and  
 3862 cancer hazard endpoints. Factors considered in weighing the scientific evidence included  
 3863 consistency and coherence among human and animal studies, quality of the studies (such as  
 3864 whether studies exhibited design flaws that made them unacceptable) and biological plausibility.  
 3865 Relevance of data was considered primarily during the screening process but may also have been  
 3866 considered when weighing the evidence.

#### 3867 **3.2.4.1 Non-Cancer Hazards**

3868 The following sections consider and describe the weight of the scientific evidence of health  
 3869 hazard domains discussed in section 3.2.3.1. These domains include: toxicity from acute  
 3870 exposure; liver effects; nervous system effects; kidney effects; and reproductive and  
 3871 developmental effects.



3872

#### 3.2.4.1.1 Acute Toxicity

---

3873 EPA is basing the evidence integration for the acute toxicity of carbon tetrachloride on the  
3874 conclusions of the AEGL program. NAC/AEGL evaluated reports describing nonlethal effects of  
3875 acute exposure of humans to carbon tetrachloride in addition of relevant animal data to derive  
3876 AEGL values. The AGL-2 values are based on observations of CNS effects ([Davis, 1934](#)), (i.e.,  
3877 nausea, vomiting, dizziness, and headaches) despite normal clinical assessments (i.e., urinalysis,  
3878 blood count, hemoglobin levels, blood pressure, and heart rate) for individuals exposed to 317  
3879 ppm carbon tetrachloride for 30 min. The observed effects were apparently not long-lasting but  
3880 are considered severe enough to impair escape or normal function. The same study also reported  
3881 notable renal effects in a worker experimentally exposed to carbon tetrachloride at 200 ppm for 8  
3882 hrs.

3883

3884 Testing for developmental toxicity by the inhalation route is limited to one study in the rat that  
3885 found effects only at high, maternally toxic exposure concentrations. Reduced fetal body weight  
3886 and crown-rump length was reported in the single inhalation study ([Schwetz et al., 1974](#)) at a  
3887 concentration that also produced toxicity in the dam (i.e., hepatotoxicity reflected by increase in  
3888 serum glutamic-pyruvic transaminase activity). This inhalation developmental toxicity study has  
3889 been reviewed in the ATSDR, IRIS, and AEGL assessments. NAC/AEGL ([NRC, 2014](#))  
3890 determined that these results were inconclusive for identifying any fetal end points for deriving  
3891 AEGL (acute) values. NAC/AEGL further concluded that these developmental effects are likely  
3892 associated with the sustained lower maternal weight over gestation days 6-15 rather than the  
3893 result of exposure to carbon tetrachloride on a single day of the study (see section 3.2.5.1).

3894

3895 The systematic review did not identify additional developmental toxicity studies with carbon  
3896 tetrachloride with acceptable data quality based on the quality criteria in the *Application of*  
3897 *Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018a](#)).

3898

3899 Limited available acute animal studies by the dermal route, described above, provide evidence of  
3900 mortality and liver changes from single, continuous ( $\geq 19$  hrs) dermal exposure conditions. The  
3901 systematic review did not identify additional dermal acute toxicity studies with carbon  
3902 tetrachloride with acceptable data quality based on the quality criteria in the *Application of*  
3903 *Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018a](#)).

3904

#### 3.2.4.1.2 Chronic Toxicity

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3905 Limited evidence from gestational exposure studies in animals suggest that developmental  
3906 toxicity is not an acute effect (see section 3.2.4.1.1) nor the most sensitive effect for carbon  
3907 tetrachloride. Developmental toxicity has been observed at doses accompanied by some degree  
3908 of maternal toxicity. Increased resorptions were observed in developmental toxicity studies  
3909 following maternal exposure to doses  $\geq 50$  mg/kg-day during pregnancy ([Narotsky et al., 1997](#)),  
3910 which were attributed to maternally-mediated effects, including reduced progesterone and  
3911 luteinizing hormone levels in dams. EPA ([2010](#)) concluded that the most detailed developmental  
3912 toxicity study by inhalation exposure ([Schwetz et al., 1974](#)) suggests that developmental effects  
3913 of carbon tetrachloride occur at concentrations toxic to the mother and at exposure  
3914 concentrations higher than those associated with liver and kidney toxicity. EPA ([2010](#)) notes that  
3915 the LOAEL for developmental effects (in the presence of maternal toxicity) in this study (300

3916 ppm) was 66-fold higher than the NOAEL (5 ppm) for liver toxicity from chronic inhalation  
3917 exposures identified by IRIS for the development of the RfC.

3918  
3919 The EPA IRIS Assessment ([U.S. EPA, 2010](#)) identified the liver as the target organ for carbon  
3920 tetrachloride after repeated inhalation and oral exposure in animals and humans. Limited  
3921 available dermal exposure data suggest that liver changes can be induced by exposure to carbon  
3922 tetrachloride through the skin in animals.

3923  
3924 Primary animal evidence on the liver toxicity from inhalation exposures is from the chronic (104  
3925 week) inhalation toxicity study in F344/DuCrj rats ([Nagano et al., 2007a](#)). Increased incidence  
3926 and severity of nonneoplastic liver lesions (fatty change, fibrosis, cirrhosis) were seen at 25 and  
3927 125 ppm in both male and female rats in this study. Fatty change in the liver of rats was selected  
3928 by EPA IRIS as the specific endpoint indicative of cellular damage and most sensitive endpoint  
3929 among the histopathologic changes observed in the 25-ppm group rats in the study. This critical  
3930 effect is the basis for the derivation of the IRIS Inhalation Reference Concentration (RfC).

3931  
3932 Kidney toxicity was identified as a target for carbon tetrachloride toxicity after repeated  
3933 inhalation exposure ([U.S. EPA, 2010](#)). Similar to the evidence for liver toxicity, the primary  
3934 evidence for kidney toxicity is the chronic (104 week) inhalation toxicity study in F344/DuCrj  
3935 rats ([Nagano et al., 2007a](#)). increased severity of glomerulonephrosis, accompanied by evidence  
3936 of impaired glomerular function, including increases in serum BUN, creatinine, inorganic  
3937 phosphorus and proteinuria were observed following exposure to  $\geq 25$  ppm. The interpretation of  
3938 the observed proteinuria in the F344 rat, a strain with a high spontaneous incidence of renal  
3939 lesions, was deemed problematic and not an appropriate basis for the RfC in the IRIS  
3940 assessment.

3941  
3942 The kidney was not identified as a critical target for carbon tetrachloride toxicity following oral  
3943 exposure. In oral gavage studies, no exposure-related kidney effects were observed in Sprague-  
3944 Dawley rats exposed to doses up to 2,000 mg/kg-day for 1-3 days ([Sun et al., 2014](#)), Sprague-  
3945 Dawley rats exposed to doses up to 33 mg/kg-day for 12 weeks ([Bruckner et al., 1986](#)), or CD-1  
3946 mice exposed to doses up to 1,200 mg/kg-day for 90 days ([Hayes et al., 1986](#)).

3947  
3948 The systematic review did not identify additional chronic toxicity studies with carbon  
3949 tetrachloride with acceptable data quality based on the quality criteria in the *Application of*  
3950 *Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018a](#)).

#### 3951 **3.2.4.2 Genotoxicity and Cancer**

3952 The available data for carbon tetrachloride do not support a conclusion that this compound  
3953 induces cancer though a mutagenic mode of action, however, there are important limitations to  
3954 the database. While there is little direct evidence that carbon tetrachloride induces intragenic or  
3955 point mutations in mammalian systems, studies have characterized formation of DNA adducts  
3956 and chromosomal damage. Lipid peroxidation products (e.g., reactive aldehydes) may contribute  
3957 to observed effects. The presence of cellular toxicity complicates the evaluation of the database  
3958 and genetic damage has not been well studied at or below the doses at which tumors are  
3959 observed.

3960

3961 The EPA IRIS assessment of carbon tetrachloride classifies this compound as “likely to be  
3962 carcinogenic to humans” based on sufficient evidence in animals by oral and inhalation  
3963 exposure, i.e., hepatic tumors in multiple species (rat, mouse, and hamster) and  
3964 pheochromocytomas (adrenal gland tumors) in male and female mice exposed by oral and  
3965 inhalation exposures ([U.S. EPA, 2010](#)).

3966  
3967 The systematic review did not identify additional genotoxicity studies with carbon tetrachloride  
3968 with acceptable data quality based on the quality criteria in the *Application of Systematic Review*  
3969 *in TSCA Risk Evaluations* ([U.S. EPA, 2018a](#)).

3970

### 3971 **3.2.4.3 MOA for Carcinogenicity**

---

3972 This section summarizes available information on mode of action (MOA) for carbon  
3973 tetrachloride carcinogenicity based on the MOA analysis performed in the 2010 EPA IRIS  
3974 assessment ([U.S. EPA, 2010](#)) and additional information made available since 2010. The  
3975 Guidelines for Carcinogen Risk Assessment ([U.S. EPA, 2005a](#)) identifies steps for determining  
3976 whether a hypothesized MOA is operative. The steps include an outline of the sequence of events  
3977 leading to cancer, identification of the key events, and determination of whether there is a causal  
3978 relationship between events and cancer. The EPA IRIS assessment reviewed MOA information  
3979 for liver tumors and pheochromocytomas. IRIS described evidence in support of several  
3980 potential mechanisms of action (described below) but concluded that “the overall MOA for  
3981 carbon tetrachloride carcinogenicity across all levels of exposure is unknown at this time” ([U.S.](#)  
3982 [EPA, 2010](#)). The IRIS assessment did not review information on potential MOAs for brain  
3983 cancers and the MOA for brain cancer is also unknown.

#### 3984 **3.2.4.3.1 Mode of Action for Liver Tumors**

---

3985 EPA has qualitatively evaluated the weight of evidence for several proposed MOAs for liver  
3986 carcinogenicity using the framework outlined in EPA cancer risk guidelines ([U.S. EPA, 2005a](#)).  
3987 This analysis considers the MOA analysis previously conducted by the IRIS program ([U.S. EPA,](#)  
3988 [2010](#)), more recent evidence, and information submitted to EPA through public comment (see  
3989 Appendix K) to evaluate supporting and counterfactual evidence for proposed MOAs.

3990

3991 A general correspondence has been observed between hepatocellular cytotoxicity and  
3992 regenerative hyperplasia and the induction of liver tumors. At lower exposure levels, this  
3993 correspondence is less consistent ([U.S. EPA, 2010](#)). A hypothesized carcinogenic MOA for  
3994 carbon tetrachloride-induced liver tumors has been proposed and includes the following key  
3995 events:

3996

- 3997 (1) metabolism to the trichloromethyl radical by CYP2E1 and subsequent formation of the
- 3998 trichloromethyl peroxy radical,
- 3999 (2) radical-induced mechanisms leading to hepatocellular cytotoxicity, and
- 4000 (3) sustained regenerative and proliferative changes in the liver in response to hepatotoxicity.

4001

4002 This MOA appears to play a significant role at relatively high exposures, driving the steep  
4003 increase in liver tumors in this exposure range. Data to characterize key events at low-exposure

4004 levels, however, are limited. Therefore, EPA also considered an alternate MOA that combines  
 4005 cytotoxic mechanisms at high doses with alternate, non-cytotoxic mechanisms as lower doses.  
 4006

4007 Based on information in the IRIS assessment and public comments [EPA-HQ-OPPT-2016-0733-](#)  
 4008 [0066](#) and [EPA-HQ-OPPT-2016-0733-0088](#), the following potential MOAs, including evidence  
 4009 for key events, are evaluated in Table 3-11 and Appendix K.  
 4010

- 4011 • Liver cytotoxic MOA (Lipid peroxidation and cytotoxicity as proposed in comments  
 4012 submitted by ACC)
- 4013 • Combined MOA (non-cytotoxic at low dose and cytotoxic at high dose)  
 4014

4015 **Table 3-11. Cytotoxic MOA (key events as proposed by [EPA-HQ-OPPT-2016-0733-0066](#)**  
 4016 **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 <a href="#">EPA-HQ-OPPT-2016-0733-0066</a> and <a href="#">EPA-HQ-OPPT-2016-0733-0088</a> : 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 $\alpha$ -tocopherol, Vitamin E antioxidant, had been shown to reduce lipid peroxidation ( <a href="#">Gee et al., 1981</a> ). 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., ( <a href="#">1999</a> ) 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 <a href="#">EPA-HQ-OPPT-2016-0733-0066</a> and <a href="#">EPA-HQ-OPPT-2016-0733-0088</a> : 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 ( <a href="#">Mccay et al., 1984</a> ; <a href="#">Slater and Sawyer, 1977</a> ; <a href="#">Recknagel and Glende, 1973</a> ), 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 ( <a href="#">U.S. EPA, 2010</a> ) 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)	<p>Multiple studies have characterized the formation of endogenously produced DNA adducts, chromosomal aberrations, and micronucleus formation.</p> <p>Lipid peroxidation products generate compounds (e.g. reactive aldehydes) that may covalently bind to DNA</p> <p>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.</p>	Carbon tetrachloride has consistently been negative in studies using Salmonella and certain strains of E. coli, at high exposure concentrations.	<p>Measurement of genetic damage to DNA has not been well characterized at or below doses at which tumors are observed.</p> <p>Technical challenges for the evaluation the genotoxicity of carbon tetrachloride are summarized in Appendix I.</p> <p>It is unknown what are the major radical-induced mechanisms driving carcinogenesis.</p>
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 ( <a href="#">U.S. EPA, 2010</a> ) 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

4019  
4020 Based on the qualitative MOA WOE for the alternative MOAs, there are significant data  
4021 limitations to assess within certainty the causal considerations (i.e., biological plausibility,  
4022 essentiality, dose-response concordance, consistency) for the postulated non-cytotoxic and  
4023 cytotoxic key events that are expected to occur after carbon tetrachloride metabolism. The  
4024 available data suggest that cytotoxicity is one major mechanism in the MOA of carcinogenesis at  
4025 high exposures, however data also indicate that carbon tetrachloride can induce tumors in the  
4026 absence of cytotoxicity, i.e., tumorigenesis in low dose female mice. There is limited information  
4027 about mechanisms at lower doses.

4028 **3.2.4.3.2 Mode of Action for Pheochromocytomas (Adrenal**  
4029 **Tumors)**

---

4030 EPA has reviewed the available literature and concludes that the MOA by which carbon  
4031 tetrachloride induces pheochromocytomas in mice is unknown. Animal and in vitro evidence  
4032 suggests that metabolism is an important contributor to the toxicity of carbon tetrachloride in the  
4033 adrenal gland (([U.S. EPA, 2010](#)) (see page 168)).

4034  
4035 Pheochromocytomas are relatively rare in people. Only a small number of chemicals have been  
4036 associated with pheochromocytomas in mice, and there does not appear to be a common  
4037 mechanism shared across these chemicals ([U.S. EPA, 2010](#)). Several potential MOAs for  
4038 induction of pheochromocytomas in mice have been hypothesized but not experimentally  
4039 supported, including endocrine disturbances, uncoupling of oxidative phosphorylation,  
4040 disturbances in calcium homeostasis, impaired mitochondrial function, and hepatotoxicity ([Greim](#)  
4041 [et al., 2009](#)).

4042

4043 **3.2.5 Dose-Response Assessment**

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4044 **3.2.5.1 Selection of Studies for Dose-Response Assessment**

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4045 EPA evaluated data from studies described in sections 3.2.3 and 3.2.4 to characterize the dose-  
4046 response relationships of carbon tetrachloride and selected studies and endpoints to quantify risks  
4047 for specific exposure scenarios. The selected studies had adequate information to select PODs.

4048 **3.2.5.1.1 Toxicity After Acute Inhalation Exposures in**  
4049 **Humans**

---

4050 Acute inhalation exposures to carbon tetrachloride above the AEGL-2 values are expected to  
4051 induce immediate and temporary CNS effects, which consist of escape-impairing symptoms in  
4052 occupational settings (i.e., dizziness). Acute inhalation human data were used by the AEGL  
4053 program for the identification of a NOAEL for transient CNS effects of 76 ppm in humans  
4054 exposed carbon tetrachloride for 4 h ([Davis, 1934](#)). EPA considers that the acute NOEL  
4055 identified by the AEGL program is adequate for assessing acute effects in inhalation  
4056 occupational exposure scenarios for TSCA conditions of use of carbon tetrachloride. EPA  
4057 reviewed the acute dose-response information in the AEGL report ([NRC, 2014](#)) including the  
4058 identification of the PODs and uncertainty factors identified for CNS effects but did not conduct  
4059 further dose-response analysis.

4060 The endpoint and effect level identified by NAC/AEGL for the AEGL-2 values are considered to  
4061 provide both a relevant effect and robust POD because the values represent the concentration  
4062 above which it is predicted that irreversible or other serious, long-lasting adverse health effects  
4063 or an impaired ability to escape can be experienced by workers. On the other hand, the AEGL-3  
4064 values protect from life-threatening health effects or death, which are appropriate for emergency  
4065 or accidental releases of the chemical.

4066  
4067 Developmental toxicity studies were also considered in the derivation of acute toxicity values as  
4068 adverse effects in the fetus related to the unique susceptibility of the fetus at discrete times  
4069 during gestation ([U.S. EPA, 1991](#)). Therefore, EPA conservatively assumes that the adverse fetal  
4070 effects observed in a developmental toxicity study that includes exposures across multiple days

4071 of embryonic or fetal development, or even throughout gestation, could have occurred as the  
4072 result of exposure on a single day of the study ([U.S. EPA, 1991](#)). Among the reasonably  
4073 available developmental toxicity data for carbon tetrachloride, Schwetz et al., (1974) is the only  
4074 developmental study by the inhalation route with acceptable data quality. This inhalation  
4075 developmental study has been reviewed in the ATSDR, IRIS, and AEGL assessments. ATSDR,  
4076 IRIS, and AEGL describe that the developmental effects (decreased fetal body weight and  
4077 crown-rump length) occur at the same LOAEL that results in maternal toxicity (a NOAEL was  
4078 not identified). ATSDR categorized these effects as less serious. The maternal effects were  
4079 reduced body weight (decreased food consumption), increased liver weight and ALT. Based on  
4080 this consideration as well as experimental variability over the 3-fold dose range, AEGL  
4081 determined that these results were inconclusive for identifying any fetal end points for deriving  
4082 AEGL values. They further concluded that these developmental effects are likely associated with  
4083 the sustained lower maternal weight over gestation days 6-15 rather than the result of exposure to  
4084 carbon tetrachloride on a single day of the study.

4085

4086 The oral developmental studies by Narotsky et al., (1997), which were rated of high quality in  
4087 the systematic review, identified a developmental NOAEL of 25 mg/kg-d based on observed  
4088 full-litter resorption at 50 mg/kg-d. However oral exposures to carbon tetrachloride undergo  
4089 first-pass metabolism in the liver, the organ with the highest concentration of CYP2E1 enzymes  
4090 involved in the generation of carbon tetrachloride's toxic metabolites.<sup>14</sup> This major difference in  
4091 the metabolism of carbon tetrachloride between oral and inhalation routes of exposure limits the  
4092 usefulness of extrapolating a developmental inhalation POD from the oral developmental study,  
4093 given that different developmental toxicity processes may be involved between the two routes of  
4094 exposure.

4095

### 3.2.5.1.2 Toxicity from Chronic Inhalation Exposures

4096 EPA's systematic review process rated as high the overall quality of the 13-week and 104-week  
4097 inhalation studies by Nagano et al., (2007a; 2007b). The IRIS assessment concluded that among  
4098 the animal studies for carbon tetrachloride the most robust inhalation study was the 104-weeks  
4099 (2-year) inhalation study with F344/DuCrj rats in which the lowest exposure concentration in  
4100 this study, 5 ppm, was considered a NOAEL based on liver and kidney toxicity at  $\geq 25$  ppm. A  
4101 human PBPK model was used in the IRIS Assessment to estimate continuous HECs (in  $\text{mg}/\text{m}^3$ )  
4102 that would result in values for the internal dose metrics, equal to the  $\text{BMDL}_{10}$  values for fatty  
4103 changes of the liver. *The  $\text{BMDL}_{10}$  based on male rat data was calculated as  $14.3 \text{ mg}/\text{m}^3$  for*  
4104 *continuous exposures.*

4105

---

<sup>14</sup> 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.



4106 The systematic review conducted did not identify information that challenges the observations or  
4107 conclusions from this critical study used in the IRIS assessment to derive a reference  
4108 concentration and inhalation unit risk for carbon tetrachloride.

### 4109 **3.2.5.1.3 Toxicity from Dermal Exposures**

4110 Kronevi et. al., (1979) (data quality rating = unacceptable due to lack of negative controls and  
4111 small number of animals) is the only available animal dermal study that includes  
4112 histopathological observations of liver and kidney in addition to skin. In the study guinea pigs  
4113 dermally exposed to a single application of 1 mL of carbon tetrachloride in a 3.1 cm<sup>2</sup> skin depot  
4114 (513 mg/cm<sup>2</sup>)<sup>15</sup> for 16 hours showed hydropic changes and necrosis in liver cells. Animals  
4115 exposed to the same dose levels for 15 minutes, 1 hr or 4 hr did not show liver morphology  
4116 alterations. The study provides suggestive evidence on the lower systemic availability of carbon  
4117 tetrachloride from dermal exposures in comparison with other routes of exposure. The results of  
4118 Kronevi et al., (1979) can be considered in conjunction with the findings from Wahlberg and  
4119 Boman, (1979), in which guinea pigs exposed to a higher dose level of 1 mL with a similar size  
4120 skin depot as Kronevi et al., (1979) did not show mortality during the first 2 days of continuous  
4121 dermal exposure. Collectively, these studies provide evidence suggesting that the induction of  
4122 liver toxicity in animals dermally exposed for 4 hrs to 0.5 mL carbon tetrachloride from a skin  
4123 depot of 3.1 cm<sup>2</sup> is unlikely.

4124  
4125 A study briefly described in the IRIS assessment: Tsuruta, (1975) (Klimisch score = 4: ‘Not  
4126 assignable’) reports a percutaneous absorption rate for carbon tetrachloride in mice of 53.6 ± 9.3  
4127 nmoles/ minute/cm<sup>2</sup>. This study, which is equivalent in design to OECD Guideline 427 (Skin  
4128 Absorption: In Vivo Method)<sup>16</sup> is considered to provide an underestimation of the skin absorption  
4129 rate for occluded exposures because of the possibility of carbon tetrachloride volatilization  
4130 during dose preparation or application. The aspect of volatilization is not considered in this study  
4131 to address potential loss of the analyte. In addition, the IRIS assessment states that Morgan et al.,  
4132 (1991) (Klimisch Score =3: ‘Not reliable’) showed that approximately one quarter of an applied  
4133 volume (i.e., 0.54 mL of neat carbon tetrachloride application) was absorbed in a 24-hour period  
4134 under occluded conditions.

4135  
4136 The systematic review did not identify additional information for refining the skin absorption  
4137 rate for carbon tetrachloride. Therefore, the available dermal toxicity information, with its  
4138 uncertainties and limitations has been used under a weight of evidence approach in the derivation  
4139 of dermal PODs for liver toxicity from acute dermal exposures.

4140  
4141 Due to the lack of repeated-dose dermal toxicity data and the irritating properties of carbon  
4142 tetrachloride (i.e., irritation is associated with increased dermal absorption for repeated dermal  
4143 exposures), the limited acute dermal data with histopathology observations and information on  
4144 dermal absorption rate were used in the derivation of PODs for chronic dermal exposures for the  
4145 chemical.

4146

---

<sup>15</sup> 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.

<sup>16</sup> Equivalency based on information in ECHA dossier for carbon tetrachloride; ECHA reliability score =4.

4147 PODs for chronic dermal exposures were derived using reasonably available inhalation data.  
 4148 Extrapolation from oral exposure data is not recommended due to differences in the  
 4149 biotransformation process between the oral and other routes of exposures for carbon  
 4150 tetrachloride. First-pass metabolism and activation of carbon tetrachloride in the liver is only a  
 4151 metabolic step for oral exposures to the chemical.

4152 **3.2.5.2 Derivation of PODs and UF for Benchmark Margins of Exposure**  
 4153 **(MOEs)**

4154 **3.2.5.2.1 PODs for Acute Inhalation Exposure**

4155 The AEGL Program identified a NOEL of 76 ppm (480 mg/m<sup>3</sup>) for CNS effects (i.e., dizziness)  
 4156 in humans exposed to carbon tetrachloride for 4 hrs.<sup>17</sup> The resulting AEGL-2 value is 7.6 ppm  
 4157 (48 mg/m<sup>3</sup>) for 4 hrs and 5.8 ppm (36 mg/m<sup>3</sup>) for 8 hrs based on a UF<sub>H</sub> of 10 to account for  
 4158 individuals who may be more susceptible to the toxic effects of carbon tetrachloride (e.g.,  
 4159 variability in metabolism and disposition from alcohol usage).

4160  
 4161 Based on AEGL program recommendations for carbon tetrachloride, the POD for acute  
 4162 inhalation exposures in this risk evaluation is 360 mg/m<sup>3</sup> – 8 hr for disabling effects (CNS effects  
 4163 such as dizziness) from elevated, but short inhalation exposures. For 12-hrs of exposure, the  
 4164 acute inhalation POD is 310 mg/m<sup>3</sup> (49 ppm) based on temporal scaling using the equation  $C^n \times t$   
 4165 = k, where an empirical value of n was determined to be 2.5 on the basis of rat lethality data  
 4166 (NRC, 2014). A benchmark MOE of 10 is used for intraspecies variability to account for  
 4167 susceptible individuals, such as moderate to heavy alcohol users, in agreement with the AEGL  
 4168 program conclusions. NRC (2014) explains that the intraspecies uncertainty factor of 10 was  
 4169 retained for protection of susceptible individuals due to the known variability in the metabolic  
 4170 disposition of carbon tetrachloride that may result in an altered toxic response.

4171  
 4172 **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 <sup>3</sup> -8 hr <sup>A</sup>	UF <sub>H</sub> 10	10
			310 mg/m <sup>3</sup> -12 hr		
			310 mg/m <sup>3</sup> -12 hr		

4173 Temporal scaling was performed using the equation  $C^n \times t = k$  (Ten Berge et al., 1986), where an empirical value of  
 4174 n was determined to be 2.5 on the basis of rat lethality data (NRC, 2014).

4175 **3.2.5.2.2 PODs for Chronic Inhalation Exposure**

4176 The basis for the chronic inhalation PODs is the 104-weeks (2-year) inhalation study with  
 4177 F344/DuCrj rats (Nagano et al., 2007b), in which the lowest exposure concentration in this study,  
 4178 5 ppm, was considered a NOAEC based on liver and kidney toxicity at ≥25 ppm. A human

<sup>17</sup> Transient kidney effects were also reported for acute exposures, but at higher exposure concentrations (see Section 3.2.3.1).

4179 PBPK model was used in the IRIS Assessment to estimate HEC (in  $\text{mg}/\text{m}^3$ ) consisting of  
4180 *calculated*  $\text{BMDL}_{10}$  for fatty changes of the liver of  $14.3 \text{ mg}/\text{m}^3$  for continuous exposures.

4181  
4182 Because the relationship between the PBPK-estimated internal dose metric and the external  
4183 concentration is linear, a periodic time adjustment of the 24-hour chronic HEC would produce a  
4184 nearly equivalent result as running the PBPK model assuming periodic exposures. While  
4185 additional nonlinearities in the model can be introduced when simulating periodic (as opposed to  
4186 continuous) exposures, the difference is small for chemicals that are rapidly absorbed and cleared  
4187 from the body. Such is the case with carbon tetrachloride. The linearity of the PBPK model was  
4188 determined by analysis of Tables C-6 and C-10 of the IRIS assessment (see Appendix J, below).  
4189 These tables presented the external:internal dose ratios for the human PBPK model over a span  
4190 of concentrations, using the model assumptions adopted by the IRIS assessment (model  
4191 parameter  $V_{\text{maxC}} = 1.49 \text{ mg}/\text{hr}/\text{kg BW}^{0.70}$ , continuous 24 hour/day, 7 days/week exposure).  
4192 Table C-6 presented PBPK model results for the MCA (mean arterial concentration) internal  
4193 dose metric, while Table C-10 presented results for the MRAMKL (mean rate of metabolism in  
4194 the liver) internal dose metric. An adaptation of these tables is presented in Appendix J. The  
4195 MRAMKL dose metric was used for RfC derivation in the IRIS assessment. For the inhalation  
4196 unit risk derivation, the MCA dose metric was used. For the MRAMKL internal dose metric, the  
4197 external:internal dose ratio remains relatively constant (within 10% of the value estimated at the  
4198 lowest simulated concentration) at external concentrations (ECs) below  $95 \text{ mg}/\text{m}^3$ . The value of  
4199 the (24-hour continuous) HEC ( $\text{BMDL}_{10}$ ) used for RfC derivation was  $14.3 \text{ mg}/\text{m}^3$ , and thus is  
4200 within the linear range. This supports the use of the Haber's law equation,  $C^n \times t = k$  with  $n=1$  to  
4201 estimate HEC values for non-continuous exposures.

4202 U.S. EPA (2002) notes that extrapolation from longer to shorter time durations will result in a  
4203 higher extrapolated exposure concentration value when using downward slope equations such as  
4204  $C^n \times t = k$ , especially when  $n = 1$  or  $0.8$ . When  $n = 3$  in the equation, the downward slope is less  
4205 appreciable than for  $n = 1$  or  $0.8$ . For instance, the slope for the equation with  $n = 2.5$  (equation  
4206 for carbon tetrachloride) is  $-0.1$ , while the slopes for the equations with  $n = 3$  and  $n = 1$  are  $-0.07$   
4207 and  $-2$ , respectively based in a  $k$  value of  $343$ . The slope of  $-0.1$  for  $n = 2.5$  suggests that the  
4208 extrapolated concentrations of carbon tetrachloride for shorter times of exposure are less shifted  
4209 to higher values because they are influenced by a much lower downward slope.

4210  
4211 Conservatively, the  $\text{BMDL}_{10}$  value for continuous exposures was extrapolated to shorter  
4212 exposure durations using the equation  $C^n \times t = k$ , where an empirical value of  $n$  was determined  
4213 to be  $2.5$  on the basis of rat lethality data (Ten Berge et al., 1986).

4214  
4215 A benchmark MOE of  $30$  (based on  $\text{UF}_H 10$  and  $\text{UF}_A 3$ ) is used to evaluate risk for workers and  
4216 ONUs.

4217

4218 **Table 3-14. PODs for Chronic Inhalation Exposures based on Animal data**

Study	Study Details	Endpoint	POD	UFs/Dose Metric	Benchmark MOE
( <a href="#">Nagano et al., 2007a</a> )	Chronic inhalation rat	Fatty changes in the liver	BMCL <sub>10[HEC]</sub> : 14.3 mg/m <sup>3</sup> for continuous exposures, which is equivalent to <b>31.1 mg/m<sup>3</sup> for 8 hrs/d and 5 days per week of exposure and 26.4 mg/m<sup>3</sup> for 12 hrs/d and 5 days per week*</b>	UF <sub>H</sub> 10 UF <sub>A</sub> 3	30

4219 \*Time adjustments based on  $C^n \times t = k$ , where  $n = 2.5$  and adjustment for 5 days/week exposures

### 4220 **3.2.5.2.3 PODs for Acute Dermal Exposures**

4221 Given the limited information on non-cancer effects after acute dermal toxicity from carbon  
 4222 tetrachloride, the POD for acute dermal exposures is based on the only reasonably available  
 4223 acute toxicity study with histopathological information on liver and kidney tissues ([Kronevi et](#)  
 4224 [al., 1979](#)). The study was found to be unacceptable in the systematic review due to the lack of  
 4225 negative controls and small number of animal per dose group. However, the study findings  
 4226 provide a rough comparison of liver and kidney changes from acute dermal exposure to carbon  
 4227 tetrachloride during different time periods (i.e., 4 hrs, 19 hrs). The use of the study findings in  
 4228 conjunction with findings from another dermal toxicity study with similar experimental  
 4229 conditions and acceptable quality data (i.e., ([Wahlberg and Boman, 1979](#))) were used to derive a  
 4230 POD for acute dermal exposures. An alternative approach, in which the POD for acute dermal  
 4231 exposures is extrapolated from the POD for chronic inhalation exposures results in a similar  
 4232 POD for acute exposures (2,450 mg/kg vs 2,750 mg/kg).<sup>18</sup> Extrapolation of the acute dermal  
 4233 POD from acute inhalation POD was not performed because the critical acute inhalation effects  
 4234 of neurotoxicity are influenced by the accessibility to brain tissue by inhaled carbon  
 4235 tetrachloride.

4236  
 4237 Based on the assumption that induction of liver toxicity is unlikely for animals dermally exposed  
 4238 for 4 hrs to 0.5 mL carbon tetrachloride from a skin depot of 3.1 cm<sup>2</sup> (see section 3.2.5.1), an  
 4239 acute dose for occluded conditions, which is associated with non-adverse liver effects was  
 4240 estimated. Dose for occluded exposures =  $[(260 \text{ mg/cm}^2 \times 3.1 \text{ cm}^2) / 0.440 \text{ kg}] - 4 \text{ hrs}$  or 1,832  
 4241 mg/kg – 4 hrs

4242  
 4243 A NOAEL value for the acute dermal exposure dose was then obtained by estimating how much  
 4244 of the acute dose is absorbed in 4 hrs under by using the reasonably available dermal absorption  
 4245 information for carbon tetrachloride. The available information includes a (underestimated)  
 4246 percutaneous absorption rate for carbon tetrachloride in mice of  $53.6 \pm 9.3 \text{ nmoles/minute/cm}^2$   
 4247 ([Tsuruta, 1975](#)), which shows dermal absorption of carbon tetrachloride has linear dependency to

<sup>18</sup> 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.

4248 the time and area of exposure and the experimental observations from Morgan et al., (1991)  
 4249 showing that about 25% of a total dose was absorbed in a 24-hr period under occluded conditions  
 4250 were used to extrapolate NOAEL for retained/absorbed carbon tetrachloride for acute dermal  
 4251 exposures.

4252  
 4253 By considering the reasonably available animal evidence on dermal absorption (i.e., 25% of a  
 4254 dermal dose is absorbed in 24 hrs, and linear time dependency for dermal absorption), a  
 4255 conservative assumption of 6% of an applied dose of carbon tetrachloride under occluded dermal  
 4256 conditions been absorbed in 4 hrs, was used to account for experimental underestimation.  
 4257 Therefore, the estimated NOAEL for acute (retained/absorbed) for occluded dermal exposures =  
 4258  $1,832 \text{ mg/kg} \times 0.06 = 110 \text{ mg/kg-d}$ .

4259  
 4260 This NOAEL for acute (retained/absorbed) occluded exposures can be adjusted to a larger  
 4261 NOAEL value for non-occluded exposures to account for volatilization of carbon tetrachloride  
 4262 during non-occluded dermal exposures. Loss of carbon tetrachloride from volatilization in non-  
 4263 occluded scenarios results in the need for a higher amount of applied dose to reach effect levels.  
 4264 The supplemental file (U.S. EPA, 2019b) explains that because carbon tetrachloride is a volatile  
 4265 liquid, its dermal absorption depends on the type and duration of exposure. Where exposure is  
 4266 not occluded, only a fraction of carbon tetrachloride that comes into contact with the skin will be  
 4267 absorbed as the chemical readily evaporates from the skin. The default fraction of applied mass  
 4268 that is absorbed for carbon tetrachloride is 0.04. This fractional absorption factor is estimated  
 4269 based on a theoretical framework by Kasting and Miller (2006).

4270  
 4271 The NOAEL for non-occluded retained doses of carbon tetrachloride is estimated by dividing the  
 4272 NOAEL of 110 mg/kg-d for occluded dermal exposures by the default absorbed fraction factor  
 4273 of 0.04. Therefore, a NOAEL for acute non-occluded retained doses of 2,750 mg/kg was  
 4274 estimated.

4275  
 4276 **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 <sub>H</sub> 10 UF <sub>A</sub> 10	100

4277  
 4278 **3.2.5.2.4 PODs for Chronic Dermal Exposures**

4279 The chronic inhalation HEC was converted to a dermal HED for non-occluded retained doses by  
 4280 using a modified equation based on (Jongeneel, 2012) equation (Equation 3-1) for transposing an  
 4281 inhalation Occupational exposure level (OEL) to a dermal OEL. In the modified equation a  
 4282 dermal absorption factor is not used, which allows the estimation of the absorbed dermal dose  
 4283 instead of the OEL. This modification is necessary because dermal exposures in 2.4.1.8 are  
 4284 retained doses.

4285 **Equation 3-1.  $HED_{Dermal} = HEC_{human,respiratory} \times V_{rate} \times T \times \text{absorption}_{(inhalation)}/\text{absorption}_{(dermal)} \times 1/\text{bodyweight}$**

4286  
4287  
4288 **Equation 3-2.  $HED_{Dermal} = HEC_{human,respiratory} \times V_{rate} \times T \times \text{absorption}_{(inhalation)} \times$**   
4289  **$1/\text{bodyweight}$**

4290  
4291 Where:

4292  **$HEC_{human,respiratory}$**  = extrapolated  $BMCL_{10[HEC]}$  of 31.1 mg/m<sup>3</sup> for 8 hrs/d, 5 days/week,

4293  **$V_{rate}$**  = a default worker ventilation rate of 1.25 m<sup>3</sup> per hour for light activities;

4294 **T** = 8 hrs /day of exposure

4295 **Absorption (inhalation)** = 63%; based on inhalation absorption information in

4296 ([U.S. EPA, 2010](#))

4297 **Absorption (dermal)** = 4% for non-occluded exposures, for 8-hrs exposure and  
4298 absorption assumptions used to derive PODs for acute dermal exposures in  
4299 section 3.2.5.2.3.

4300 **bodyweight** = 80 kg.

4301  
4302  
4303 **Table 3-16. PODs for Chronic Dermal Exposures**

Study	Study Details	Endpoint	POD	UFs/Dose Metric	Benchmark MOE
( <a href="#">Nagano et al., 2007a</a> )	Chronic inhalation rat	Fatty changes in the liver	$BMCL_{10[HEC]}$ : 14.3 mg/m <sup>3</sup> for continuous exposures, which is equivalent to <b><math>HED_{Dermal} = 245 \text{ mg/kg-d}</math></b>	UF <sub>H</sub> 10 UF <sub>A</sub> 3	30

4304  
4305 **3.2.5.2.5 Cancer Inhalation Unit Risk and Dermal Slope Factor**

4306 *Cancer Inhalation Unit Risk (IUR)*

4307 In the IRIS Toxicological Review of Carbon Tetrachloride ([U.S. EPA, 2010](#)) two quantitative  
4308 approaches for assessment of carbon tetrachloride carcinogenicity are presented:

4309  
4310 1- a low dose linear cancer risk model for carbon tetrachloride, which is EPA's default  
4311 approach to risk assessment when the MOA is unknown. The IRIS program estimated an  
4312 IUR of  $6 \times 10^{-6}$  per  $\mu\text{g}/\text{m}^3$  for continuous lifetime exposure. The question of combining  
4313 risks from the liver and adrenal tumors was considered in the IRIS Tox Review. As noted  
4314 in the Tox Review, it is not possible to combine the tumor risks directly because each  
4315 tumor risk was based on a different internal dose metric from the PBPK model. The risks  
4316 in the male mice could not be combined because the liver cancer IUR was too uncertain  
4317 and the upper bound combination of the risks in female mice was still lower than just the  
4318 pheochromocytomas in male mice and thus would not have affected the bottom-line  
4319 results.

4321 In summary, the MS-combo model could not be applied because the dose metric is  
 4322 different for the two different tumor types, and even if they could be combined, the risk  
 4323 estimates would not change.

4324  
 4325 2- nonlinear approach with exposures exceeding the POD (18 mg/m<sup>3</sup>, lower 95% bound  
 4326 on exposure associated with 10% extra risk) for continuous exposure, because above this  
 4327 level, the fitted dose-response model better characterizes what is known about the  
 4328 carcinogenicity of carbon tetrachloride. This threshold approach is used in this risk  
 4329 evaluations for high exposures based on a benchmark MOE of 30 (UF<sub>H</sub> = 10 and UF<sub>A</sub> =  
 4330 3).

4331

### 4332 *Cancer Slope Factor for Dermal Exposures*

4333 To avoid uncertainties related to the first-pass biotransformation of carbon tetrachloride from  
 4334 oral exposures, a cancer slope factor for dermal exposures was derived using the IUR of  
 4335  $6 \times 10^{-6}$  per  $\mu\text{g}/\text{m}^3$  and similar approach presented in section 3.2.5.2.4.

4336

4337 Starting with time adjusted IUR of  $6 \times 10^{-6}$  per  $\mu\text{g}/\text{m}^3$

- 4338 • Adjusting for a default worker ventilation rate of 1.25 m<sup>3</sup> per hour for light activities for  
 4339 8 hrs/day (10 m<sup>3</sup>/day).
  - 4340 ○  $6 \times 10^{-6}$  per  $\mu\text{g}/\text{m}^3 \times 1 \text{ day}/10 \text{ m}^3 = 6 \times 10^{-7}$  per  $\mu\text{g}/\text{d}$
- 4341 • Adjusting for average worker bodyweight of 80 kg
  - 4342 ○  $6 \times 10^{-7}$  per  $\mu\text{g}/\text{d} \times 80 \text{ kg} = 5 \times 10^{-5}$  per  $\mu\text{g}/\text{kg}\text{-d}$  or  $5 \times 10^{-2}$  per  $\text{mg}/\text{kg}\text{-d}$
- 4343 • Adjusting for absorption: 63% inhalation absorption.
  - 4344 ○ Dermal Cancer Slope Factor =  $(5 \times 10^{-2} \text{ per mg}/\text{kg}\text{-d}) (1/63) = 8 \times 10^{-4}$  per  $\text{mg}/\text{kg}\text{-}$   
 4345 d

### 4346 **3.2.5.3 PODs for Human Health Hazard Endpoints and Confidence Levels**

4347 Section 3.2.5.2 summarizes the PODs derived for evaluating human health hazards from acute  
 4348 and chronic inhalation scenarios, acute dermal scenarios and PODs extrapolated from inhalation  
 4349 studies to evaluate human health hazards from chronic dermal scenarios. EPA has also  
 4350 determined confidence levels for the acute, non-cancer chronic and cancer chronic values used in  
 4351 the risk evaluation. These confidence levels consider the data quality ratings of the study chosen  
 4352 as the basis of dose-response modeling and also consider the strengths and limitations of the  
 4353 body of evidence including the strengths and limitations of the human, animal and MOA  
 4354 information to support the endpoint both qualitatively and quantitatively.

4355

#### 4356 *Confidence Levels*

4357 NAS/AEGL considered several reports providing data on nonlethal effects of acute exposure of  
 4358 humans to carbon tetrachloride to establish an AEGL-2 value. Some of the reports include Davis  
 4359 (1934), which includes a series of controlled exposure experiments that allowed the  
 4360 determination of a no-effect level for non-lasting CNS effects (i.e., dizziness). The data set was  
 4361 determined to provide suitable data to derive AEGL-2 values by NAS/AEGL. Overall, there is  
 4362 high confidence in this endpoint because the quantitative dataset consists of a series of controlled  
 4363 exposure experiments that identify a no-effect level for CNS effects in humans. EPA found that  
 4364 this study is an acceptable study with low data quality based upon our review using the

4365 systematic review protocol. Further information on the data quality evaluation of this study can  
 4366 be found in the *Draft Risk Evaluation for Carbon Tetrachloride, Systematic Review*  
 4367 *Supplemental File: Data Quality Evaluation of Epidemiological Studies. Docket EPA-HQ-*  
 4368 *OPPT-2019-0499* ([U.S. EPA, 2019g](#)).

4369  
 4370 For the chronic non-cancer endpoint, confidence in the Nagano et al., ([2007a](#)) the principal study  
 4371 is high. According to EPA ([2010](#)) and systematic review for this risk evaluation, this chronic  
 4372 study was well conducted, using two species and 50 animals/sex/group. The chronic study was  
 4373 preceded by a 13-week subchronic study, and an extensive set of endpoints was examined in  
 4374 both studies. Thus, EPA has high confidence in the chronic non-cancer endpoint based on liver  
 4375 effects.

4376  
 4377 For the chronic cancer endpoint, the same high-quality chronic cancer bioassay in rats and mice  
 4378 provided data adequate for dose-response modeling. The IUR is based on pheochromocytomas  
 4379 observed in only one of the rodent species, mice. Furthermore, the cancer MOA for carbon  
 4380 tetrachloride is not fully elucidated, especially at low doses. Thus, EPA has medium confidence  
 4381 in the chronic cancer endpoint and dose-response model used in this risk evaluation.  
 4382

4383 **Table 3-17. Summary of PODs for Evaluating Human Health Hazards from Acute and**  
 4384 **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 <sup>3</sup> -8hr	10 (UF <sub>H</sub> 10)	Study duration and endpoint relevant to worker acute exposures; in agreement with AEGL acute exposure guidelines	( <a href="#">Davis, 1934</a> )
	Non-cancer	Extrapolated BMCL <sub>10[HEC]</sub>	31.1	mg/m <sup>3</sup> - 8 hrs	30 (UF <sub>H</sub> 10; UF <sub>A</sub> 3)	POD relevant for liver effects; in agreement with IRIS non-cancer conclusions	( <a href="#">Nagano et al., 2007a</a> )
	Cancer	Inhalation Unit Risk (IUR)	6 × 10 <sup>-6</sup>	(µg/m <sup>3</sup> ) <sup>-1</sup>	1 in 10 <sup>4</sup> for occupational risk	In agreement with IRIS cancer conclusions for carbon tetrachloride	( <a href="#">Nagano et al., 2007a</a> )
Dermal	Short term-Liver effects	Single exposure	2,750	mg/kg-d	100 (UF <sub>H</sub> 10; UF <sub>A</sub> 10)	POD relevant for liver effects	( <a href="#">Kronevi et al., 1979</a> ) ( <a href="#">Wahlberg and Boman, 1979</a> )
	Non-cancer	Extrapolated Human Equivalent Dose (HED)	245	mg/kg-d	30 (UF <sub>H</sub> 10; UF <sub>A</sub> 3)	POD relevant for liver effects	( <a href="#">Nagano et al., 2007a</a> )
	Cancer	Cancer Slope Factor (CSF)	8 × 10 <sup>-4</sup> (derived from IUR)	(mg/kg-d) <sup>-1</sup>	1 in 10 <sup>4</sup> for occupational risk	In agreement with IRIS cancer conclusions for carbon tetrachloride	( <a href="#">Nagano et al., 2007a</a> )



4385 Uncertainty Factors =  $UF_A$  = interspecies UF;  $UF_H$  = intraspecies UF

#### 4386 **3.2.5.4 Potentially Exposed or Susceptible Subpopulations**

4387 EPA evaluated reasonably available information to identify human subpopulations that may have  
4388 greater susceptibility to carbon tetrachloride than the general population. Because the scope of  
4389 this human health assessment is limited to workers and ONUs, this section focuses on identifying  
4390 subpopulations within workers and ONUs who may have greater susceptibility to carbon  
4391 tetrachloride. This hazard assessment does not address factors that may make non-  
4392 workers/ONUs more susceptible to carbon tetrachloride. Based on reasonably available  
4393 information, some individuals in the workplace may be more biologically susceptible to the  
4394 effects of carbon tetrachloride due to age, alcohol consumption, nutritional status, pre-existing  
4395 disease (e.g. diabetes or liver disease), exposure to other chemicals, and genetic variation.  
4396

4397 Metabolism of carbon tetrachloride to reactive metabolites by cytochrome p450 enzymes  
4398 (particularly CYP2E1 and CYP3A) is hypothesized to be a key event in the toxicity of this  
4399 compound. Differences in the metabolism due to alcohol consumption, exposure to other  
4400 chemicals, age, nutritional status, genetic variability in CYP expression, or impaired liver  
4401 function due to liver disease can increase susceptibility to carbon tetrachloride ([U.S. EPA, 2010](#)).  
4402 For example, alcohol is known to induce CYP2E1 expression. Cases of acute toxicity from  
4403 occupational exposures indicate that heavy drinkers are more susceptible to carbon tetrachloride  
4404 and this observation has been verified in numerous animal studies. Exposure to other chemicals  
4405 that induce p450 enzymes, including isopropanol, methanol, acetone, methyl ethyl ketone,  
4406 methyl isobutyl ketone, 2-butanone, phenobarbital, methamphetamine, nicotine,  
4407 trichloroethylene, polychlorinated and polybrominated biphenyls, DDT, mirex, and chlordecone  
4408 have also been shown to potentiate carbon tetrachloride liver toxicity ([U.S. EPA, 2010](#); [ATSDR,  
4409 2005](#)).

4410  
4411 Age can influence susceptibility to carbon tetrachloride due to differences in metabolism,  
4412 antioxidant responses, and reduced kidney function in older adults. While lower CYP expression  
4413 may reduce susceptibility of older adults to carbon tetrachloride in some tissues, reduced kidney  
4414 function and increased CYP3A activity in the liver (indicated by animal studies) suggest that  
4415 older populations could be at greater risk of carbon tetrachloride-associated kidney damage ([U.S.  
4416 EPA, 2010](#)).

4417  
4418 Nutrition has also been shown to influence susceptibility to carbon tetrachloride in animals. Food  
4419 restriction has been shown to increase liver toxicity of carbon tetrachloride. Diets low in  
4420 antioxidants increase lipid peroxidation and liver damage in following carbon tetrachloride  
4421 exposure (reversed with antioxidant supplementation) and zinc deficient diets increase carbon  
4422 tetrachloride-induced liver toxicity ([U.S. EPA, 2010](#)).

4423  
4424 The AEGL-2 values (See section 3.2.3.1), which are the basis for the PODs for acute inhalation  
4425 exposures in this draft risk evaluation, were derived using an intraspecies uncertainty factor of 10  
4426 to account for individuals who may be more susceptible to the toxic effects of carbon  
4427 tetrachloride, including greater potential of carbon tetrachloride-induced toxicity in individuals  
4428 with histories of alcohol usage. Susceptibility to carbon tetrachloride due to elevated (i.e.,  
4429 moderate-high) alcohol use is in agreement with the known dispositional potentiation of carbon  
4430 tetrachloride toxicity by inducers of cytochrome CYP2E1 enzymes. The AEGL document states

4431 that the variability in response to carbon tetrachloride is emphasized by the fact that an estimated  
4432 exposure at 63 ppm-h was fatal in a heavy drinker whereas controlled exposures at 190 ppm-h  
4433 were without effect for individuals not categorized as heavy drinkers.

## 4434 **4 RISK CHARACTERIZATION**

---

### 4435 **4.1 Environmental Risk**

---

4436 EPA integrated fate, exposure, and environmental hazard information when characterizing the  
4437 environmental risk of carbon tetrachloride. As stated in section 2.1, carbon tetrachloride is not  
4438 expected to bioconcentrate in biota or accumulate in wastewater biosolids, soil, sediment, or  
4439 biota. Releases of carbon tetrachloride to the environment are likely to volatilize into the  
4440 atmosphere, where it will photodegrade under stratospheric conditions. It may migrate to  
4441 groundwater, where it will slowly hydrolyze. Section 2.1 also explains that the bioconcentration  
4442 potential of carbon tetrachloride is low. EPA modeled environmental exposure with surface  
4443 water concentrations of carbon tetrachloride ranging from 4.9E-05 µg/L to 1.3E+02 µg/L for  
4444 acute exposures and 4.1E-06 µg/L to 1.0E+01 µg/L for chronic exposures from facilities  
4445 releasing the chemical to surface water. The modeled data represents estimated concentrations  
4446 near facilities that are actively monitoring and reporting carbon tetrachloride releases to surface  
4447 receiving water via EPA's Discharge Monitoring Reports as required under the National  
4448 Pollutant Discharge Elimination System (NPDES) permitting rules.

4450 EPA concludes that carbon tetrachloride poses a hazard to environmental aquatic receptors  
4451 (section 3.1). Amphibians are the most sensitive taxa for acute and chronic exposures,  
4452 respectively. For acute exposures, a hazard value of 0.9 mg/L was established for amphibians  
4453 using data on teratogenesis leading to lethality in frog embryos and larvae. For acute exposures,  
4454 carbon tetrachloride also has hazard values for fish as low as 10.4 mg/L and for freshwater  
4455 aquatic invertebrates as low as 11.1 mg/L. For chronic exposures, carbon tetrachloride has a  
4456 hazard value for amphibians of 0.03 mg/L based on teratogenesis and lethality in frog embryos  
4457 and larvae. For chronic exposures, carbon tetrachloride also has hazard values as low as 1.97  
4458 mg/L for fish and 1.1 mg/L (acute to chronic ratio of 10) for aquatic invertebrates. In algal  
4459 studies, carbon tetrachloride has hazard values ranging from 0.07 to 23.59 mg/L.

4461 EPA considered the biological relevance of the species that the COCs were based on when  
4462 integrating the COCs with surface water concentration data to produce risk quotients (RQs). For  
4463 example, life-history and the habitat-use influence the likelihood of exposure above the hazard  
4464 benchmark in an aquatic environment. In general, amphibian distribution is typically limited to  
4465 freshwater environments. Larvae of the amphibian species (*Lithobates* sp. and *Rana* sp.)  
4466 evaluated for hazards from chronic exposure (see Appendix G.2) can occupy a wide range of  
4467 freshwater habitats including wetlands, lakes, springs, and streams throughout development and  
4468 metamorphosis. However, as adults these species are semi-aquatic and may interact with surface  
4469 water for fewer days per year. In contrast, fish occupy a wide range of freshwater habitats  
4470 throughout their entire life cycle. If hazard benchmarks are exceeded by both larval amphibians  
4471 and fish from a modeled and estimated chronic exposure, it provides additional evidence that the  
4472 site-specific releases could affect that specific aquatic environment.

4473

4474 A total of 14 aquatic environmental hazard studies were reviewed and determined to have  
4475 acceptable data quality for carbon tetrachloride. EPA's evaluation of these studies was either  
4476 high or medium during data quality evaluation (Appendix G). The document *Risk Evaluation for*  
4477 *Carbon Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of*  
4478 *Environmental Hazard Studies*. EPA, (2019e) presents details of the data evaluations for each  
4479 study, including scores for each metric and the overall study score.  
4480

4481 For this risk evaluation, EPA conducted a multi-year analysis of 21 facilities that released the  
4482 highest concentration of carbon tetrachloride from 2014-2018 as reported in the EPA Discharge  
4483 Monitoring Reports. Given carbon tetrachloride's conditions of use under TSCA outlined during  
4484 problem formulation (U.S. EPA, 2018d), EPA determined that significant environmental  
4485 exposures are not expected to exceed the acute and chronic COCs for aquatic species, as  
4486 presented in section 3.1.2. Environmental releases of carbon tetrachloride occur through disposal  
4487 from industrial/commercial facilities as well as from POTWs. Sources of carbon tetrachloride  
4488 from POTWs releases may not be tied to a specific condition of use given that POTWs may have  
4489 multiple release sources. However, EPA is confident that the risks from releases of carbon  
4490 tetrachloride include all conditions of use considered within the scope of the risk evaluation  
4491 because EPA is using the worst-case, high end exposures and modeled surface water  
4492 concentrations.  
4493

4494 At problem formulation, EPA made refinements to the conceptual models resulting in the  
4495 elimination of the sediment exposure pathway from further analysis. Based on physical chemical  
4496 and fate properties of carbon tetrachloride, EPA did not conduct a full quantitative assessment to  
4497 further evaluated exposure to sediment-dwelling aquatic organisms through the sediment. There  
4498 is no data to suggest that sediment-dwelling aquatic organisms are exposed to carbon  
4499 tetrachloride.  
4500

4501 During problem formulation, exposure pathways to terrestrial species (e.g., through soil, land-  
4502 applied biosolids, and ambient air) were determined to be adequately assessed and effectively  
4503 managed under programs of other environmental statutes administered by EPA. These pathways  
4504 were excluded from the scope of this risk evaluation. Thus, environmental hazard data sources  
4505 on terrestrial organisms were excluded from data quality evaluation.

#### 4506 **4.1.1 Aquatic Pathway**

---

4507 The purpose of the environmental risk characterization is to determine whether there are risks to  
4508 the aquatic environment from levels of carbon tetrachloride found in surface water based on the  
4509 fate properties, relatively high potential for release, and the availability of environmental  
4510 monitoring data and hazard data. Although EPA did not calculate risks to the aquatic  
4511 environment at problem formulation, EPA conducted further analysis of the environmental  
4512 release pathway in this risk evaluation during data quality evaluation. Due to the physical,  
4513 chemical, and fate properties of carbon tetrachloride in the environment (e.g., volatility, water  
4514 solubility) and a quantitative comparison of hazards and exposures for aquatic organisms, EPA  
4515 has high confidence that there are no environmental risks to the aquatic species posed by carbon  
4516 tetrachloride under the conditions of use within the scope of the risk evaluation. The results of  
4517 the analyses are presented in Appendix E and Appendix G.  
4518

4519 The environmental risk of carbon tetrachloride is characterized by calculating risk quotients or  
 4520 RQs ([U.S. EPA, 1998](#)). The RQ is defined as:

4521  
 4522 
$$\text{RQ} = \text{Environmental Concentration} / \text{Effect Level}$$

4523  
 4524 An RQ equal to 1 indicates that the exposures are the same as the concentration that causes  
 4525 effects. If the RQ is above 1, the exposure is greater than the effect concentration. If the RQ is  
 4526 below 1, the exposure is less than the effect concentration. The Concentrations of Concern  
 4527 (COCs) for aquatic organisms shown in Table 4-1 were used to calculate RQs. The  
 4528 environmental concentration for surface water is determined based on experimental test data of  
 4529 carbon tetrachloride (Appendix E and Appendix G).

4530  
 4531  
 4532  
 4533

**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 <sub>50</sub>	10	90 µg/L
Chronic Toxicity, aquatic organisms	9-day amphibians LC <sub>10</sub>	10	3 µg/L
Algae	72-hour algal EC <sub>10</sub>	10	7 µg/L

4534 \*The Concentration of Concern is derived from the most sensitive acute, chronic, and algal toxicity values (hazard  
 4535 values) divided by an assessment factor of 10.

4536 \*\*Assessment factors are applied to account for variation within and across taxa.

4537

4538 As described in Appendix E and Appendix G, EPA used model exposure data that was calculated  
 4539 from E-FAST, monitored data from Discharge Monitoring Reports (DMR), and aquatic COCs  
 4540 from the available hazard data to determine the risk of carbon tetrachloride to aquatic species  
 4541 using the RQ method.

4542

4543 EPA quantitatively evaluated risk to aquatic organisms from exposure to surface water and  
 4544 assessed the available monitoring data for carbon tetrachloride to adequately evaluate any  
 4545 potential environmental risk to aquatic organisms posed by carbon tetrachloride. The results of  
 4546 the review are summarized in Appendix E. All facilities were modeled in E-FAST. Facilities  
 4547 with an RQ ≥ 1 for the acute COC, or an RQ ≥ 1 and 20 days or more of exceedance for the  
 4548 chronic and algal COCs suggest the potential for environmental risks posed by carbon  
 4549 tetrachloride.

4550

4551 EPA used the acute COC (90 µg/L), chronic COC (3 µg/L), and algal COC (7 µg/L) based on  
 4552 environmental toxicity LC<sub>50</sub> from ([Brack and Rottler, 1994](#)), LC<sub>10</sub> from ([Black et al., 1982](#); [Birge  
 4553 et al., 1980](#)), and EC<sub>10</sub> from ([Brack and Rottler, 1994](#)) endpoint values, respectively, to represent

4554 the lowest bound of all carbon tetrachloride data available in the public domain and provide the  
4555 most conservative hazard values.

4556  
4557 EPA estimated carbon tetrachloride concentrations in surface water resulting from individual  
4558 industrial direct discharges as well as from indirect discharges that receive and treat wastewater  
4559 from multiple facilities and sources such as the municipal Publicly-Owned Treatment Works  
4560 (POTWs). EPA compiled five years of carbon tetrachloride NPDES permit Discharge  
4561 Monitoring Report (DMR) release data (2014 through 2018). This expanded data set provides a  
4562 range of facilities and a range of discharge amounts for this time period within the United States.  
4563 EPA used the Probabilistic Dilution Model (PDM) in E-FAST to estimate site-specific receiving  
4564 water concentrations of carbon tetrachloride at the point of discharge. Based on carbon  
4565 tetrachloride physical-chemical properties, EPA anticipates that in surface waters, carbon  
4566 tetrachloride will dissipate and volatilize. The E-FAST model, however, did not include these  
4567 processes in surface water estimates, thereby providing conservative estimates. The largest  
4568 releases of carbon tetrachloride were modeled for releases over 20 days and 250 days per year as  
4569 estimates of releases that could lead to chronic risk. The 20-day time frame was derived from  
4570 partial life cycle tests (e.g., daphnid chronic and fish early life stage tests) that typically range  
4571 from 21 to 28 days in duration and the 250-day time frame represents annual full-time industrial  
4572 operations. The surface water concentrations are summarized in Table 4-2 below.

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4574

4575

**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 <sup>a</sup> 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 <sup>b</sup> 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	<b>3.4E+00</b>	<b>1.5E+00</b>
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	<b>6.4E+00</b>	0.02	3.6	2	<b>1.2E+00</b>	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 <sup>c</sup>										
OH0007269	Dover Chemical Corp	1.8	1.3E+2	0	<b>1.4E+00<sup>d</sup></b>	<b>1.8E+01</b>	0.14	10	15	<b>3.3E+00</b>	<b>1.4E+00</b>
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

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NPDES	Facility Name	Amount Discharged for 20 days (kg/day)	20 Day Stream Conc. (µg/L)	Days Acute COC <sup>a</sup> 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 <sup>b</sup> 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	<b>7.0E+00</b>	0.02	3.9	2	<b>1.3E+00</b>	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	<b>10.0E+00</b>	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

4576 <sup>a</sup>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.

4577 <sup>b</sup>Chronic COC = 3 µg/L

4578 <sup>c</sup>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.

4580 <sup>d</sup>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

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4581  
4582 To characterize potential risk from exposures to carbon tetrachloride, EPA calculated RQs based  
4583 on modeled data from E-FAST for sites that had surface water discharges according to carbon  
4584 tetrachloride DMR data (Appendix E).

4585  
4586 All facilities assessed in this risk evaluation were modeled in E-FAST. The RQs and days of  
4587 exceedance that indicate risk for aquatic organisms (facilities with an  $RQ \geq 1$  for the acute COC,  
4588 or an  $RQ \geq 1$  and 20 days or more of exceedance for the chronic and algal COCs) for all facilities  
4589 analyzed in this risk evaluation are presented in Table 4-2.

4590  
4591 Using conservative scenarios, EPA concluded that the surface water concentrations did not  
4592 exceed the acute COC (i.e., acute RQs  $< 1$ ) for aquatic species for all sites except one site at  
4593 Dover Chemical Corp (i.e., worst-case scenario;  $RQ = 1.4$ ), as summarized in Table 4-2. EPA  
4594 determined there is not an acute aquatic concern for carbon tetrachloride after further review of  
4595 the Dover Chemical Corp site (see Section 2).

4596  
4597 The predicted exposure concentrations in surface water of carbon tetrachloride (from  $4.9E-05$   
4598  $\mu\text{g/L}$  to  $1.3E+02$   $\mu\text{g/L}$  for acute exposures and  $4.1E-06$   $\mu\text{g/L}$  to  $1.0E+1$   $\mu\text{g/L}$  for chronic  
4599 exposures; see 7Appendix E) were based on conservative assumptions, including 0% removal of  
4600 carbon tetrachloride by the waste water treatment facility. As explained in section 2.1, the EPI  
4601 Suite™ STP module estimates that about 90% of carbon tetrachloride in wastewater will be  
4602 removed by volatilization and 2% by adsorption. Also due to its physical-chemical properties,  
4603 carbon tetrachloride is not anticipated to bioaccumulate in fish (BCF 30- 40) thus there is no  
4604 bioconcentration or bioaccumulation concern. Although the chronic COC was exceeded by four  
4605 facilities ranging from 1.2 to 3.4 (i.e., worst-case scenario;  $RQ = 3.4$ ) and the algae COC was  
4606 exceeded by four facilities ranging from 6.4 to 18 based on the 20-day stream concentration and  
4607 by two facilities ranging from 1.4 to 1.5 based on the 250-day stream concentration, these carbon  
4608 tetrachloride releases are not continuously released over time (i.e., chronic exposure). Frequency  
4609 and duration of exposure also affects potential for adverse effects in aquatic organisms,  
4610 especially for chronic exposures. Therefore, the number of days that a COC was exceeded was  
4611 also calculated using E-FAST. The days of exceedance modeled in E-FAST are not necessarily  
4612 consecutive and could occur sporadically throughout the year. For carbon tetrachloride,  
4613 continuous aquatic exposures are more likely for the longer exposure scenarios (i.e., 100-365  
4614 days/yr of exceedance of a COC), and more of an interval or pulse exposure for shorter exposure  
4615 scenarios (i.e., 1-99 days/yr of exceedances of a COC). Due to the volatile properties of carbon  
4616 tetrachloride, it is more likely that a chronic exposure duration will occur when there are long-  
4617 term consecutive days of release versus an interval or pulse exposure which would more likely  
4618 result in an acute exposure duration. For all the sites analyzed in this risk evaluation of carbon  
4619 tetrachloride, all of the release sites had  $< 20$  days of exceedance of the chronic COC.  
4620 Consequently, EPA determined there is not an acute, chronic, algal concern of carbon  
4621 tetrachloride from the conditions of use for aquatic organisms.

#### 4.1.3 Risk Estimation for Sediment

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4622  
4623 EPA did not quantitatively estimate sediment-bound carbon tetrachloride exposure to sediment-  
4624 dwelling aquatic organisms. On-topic hazard studies for sediment exposures are not available in  
4625 the scientific literature (and would not be expected due to the physical, chemical, and fate



4626 properties of the chemical). Carbon tetrachloride is not expected to partition to or be retained in  
 4627 sediment and is expected to remain in aqueous phase due to its water solubility (793 mg/L) and  
 4628 low partitioning to organic matter ( $\log K_{OC} = 0.79 - 1.93$  (aquifer sediments) and 1.67 (marine  
 4629 and estuary sediments)) (see section 2.1). According to this reasonably available information,  
 4630 carbon tetrachloride is likely to be in pore water and not adsorbed to the sediment organic matter  
 4631 because the chemical has low partitioning to organic matter. Thus, qualitatively, sediment-bound  
 4632 carbon tetrachloride exposure concentrations are expected to be low. Consequently, EPA  
 4633 determined there is not an acute or chronic sediment-bound concern of carbon tetrachloride from  
 4634 the COUs and did not further analyze exposure pathways to ecological sediment-dwelling  
 4635 species in the risk evaluation.

#### 4.1.4 Risk Estimation for Terrestrial

4636 During problem formulation, EPA made refinements to the conceptual models resulting in the  
 4637 elimination of the terrestrial exposure pathway. As explained in section 2.5.3.2 of the problem  
 4638 formulation (U.S. EPA, 2018d), exposure to terrestrial organisms was removed from the scope of  
 4639 the evaluation. This exposure pathway is under programs of other environmental statutes,  
 4641 administered by EPA, which adequately assess and effectively manage exposures and for which  
 4642 long-standing regulatory and analytical processes already exist.

## 4.2 Human Health Risk

### 4.2.1 Risk Estimation Approach

4644 Development of the carbon tetrachloride hazard and dose-response assessment used for the  
 4645 selection of PODs for non-cancer and cancer endpoints and the benchmark dose analyses used in  
 4646 the risk characterization are found in section 3.2.5.2.

4648 The use scenarios, populations of interest and toxicological endpoints that were selected for  
 4649 determining potential risks from acute and chronic exposures are presented in Table 4-3, Table  
 4650 4-4, Table 4-5 and Table 4-6.

4651 **Table 4-3. Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing**  
 4652 **Occupational Risks Following Acute Inhalation Exposures to Carbon Tetrachloride**

Populations and Toxicological Approach	Occupational Use Scenarios of Carbon Tetrachloride
<b>Population of Interest and Exposure Scenario:</b>	<p><i>Occupational Users:</i> Adult worker (&gt;16 years old) exposed to carbon tetrachloride for a single 8-hr exposure.</p> <p><i>Occupational Non-users:</i> Adult (&gt;16 years old) exposed to carbon tetrachloride indirectly by being in the same work area of building.</p>
<b>Health Effects of Concern, Concentration and Time Duration</b>	<p><u>Non-Cancer Health Effects:</u> CNS  <b>1. Non-Cancer Hazard values or Point of Departures (PODs):</b> 58 ppm-8 hr (or 360 mg/m<sup>3</sup> – 8 hr) for temporary disabling CNS effects;</p> <p><u>Cancer Health Effects:</u> 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.</p>

Populations and Toxicological Approach	Occupational Use Scenarios of Carbon Tetrachloride
<b>Uncertainty Factors (UF) used in Non-Cancer Margin of Exposure (MOE) calculations</b>	UF <sub>H</sub> = 10 (based on human data and susceptibility from alcohol consumption) Total UF=Benchmark MOE= 10
<b>Notes:</b> Adult workers (>16 years old) include both healthy female and male workers. UF <sub>H</sub> =intraspecies UF	

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4657

**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
<b>Population of Interest and Exposure Scenario:</b>	<i>Occupational Users:</i> Adult worker (>16 years old) exposed to carbon tetrachloride for the entire 8-hr workday for 250 days per year for 40 working years. <i>Occupational Non-users:</i> Adult worker (>16 years old) repeatedly exposed to indirect carbon tetrachloride exposures by being in the same work area of building.
<b>Health Effects of Concern, Concentration and Time Duration</b>	Non-Cancer <b>1.</b> Non-cancer health effects: Fatty changes in the liver <b>2.</b> Non-Cancer Hazard values or Point of Departure (POD): BMCL <sub>10</sub> [HEC]: 14.3 mg/m <sup>3</sup> for continuous exposures, which is equivalent to 31.1 mg/m <sup>3</sup> for 8 hrs, EPA IRIS Assessment ( <a href="#">U.S. EPA, 2010</a> ) Cancer <b>1.</b> Cancer health effects: carbon tetrachloride is classified as "likely to be carcinogenic to humans" <b>2.</b> Cancer Inhalation Unit Risk (IUR): $6 \times 10^{-6}$ per $\mu\text{g}/\text{m}^3$ for lifetime continuous exposure
<b>Uncertainty Factors (UF) Used in Non-Cancer Margin of Exposure (MOE) calculations</b>	(UF <sub>H</sub> = 10) × (UF <sub>A</sub> = 3) = 30 Total UF=Benchmark MOE=30
<b>Cancer Benchmark</b>	1 in 10 <sup>4</sup> cancer risk for worker populations
<b>Notes:</b> Adult workers (>16 years old) include both healthy female and male workers. UF <sub>H</sub> =intraspecies UF; UF <sub>A</sub> =interspecies UF	

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**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
<b>Population of Interest and Exposure Scenario:</b>	<i>Occupational Users:</i> Adult worker (>16 years old) exposed to carbon tetrachloride for a single 8-hr exposure.
<b>Health Effects of Concern, Concentration and Time Duration</b>	<u>Non-Cancer Health Effects:</u> CNS <b>1. Non-Cancer Hazard values or Point of Departures (PODs):</b> 2,750 mg/kg-d for liver effects  <u>Cancer Health Effects:</u> 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.
<b>Uncertainty Factors (UF) used in Non-Cancer Margin of Exposure (MOE) calculations</b>	$(UF_H = 10) \times (UF_A = 10) = 100$ Total UF=Benchmark MOE=100
<b>Notes:</b> Adult workers (>16 years old) include both healthy female and male workers. $UF_H$ =intraspecies UF; $UF_A$ =interspecies UF	

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**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
<b>Population of Interest and Exposure Scenario:</b>	<i>Occupational Users:</i> Adult worker (>16 years old) exposed to carbon tetrachloride for the entire 8-hr workday for 250 days per year for 40 working years.
<b>Health Effects of Concern, Concentration and Time Duration</b>	<u>Non-Cancer</u> <b>1.</b> Non-cancer health effects: Fatty changes in the liver <b>2.</b> Non-Cancer POD: 245 mg/kg-d based on route to route extrapolation from $BMCL_{10[HEC]}$ : 14.3 mg/m <sup>3</sup> for continuous exposures.  <u>Cancer</u> <b>1.</b> Cancer health effects: carbon tetrachloride is classified as "likely to be carcinogenic to humans" <b>2.</b> Cancer Slope factor derived from Inhalation Unit Risk (IUR) of $6 \times 10^{-6}$ per $\mu\text{g}/\text{m}^3$ for lifetime continuous exposure
<b>Uncertainty Factors (UF) Used in Non-Cancer Margin of Exposure (MOE) calculations</b>	$(UF_H = 10) \times (UF_A = 3) = 30$ Total UF=Benchmark MOE=30
<b>Cancer Benchmark</b>	1 in 10 <sup>4</sup> cancer risk for worker populations
<b>Notes:</b> 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	

4674  
 4675 EPA used a Margin of Exposure (MOE) approach to identify potential non-cancer risks. The  
 4676 MOE is the ratio of the non-cancer POD divided by a human exposure dose, which is then  
 4677 compared to a benchmark MOE. If the calculated MOE is less than the benchmark MOE, this  
 4678 indicates potential risk to human health, whereas if the calculated MOE is equal to or greater  
 4679 than the benchmark MOE, it suggests that the risks are negligible.

4680  
 4681 Acute or chronic MOEs ( $MOE_{acute}$  or  $MOE_{chronic}$ ) were used in this assessment to estimate non-  
 4682 cancer risks using Equation 4-1.

4683  
 4684 **Equation 4-1. Equation to Calculate Non-Cancer Risks Following Acute or Chronic**  
 4685 **Exposures Using Margin of Exposures**

4686  
 4687 
$$MOE_{acute\ or\ chronic} = \frac{\text{Non-cancer Hazard value (POD)}}{\text{Human Exposure}}$$

4688  
 4689 Where:

<b>MOE</b>	= <b>Margin of exposure (unitless)</b>
<b>Hazard value (POD)</b>	= NOAEC or HEC (mg/m <sup>3</sup> )
<b>Human Exposure</b>	= Exposure estimate (in mg/m <sup>3</sup> ) from occupational exposure assessment

4690  
 4691 The Acute Exposure Concentration (AEC) was used to estimate acute/short-term inhalation risks,  
 4692 whereas the Average Daily Concentration/Dose (ADC)/D) was used to estimate chronic non-  
 4693 cancer inhalation/dermal.

4694  
 4695 EPA used MOEs<sup>19</sup> to estimate acute and chronic risks for non-cancer based on the following:

- 4696  
 4697 **1.** the HECs/HEDs identified for the highest quality studies within each health effects domain;  
 4698 **2.** the endpoint/study-specific UFs applied to the HECs/HEDs per the review of the EPA  
 4699 Reference Dose and Reference Concentration Processes ([U.S. EPA, 2002](#)); and  
 4700 **3.** the exposure estimates calculated for carbon tetrachloride conditions under the conditions  
 4701 of use (see section 2.4).

4702  
 4703 MOEs allow for the presentation of a range of risk estimates. The occupational exposure  
 4704 scenarios considered both acute and chronic exposures. Different adverse endpoints were used  
 4705 based on the expected exposure durations. For occupational exposure calculations, the 8 hr and  
 4706 12 hr TWAs was used to calculate MOEs for risk estimates for acute and chronic exposures. The  
 4707 occupational inhalation exposure scenarios considered both acute and chronic exposures. For  
 4708 non-cancer effects, risks for transient CNS effects were evaluated for acute (short-term)  
 4709 exposures, whereas risks for toxicity to the liver was evaluated for repeated (chronic) exposures  
 4710 to carbon tetrachloride because of their human relevance and relevance to occupational  
 4711 exposures as discussed in section 3.2.3.

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<sup>19</sup> 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.

4713 The total UF for each non-cancer POD was the benchmark MOE used to interpret the MOE risk  
 4714 estimates for each use scenario. The MOE estimate was interpreted as human health risk if the  
 4715 MOE estimate was less than the benchmark MOE (i.e., the total UF). On the other hand, the  
 4716 MOE estimate indicated negligible concerns for adverse human health effects if the MOE  
 4717 estimate exceeded the benchmark MOE. Typically, the larger the MOE, the more unlikely it is  
 4718 that a non-cancer adverse effect would occur.

4719  
 4720 To determine the level of personal protection needed by workers to reduce the high-end exposures  
 4721 to below the level of concern for non-cancer risks, EPA evaluated the impact of respirator use.  
 4722 Typical APF values of 10, 25 and 50 were compared to the calculated MOE and the benchmark  
 4723 MOE to determine the level of APF required to reduce exposure so that risk is below the level of  
 4724 concern for noncancer risks (i.e., calculated MOE  $\geq$  benchmark MOE).

4725  
 4726 EPA estimated potential cancer risks from chronic exposures to carbon tetrachloride using  
 4727 probabilistic approaches, which consisted of calculating the added cancer risk. Each of these  
 4728 approaches is discussed below.

4729  
 4730 Added cancer risks for repeated exposures to carbon tetrachloride were estimated using Equation  
 4731 4-2. Estimates of added cancer risks should be interpreted as the incremental probability of an  
 4732 individual developing cancer over a lifetime as a result of exposure to the potential carcinogen  
 4733 (i.e., incremental or added individual lifetime cancer risk).

4734  
 4735 **Equation 4-2. Equation to Calculate Cancer Risks**

4736  
 4737 
$$\text{Inhalation Cancer Risk} = \text{Human Exposure} \times \text{IUR}$$
  
 4738 *or*  
 4739 
$$\text{Dermal Cancer Risk} = \text{Human Exposure} \times \text{CSF}$$

4740  
 4741 Where:  
 4742

<b>Risk</b>	= Added cancer risk (unitless)
<b>Human exposure</b>	= Occupational exposure estimate (LADC in ppm)
<b>IUR</b>	= Inhalation unit risk ( $6 \times 10^{-6}$ per $\mu\text{g}/\text{m}^3$ for continuous exposures)
<b>CSF</b>	= Inhalation unit risk adjusted for 0.8% dermal absorption

4743  
 4744 For carbon tetrachloride, EPA, consistent with OSHA (878 F.2d 389, 392 (D.C. Cir. 1989) and  
 4745 2017 NIOSH guidance *NIOSH [2017] Current intelligence bulletin 68: NIOSH chemical*  
 4746 *carcinogen policy*, available at <https://www.cdc.gov/niosh/docs/2017-100/pdf/2017-100.pdf>.,  
 4747 used  $1 \times 10^{-4}$  as the benchmark for the purposes of this risk determination for individuals in  
 4748 industrial/commercial work environments subject to Occupational Safety and Health Act  
 4749 (OSHA) requirements. It is important to note that  $1 \times 10^{-4}$  is not a bright line and EPA has  
 4750 discretion to find unreasonable risks based on other benchmarks as appropriate based on  
 4751 analysis. It is important to note that exposure related considerations (duration, magnitude,  
 4752 population exposed) can affect EPA's estimates of the added cancer risk.

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**4.2.2 Risk Estimation for Non-Cancer Effects Following Acute Inhalation Exposures**

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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 (95<sup>th</sup> percentile) and 50<sup>th</sup> 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.

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4763 **Table 4-7. Risk Estimates for Acute Inhalation Exposures based on POD of 360 mg/m<sup>3</sup> – 8hrs (= 310 mg/m<sup>3</sup>-12 hrs); and**  
 4764 **Benchmark MOE of 10**

Condition of Use	EXPOSURE		Calculated MOE without Respirator (Worker and ONU)		Calculated MOE with Respirator (Worker)*					
	ADC (mg/m <sup>3</sup> )				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.									

4765 \* 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  
 4766 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  
 4767 concentrations.

4768 **4.2.3 Risk Estimation for Non-Cancer Effects Following Chronic Inhalation**  
4769 **Exposures**

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4770 Chronic non-cancer risk estimates for inhalation exposures to carbon tetrachloride were derived  
4771 for occupational scenarios using estimated inhalation average daily concentrations (ADCs). The  
4772 risk estimates for chronic non-cancer health effects are based on the BMCL<sub>10</sub>[HEC] for liver  
4773 effects: 14.3 mg/m<sup>3</sup> for continuous exposures, which is equivalent to 31.1 mg/m<sup>3</sup> for 8 hrs of  
4774 exposure and 26.4 mg/m<sup>3</sup> for 12 hrs.<sup>20</sup> Non-cancer risk estimates for chronic exposures for each  
4775 occupational use scenario are presented in Table 4-8 below.

4776  
4777 The calculated MOEs are greater than the benchmark MOEs of 30 for the high-end and central  
4778 tendency exposures for most conditions of use without respirator use, except for the high-end  
4779 exposures for manufacturing and processing as reactant/intermediate (8 hr and 12 hr TWA)  
4780 COUs. The high-end exposures with MOEs below the benchmark MOE have exposure  
4781 reductions during use of respirator with APF 10 that result in MOEs greater than the benchmark  
4782 MOE.

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<sup>20</sup> Time adjustment from continuous exposure to 5 days per week and to 8 or 12 hrs/day



4783 **Table 4-8. Risk Estimates for Chronic Inhalation Exposures based on POD of 31.1mg/m<sup>3</sup>- 8 hrs (= 26.4 mg/m<sup>3</sup>-12 hrs) and**  
 4784 **Benchmark MOE of 30**

Condition of Use	EXPOSURE		Calculated MOE without Respirator (Worker and ONU)		Calculated MOE with Respirator (Worker)*					
	ADC (mg/m <sup>3</sup> )				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	<b>8</b>	41	80	410	200	1,025	400	2,050
Manufacturing - 12-hr TWA	4.8	0.50	<b>6</b>	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	<b>8</b>	41	80	410	200	1,025	400	2,050
Processing as Reactant/Intermediate – 12-hr TWA	4.8	0.50	<b>6</b>	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.									

4785 **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.  
 4786 OSHA’s occupational safety and health standards for carbon tetrachloride include respiratory protection recommendations starting with APF =10 (any supplied-air respirator) up to  
 4787 APF =10,000 for emergency or planned entry into unknown concentrations.

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

4788  
4789  
4790 Results from dermal studies with guinea pigs ([Kronevi et al., 1979](#); [Wahlberg and Boman, 1979](#))  
4791 were used in conjunction with dermal absorption information for carbon tetrachloride to derive a  
4792 POD for acute dermal exposures of 2,750 mg/kg (see section 3.2.5.2.3). Table 4-9 outlines the  
4793 non-cancer dermal risk estimates to workers with and without the use of gloves for all conditions  
4794 of use.  
4795  
4796

**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	<b>Liver</b> Liver toxicity for non to light alcohol users - Histopathological changes in the liver (guinea pigs) ( <a href="#">Kronevi et al., 1979</a> ; <a href="#">Wahlberg and Boman, 1979</a> )	2750	High End	1.1	100	2,500	12,500
Import and repackaging							
Additive							
Processing as a Reactant							
Processing Agent/Aid			Central Tendency	0.37	100	7,432	37,160
Recycling							
Waste disposal							
Laboratory Chemicals							
Specialty Uses – Department of Defense Data							
Reactive Ion Etching	Negligible - Highly controlled work areas with small quantities applied						

**4.2.5 Risk Estimation for Non-Cancer Effects Following Chronic Dermal Exposures**

4797  
4798  
4799 The HED<sub>Dermal</sub> of 245 mg/kg-d for non-occluded exposures was extrapolated from the chronic  
4800 inhalation BMCL<sub>10[HEC]</sub>: 14.3 mg/m<sup>3</sup> for continuous exposures, which was derived in the EPA  
4801 IRIS assessment ([U.S. EPA, 2010](#)) using data from Nagano et al., ([2007a](#)).  
4802

4803 Table 4-10 outlines the non-cancer dermal risk estimates to workers for endpoints with and  
4804 without the use of gloves.  
4805

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	<b>Liver</b> Liver toxicity for non to light alcohol users - Histopathological changes in the liver (guinea pigs) ( <a href="#">Kronevi et al., 1979</a> ; <a href="#">Wahlberg and Boman, 1979</a> )	245	High End	1.1	30	223	1,115
Import and repackaging							
Additive							
Processing as a Reactant							
Processing Agent/Aid							
Recycling			Central Tendency	0.37	30	662	3,310
Waste disposal							
Laboratory Chemicals							
Specialty Uses – Department of Defense Data							
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.

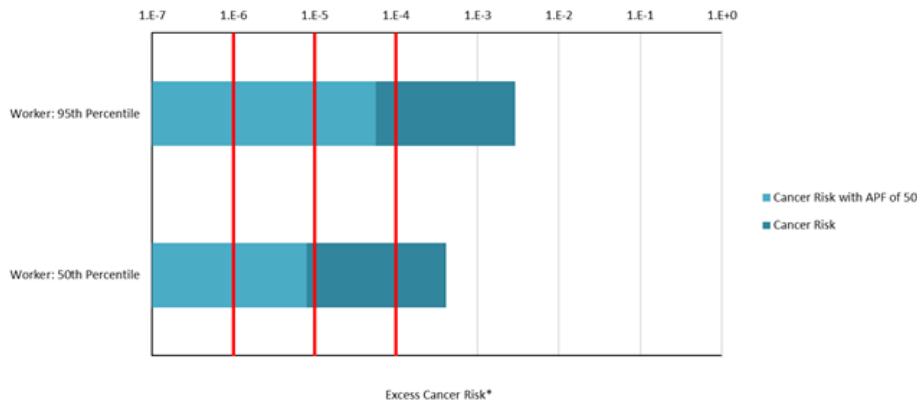
4816  
 4817 In general terms, the exposure frequency (i.e., the amount of days per year for workers or  
 4818 occupational non-users exposed to carbon tetrachloride) was considered to be 250 days per year  
 4819 and the occupational exposure duration was 40 years over a 70-year lifespan. It is recognized that  
 4820 these exposure assumptions are likely yielding conservative cancer risk estimates, but EPA does  
 4821 not have additional information for further refinement.

4822 **Table 4-11. Risk Estimates for Cancer Effects from Chronic Inhalation Exposures for Workers Based on IUR of  $6 \times 10^{-6}$  per**  
 4823  **$\mu\text{g}/\text{m}^3$  and Benchmark Risk = 1 in  $10^4$**

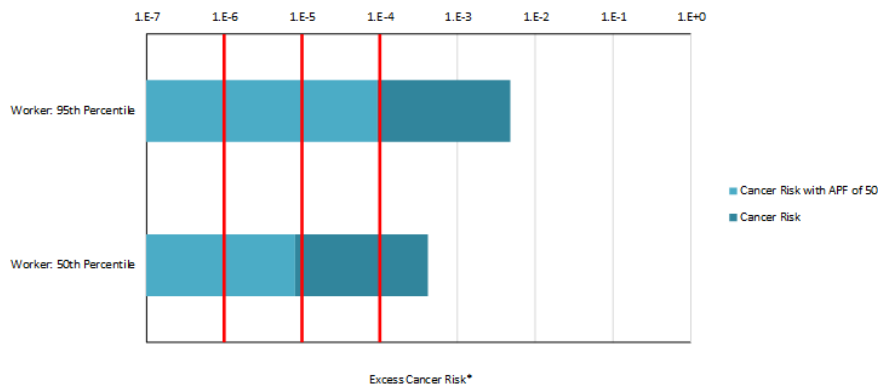
Condition of Use	Chronic, Cancer Exposures		Calculated Cancer Risk without Respirator (Worker and ONU)		Calculated Cancer Risk with Respirator (Worker)*					
	LADC ( $\mu\text{g}/\text{m}^3$ )				APF =10		APF =25		APF =50	
	High-End (Worker)	Central Tendency (Worker and ONU)	High-End	Central Tendency	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.									

4824 **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  
 4825 Tendency LADC ( $\mu\text{g}/\text{m}^3$ )” or “High-end LADC ( $\mu\text{g}/\text{m}^3$ )”  $\times$  IUR (i.e.,  $6 \times 10^{-6}$  per  $\mu\text{g}/\text{m}^3$ )  
 4826 \*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  
 4827 the MOE without a respirator by the respirator APF. OSHA’s occupational safety and health standards for carbon tetrachloride include respiratory protection recommendations  
 4828 starting with APF = 10 (any supplied-air respirator) up to APF = 10,000 for emergency or planned entry into unknown concentrations.  
 4829

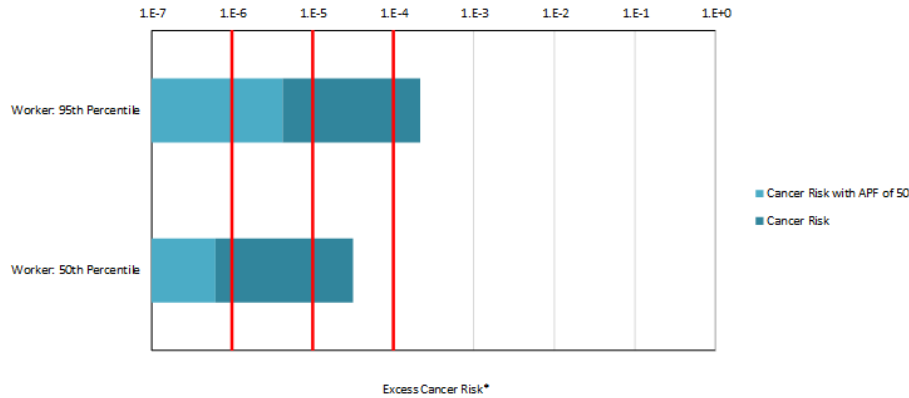
4830 Figure 4-1 through Figure 4-4 present the incremental individual lifetime cancer risks for the 95<sup>th</sup>  
4831 percentile/high-end and 50<sup>th</sup> percentile/central tendency exposures to carbon tetrachloride  
4832 occurring in occupational exposure scenarios. The figures consist of graphical representations of  
4833 the cancer risks presented in Table 4-11 by COU.  
4834



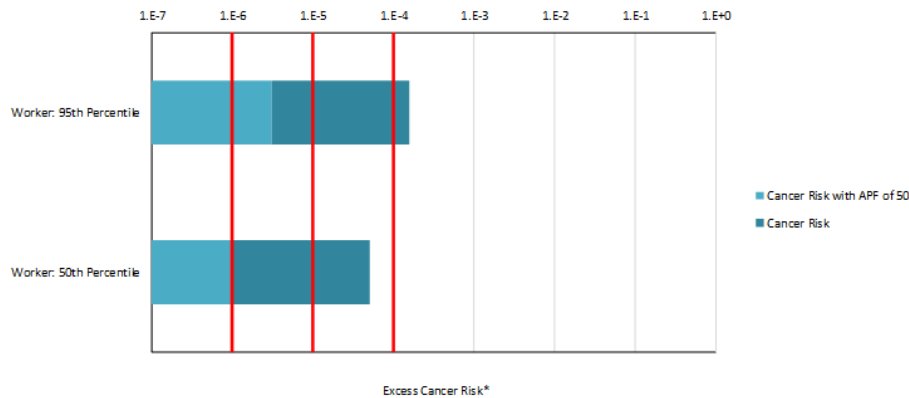
4835 **Figure 4-1. Cancer Risk Estimates for Occupational Use of Carbon Tetrachloride in**  
4836 **Manufacturing and Processing as Reactant/Intermediate Based on Monitoring or**  
4837 **Surrogate Monitoring Data 8 hr TWA**  
4838  
4839  
4840



4841 **Figure 4-2. Cancer Risk Estimates for Occupational Use of Carbon Tetrachloride in**  
4842 **Manufacturing and Processing as Reactant/Intermediate Based on Monitoring or**  
4843 **Surrogate Monitoring Data 12 hr TWA**  
4844  
4845  
4846



4847  
4848 **Figure 4-3. Cancer Risk Estimates for Occupational Use of Carbon Tetrachloride in**  
4849 **Import, Processing Agent, Additive and Disposal/Recycling Based on Modeling**  
4850  
4851  
4852



4853  
4854 **Figure 4-4. Cancer Risk Estimates for Occupational Use of Carbon Tetrachloride in**  
4855 **Specialty Uses-DoD Based on Monitoring Data**

4856 **4.2.7 Risk Estimations for Cancer Effects Following Chronic Dermal Exposures**

4857 EPA estimated the added cancer risks associated with chronic dermal exposures to carbon  
4858 tetrachloride in the workplace. The added cancer risk estimation for carbon tetrachloride was  
4859 calculated by multiplying the occupational scenario-specific dermal exposure estimates for  
4860 workers by the derived  $CSF_{Dermal}$  to estimate the added cancer risk. The  $CSF_{Dermal}$  was  
4861 extrapolated from the EPA's inhalation unit risk (IUR) of  $6 \times 10^{-6}$  per  $\mu\text{g}/\text{m}^3$  for continuous  
4862 lifetime exposure resulting in a derived  $CSF_{Dermal}$  of  $8 \times 10^{-4}$  per  $\text{mg}/\text{kg}$  for non-occluded  
4863 exposures (see section 3.2.5.2.4). Table 4-12 outlines the non-cancer dermal risk estimates to  
4864 workers for endpoints with and without gloves.

4865  
4866  
4867  
4868

4869 **Table 4-12. Risk Estimates for Cancer Effects from Chronic Dermal Exposures for**  
 4870 **Workers; Benchmark Risk = 1 in 10<sup>4</sup>**

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			
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		

4871 **4.2.8 Summary of Non-cancer and Cancer Estimates for Inhalation and Dermal**  
 4872 **Exposures**

4873 Table 4-13 presents a summary of the MOEs and estimated cancer risks for the inhalation  
 4874 exposures from the conditions of use for carbon tetrachloride. The high-end chronic inhalation  
 4875 exposures for manufacturing and processing (8hr and 12hr TWA) COUs have MOEs below the  
 4876 benchmark MOE and cancer risks greater than the benchmark cancer risk. The central tendency  
 4877 chronic inhalation exposures for the same COUs have cancer risks greater than the benchmark.  
 4878 However, all those inhalation exposures are reduced with respirator use (APF 10, 25 or 50)  
 4879 resulting in MOEs greater than benchmark MOEs and cancer risks below the benchmark cancer  
 4880 risk.

4881  
 4882 There are cancer risks above the cancer risk benchmark for the high-end exposures for the  
 4883 additive, processing agent/aid, import and repackaging, specialty uses-DoD and

4884 disposal/recycling COUs. Those high-end exposures are reduced with respirator use (APF 10)  
4885 resulting in cancer risks below the benchmark.

4886  
4887 The calculated MOEs for all the occupational dermal exposures without gloves are greater than  
4888 the benchmark MOEs. The calculated cancer risks are lower than the benchmark cancer risk for  
4889 the central tendency dermal exposures from all the COUs for carbon tetrachloride. The  
4890 calculated cancer risks for the high-end dermal exposures for all COUs is higher than the  
4891 benchmark cancer risk without the use of gloves. Those dermal high-end exposures are reduced  
4892 with the use of gloves (PF =5) resulting in cancer risks below the benchmark.

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4893

Table 4-13. Summary of Estimated Non-cancer and Cancer Risks from Inhalation and Dermal Exposures<sup>1</sup>

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 <sup>4</sup> )	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 <sup>4</sup>
Manufacture	Domestic Manufacture	Domestic Manufacture	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)
					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)	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)
Processing	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)

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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 <sup>4</sup> )	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 <sup>4</sup>
			ONU (central tendency inhalation exposures)	Dermal	High -End	65	6	5E-03	N/A	60 (APF = 10)	1E-04 (APF =50)
					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)
				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

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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 <sup>4</sup> )	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 <sup>4</sup>			
			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)	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)	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.									

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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 <sup>4</sup> )	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 <sup>4</sup>
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	<b>2E-04</b>	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	<b>3E-04</b>	N/A	N/A	6E-05 (PF =5)

4894  
4895  
4896  
4897  
4898  
4899

<sup>1</sup>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

4900  
4901 TSCA requires that the determination of whether a chemical substance presents an unreasonable  
4902 risk include consideration of unreasonable risk to “a potentially exposed or susceptible  
4903 subpopulation identified as relevant to the risk evaluation” by EPA. TSCA § 3(12) states that  
4904 “the term ‘*potentially exposed or susceptible subpopulation*’ means a group of individuals within  
4905 the general population identified by the Administrator who, due to either greater susceptibility or  
4906 greater exposure, may be at greater risk than the general population of adverse health effects  
4907 from exposure to a chemical substance or mixture, such as infants, children, pregnant women,  
4908 workers, or the elderly.”

4909  
4910 In developing the exposure assessment for carbon tetrachloride, EPA analyzed reasonably  
4911 available information to identify groups that may have greater exposure or susceptibility than the  
4912 general population to the hazard posed by carbon tetrachloride. Exposures of carbon  
4913 tetrachloride could be higher amongst workers and ONUs who use or are exposed to carbon  
4914 tetrachloride as part of typical processes.

4915  
4916 The scope of this human health assessment is limited to workers and ONUs. Thus, this section  
4917 focuses on identifying subpopulations within workers and ONUs who may have greater  
4918 susceptibility to carbon tetrachloride. Assessment of susceptible subpopulations does not include  
4919 children or non-workers/non-ONUs.

4920  
4921 Some workers and ONUs may be more biologically susceptible to the effects of carbon  
4922 tetrachloride due to age, alcohol consumption, nutritional status, pre-existing disease (e.g.,  
4923 diabetes or liver disease), exposure to other chemicals, and genetic variation (described in more  
4924 detail in section 3.2.5.4).

4925  
4926 Metabolism of carbon tetrachloride to reactive metabolites by cytochrome p450 enzymes  
4927 (particularly CYP2E1 and CYP3A) is hypothesized to be a key event in the toxicity of this  
4928 compound. Differences in the metabolism due to alcohol consumption, exposure to other  
4929 chemicals, age, nutritional status, genetic variability in CYP expression, or impaired liver  
4930 function due to liver disease can increase susceptibility to carbon tetrachloride ([U.S. EPA, 2010](#)).  
4931 For example, alcohol is known to induce CYP2E1 expression. Cases of acute toxicity from  
4932 occupational exposures indicate that heavy drinkers are more susceptible to carbon tetrachloride  
4933 and this observation has been verified in numerous animal studies. Exposure to other chemicals  
4934 that induce p450 enzymes, including isopropanol, methanol, acetone, methyl ethyl ketone,  
4935 methyl isobutyl ketone, 2-butanone, phenobarbital, methamphetamine, nicotine,  
4936 trichloroethylene, polychlorinated and polybrominated biphenyls, DDT, mirex, and chlordecone  
4937 have also been shown to potentiate carbon tetrachloride liver toxicity ([U.S. EPA, 2010](#); [ATSDR, 2005](#)).  
4938

4939  
4940 Age can influence susceptibility to carbon tetrachloride due to differences in metabolism,  
4941 antioxidant responses, and reduced kidney function in older adults. While lower CYP expression  
4942 may reduce susceptibility of older adults to carbon tetrachloride in some tissues, reduced kidney  
4943 function and increased CYP3A activity in the liver (indicated by animal studies) suggest that

4944 older populations could be at greater risk of carbon tetrachloride-associated kidney damage ([U.S.](#)  
4945 [EPA, 2010](#)).

4946  
4947 Nutrition has also been shown to influence susceptibility to carbon tetrachloride in animals. Food  
4948 restriction has been shown to increase liver toxicity of carbon tetrachloride. Diets low in  
4949 antioxidants increase lipid peroxidation and liver damage in following carbon tetrachloride  
4950 exposure (reversed with antioxidant supplementation) and zinc deficient diets increase carbon  
4951 tetrachloride-induced liver toxicity ([U.S. EPA, 2010](#)).

4952  
4953 EPA identified groups of individuals with greater inhalation exposure as workers in occupational  
4954 scenarios. EPA examined worker exposures in this risk evaluation for several occupational  
4955 scenarios (see section 2.4.1 for these exposure scenarios).

4956  
4957 To account for variation in sensitivity within human populations intraspecies UFs were applied  
4958 for non-cancer effects. The UF values selected are described in section 3.2.5.2.

## 4959 **4.4 Assumptions and Key Sources of Uncertainty**

---

4960 The characterization of assumptions, variability and uncertainty may raise or lower the  
4961 confidence of the risk estimates. This section describes the assumptions and uncertainties in the  
4962 exposure assessment, hazard/dose-response and risk characterization.

### 4963 **4.4.1 Occupational Exposure Assumptions and Uncertainties**

---

4964 EPA addressed variability in models by identifying key model parameters to apply a statistical  
4965 distribution that mathematically defines the parameter's variability. EPA defined statistical  
4966 distributions for parameters using documented statistical variations where available. Uncertainty  
4967 is "the lack of knowledge about specific variables, parameters, models, or other factors" and can  
4968 be described qualitatively or quantitatively ([U.S. EPA, 2001](#)). The following sections discuss  
4969 uncertainties in each of the assessed carbon tetrachloride use scenarios.

#### 4970 4971 *Number of Workers*

4972 There are a number of uncertainties surrounding the estimated number of workers potentially  
4973 exposed to carbon tetrachloride, as outlined below.

4974  
4975 First, BLS' OES employment data for each industry/occupation combination are only available  
4976 at the 3-, 4-, or 5-digit NAICS level, rather than the full 6-digit NAICS level. This lack of  
4977 granularity could result in an overestimate of the number of exposed workers if some 6-digit  
4978 NAICS are included in the less granular BLS estimates but are not, in reality, likely to use  
4979 carbon tetrachloride for the assessed applications. EPA addressed this issue by refining the OES  
4980 estimates using total employment data from the U.S. Census' SUSB. However, this approach  
4981 considers that the distribution of occupation types (SOC codes) in each 6-digit NAICS is equal to  
4982 the distribution of occupation types at the parent 5-digit NAICS level. If the distribution of  
4983 workers in occupations with carbon tetrachloride exposure differs from the overall distribution of  
4984 workers in each NAICS, then this approach will result in inaccuracy.

4985  
4986 Second, EPA's judgments about which industries (represented by NAICS codes) and  
4987 occupations (represented by SOC codes) are associated with the uses assessed in this report are  
4988 based on EPA's understanding of how carbon tetrachloride is used in each industry. Designations

4989 of which industries and occupations have potential exposures is nevertheless subjective, and  
4990 some industries/occupations with few exposures might erroneously be included, or some  
4991 industries/occupations with exposures might erroneously be excluded. This would result in  
4992 inaccuracy but would be unlikely to systematically either overestimate or underestimate the  
4993 count of exposed workers.  
4994

4995 ***Occupational non-users (ONUs)***

4996 EPA evaluated inhalation risks for acute and chronic exposures for ONUs. However, EPA did  
4997 not separately calculate inhalation risk estimates for ONUs and workers. There is uncertainty in  
4998 the ONU inhalation risk estimate since the data did not distinguish between worker and ONU  
4999 inhalation exposure estimates. While the difference between the exposures of ONUs and the  
5000 exposures of workers directly handling the chemical generally cannot be quantified, ONU  
5001 inhalation exposures are expected to be lower than inhalation exposures for workers directly  
5002 handling the chemical. EPA considered the ONU exposures to be equal to the central tendency  
5003 risk estimates for workers when determining ONU risk attributable to inhalation. While this is  
5004 likely health protective as it assumes ONU exposure is greater than that of 50% of the workers,  
5005 this is highly uncertain, and EPA has low confidence in these exposure estimates for ONUs.  
5006

5007 ***Analysis of Exposure Monitoring Data***

5008 This draft risk evaluation uses existing worker exposure monitoring data to assess exposure to  
5009 carbon tetrachloride during manufacturing. Some data sources may be inherently biased. For  
5010 example, bias may be present if exposure monitoring was conducted to address concerns  
5011 regarding adverse human health effects reported following exposures during use.  
5012

5013 Some scenarios have limited exposure monitoring data in literature, if any. Where there are few  
5014 data points available, it is unlikely the results will be representative of worker exposure across  
5015 the industry.  
5016

5017 In cases where there was no exposure monitoring data, EPA used monitoring data from similar  
5018 conditions of use as surrogate (i.e., monitoring data from manufacturing were used as surrogate  
5019 monitoring data for the processing COUs). While these conditions of use have similar worker  
5020 activities contributing to exposures, it is unknown whether the results will be fully representative  
5021 of worker exposure across different conditions of use.  
5022

5023 Where sufficient data were available, the 95th and 50th percentile exposure concentrations were  
5024 calculated using available data. The 95th percentile exposure concentration is intended to  
5025 represent a high-end exposure level, while the 50th percentile exposure concentration represents  
5026 typical exposure level. The underlying distribution of the data, and the representativeness of the  
5027 available data, are not known. Where discrete data was not available, EPA used reported  
5028 statistics (i.e., median, mean, 90th percentile, etc.). Since EPA could not verify these values,  
5029 there is an added level of uncertainty.  
5030

5031 EPA generally calculated ADC and LADC values assuming a high-end exposure duration of 250  
5032 days per year over 40 years and a typical exposure duration of 250 days per year over 31 years.  
5033 This assumes the workers and occupational non-users are regularly exposed during their entire  
5034 working lifetime, which likely results in an overestimate. Individuals may change jobs during the

5035 course of their career such that they are no longer exposed to carbon tetrachloride, resulting in  
5036 actual ADC and LADC values that are lower than the estimates presented.

5037

### 5038 ***Modeling Dermal Exposures***

5039 To assess dermal exposure, EPA used a modified equation from the *EPA/OPPT 2-Hand Dermal*  
5040 *Exposure to Liquids* Model to calculate the dermal absorbed dose for both non-occluded and  
5041 occluded scenarios. The modified equation incorporates a “fraction absorbed (fabs)” parameter  
5042 to account for the evaporation of volatile chemicals and a “protection factor (PF)” to account for  
5043 glove use. PF values will vary depending on the type of glove used and the presence of employee  
5044 training program.

5045

5046 The model considers an infinite dose scenario and does not account for the transient exposure  
5047 and exposure duration effect, which likely overestimates exposures. The model assumes one  
5048 exposure event per day, which likely underestimates exposure as workers often come into repeat  
5049 contact with the chemical throughout their work day. Surface areas of skin exposure are based on  
5050 skin surface area of hands from EPA’s Exposure Factors Handbook, but actual surface areas with  
5051 liquid contact are unknown and uncertain for all occupational exposure scenarios. For many  
5052 scenarios, the assumption of contact over the full area of two hands likely overestimates  
5053 exposures. Weight fractions are usually reported to CDR and shown in other literature sources as  
5054 ranges, and EPA assessed only upper ends of ranges. While the glove protection factors are  
5055 based on the ECETOC TRA model as described in section 2.4.1.5 they are “what-if”  
5056 assumptions and are highly uncertain. EPA does not know the actual frequency, type, and  
5057 effectiveness of glove use in specific workplaces of the occupational exposure scenarios. Except  
5058 where specified above, it is unknown whether most of these uncertainties overestimate or  
5059 underestimate exposures. The representativeness of the modeling results toward the true  
5060 distribution of dermal doses for the occupational scenarios is uncertain.

5061

5062 More details on the dermal methodology are discussed in the supplemental document *Risk*  
5063 *Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and Occupational*  
5064 *Exposure Assessment* ([U.S. EPA, 2019b](#)).

### 5065 **4.4.2 Environmental Exposure Assumptions and Uncertainties**

5066 As described in Appendix E and section 2.3.1, a screening-level aquatic exposure assessment  
5067 was undertaken to evaluate ecological exposures in the U.S. that may be associated with releases  
5068 of carbon tetrachloride to surface waters. This assessment was intended as a first-tier, or  
5069 screening-level, evaluation. The top ten (by annual release/discharge amount) facilities as  
5070 reported in EPA’s Discharge Monitoring Reports (DMRs) were selected for use in exposure  
5071 modeling for each of five years from 2014 through 2018. Thus, not all reporting sites were  
5072 modeled, and the selected sites were not cross-walked with the conditions of use included in the  
5073 occupational engineering assessment.

5074

5075 For the purposes of this assessment, the number of release days were either 20 days or 250 days.  
5076 The reported annual release amounts from DMR were divided by these numbers of release days  
5077 to obtain the necessary kg/site-day release input. These assumptions are not based on associated  
5078 industry-specific data or standards, but on the assumptions to capture conservative environmental  
5079 concentrations for acute and chronic release scenarios. The 20 days of release is the assumption  
5080 for a chronic scenario, appropriate for comparison against a chronic COC, whereas 250 days of



5081 release may be more typical for facilities that operate and release effluent frequently, such as  
5082 POTWs or treatment plants.

5083  
5084 Uncertainties in the modeled surface water concentration estimates include the variable amount  
5085 of releases of carbon tetrachloride captured in the DMR database and regulated by the Office of  
5086 Water's NPDES permitting process.

5087  
5088 Lastly, some facilities releasing carbon tetrachloride, such as POTWs, may not be associated  
5089 with a TSCA condition of use covered in this risk evaluation. Use of facility data to estimate  
5090 environmental exposures is constrained by a number of other uncertainties including: the  
5091 heterogeneity of processes and releases among facilities grouped within a given sector;  
5092 assumptions made regarding sector definitions used to select facilities covered under the scope;  
5093 and fluctuations in the level of production and associated environmental releases incurred as a  
5094 result of changes in standard operating procedures. Nevertheless, it is important to note that the  
5095 DMR dataset is based on the most comprehensive, best reasonably available data at a nationwide  
5096 scale. DMR is based on representative pollutant monitoring data at facility outfalls and  
5097 corresponding wastewater discharges. Any exceedances of permit levels are referred to EPA's  
5098 Enforcement and Compliance.

#### 5099 **4.4.3 Environmental Hazard Assumptions and Uncertainties**

---

5100 While the EPA has determined that sufficient data are available to characterize the overall  
5101 environmental hazards of carbon tetrachloride, uncertainties exist. To begin, while reasonable  
5102 attempts were made, the Agency was not able to obtain all of the full scientific reports listed in  
5103 ECHA, SIAP, and NICNAS on carbon tetrachloride due to challenges that include ownership of  
5104 the studies by foreign sources. EPA did not use its information collection authority to obtain the  
5105 full scientific reports or translate foreign language studies listed in ECHA, SIAP, and NICNAS  
5106 because the robust summary endpoints from these sources align with the dataset EPA used to  
5107 assess the hazards of carbon tetrachloride. Additionally, EPA has successfully obtained the full  
5108 study reports for the most conservative endpoint values in the scientific literature that are driving  
5109 the acute and chronic concentrations of concern.

5110  
5111 Furthermore, EPA used sub-chronic data, measuring a developmental effect in embryo and  
5112 larvae, to calculate the amphibian chronic COC, which introduces some uncertainty about  
5113 whether EPA is overestimating or underestimating chronic risk. Assessment factors (AFs) were  
5114 used to calculate the acute and chronic concentrations of concern for carbon tetrachloride. As  
5115 described in Appendix G, AFs account for differences in inter- and intra-species variability, as  
5116 well as laboratory-to-field variability and are routinely used within TSCA for assessing the  
5117 hazard of new industrial chemicals (with very limited environmental test data). Some  
5118 uncertainty may be associated with the use of the specific AFs used in the hazard assessment.  
5119 There is no way of knowing exactly how much uncertainty to account for in the AFs. Therefore,  
5120 there is uncertainty associated with the use of the specific AFs used in the hazard assessment.  
5121 For example, a standard AF has not been established for amphibians by the EPA under TSCA,  
5122 because there are few amphibian studies for industrial chemicals. It is unclear whether using an  
5123 assessment factor of 10 to calculate the acute COC value for amphibians using the sub-chronic  
5124 embryo-larvae test data is sufficiently protective or is overly protective of amphibian exposures  
5125 to carbon tetrachloride. There are additional factors that affect the potential for adverse effects in

5126 aquatic organisms. Life-history factors and the habitat of aquatic organisms influences the  
5127 likelihood of exposure above the hazard benchmark in an aquatic environment.

#### 5128 **4.4.4 Human Health Hazard Assumptions and Uncertainties**

---

5129 Toxicity data are limited for dermal exposures to carbon tetrachloride and for developmental  
5130 toxicity by the inhalation route. The available developmental toxicity by the inhalation route  
5131 suggests that carbon tetrachloride does not induce developmental effects from single exposures  
5132 during gestation (see section 3.2.4.1.1). The available dermal data were used in a weight of  
5133 evidence approach to derive points of departures (POD) for occupational dermal exposures and  
5134 estimates of dermal absorption.

5135  
5136 The main source of uncertainty for the human health hazard is the lack of evidence in support of  
5137 a mode of action (MOA) for carcinogenesis of carbon tetrachloride at low dose levels. Therefore,  
5138 a low dose linear cancer risk model for carbon tetrachloride was used to calculate cancer risk,  
5139 which is EPA's baseline approach to risk assessment when the MOA is unknown or not  
5140 sufficiently supported by the evidence.

5141  
5142 Several uncertainties affected the dermal risk assessment. Evaporation from skin could occur (if  
5143 in an aqueous solution, evaporation may be less likely). Route-to-route extrapolation was used to  
5144 calculate a human equivalent dermal dose for chronic exposures based on an equation in  
5145 Jongeneel (2012). Inhalation to dermal route-to-route extrapolation assumes that the inhalation  
5146 route of exposure is most relevant to dermal exposures, as carbon tetrachloride undergoes first-  
5147 pass bioactivation in the liver for oral exposures.

5148  
5149 The BMDL<sub>10</sub> value for continuous inhalation exposures was extrapolated to shorter exposure  
5150 durations using the equation  $C^n \times t = k$ , where an empirical value of n was determined to be 2.5  
5151 based on rat lethality data (Ten Berge et al., 1986). The validity of this extrapolation is supported  
5152 by similar time scaling processes conducted in the generation of AEGL values. Uncertainties  
5153 associated to this extrapolation are discussed in U.S. EPA, (2002) (see section 3.2.5.2.2).

### 5154 **4.5 Risk Characterization Confidence Levels**

---

#### 5155 **4.5.1 Environmental Risk**

---

5156 EPA has high confidence that there are no identified ecological risks from the TSCA conditions  
5157 of use and exposure pathways within the scope of the risk evaluation for carbon tetrachloride.  
5158 This is based on EPA using conservative, high end exposures and modeled surface water  
5159 concentrations and the most conservative (highest toxicity)/environmentally-protective acute and  
5160 chronic COC.

#### 5161 **4.5.2 Human Health Risk**

---

5162 There is medium to high confidence in the risk estimates for inhalation exposures. The PODs for  
5163 non-cancer and cancer effects from acute or chronic exposures are rated with at least medium  
5164 confidence (see section 3.2.5.3). Exposure estimates from monitoring/surrogate monitoring data  
5165 (i.e., manufacturing and processing COUs) are based on a robust monitoring dataset (i.e., > 100  
5166 data points), reflecting high confidence in resulting exposure estimates. Exposure estimates for  
5167 all the other COUs are based on modeling or monitoring data with limited datapoints (i.e.,  
5168 OBOD cleanup process in DoD). There is congruency between the exposure estimates based on

5169 the limited monitoring data for the OBOD cleanup (i.e., a process that last 1-2 hrs/day) and  
5170 estimates based on the *Tank Truck and Railcar Loading and Unloading Release and Inhalation*  
5171 *Exposure Model* that estimates worker exposure during container and truck unloading activities  
5172 that occur at industrial facilities. The fact that there is congruency in the resulting exposure  
5173 estimates suggest at least medium confidence in those exposure estimates.  
5174

5175 There is low confidence in the risk estimates for dermal exposures. The lack of quantitative data  
5176 on dermal absorption for carbon tetrachloride affects the derivation of accurate dermal PODs and  
5177 the modeling of dermal exposures. The conservative assumptions used to derive the PODs and  
5178 exposure estimate are likely to result in risk overestimations.

#### 5179 **4.6 Aggregate or Sentinel Exposures**

---

5180 Section 6(b)(4)(F)(ii) of TSCA requires the EPA, as a part of the risk evaluation, to describe  
5181 whether aggregate or sentinel exposures under the conditions of use were considered and the  
5182 basis for their consideration. The EPA has defined aggregate exposure as “*the combined*  
5183 *exposures to an individual from a single chemical substance across multiple routes and across*  
5184 *multiple pathways*” (40 CFR § 702.33). In this risk evaluation exposure is limited to exposure to  
5185 carbon tetrachloride by both inhalation and dermal contact only. Inhalation exposure is specified  
5186 by the air concentration encountered as a function of time during the work-day. Dermal contact  
5187 is characterized by the surface area of skin (hands) exposed, and the duration of the dermal  
5188 exposure. For workplace exposures inhalation and dermal exposures are assumed to be only  
5189 simultaneous (both end at the end of the task, shift, or work day).  
5190

5191 Quantitative information on the dermal absorption of carbon tetrachloride is limited. This data  
5192 limitation hinders the accuracy of estimated internal doses from dermal exposures. On the other  
5193 hand, carbon tetrachloride is a skin irritant and sensitizer, which suggests that workers are  
5194 persuaded on their own (in addition to the workplace industrial hygiene program and OSHA  
5195 regulations) to wear gloves when handling the chemical. Based on this assumption, the  
5196 occurrence of aggregate exposures including dermal exposures without gloves is expected to be  
5197 highly unlikely especially for chronic aggregate exposures. Aggregate exposures including  
5198 dermal exposures with gloves are expected to be greatly influenced by the higher inhalation  
5199 exposures (see retained absorbed doses from dermal exposures with gloves in Table 2-20). This  
5200 greater influence by the inhalation route of exposure is also suggested by the high inhalation  
5201 absorption for carbon tetrachloride and the number of activities that may generate fugitive  
5202 emissions in the COUs (see section 2.4.1.7).  
5203

5204 The EPA defines sentinel exposure as “*the exposure to a single chemical substance that*  
5205 *represents the plausible upper bound of exposure relative to all other exposures within a broad*  
5206 *category of similar or related exposures* (40 CFR § 702.33).” In this risk evaluation, the EPA  
5207 considered sentinel exposure the highest exposure given the details of the conditions of use and  
5208 the potential exposure scenarios – for example, workers who perform activities with higher  
5209 exposure potential, or certain physical factors like body weight or skin surface area exposed.  
5210 EPA characterized high-end exposures in evaluating exposure using both monitoring data and  
5211 modeling approaches. Where statistical data are available, EPA typically uses the 95th percentile  
5212 value of the available dataset to characterize high-end exposure for a given condition of use.  
5213

5214 Greater inhalation exposures to carbon tetrachloride are estimated for the Domestic  
5215 Manufacturing and Processing as Reactant/Intermediate COUs than all the other COUs in this  
5216 draft risk evaluation (see Table 2-18, Table 4-7 and Table 4-8).

## 5217 **5 Risk Determination**

---

### 5218 **5.1 Unreasonable Risk**

---

#### 5219 **5.1.1 Overview**

---

5220 In each risk evaluation under TSCA section 6(b), EPA determines whether a chemical substance  
5221 presents an unreasonable risk of injury to health or the environment, under the conditions of use.  
5222 These determinations do not consider costs or other non-risk factors. In making these  
5223 determinations, EPA considers relevant risk-related factors, including, but not limited to: the  
5224 effects of the chemical substance on health and human exposure to such substance under the  
5225 conditions of use (including cancer and non-cancer risks); the effects of the chemical substance  
5226 on the environment and environmental exposure under the conditions of use; the population  
5227 exposed (including any potentially exposed or susceptible subpopulations (PESS)); the severity  
5228 of hazard (including the nature of the hazard and the irreversibility of the hazard); and  
5229 uncertainties. EPA also takes into consideration the Agency's confidence in the data used in the  
5230 risk estimate. This includes an evaluation of the strengths, limitations and uncertainties  
5231 associated with the information used to inform the risk estimate and the risk characterization.  
5232 This approach is in keeping with the Agency's final rule, *Procedures for Chemical Risk*  
5233 *Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726).<sup>21</sup>

5234  
5235 Under TSCA, conditions of use are defined as the circumstances, as determined by the  
5236 Administrator, under which the substance is intended, known, or reasonably foreseen to be  
5237 manufactured, processed, distributed in commerce, used, or disposed of. TSCA §3(4).

5238  
5239 An unreasonable risk may be indicated when health risks under the conditions of use are  
5240 identified by comparing the estimated risks with the risk benchmarks and where the risks affect  
5241 the general population or PESS, identified as relevant. For workers (which are one example of  
5242 PESS), an unreasonable risk may be indicated when risks are not adequately addressed through  
5243 expected use of workplace practices and exposure controls, including engineering controls or use  
5244 of personal protective equipment (PPE). An unreasonable risk may also be indicated when  
5245 environmental risks under the conditions of use are greater than environmental risk benchmarks.  
5246 The risk estimates contribute to the evidence EPA uses to determine unreasonable risk.

5247  
5248 EPA uses the term "indicates unreasonable risk" to indicate EPA concern for potential  
5249 unreasonable risk. For non-cancer endpoints, "less than MOE benchmark" is used to indicate  
5250 potential unreasonable risk; this occurs if an MOE value is less than the benchmark MOE (e.g.,  
5251 MOE 0.3 < benchmark MOE 30). For cancer endpoints, EPA uses the term "greater than risk  
5252 benchmark" to indicate potential unreasonable risk; this occurs, for example, if the lifetime

---

<sup>21</sup> 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.

5253 cancer risk value is greater than 1 in 10,000 (e.g., cancer risk value is  $5 \times 10^{-2}$  which is greater  
5254 than the standard range of acceptable cancer risk benchmarks of  $1 \times 10^{-4}$  to  $1 \times 10^{-6}$ ). For  
5255 environmental endpoints, to indicate potential unreasonable risk EPA uses a risk quotient (RQ)  
5256 value “greater than 1” (i.e.,  $RQ > 1$ ). Conversely, EPA uses the term “does not indicate  
5257 unreasonable risk” to indicate that it is unlikely that EPA has a concern for potential  
5258 unreasonable risk. More details are described below.

5259  
5260 The degree of uncertainty surrounding the MOEs, cancer risk or RQs is a factor in determining  
5261 whether or not unreasonable risk is present. Where uncertainty is low, and EPA has high  
5262 confidence in the hazard and exposure characterizations (for example, the basis for the  
5263 characterizations is measured or monitoring data or a robust model and the hazards identified for  
5264 risk estimation are relevant for conditions of use), the Agency has a higher degree of confidence  
5265 in its risk determination. EPA may also consider other risk factors, such as severity of endpoint,  
5266 reversibility of effect, or exposure-related considerations, such as magnitude or number of  
5267 exposures, in determining that the risks are unreasonable under the conditions of use. Where  
5268 EPA has made assumptions in the scientific evaluation, whether or not those assumptions are  
5269 protective will also be a consideration. Additionally, EPA considers the central tendency and  
5270 high-end scenarios when determining the unreasonable risk. High-end risk estimates (i.e., 95th  
5271 percentile) are generally intended to cover individuals or sub-populations with greater exposure  
5272 (PESS) and central tendency risk estimates are generally estimates of average or typical  
5273 exposure.

5274  
5275 EPA may make a no unreasonable risk determination for conditions of use where the substance’s  
5276 hazard and exposure potential, or where the risk-related factors described previously, lead EPA  
5277 to determine that the risks are not unreasonable.

5278  
5279 EPA’s general approach to determining unreasonable risks to health or the environment is  
5280 described in more detail in sections 5.1.2 and 5.1.3; these are not chemical-specific  
5281 considerations and the examples listed may not necessarily be evaluated or considered for this  
5282 chemical substance.

## 5283 **5.1.2 Risks to Human Health**

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### 5284 **5.1.2.1 Determining Non-Cancer Risks**

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5285 Margins of exposure (MOEs) are used in EPA’s risk evaluations as a starting point to estimate  
5286 non-cancer risks for acute and chronic exposures. The non-cancer evaluation refers to potential  
5287 adverse health effects associated with health endpoints other than cancer, including to the body’s  
5288 organ systems, such as reproductive/developmental effects, cardiac and lung effects, and kidney  
5289 and liver effects. The MOE is the point of departure (POD) (an approximation of the no-  
5290 observed adverse effect level (NOAEL) or benchmark dose level (BMDL)) for a specific health  
5291 endpoint divided by the exposure concentration for the specific scenario of concern. The  
5292 benchmark for the MOE that is used accounts for the total uncertainty in a POD, including, as  
5293 appropriate: (1) the variation in sensitivity among the members of the human population (i.e.,  
5294 intrahuman/intraspecies variability); (2) the uncertainty in extrapolating animal data to humans  
5295 (i.e., interspecies variability); (3) the uncertainty in extrapolating from data obtained in a study  
5296 with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to  
5297 chronic exposure); and (4) the uncertainty in extrapolating from a lowest observed adverse effect

5298 level (LOAEL) rather than from a NOAEL. MOEs can provide a non-cancer risk profile by  
5299 presenting a range of estimates for different non-cancer health effects for different exposure  
5300 scenarios and are a widely recognized point estimate method for evaluating a range of potential  
5301 non-cancer health risks from exposure to a chemical.

5302  
5303 A calculated MOE that is less than the benchmark MOE indicates the possibility of risk to  
5304 human health. Whether those risks are unreasonable will depend upon other risk-related factors,  
5305 such as severity of endpoint, reversibility of effect, exposure-related considerations (e.g.,  
5306 duration, magnitude, frequency of exposure, population exposed), and the confidence in the  
5307 information used to inform the hazard and exposure values. If the calculated MOE is greater than  
5308 the benchmark MOE, generally it is less likely that there is risk.

5309  
5310 Uncertainty factors (UFs) also play an important role in the risk estimation approach and in  
5311 determining unreasonable risk. A lower benchmark MOE (e.g., 30) indicates greater certainty in  
5312 the data (because fewer of the default UFs relevant to a given POD as described above were  
5313 applied). A higher benchmark MOE (e.g., 1000) would indicate more uncertainty in risk  
5314 estimation and extrapolation for the MOE for specific endpoints and scenarios. However, these  
5315 are often not the only uncertainties in a risk evaluation.

#### 5316 **5.1.2.2 Determining Cancer Risks**

5317 EPA estimates cancer risks by determining the incremental increase in probability of an  
5318 individual in an exposed population developing cancer over a lifetime (excess lifetime cancer  
5319 risk (ELCR)) following exposure to the chemical under specified use scenarios. Standard cancer  
5320 benchmarks used by EPA and other regulatory agencies are an increased cancer risk above  
5321 benchmarks ranging from 1 in 1,000,000 to 1 in 10,000 (i.e.,  $1 \times 10^{-6}$  to  $1 \times 10^{-4}$ ) depending on  
5322 the subpopulation exposed. Generally, EPA considers  $1 \times 10^{-6}$  to  $1 \times 10^{-4}$  as the appropriate  
5323 benchmark for the general population, consumer users, and non-occupational PESS.<sup>22</sup>

5324  
5325 For the subject chemical substance, the EPA, consistent with case law and 2017 NIOSH  
5326 guidance,<sup>23</sup> used  $1 \times 10^{-4}$  as the benchmark for the purposes of this risk determination for  
5327 individuals in industrial/commercial work environments subject to Occupational Safety and  
5328 Health Act (OSHA) requirements. It is important to note that  $1 \times 10^{-4}$  is not a bright line and  
5329 EPA has discretion to make risk determinations based on other benchmarks as appropriate. It is

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<sup>22</sup> 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).

<sup>23</sup> 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>.

5330 important to note that exposure-related considerations (duration, magnitude, population exposed)  
5331 can affect EPA's estimates of the excess lifetime cancer risk.

### 5332 **5.1.3 Determining Environmental Risk**

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5333 To assess environmental risk, EPA generally identifies and evaluates environmental hazard data  
5334 for aquatic, sediment-dwelling, and terrestrial organisms exposed under acute and chronic  
5335 exposure conditions. The environmental risk includes any risks that exceed benchmark values to  
5336 the aquatic and terrestrial environment from levels of the evaluated chemical found in the  
5337 environment (e.g., surface water, sediment, soil, biota) based on the fate properties, relatively  
5338 high potential for release, and the availability of environmental monitoring data and hazard data.

5339  
5340 Environmental risks are estimated by calculating a RQ. The RQ is defined as:

$$5341 \text{RQ} = \text{Environmental Concentration} / \text{Effect Level}$$

5343  
5344 An RQ equal to 1 indicates that the exposures are the same as the concentration that causes  
5345 effects. If the RQ is greater than 1, the exposure is greater than the effect concentration and there  
5346 is potential for risk presumed. If the RQ is less than 1, the exposure is less than the effect  
5347 concentration and unreasonable risk is not likely. The Concentrations of Concern (COC) or  
5348 hazard value for certain aquatic organisms are used to calculate RQs for acute and chronic  
5349 exposures. For environmental risk, EPA is more likely to determine that there is unreasonable  
5350 risk if the RQ exceeds 1 for the conditions of use being evaluated. Consistent with EPA's human  
5351 health evaluations, the RQ is not treated as a bright line and other risk-based factors may be  
5352 considered (e.g., exposure scenario, uncertainty, severity of effect) for purposes of making a risk  
5353 determination.

## 5354 **5.2 Risk Determination for Carbon Tetrachloride**

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5355 EPA's preliminary determinations of unreasonable risk for specific conditions of use of carbon  
5356 tetrachloride listed below are based on health risks to occupational non-users (ONUs) during  
5357 occupational exposures.

5358  
5359 As described in section 4, significant risks associated with more than one adverse effect (e.g.  
5360 liver toxicity and cancer) were identified for particular conditions of use. In Table 5-1 and  
5361 section 5.3 below, EPA identifies cancer as the driver endpoint for the conditions of use that  
5362 EPA has determined present unreasonable risks. This is the effect that is most sensitive, and it is  
5363 expected that addressing risks for this effect would address other identified risks.

- 5364
- 5365 • **Occupational non-users (ONUs):** EPA evaluated inhalation risks for acute and chronic  
5366 exposures for occupational non-users (ONUs). However, EPA did not separately calculate  
5367 inhalation risk estimates for ONUs and workers. There is uncertainty in the ONU inhalation  
5368 risk estimate since the data did not distinguish between worker and ONU inhalation exposure  
5369 estimates. While the difference between the exposures of ONUs and the exposures of  
5370 workers directly handling the chemical generally cannot be quantified, ONU inhalation  
5371 exposures are expected to be lower than inhalation exposures for workers directly handling  
5372 the chemical. EPA considered the ONU exposures to be equal to the central tendency risk  
5373 estimates for workers when determining ONU risk attributable to inhalation. While this is

5374 likely health protective as it assumes ONU exposure is greater than that of 50% of the  
5375 workers, this is highly uncertain, and EPA has low confidence in these exposure estimates for  
5376 ONUs. Recognizing the significant uncertainty surrounding EPA's inhalation exposure  
5377 estimates for ONUs, EPA will continue to seek data on ONU inhalation exposures during the  
5378 public comment period on the draft risk evaluation. In addition, because EPA is preliminarily  
5379 making a finding that four COUs present an unreasonable risk for ONUs based on an  
5380 increased cancer risk estimate of  $4 \times 10^{-4}$ , EPA will further analyze this information to  
5381 determine whether this four-fold difference from the cancer risk benchmark falls within the  
5382 range of uncertainty for these estimates. Dermal exposures are not expected because ONUs  
5383 do not typically directly handle the carbon tetrachloride, nor they are in the immediate  
5384 proximity of carbon tetrachloride. Estimated numbers of occupational non-users are  
5385 in section 2.4.1.  
5386

5387 As described below, risks to workers, general population, consumers, bystanders to consumer  
5388 use, and the environment either were not relevant for these conditions of use or were evaluated  
5389 and not found to be unreasonable. For the conditions of use where EPA found no unreasonable  
5390 risk, EPA describes the estimated risks in section 4.2 (Table 4-7, Table 4-8, and Table 4-11)  
5391

- 5392 • **Workers:** EPA evaluated workers' acute and chronic inhalation and dermal occupational  
5393 exposures for cancer and non-cancer risks and determined whether any risks indicated are  
5394 unreasonable. For all applicable conditions of use, acute and chronic inhalation and dermal  
5395 exposure scenarios resulted in calculated MOEs and cancer risk levels that did not indicate  
5396 risk (Table 4-7, Table 4-8, Table 4-9, Table 4-10, Table 4-11, Table 4-12) with expected PPE. As  
5397 a result, EPA does not find unreasonable risks of injury to health of workers from acute and  
5398 chronic inhalation and dermal exposures to carbon tetrachloride. EPA expects there is  
5399 compliance with federal and state laws, such as worker protection standards, unless case-  
5400 specific facts indicate otherwise, and therefore existing OSHA regulations for worker  
5401 protection and hazard communication will result in use of appropriate PPE consistent with  
5402 the applicable SDSs in a manner adequate to protect employees. Estimated numbers of  
5403 workers are in section 2.4.1.  
5404
- 5405 • **General population:** The Office of Chemical Safety and Pollution Prevention works closely  
5406 with the offices within EPA that administer and implement the regulatory programs under  
5407 these statutes. EPA believes that the TSCA risk evaluation should focus on those exposure  
5408 pathways associated with TSCA uses that are not subject to the regulatory regimes discussed  
5409 above because these pathways are likely to represent the greatest areas of concern to EPA.  
5410 Examples of exposure pathways covered by other statutes for carbon tetrachloride such as:  
5411 the ambient air pathway (i.e., carbon tetrachloride is listed as a Hazardous Air Pollutant in  
5412 the Clean Air Act (CAA)), the drinking water pathway (i.e., National Primary Drinking  
5413 Water Regulations (NPDWRs) are promulgated for carbon tetrachloride under the Safe  
5414 Drinking Water Act), ambient water pathways (i.e., carbon tetrachloride is a priority  
5415 pollutant with recommended water quality criteria for protection of human health under the  
5416 CWA), the biosolids pathway (i.e., the biosolids pathway for carbon tetrachloride is currently  
5417 being addressed in the CWA regulatory analytical process), and disposal pathways (i.e.,  
5418 carbon tetrachloride disposal is managed and prevented from further environmental release  
5419 by RCRA and SDWA regulations). In addition, the Montreal Protocol and Title VI of the



5420 CAA Amendments of 1990 led to a phase-out of carbon tetrachloride production in the  
5421 United States for most non feedstock domestic uses in 1996.

5422

5423 • **Consumers and bystanders to consumer use:** EPA did not include any consumer uses  
5424 among the conditions of use within the scope of the risk evaluation for carbon tetrachloride.  
5425 The CPSC banned the use of carbon tetrachloride in consumer products (excluding  
5426 unavoidable residues not exceeding 10 ppm atmospheric concentration) in 1970. Therefore,  
5427 EPA did not evaluate hazards or exposures to consumers or bystanders to consumer use in  
5428 this risk evaluation, and there are no risk determinations for these populations.

5429

5430 • **Environmental risks:** EPA concluded that the surface water concentrations did not exceed  
5431 the acute COC (i.e., acute RQs < 1) for aquatic species for all but one of the sites assessed  
5432 (see Table 4-2). EPA determined there is not an acute aquatic concern for carbon tetrachloride  
5433 after further review indicated that the one site had a one-time increased environmental  
5434 release of carbon tetrachloride in 2014 due to an unexpected chemical spill. With respect to  
5435 the chronic COC, due to the volatile properties of carbon tetrachloride, EPA determined that  
5436 it is more likely that a chronic exposure duration will occur when there are long-term  
5437 consecutive days of release versus an interval or pulse exposure, which would more likely  
5438 result in an acute exposure duration. For all sites analyzed, none had more than 20 days  
5439 where the chronic COC was exceeded (see Table 4-2). Consequently, EPA determined there  
5440 is not an acute or chronic aquatic concern for carbon tetrachloride from the conditions of use.  
5441 With respect to algae, no sites had more than 20 days where the algal COC was exceeded  
5442 (see Table 4-2). Due to the quick regeneration time of many algae species, impacts to algae  
5443 populations would be most likely to over long-term consecutive days of release (i.e., > 20)  
5444 versus an interval or pulse exposure. Consequently, EPA determined there is not a concern  
5445 for carbon tetrachloride exposure to algae from the conditions of use. With respect to  
5446 sediment-dwelling aquatic species, carbon tetrachloride is not expected to partition to or be  
5447 retained in sediment and is expected to remain in aqueous phase due to its water solubility  
5448 and low partitioning to organic matter, so EPA did not further evaluate exposure to sediment-  
5449 dwelling organisms. Therefore, EPA does not find unreasonable environmental risks to  
5450 aquatic species from the conditions of use for carbon tetrachloride (see section 4.1). Also, as  
5451 explained in section 2.5.3.2 of the problem formulation ([U.S. EPA, 2018d](#)), exposure to  
5452 terrestrial organisms was removed from the scope of the evaluation. This exposure pathway  
5453 is considered to be covered under programs of other environmental statutes administered by  
5454 EPA (e.g., CWA, RCRA, and CAA) which adequately assess and effectively manage  
5455 exposures and for which long-standing regulatory and analytical processes already exist.  
5456 Therefore, EPA did not evaluate hazards and exposures to terrestrial organisms in this risk  
5457 evaluation, and there is no risk determination for terrestrial organisms.

5458

5459 Table 5-1 below presents an overview of risk determinations by condition of use. An in-  
5460 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	<b>Presents an unreasonable risk of injury to health (occupational non-users)</b>
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	<b>Presents an unreasonable risk of injury to health (occupational non-users)</b>
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)	<b>Presents an unreasonable risk of injury to health (occupational non-users)</b> (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)	<b>Presents an unreasonable risk of injury to health (occupational non-users)</b>
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

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### 5.3.1 Manufacture-Domestic manufacture

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

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Unreasonable risk driver – ONUs:

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Driver benchmark – ONUs:

- Cancer: Benchmark =  $1 \times 10^{-4}$

Risk estimate – ONUs:

Cancer: Chronic inhalation risk estimate  $4 \times 10^{-4}$  and  $5 \times 10^{-3}$  (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 =  $1 \times 10^{-4}$ .

Risk estimates – workers:

- Liver toxicity: Chronic inhalation MOE 104 (high end) (Table 4-8).
- Cancer: Dermal risk estimate  $6 \times 10^{-5}$  (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  $3 \times 10^{-5}$  and  $2 \times 10^{-4}$  (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

5543 **5.3.3 Processing-Processing as a reactant in the production of**  
 5544 **hydrochlorofluorocarbon, hydrofluorocarbon, hydrofluoroolefin, and**  
 5545 **perchloroethylene**

5546 Section 6(b)(4)(A) unreasonable risk determination for processing carbon tetrachloride as a  
 5547 reactant in the production of hydrochlorofluorocarbon, hydrofluorocarbon, hydrofluoroolefin,  
 5548 and perchloroethylene:

- 5550 • **Presents an unreasonable risk of injury to health (ONUs).**
- 5551 • Does not present an unreasonable risk of injury to health (workers).
- 5552 • Does not present an unreasonable risk of injury to the environment (aquatic, sediment
- 5553 dwelling and terrestrial organisms).

5554  
 5555 Unreasonable risk driver – ONUs:

- 5556 • Cancer from chronic inhalation exposure.

5557  
 5558 Driver benchmark – ONUs:

- 5559 • Cancer: Benchmark =  $1 \times 10^{-4}$

5560  
 5561 Risk estimate – ONUs:

- 5562 • Cancer: Chronic inhalation risk estimates  $4 \times 10^{-4}$  and  $5 \times 10^{-3}$  (12-hr TWA) (central
- 5563 tendency and high end) (Table 4-11)

5564  
 5565 Risk Considerations: EPA assessed inhalation exposures using submitted monitoring data  
 5566 containing information on 8-hour and 12-hour shifts for this and other conditions of use for  
 5567 which this occupational exposure scenario is relevant. The unreasonable risk determination was  
 5568 based on the submitted monitoring data for 12-hour shifts. The submitted data cover two  
 5569 companies and are summarized in Table 2-6. There is uncertainty in the ONU risk estimate since  
 5570 the data did not distinguish between worker and ONU inhalation exposure estimates. To account  
 5571 for this uncertainty, EPA considered the central tendency estimate when determining ONU risk.  
 5572 As noted previously, EPA has low confidence in the exposure estimates for ONUs. For the  
 5573 purpose of making a risk determination for workers, EPA considered the high-end estimates.  
 5574 While those risk estimates for this condition of use indicate risk in the absence of PPE, the risk  
 5575 estimates for these pathways do not indicate risk for workers when expected use of PPE, a  
 5576 respirator with an APF of 50, was considered (Table 4-8 and Table 4-11). EPA’s unreasonable  
 5577 risk determination for ONUs reflects the hazards associated with chronic exposure to carbon  
 5578 tetrachloride and is based on an expected absence of PPE for ONUs.  
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 5580  
 5581  
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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)

5583 **5.3.4 Processing- Processing as reactant/intermediate in reactive ion etching**  
 5584 Section 6(b)(4)(A) unreasonable risk determination for processing of carbon tetrachloride as a  
 5585 reactant/intermediate in reactive ion etching (e.g., semiconductor manufacture):  
 5586

- 5587 • Does not present an unreasonable risk of injury to health (workers and ONUs).
- 5588 • Does not present an unreasonable risk of injury to the environment (aquatic, sediment  
 5589 dwelling and terrestrial organisms).

5590  
 5591 Risk Considerations: A quantitative evaluation of the occupational exposures attributable to this  
 5592 condition of use is not included in the risk evaluation because EPA estimates that worker  
 5593 exposures to carbon tetrachloride during reactive ion etching are negligible. Due to the  
 5594 performance requirements of products typically produced using this technique, carbon  
 5595 tetrachloride is typically applied in small quantities under a fume hood and/or inside a highly  
 5596 controlled work area (a Class 1 clean room), thus eliminating or significantly reducing the  
 5597 potential for exposures (section 2.4.1.7.5).  
 5598

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

5599 **5.3.5 Processing – Incorporation into formulation, mixture or reaction**  
 5600 **products-Petrochemicals-derived manufacturing, agricultural products**  
 5601 **manufacturing, and other basic organic and inorganic chemical**  
 5602 **manufacturing**

5603 Section 6(b)(4)(A) unreasonable risk determination for processing carbon tetrachloride to  
 5604 incorporate into a formulation, mixture or reaction product (other basic organic and inorganic  
 5605 chemical manufacturing):  
 5606

- 5607 • **Presents an unreasonable risk of injury to health (ONUs).**
- 5608 • Does not present an unreasonable risk of injury to health (workers).
- 5609 • Does not present an unreasonable risk of injury to the environment (aquatic, sediment  
 5610 dwelling and terrestrial organisms).

5611 Unreasonable risk driver – ONUs:

- 5612 • Cancer from chronic inhalation exposure

5613 Driver benchmark – ONUs:

- 5614 • Cancer: Benchmark =  $1 \times 10^{-4}$

5615  
 5616  
 5617  
 5618  
 5619

5620 Risk estimate – ONUs:

5621

- 5622 • Cancer: Chronic inhalation risk estimates  $4 \times 10^{-4}$  and  $5 \times 10^{-3}$  (central tendency and
- 5623 high end) (Table 4-11)

5624

5625 Risk Considerations: EPA assessed inhalation exposures using submitted monitoring data  
5626 containing information on 8-hour and 12-hour shifts for this and other conditions of use for  
5627 which this occupational exposure scenario is relevant. The unreasonable risk determination was  
5628 based on the submitted monitoring data for 12-hour shifts. The submitted data cover two  
5629 companies and are summarized in Table 2-6. There is uncertainty in the ONU risk estimate since  
5630 the data did not distinguish between worker and ONU inhalation exposure estimates. To account  
5631 for this uncertainty, EPA considered the central tendency estimate when determining ONU risk.  
5632 As noted previously, EPA has low confidence in the exposure estimates for ONUs. For the  
5633 purpose of making a risk determination for workers, EPA considered the high-end estimates.  
5634 While those risk estimates for this condition of use indicate risk in the absence of PPE, the risk  
5635 estimates for these pathways do not indicate risk for workers when expected use of PPE, a  
5636 respirator with an APF of 50, was considered (Table 4-8, Table 4-11). EPA's unreasonable risk  
5637 determination for ONUs reflects the hazards associated with chronic exposure to carbon  
5638 tetrachloride and is based on an expected absence of PPE for ONUs.

5639

5640 Section 6(b)(4)(A) unreasonable risk determination for processing carbon tetrachloride to  
5641 incorporate into a formulation, mixture or reaction product (petrochemicals-derived  
5642 manufacturing, agricultural products manufacturing):

5643

- 5644 • Does not present an unreasonable risk of injury to health (workers, ONUs).
- 5645 • Does not present an unreasonable risk of injury to the environment (aquatic, sediment
- 5646 dwelling and terrestrial organisms).

5647

5648 Exposure scenario with highest risk estimate – workers and ONUs:

5649

- 5650 • Liver toxicity from chronic inhalation exposure and cancer from chronic dermal
- 5651 exposure.

5652

5653 Benchmarks – workers and ONUs:

5654

- 5655 • Liver toxicity: Benchmark MOE = 30.
- 5656 • Cancer: Benchmark =  $1 \times 10^{-4}$ .

5657

5658 Risk estimates – workers:

5659

- 5660 • Liver toxicity: Chronic inhalation MOE 104 (high end) (Table 4-8).
- 5661 • Cancer: Chronic dermal risk estimate  $6 \times 10^{-5}$  (high end) with PPE (gloves PF 5) (Table
- 5662 4-12).

5663

5664 Risk estimates – ONUs:

5665

- 5666 • Liver toxicity: Chronic inhalation MOEs 546 and 104 (central tendency and high end)  
5667 (Table 4-8).
- 5668 • Cancer: Chronic inhalation risk estimates  $3 \times 10^{-5}$  and  $2 \times 10^{-4}$  (central tendency and high  
5669 end) (Table 4-11).

5670  
5671 **Risk Considerations:** Risk estimates for workers and ONUs for acute and chronic inhalation and  
5672 for workers, chronic dermal do not indicate risk. While high-end risk estimates for this condition  
5673 of use indicate risk in the absence of PPE, risk estimates for these pathways do not indicate risk  
5674 for workers when expected use of PPE, a respirator with an APF of 10 and gloves with PF of 5,  
5675 was considered (Table 4-8, Table 4-11 and Table 4-12). EPA did not separately calculate risk  
5676 estimates for ONUs and workers. ONU inhalation exposures are expected to be lower than  
5677 inhalation exposures for workers directly handling the chemical substance; however, the relative  
5678 exposure of ONUs to workers in these cases cannot be quantified. To account for this  
5679 uncertainty, EPA considered the central tendency estimate when determining ONU risk. EPA's  
5680 risk determination for ONUs is based on an expected absence of PPE. Dermal exposures are not  
5681 expected for ONUs.  
5682

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.

### 5683 **5.3.6 Processing-Repackaging of carbon tetrachloride for use in laboratory** 5684 **chemicals**

5685 Section 6(b)(4)(A) unreasonable risk determination for repackaging of carbon tetrachloride for  
5686 use in laboratory chemicals:

- 5687
- 5688 • Does not present an unreasonable risk of injury to health (workers and ONUs).
- 5689 • Does not present an unreasonable risk of injury to the environment (aquatic, sediment  
5690 dwelling and terrestrial organisms).

5691  
5692 Exposure scenario with highest risk estimate – workers and ONUs:

- 5693
- 5694 • Liver toxicity from chronic inhalation exposure and cancer from chronic dermal  
5695 exposure.

5696  
5697 Benchmarks – workers and ONUs:

- 5698
- 5699 • Liver toxicity: Benchmark MOE = 30.
- 5700 • Cancer: Benchmark =  $1 \times 10^{-4}$ .

5701  
5702 Risk estimates – workers:

5703



- 5704
- Liver toxicity: Chronic inhalation MOE 104 (high end) (Table 4-8).
- 5705
- Cancer: Chronic dermal risk estimate  $6 \times 10^{-5}$  (high end) with PPE (gloves PF 5) (Table
- 5706
- 4-12).

5707

5708 Risk estimates – ONUs:

- 5709
- Liver toxicity: Chronic inhalation MOEs 546 and 104 (central tendency and high end) (Table 4-8).
- 5710
- Cancer: Chronic inhalation risk estimates  $3 \times 10^{-5}$  and  $2 \times 10^{-4}$  (central tendency and high
- 5711
- end) (Table 4-11).

5712

5713

5714

5715 Risk Considerations: Risk estimates for workers and ONUs for acute and chronic inhalation and

5716 for workers, chronic dermal do not indicate risk. While high-end risk estimates for this condition

5717 of use indicate risk in the absence of PPE, risk estimates for these pathways do not indicate risk

5718 for workers when expected use of PPE, a respirator with an APF of 10 and gloves with PF of 5,

5719 was considered (Table 4-8, Table 4-11 and Table 4-12). EPA did not separately calculate risk

5720 estimates for ONUs and workers. ONU inhalation exposures are expected to be lower than

5721 inhalation exposures for workers directly handling the chemical substance; however, the relative

5722 exposure of ONUs to workers in these cases cannot be quantified. To account for this

5723 uncertainty, EPA considered the central tendency estimate when determining ONU risk. EPA’s

5724 risk determination for ONUs is based on an expected absence of PPE. Dermal exposures are not

5725 expected for ONUs.

5726

Life Cycle Stage	Category	Subcategory
Processing	Processing - repackaging	Laboratory Chemicals

5727

### 5.3.7 Processing-Recycling

5728 Section 6(b)(4)(A) unreasonable risk determination for recycling of carbon tetrachloride:

- 5729
- Does not present an unreasonable risk of injury to health (workers and ONUs).
- 5730
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment
- 5731
- dwelling and terrestrial organisms).

5732

5733

5734 Exposure scenario with highest risk estimate – workers and ONUs:

- 5735
- Liver toxicity from chronic inhalation exposure and cancer from chronic dermal
- 5736
- exposure.

5737

5738

5739 Benchmarks – workers and ONUs:

- 5740
- Liver toxicity: Benchmark MOE = 30.
- 5741
- Cancer: Benchmark =  $1 \times 10^{-4}$ .

5742

5743

5744 Risk estimates – workers:

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5768

- Liver toxicity: Chronic inhalation MOE 104 (high end) (Table 4-8).
- Cancer: Chronic dermal risk estimate  $6 \times 10^{-5}$  (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  $3 \times 10^{-5}$  and  $2 \times 10^{-4}$  (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

5769  
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5771  
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**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

5780 **5.3.9 Industrial/ Commercial Use - Industrial Processing Aid – Manufacturing**  
5781 **of petrochemical-derived products and agricultural products**

5782 Section 6(b)(4)(A) unreasonable risk determination for use of carbon tetrachloride as an  
5783 industrial processing aid in the manufacture of petrochemicals-derived products and agricultural  
5784 products:

- 5785
- 5786 • Does not present an unreasonable risk of injury to health (workers and ONUs).
- 5787 • Does not present an unreasonable risk of injury to the environment (aquatic, sediment
- 5788 dwelling and terrestrial organisms).
- 5789

5790 Exposure scenario with highest risk estimate – workers and ONUs:

- 5791
- 5792 • Liver toxicity from chronic inhalation exposure and cancer from chronic dermal
- 5793 exposure.
- 5794

5795 Benchmarks – workers and ONUs:

- 5796
- 5797 • Liver toxicity: Benchmark MOE = 30.
- 5798 • Cancer: Benchmark =  $1 \times 10^{-4}$ .
- 5799

5800 Risk estimates – workers:

- 5801
- 5802 • Liver toxicity: Chronic inhalation MOE 104 (high end) (Table 4-8).
- 5803 • Cancer: Chronic dermal risk estimate  $6 \times 10^{-5}$  (high end) with PPE (gloves PF 5) (Table
- 5804 4-12).
- 5805

5806 Risk estimates – ONUs:

- 5807
- 5808 • Liver toxicity: Chronic inhalation MOEs 546 and 104 (central tendency and high end)
- 5809 (Table 4-8).
- 5810 • Cancer: Chronic inhalation risk estimates  $3 \times 10^{-5}$  and  $2 \times 10^{-4}$  (central tendency and high
- 5811 end) (Table 4-11).
- 5812

5813 Risk Considerations: Risk estimates for workers and ONUs for acute and chronic inhalation and  
5814 for workers, chronic dermal do not indicate risk. While high-end risk estimates for this condition  
5815 of use indicate risk in the absence of PPE, risk estimates for these pathways do not indicate risk  
5816 for workers when expected use of PPE, a respirator with an APF of 10 and gloves with a PF of 5,  
5817 was considered (Table 4-8, Table 4-11 and Table 4-12). EPA did not separately calculate risk  
5818 estimates for ONUs and workers. ONU inhalation exposures are expected to be lower than  
5819 inhalation exposures for workers directly handling the chemical substance; however, the relative  
5820 exposure of ONUs to workers in these cases cannot be quantified. To account for this  
5821 uncertainty, EPA considered the central tendency estimate when determining ONU risk. EPA's  
5822 risk determination for ONUs is based on an expected absence of PPE. Dermal exposures are not  
5823 expected for ONUs.  
5824

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

5825 **5.3.10 Industrial/Commercial Use – Other Basic Organic and Inorganic**  
 5826 **Chemical Manufacturing (manufacturing of chlorinated compounds used**  
 5827 **in solvents for cleaning and degreasing, adhesives and sealants, paints and**  
 5828 **coatings, asphalt, and elimination of nitrogen trichloride in the production**  
 5829 **of chlorine and caustic)**

5830 Section 6(b)(4)(A) unreasonable risk determination for use of carbon tetrachloride in the  
 5831 manufacture of other basic chemicals:

- 5832
- 5833 • **Presents an unreasonable risk of injury to health (ONUs).**
- 5834 • Does not present an unreasonable risk of injury to health (workers).
- 5835 • Does not present an unreasonable risk of injury to the environment (aquatic, sediment
- 5836 dwelling and terrestrial organisms).

5837

5838 Unreasonable risk driver – ONUs:

- 5839
- 5840 • Cancer from chronic inhalation exposure.

5841

5842 Driver benchmark – ONUs:

- 5843
- 5844 • Cancer: Benchmark =  $1 \times 10^{-4}$

5845

5846 Risk estimate – ONUs:

- 5847
- 5848 • Cancer: Chronic inhalation risk estimates  $4 \times 10^{-4}$  and  $5 \times 10^{-3}$  (12-hr TWA) (central
- 5849 tendency and high end) (Table 4-11)

5850

5851 Risk Considerations: EPA assessed inhalation exposures using submitted monitoring data  
 5852 containing information on 8-hour and 12-hour shifts for this and other conditions of use for  
 5853 which this occupational exposure scenario is relevant. The unreasonable risk determination was  
 5854 based on the submitted monitoring data for 12-hour shifts. The submitted data cover two  
 5855 companies and are summarized in Table 2-6. There is uncertainty in the ONU risk estimate since  
 5856 the data did not distinguish between worker and ONU inhalation exposure estimates. To account  
 5857 for this uncertainty, EPA considered the central tendency estimate when determining ONU risk.  
 5858 As noted previously, EPA has low confidence in the exposure estimates for ONUs. For the  
 5859 purpose of making a risk determination for workers, EPA considered the high-end estimates.  
 5860 While those risk estimates for this condition of use indicate risk in the absence of PPE, the risk  
 5861 estimates for these pathways do not indicate risk for workers when expected use of PPE, a

5862 respirator with an APF of 50, was considered (Table 4-8 and Table 4-11). EPA’s unreasonable  
 5863 risk determination for ONUs reflects the hazards associated with chronic exposure to carbon  
 5864 tetrachloride and is based on an expected absence of PPE for ONUs.  
 5865

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

5866 **5.3.11 Industrial/Commercial Use – Metal recovery**

5867 Section 6(b)(4)(A) unreasonable risk determination for use of carbon tetrachloride in metal  
 5868 recovery:

- 5869 • Does not present an unreasonable risk of injury to health (workers and ONUs).
- 5870 • Does not present an unreasonable risk of injury to the environment (aquatic, sediment
- 5871 dwelling and terrestrial organisms).
- 5872
- 5873

5874 Exposure scenario with highest risk estimate – workers and ONUs:

- 5875 • Liver toxicity from chronic inhalation exposure and cancer from chronic dermal
- 5876 exposure.
- 5877

5878 Benchmarks – workers and ONUs:

- 5879 • Liver toxicity: Benchmark MOE = 30.
- 5880 • Cancer: Benchmark =  $1 \times 10^{-4}$ .
- 5881
- 5882
- 5883

5884 Risk estimates – workers:

- 5886
- Liver toxicity: Chronic inhalation MOE 104 (high end) (Table 4-8).
- 5887
- Cancer: Chronic dermal risk estimate  $6 \times 10^{-5}$  (high end) with PPE (gloves PF 5) (Table
- 5888
- 4-12).
- 5889

5890 Risk estimates – ONUs:

- 5891
- Liver toxicity: Chronic inhalation MOEs 546 and 104 (central tendency and high end) (Table 4-8).
- 5892
- Cancer: Chronic inhalation risk estimates  $3 \times 10^{-5}$  and  $2 \times 10^{-4}$  (central tendency and high
- 5893
- end) (Table 4-11).
- 5894
- 5895
- 5896

5897 Risk Considerations: Risk estimates for workers and ONUs for acute and chronic inhalation and  
 5898 for workers, chronic dermal do not indicate risk. While high-end risk estimates for this condition  
 5899 of use indicate risk in the absence of PPE, risk estimates for these pathways do not indicate risk  
 5900 for workers when expected use of PPE, a respirator with an APF of 10 and gloves with a PF of 5,  
 5901 was considered (Table 4-8, Table 4-11 and Table 4-12). EPA did not separately calculate risk  
 5902 estimates for ONUs and workers. ONU inhalation exposures are expected to be lower than  
 5903 inhalation exposures for workers directly handling the chemical substance; however, the relative  
 5904 exposure of ONUs to workers in these cases cannot be quantified. To account for this  
 5905 uncertainty, EPA considered the central tendency estimate when determining ONU risk. EPA’s  
 5906 risk determination for ONUs is based on an expected absence of PPE. Dermal exposures are not  
 5907 expected for ONUs.  
 5908

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

5909 **5.3.12 Industrial/Commercial Use – Use an additive**

5910 Section 6(b)(4)(A) unreasonable risk determination for the use of carbon tetrachloride as an  
 5911 additive:

- 5912
- Does not present an unreasonable risk of injury to health (workers and ONUs).
- 5913
- Does not present an unreasonable risk of injury to the environment (aquatic, sediment
- 5914
- dwelling and terrestrial organisms).
- 5915
- 5916

5917 Exposure scenario with highest risk estimate – workers and ONUs:

- 5918
- Liver toxicity from chronic inhalation exposure and cancer from chronic dermal
- 5919
- exposure.
- 5920
- 5921

5922 Benchmarks – workers and ONUs:

- 5923
- Liver toxicity: Benchmark MOE = 30.
- 5924
- Cancer: Benchmark =  $1 \times 10^{-4}$ .
- 5925
- 5926

5927 Risk estimates – workers:

5928

- 5929 • Liver toxicity: Chronic inhalation MOE 104 (high end) (Table 4-8)
- 5930 • Cancer: Chronic dermal risk estimate  $6 \times 10^{-5}$  (high end) with PPE (gloves PF 5) (Table 4-12).

5931

5932

5933 Risk estimates – ONUs:

5934

- 5935 • Liver toxicity: Chronic inhalation MOEs 546 and 104 (central tendency and high end) (Table 4-8).
- 5936 • Cancer: Chronic inhalation risk estimates  $3 \times 10^{-5}$  and  $2 \times 10^{-4}$  (central tendency and high end) (Table 4-11).

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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

5952

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

5953

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

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5957

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- 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).

5960 Exposure scenario with highest risk estimate – workers and ONUs:

5961

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5964

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

5965 Benchmarks – workers and ONUs:

5966

- 5967
- Liver toxicity: Benchmark MOE = 30.
- 5968
- Cancer: Benchmark =  $1 \times 10^{-4}$ .
- 5969

5970 Risk estimates – workers:

- 5971
- Liver toxicity: Chronic inhalation MOE 141 (high end) (Table 4-8).
- 5972
- Cancer: Chronic dermal risk estimate  $6 \times 10^{-5}$  (high end) with PPE (gloves PF 5) (Table 4-12).
- 5973
- 5974
- 5975

5976 Risk estimates – ONUs:

- 5977
- Liver toxicity: Chronic inhalation MOEs 346 and 141 (central tendency and high end) (Table 4-8).
- 5978
- Cancer: Chronic inhalation risk estimates  $3 \times 10^{-5}$  and  $2 \times 10^{-4}$  (central tendency and high end) (Table 4-11).
- 5979
- 5980
- 5981
- 5982

5983 Systematic Review confidence rating (hazard): High.

5984

5985 Systematic Review confidence rating (inhalation exposure): High.

5986

5987 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.

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

5999 **5.3.14 Industrial/Commercial Use – Laboratory Chemical**

6000 Section 6(b)(4)(A) unreasonable risk determination for the use of carbon tetrachloride as a laboratory chemical:

6001

6002

- 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).
- 6003
- 6004
- 6005
- 6006



6007 Risk Considerations: As discussed in section 2.4.1.7.8, EPA does not have data to assess worker  
 6008 exposures to carbon tetrachloride during laboratory use. However, due to the expected safety  
 6009 practices when using this chemical in a laboratory setting, carbon tetrachloride is applied in  
 6010 small quantities under a fume hood, thus reducing the potential for inhalation exposures.  
 6011

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

### 6012 **5.3.15 Disposal**

#### 6013 Section 6(b)(4)(A) unreasonable risk determination for disposal of carbon tetrachloride:

- 6014 • Does not present an unreasonable risk of injury to health (workers and ONUs).
- 6016 • Does not present an unreasonable risk of injury to the environment (aquatic, sediment dwelling and terrestrial organisms).

#### 6018 Exposure scenario with highest risk estimate – workers and ONUs:

- 6019 • Liver toxicity from chronic inhalation exposure and cancer from chronic dermal exposure.

#### 6020 Benchmarks – workers and ONUs:

- 6021 • Liver toxicity: Benchmark MOE = 30.
- 6022 • Cancer: Benchmark =  $1 \times 10^{-4}$ .

#### 6023 Risk estimates – workers:

- 6024 • Liver toxicity: Chronic inhalation MOE 104 (high end) (Table 4-8).
- 6026 • Cancer: Chronic dermal risk estimate  $6 \times 10^{-5}$  (high end) with PPE (gloves PF 5) (Table 4-12).

#### 6028 Risk estimates – ONUs:

- 6029 • Liver toxicity: Chronic inhalation MOEs 546 and 104 (central tendency and high end) (Table 4-8).
- 6031 • Cancer: Chronic inhalation risk estimates  $3 \times 10^{-5}$  and  $2 \times 10^{-4}$  (central tendency and high end) (Table 4-11).

6032 Risk Considerations: Risk estimates for workers and ONUs for acute and chronic inhalation and  
 6033 for workers, chronic dermal do not indicate risk. While high-end risk estimates for this condition  
 6034 of use indicate risk in the absence of PPE, risk estimates for these pathways do not indicate risk  
 6035 for workers when expected use of PPE, a respirator with an APF of 10 and gloves with a PF of 5,  
 6036 was considered (Table 4-8, Table 4-11 and Table 4-12). EPA did not separately calculate risk  
 6037 estimates for ONUs and workers. ONU inhalation exposures are expected to be lower than  
 6047

6048 inhalation exposures for workers directly handling the chemical substance; however, the relative  
 6049 exposure of ONUs to workers in these cases cannot be quantified. To account for this  
 6050 uncertainty, EPA considered the central tendency estimate when determining ONU risk. EPA's  
 6051 risk determination for ONUs is based on an expected absence of PPE. Dermal exposures are not  
 6052 expected for ONUs.  
 6053

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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6763 **7 APPENDICES**

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6765 **Appendix A REGULATORY HISTORY**

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6767 **A.1 Federal Laws and Regulations**6768 **Table Apx A-1. Federal Laws and Regulations**

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
<b>EPA Regulations</b>		
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
	<p>or exemption from tolerance, EPA must determine that the tolerance or exemption is “safe.” Sections 408(b) and (c) of the FFDCFA 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 FFDCFA 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.</p>	
CAA - Section 112(b)	<p>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.</p>	<p>Lists carbon tetrachloride as a HAP (70 FR 75047, December 19, 2005).</p>
CAA - Section 112(d)	<p>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).</p>	<p>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)</p>

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
		<p>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)</p>
<p>CAA – Sections 112(d) and 112(f)</p>	<p>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.</p>	<p>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.</p>
<p>CAA - Section 604</p>	<p>Establishes a mandatory phase-out of ozone depleting substances.</p>	<p>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.</p>
<p>CWA - Section 304(a)(1)</p>	<p>Requires EPA to develop and publish ambient water quality criteria (AWQC) reflecting the latest scientific knowledge on the effects on human</p>	<p>In 2015, EPA published updated AWQC for carbon tetrachloride, including recommendations for “water +</p>

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
	<p>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.</p>	
<p>Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) - Sections 102(a) and 103</p>	<p>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.</p>	<p>Carbon tetrachloride is a hazardous substance under CERCLA. Releases of carbon tetrachloride in excess of 10 pounds must be reported (40 CFR 302.4).</p>
<p>RCRA - Section 3001</p>	<p>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.</p>	<p>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).</p> <p>RCRA solid waste that leaches 0.5 mg/L or more carbon</p>



Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
		<p>tetrachloride when tested using the TCLP leach test is RCRA hazardous (D019) under 40 CFR 261.24 (55 FR 11798 March 29, 1990).</p> <p>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).</p>
<b>Other Federal Regulations</b>		
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.	<p>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).</p> <p>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).</p> <p>Carbon tetrachloride is also listed as an “Inactive Ingredient for approved Drug Products” by FDA (FDA</p>

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
		Inactive Ingredient Database. Accessed April 13, 2017).
OSHA	<p>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.</p> <p>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.</p>	<p>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).</p> <p>OSHA prohibits all workplaces from using portable fire extinguishers containing carbon tetrachloride (29 CFR 1910.157(c)(3)).</p>
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).

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6771 **A.2 State Laws and Regulations**

6772 **Table\_Apx A-2. State Laws and Regulations**

State Actions	Description of Action
<b>State agencies of interest</b>	
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
<b>State agencies of interest</b>	
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).

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### A.3 International Laws and Regulations

**Table\_Apx A-3. Regulatory Actions by Other Governments and Tribes**

Country/Organization	Requirements and Restrictions
<b>Regulatory Actions by other Governments and Tribes</b>	
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
	<p>Authorisation and Restriction of Chemicals) ECHA database. Accessed April 18, 2017).</p> <p>Carbon tetrachloride is restricted by regulation (EC) No 2037/2000 on substances that deplete the ozone layer.</p>
Australia	<p>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, <i>Environment Tier II Assessment for Methane, Tetrachloro-</i>. Accessed April, 18 2017).</p>
Japan	<p>Carbon tetrachloride is regulated in Japan under the following legislation:</p> <ul style="list-style-type: none"> <li>• Industrial Safety and Health Act (ISHA)</li> <li>• Act on the Evaluation of Chemical Substances and Regulation of Their Manufacture, etc. (Chemical Substances Control Law (CSCL))</li> <li>• Act on Confirmation, etc. of Release Amounts of Specific Chemical Substances in the Environment and Promotion of Improvements to the Management Thereof</li> <li>• Poisonous and Deleterious Substances Control Act</li> <li>• Act on the Protection of the Ozone Layer through the Control of Specified Substances and Other Measures</li> <li>• Air Pollution Control Law</li> <li>• Water Pollution Control Law</li> <li>• Soil Contamination Countermeasures Act</li> </ul> <p>(National Institute of Technology and Evaluation (NITE) Chemical Risk Information Platform (CHIRP). Accessed April 13, 2017).</p>
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	<p>Occupational exposure limits (OELs) for carbon tetrachloride. (GESTIS International limit values for chemical agents (Occupational exposure limits, OELs) database. Accessed April 18, 2017).</p>
Basel Convention	<p>Halogenated organic solvents (Y41) are listed as a category of waste under the Basel Convention-Annex I. Although the United States is</p>

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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## 6778 **Appendix B LIST OF SUPPLEMENTAL DOCUMENTS**

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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](#)).*

6820 **Appendix C FATE AND TRANSPORT**

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**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	<u>Biodegradation parameter: percent removal:</u> 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.	( <a href="#">Van Eekert et al., 1998</a> )	High
Other	≤149 µg/L	activated sludge, adapted	anaerobic	54 days	<u>Biodegradation parameter: percent removal by radiolabel:</u> 100%/16d	The reviewer agreed with this study's overall quality level.	( <a href="#">Bouwer and McCarty, 1983</a> )	High
Other	≤16 µg/L	activated sludge, adapted	anaerobic	19 months	<u>Biodegradation parameter: concentration in column effluent (initial concentration: 16 µg/L, liquid retention: 2 days):</u> <0.1 µg/L	The reviewer agreed with this study's overall quality level.	( <a href="#">Bouwer and McCarty, 1983</a> )	High

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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)	<u>Biodegradation parameter: percent removal:</u> Avg. 89%/7 days	The reviewer agreed with this study's overall quality level.	( <a href="#">Tabak et al., 1981</a> )	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 )	<u>Biodegradation parameter: percent removal via dechlorination:</u> 100%/30 weeks; transformation products included chloroform and dichloro-methane.	The reviewer agreed with this study's overall quality level.	( <a href="#">de Best et al., 1997</a> )	High
Soil								
Other	100 mg/kg	Microbial colonies on agar plates revealed that autoclave controls were devoid of microbial activity.	not specified	7 days	<u>Biodegradation parameter: half-life:</u> 50%/5 days	The reviewer agreed with this study's overall quality level.	( <a href="#">Anderson et al., 1991</a> )	Medium

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6824 **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	<u>Photodegradation parameter: atmospheric lifetime or residence time:</u> 30-50 years	The reviewer agreed with this study's overall quality level.	( <a href="#">Molina and Rowland, 1974</a> )	High
Photochemical oxidation using photolysis of nitrous acid in air as a source of hydroxyl radicals	360 nm	Not reported	<u>Photodegradation parameter: Tropospheric lifetime:</u> >330 years	The reviewer agreed with this study's overall quality level.	( <a href="#">Cox et al., 1976</a> )	High
Absorption	160-275	700 seconds	<u>Photodegradation parameter: absorption: threshold wavelength =</u> 253 nm	The reviewer agreed with this study's overall quality level.	( <a href="#">Hubrich and Stuhl, 1980</a> )	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	<u>Photodegradation parameter: percent transformation via reductive dechlorination:</u> 84%/33d (Ferrous; dark); 99.9%/33d (Ferrous; light)	The reviewer agreed with this study's overall quality level.	( <a href="#">Doong and Wu, 1992</a> )	High

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6826 **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	<u>Hydrolysis parameter: half-life (298K and 1ppm):</u> 7000 years.	The reviewer agreed with this study's overall quality level.	( <a href="#">Mabey and Mill, 1978</a> )	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		<u>Sorption parameter: log K<sub>oc</sub>(sw,eq.):</u> 1.67	The reviewer agreed with this study's overall quality level.	( <a href="#">Roose et al., 2001</a> )	High
Equilibrium and two-site models applied to field and laboratory experiments to determine transport behavior (including K <sub>d</sub> )	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		<u>Sorption parameter: K<sub>d</sub>:</u> 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.	( <a href="#">Ptacek and Gillham, 1992</a> )	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		<u>Sorption parameter: log K<sub>f</sub>: lignite and peat, respectively:</u> 2.29, 1/n = 0.916 and 1.59, 1/n = 0.879	The reviewer agreed with this study's overall quality level.	( <a href="#">Endo et al., 2008</a> )	High

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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%		<u>Sorption parameter: Kd:</u> 0.39 L/kg; retardation factor (Rf) 2.64	The reviewer agreed with this study's overall quality level.	( <a href="#">Zhao et al., 1999</a> )	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		<u>Sorption parameter: Koc:</u> 48.89 +/-16.16; <u>Sorption parameter: Kp:</u> 0.323 +/-0.107	The reviewer agreed with this study's overall quality level. Study reported in ECHA (ECHA, <a href="#">Adsorption/desorption: Carbon tetrachloride, 2017.</a> )	( <a href="#">Walton et al., 1992</a> )	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		<u>Sorption parameter: log Kp: primary sludge, mixed-liquor solids and digested, sludge, respectively:</u> 2.66, 2.80, 2.49	The reviewer agreed with this study's overall quality level.	( <a href="#">Dobbs et al., 1989</a> )	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		<u>Sorption parameter: Koc:</u> 143.6 +/-32.11; <u>Sorption parameter: Kp:</u>	The reviewer agreed with this study's overall quality level. Study	( <a href="#">Walton et al., 1992</a> )	High

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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. <a href="#">Adsorption/desorption: Carbon tetrachloride. 2017.</a> )		
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		<u>Sorption parameter: Kd: T17 core sample and T18 core sample, respectively:</u> 0.367, 1.44	The reviewer agreed with this study's overall quality level.	<a href="#">(Riley et al., 2010)</a>	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,		<u>Sorption parameter: log Koc: Modern A horizon, Buried A and Loess C horizon sites, respectively:</u> 1.74 (±0.04), 1.89 (±0.10), 2.43 (±0.18)	The reviewer agreed with this study's overall quality level.	<a href="#">(Duffy et al., 1997)</a>	High

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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%		<u>Sorption parameter: Kom: peat and muck respectively: 44.6, 27.8</u>	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."	<a href="#">(Rutherford and Chiou, 1992)</a>	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		<u>Sorption parameter: Kom: peqt, peat, muck, and cellulose respectively: 73.5, 44.6, 27.8, and 1.75</u>	The reviewer agreed with this study's overall quality level.	<a href="#">(Rutherford et al., 1992)</a>	High

PEER REVIEW DRAFT, DO NOT CITE OR QUOTE

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		<u>Sorption parameter: Kd: Silty/fine sand, Medium sand, Coarse sand, and Very coarse sand, respectively:</u> 0.162, 0.233, 0.494, 0.376	The reviewer agreed with this study's overall quality level.	<a href="#">(Zhao et al., 2005)</a>	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		<u>Sorption parameter: Kd:</u> 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.	<a href="#">(Larsen et al., 1992)</a>	High
Adsorption/desorption in soil	EPA standard soil (FW Enviresponse,	OC 0.8%; sand 56.4% clay		<u>Sorption parameter: Monolayer adsorption capacity X<sub>m</sub>:</u>	The reviewer agreed with this study's overall quality level.	<a href="#">(Thibaud et al., 1992)</a>	High

PEER REVIEW DRAFT, DO NOT CITE OR QUOTE

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; <u>Sorption parameter: adsorption capacity at saturation X<sub>a</sub>:</u> 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		<u>Sorption parameter: K<sub>d</sub>:</u> 0.03-0.24, R <sub>f</sub> : .2-2.3	The reviewer agreed with this study's overall quality level.	( <a href="#">Mackay et al., 1994</a> )	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	<u>Sorption parameter: <math>\tau</math>-soil (partial lifetime of atmospheric CT due to soil removal):</u> 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.	( <a href="#">Happell and Roche, 2003</a> )	High
Calculation; Carbon tetrachloride concentrations in air	boreal forest soil in Alberta, Canada; sub-	Not reported		<u>Sorption parameter: <math>\tau</math>-soil (partial lifetime of</u>	The reviewer agreed with this study's overall quality level.	( <a href="#">Happell et al., 2014</a> )	High

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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			<u>atmospheric CT due to soil removal</u> : 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)		<u>Sorption parameter: Koc</u> : 45; <u>Sorption parameter: Kf</u> : 0.62 (Hastings); 1.18 (Overton)	The reviewer agreed with this study's overall quality level.	( <a href="#">Rogers and McFarlane, 1981</a> )	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%		<u>Sorption parameter: Kd</u> : 1.0 ± 0.2, Rf = 6 ± 1.0	The reviewer agreed with this study's overall quality level.	( <a href="#">Harmon et al., 1992</a> )	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%		<u>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</u> : 0.7, 0.4, 0.1, <0.05, <0.05	The reviewer agreed with this study's overall quality level.	( <a href="#">Urano and Murata, 1985</a> )	Medium
Other	Eglin-Florida Soil	OC 1.6%; 91.7% sand,		<u>Sorption parameter: Henry's isotherm constant K</u> :	The reviewer downgraded this study's overall quality rating.	( <a href="#">Peng and Dural, 1998</a> )	Low



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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 <u>Sorption parameter: normalized isotherm constant Ki:</u> 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		<u>Sorption parameter: Henry's isotherm constant K:</u> 1.695 <u>Sorption parameter: normalized isotherm constant Ki:</u> 0.301	The reviewer downgraded this study's overall quality rating. They noted: No controls or analytical details were reported.	( <a href="#">Peng and Dural, 1998</a> )	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		<u>Sorption parameter: Koc:</u> 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.	( <a href="#">Kile et al., 1995</a> )	Low
Other	Visalia-California Soil	OC 1.7%; 45.1% sand, 35.2% silt, 21.7% clay, pH 8.1		<u>Sorption parameter: Henry's isotherm constant K:</u> 1.483 <u>Sorption parameter: normalized isotherm constant Ki:</u> 0.459	The reviewer downgraded this study's overall quality rating. They noted: No controls or analytical details were reported.	( <a href="#">Peng and Dural, 1998</a> )	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%		<u>Sorption parameter: Koc:</u> 49-89	The reviewer downgraded this study's overall quality rating. They noted: Limited	( <a href="#">Kile et al., 1995</a> )	Low

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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%		<u>Sorption parameter: Koc:</u> 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.	( <a href="#">Kile et al., 1995</a> )	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		<u>Sorption parameter: Koc:</u> 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.	( <a href="#">Kile et al., 1995</a> )	Low
Partitioning in clays	clay:water			<u>Sorption parameter: Kgm (adsorption equilibrium constant gas/mineral):</u> 90 at 0%RH; 3.6 at 80%RH	The reviewer agreed with this study's overall quality level.	( <a href="#">Cabbar et al., 1998</a> )	Low
Vapor sorption of CT using synthetic clay pellets	Synthetic clay: montmorillonite-type natural clay and humic acid			<u>Sorption parameter: coefficient that considers:</u> (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	( <a href="#">Cabbar, 1999</a> )	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
				<p><u>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:</u>                      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</p>	<p>provided, and results were not environmentally relevant.</p>		
<p>Sorption/desorption of organic vapors on single particles using an electrodynamic thermogravimetric analyzer</p>	<p>Spherocarb, montmorillonite, and Carbopack particles</p>	<p>0.63, 0.62, 0.95 g/cm<sup>3</sup></p>		<p><u>Sorption parameter:</u> 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</p>	<p>The test method was not relevant to conceptual model for this compound.</p>	<p>(<a href="#">Tognotti et al., 1991</a>)</p>	<p>Unacceptable</p>

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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)	<p><u>Parameter: Kaw(L/g):</u>  <u>air:tree-core (sorption):</u>                      0.055±0.008; <u>air:tree-cutting (sorption):</u>                      0.042±0.007; <u>air:tree-cutting (desorption):</u>                      0.072±0.008;  <u>Parameter: Klw(L/g):</u>  <u>water:biomass:</u>                      0.0593±0.0066                      (measured) 0.0239                      (calculated)</p>	The reviewer agreed with this study's overall quality level.	( <a href="#">Ma and Burken, 2002</a> )	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.	<p><u>Parameter: partitioning:</u>                      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</p>	The reviewer agreed with this study's overall quality level.	( <a href="#">Chen et al., 2014</a> )	High

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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	<u>Parameter: effect on soil microbial respiration:</u> 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	<u>Parameter: abiotic dechlorination (50 °C):</u> 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**

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**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 <sup>a</sup>	Total On- and Off-Site Disposal or Other Releases <sup>b, c</sup>
		Stack Air Releases	Fugitive Air Releases		Class I Under-ground Injection	RCRA Subtitle C Landfills	All other Land Disposal <sup>a</sup>		
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](#)).

<sup>a</sup> Terminology used in these columns may not match the more detailed data element names used in the TRI public data and analysis access points.

<sup>b</sup> These release quantities do include releases due to one-time events not associated with production such as remedial actions or earthquakes.

<sup>c</sup> Counts release quantities once at final disposition, accounting for transfers to other TRI reporting facilities that ultimately dispose of the chemical waste.

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6842 **Appendix E SURFACE WATER ANALYSIS FOR CARBON**  
 6843 **TETRACHLORIDE**

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 6845 EPA identified additional data on ecological hazards requiring an update of the analysis of  
 6846 carbon tetrachloride releases and surface water concentrations (see Appendix H). In order to  
 6847 update the analysis, EPA expanded the release data as reported by facilities in the Discharge  
 6848 Monitoring Reports (in EPA's ECHO) to five years of releases (2014 through 2018) and  
 6849 expanded the number of facilities releasing carbon tetrachloride in any given year in order to  
 6850 capture the range and variability of releases.  
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6852 **Table E-1. Releases of Carbon Tetrachloride to Surface Waters<sup>a</sup>**

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 <sup>b</sup>	0	0	0	--	--
OH0007269	Dover Chemical Corp	320 <sup>c</sup>	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

6853 <sup>a</sup>2014 to 2018 data from the EPA [ECHO](#) website

6854 <sup>b</sup>San Diego Sea World facility (CA0107336) was not included in the analysis since the reported level is  
6855 above permit discharge limits; noncompliance and spills are not in the scope of this risk evaluation.

6856 <sup>c</sup>A 2014 accidental spill/release of carbon tetrachloride likely contributed to the larger release of the  
6857 chemical compared to the following 4 years; noncompliance and spills are not in the scope of this risk  
6858 evaluation. (<https://www.timesreporter.com/article/20140716/news/140719487>)

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

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

6864 <sup>a</sup>Acute COC = 90 µg/L

6865 <sup>b</sup>Chronic COC = 3 µg/L

6866 <sup>c</sup>San Diego Sea World facility (CA0107336) was not included in the analysis since the reported level is above permit discharge limits;  
 6867 noncompliance and spills are not in the scope of this risk evaluation.

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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 <sup>a</sup> Exceeded (PDM)	Amount Discharged for 250 days (kg/day)	250 Day Stream Conc. (µg/L)	Days Algal COC <sup>a</sup> 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 <sup>b</sup>						
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

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

6874 <sup>a</sup>Algal COC = 7 µg/L

6875 <sup>b</sup>San Diego Sea World facility (CA0107336) was not included in the analysis since the reported level is above permit discharge limits;  
 6876 noncompliance and spills are not in the scope of this risk evaluation.

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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 <sup>a</sup> Exceeded (PDM)	Amount Discharged for 250 days (kg/day)	250 Day Stream Conc. (µg/L)	Days Algae COC <sup>b</sup> 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 <sup>c</sup>						
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

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NPDES	Facility Name	Amount Discharged for 20 days (kg/day)	20 Day Stream Conc. (µg/L)	Days Algae COC <sup>a</sup> Exceeded (PDM)	Amount Discharged for 250 days (kg/day)	250 Day Stream Conc. (µg/L)	Days Algae COC <sup>b</sup> 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

6880 <sup>a,b</sup>Algal COC = 7 µg/L  
 6881 <sup>c</sup>San Diego Sea World facility (CA0107336) was not included in the analysis since the reported level is above permit discharge limits;  
 6882 noncompliance and spills are not in the scope of this risk evaluation  
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6887 **Appendix F OCCUPATIONAL EXPOSURES**

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6889 For additional information on the developmental details, methodology, approach, and results of  
6890 any part of the occupational exposure determination process, refer to the supplemental document  
6891 *Risk Evaluation for Carbon Tetrachloride, Supplemental Information on Releases and*  
6892 *Occupational Exposure Assessment* ([U.S. EPA, 2019b](#)).

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6893 **Appendix G ENVIRONMENTAL HAZARDS**

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6895 **G.1 Systematic Review**

6896 EPA reviewed ecotoxicity studies for carbon tetrachloride according to the data quality  
 6897 evaluation criteria found in the *Application of Systematic Review in TSCA Risk Evaluations* ([U.S.  
 6898 EPA, 2018a](#)). The detailed data quality evaluation results of the 14 on-topic studies for carbon  
 6899 tetrachloride environmental hazard are presented in the document Risk Evaluation for Carbon  
 6900 Tetrachloride, Systematic Review Supplemental File: Data Quality Evaluation of Environmental  
 6901 Hazard Studies ([U.S. EPA, 2019e](#)). The data quality extraction results for carbon tetrachloride  
 6902 environmental hazard are presented in Table\_Apx G-1.

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6904 **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
<b>Fish</b>								
Rainbow trout ( <i>Oncorhynchus mykiss</i> )	Fresh	24-hour	LD <sub>50</sub> = 4.75 mL/kg body weight	1.6-5.0 mL/kg	Intra- peritoneal, Nominal	Mortality	( <a href="#">Weber et al., 1979</a> )	High
Rainbow trout ( <i>Oncorhynchus mykiss</i> )	Fresh	24-hour	LOAEL = 0.2 mL/kg body weight	0, 0.2, 2.0 mL/kg	Intra- peritoneal, Nominal	Plasma clearance of sulfobromoph thalein	( <a href="#">Weber et al., 1979</a> )	High
Rainbow trout ( <i>Oncorhynchus mykiss</i> )	Fresh	48-hour	LOAEL = 2 mL/kg body weight	0, 2.0 mL/kg	Intra- peritoneal, Nominal	Plasma clearance of sulfobromoph thalein	( <a href="#">Weber et al., 1979</a> )	High
Rainbow trout ( <i>Oncorhynchus mykiss</i> )	Fresh	96-hour	LOAEL = 2 mL/kg body weight	0, 2.0 mL/kg	Intra- peritoneal, Nominal	Plasma clearance of sulfobromoph thalein	( <a href="#">Weber et al., 1979</a> )	High
Rainbow trout ( <i>Oncorhynchus mykiss</i> )	Fresh	24-hour	LOAEL = 1 mL/kg body weight	0, 1.0, 2.0 mL/kg	Intra- peritoneal, Nominal	Glutamic pyruvic transaminase activity	( <a href="#">Weber et al., 1979</a> )	High
Rainbow trout ( <i>Oncorhynchus mykiss</i> )	Fresh	48-hour	LOAEL = 1 mL/kg body weight	0, 1.0, 2.0 mL/kg	Intra- peritoneal, Nominal	Glutamic pyruvic transaminase activity	( <a href="#">Weber et al., 1979</a> )	High
Rainbow trout ( <i>Oncorhynchus mykiss</i> )	Fresh	24-hour	LOAEL = 1 mL/kg body weight	0, 1.0, 2.0 mL/kg	Intra- peritoneal, Nominal	Increased body weight gain	( <a href="#">Weber et al., 1979</a> )	High



Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Rainbow trout ( <i>Oncorhynchus mykiss</i> )	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 ( <i>Oncorhynchus mykiss</i> )	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 ( <i>Oncorhynchus mykiss</i> )	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 ( <i>Oncorhynchus mykiss</i> )	Fresh	23-day	LC <sub>50</sub> = 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 ( <i>Oncorhynchus mykiss</i> )	Fresh	27-day	LC <sub>50</sub> = 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 ( <i>Oncorhynchus mykiss</i> )	Fresh	23-day	LC <sub>100</sub> = 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 ( <i>Oncorhynchus mykiss</i> )	Fresh	27-day	LC <sub>100</sub> = 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 ( <i>Oncorhynchus mykiss</i> )	Fresh	16-day	NOAEL = 8 mg AI/L	0, 8 mg/L	Renewal, Nominal	Lipid peroxidation	(Bauder et al., 2005)	High
Rainbow trout ( <i>Oncorhynchus mykiss</i> )	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 ( <i>Oncorhynchus mykiss</i> )	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 ( <i>Oncorhynchus mykiss</i> )	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 ( <i>Oncorhynchus mykiss</i> )	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 hepatecto my at 4 months	Hepatic lesions	( <a href="#">Kotsanis and Metcalf, 1988</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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 dehydrogenas e activity	( <a href="#">Jia et al., 2013</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2013</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2013</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2013</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2013</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2013</a> )	High

Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2013</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2013</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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 malondialdeh yde in blood	( <a href="#">Jia et al., 2013</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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)	( <a href="#">Jia et al., 2013</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2013</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2013</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2014</a> )	High

Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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 malondialdeh yde in blood	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2014</a> )	High

Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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 histopatholog y	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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- $\kappa$ B cREL subunit gene expression	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2014</a> )	High

Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	16-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Hepatocyte viability	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	0-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Hepatocyte viability	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	2-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Hepatocyte viability	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	1-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Hepatocyte viability	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	4-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Hepatocyte viability	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	8-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Hepatocyte viability	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	0-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 3 activity	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	1-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 3 activity	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	2-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 3 activity	( <a href="#">Jia et al., 2014</a> )	High

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Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Common carp ( <i>Cyprinus carpio</i> )	Fresh	8-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 3 activity	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	4-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 3 activity	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	16-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 3 activity	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	0-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 8 activity	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	1-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 8 activity	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	2-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 8 activity	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	4-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 8 activity	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	8-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 8 activity	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	16-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 8 activity	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	0-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 9 activity	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	1-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 9 activity	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	2-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 9 activity	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	4-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 9 activity	( <a href="#">Jia et al., 2014</a> )	High

Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Common carp ( <i>Cyprinus carpio</i> )	Fresh	8-hour	LOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 9 activity	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	16-hour	NOAEL = 1,230.56 mg AI/L	0, 1230.56 mg/L	In vitro, Nominal	Caspase 9 activity	( <a href="#">Jia et al., 2014</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	In vitro, Nominal	Adenosine triphosphate in liver	( <a href="#">Liu et al., 2015</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	In vitro, Nominal	Glutamic pyruvic transaminase activity	( <a href="#">Liu et al., 2015</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	In vitro, Nominal	Glutamic- oxaloacetic transaminase activity	( <a href="#">Liu et al., 2015</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	In vitro, Nominal	Alkaline phosphatase activity	( <a href="#">Liu et al., 2015</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	In vitro, Nominal	Lactate dehydrogenase activity	( <a href="#">Liu et al., 2015</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	In vitro, Nominal	Malondialdehyde content in liver	( <a href="#">Liu et al., 2015</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	In vitro, Nominal	Superoxide dismutase activity	( <a href="#">Liu et al., 2015</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	In vitro, Nominal	Glutathione peroxidase activity	( <a href="#">Liu et al., 2015</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	In vitro, Nominal	Glutathione S-transferase activity	( <a href="#">Liu et al., 2015</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	In vitro, Nominal	Catalase activity	( <a href="#">Liu et al., 2015</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Liu et al., 2015</a> )	High



Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Common carp ( <i>Cyprinus carpio</i> )	Fresh	4-hour	LOAEL = 1,845.84 mg AI/L	0, 1,845.84 mg/L	In vitro, Nominal	Total antioxidant capacity	( <a href="#">Liu et al., 2015</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Liu et al., 2015</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Liu et al., 2015</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Liu et al., 2015</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	Malondialdeh yde content in liver	( <a href="#">Liu et al., 2015</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Liu et al., 2015</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Liu et al., 2015</a> )	High

Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Liu et al., 2015</a> )	High
Common carp ( <i>Cyprinus carpio</i> )	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	( <a href="#">Liu et al., 2015</a> )	High
Bluegill ( <i>Lepomis macrochirus</i> )	Fresh	21-day	BCF = 30	0.0523 mg AI/L	Flow- through, Measured, Solvent: Acetone	Residue, whole body	( <a href="#">Barrows et al., 1980</a> )	High
Bluegill ( <i>Lepomis macrochirus</i> )	Fresh	24-hour	LC <sub>50</sub> = 38 mg/L	Not reported	Static, Nominal, Solvent: Not specified	Mortality	( <a href="#">Buccafusco et al., 1981</a> )	Medium
Bluegill ( <i>Lepomis macrochirus</i> )	Fresh	96-hour	LC <sub>50</sub> = 27 mg/L	Not reported	Static, Nominal, Solvent: Not specified	Mortality	( <a href="#">Buccafusco et al., 1981</a> )	Medium
Fathead minnow ( <i>Pimephales promelas</i> )	Fresh	96-hour	LC <sub>50</sub> = 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	( <a href="#">Geiger et al., 1990</a> )	High
Fathead minnow ( <i>Pimephales promelas</i> )	Fresh	96-hour	EC <sub>50</sub> = 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	( <a href="#">Geiger et al., 1990</a> )	High
Fathead minnow ( <i>Pimephales promelas</i> )	Fresh	96-hour	LC <sub>50</sub> = 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	( <a href="#">Kimball, 1978</a> )	High
Fathead minnow ( <i>Pimephales promelas</i> )	Fresh	96-hour	LC <sub>50</sub> = 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	( <a href="#">Kimball, 1978</a> )	High
Fathead minnow ( <i>Pimephales promelas</i> )	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	( <a href="#">Kimball, 1978</a> )	High

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Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Fathead minnow ( <i>Pimephales promelas</i> )	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	( <a href="#">Kimball, 1978</a> )	High
Fathead minnow ( <i>Pimephales promelas</i> )	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	( <a href="#">Kimball, 1978</a> )	High
Fathead minnow ( <i>Pimephales promelas</i> )	Fresh	>7 days	LC <sub>100</sub> = 73.2 mg AI/L	0, 9.7, 10.5, 19.6, 37.1, 73.2, 181.0 mg/L	Flow-through, Measured	Mortality	( <a href="#">Kimball, 1978</a> )	High
Fathead minnow ( <i>Pimephales promelas</i> )	Fresh	96-hour	LC <sub>50</sub> = 10.4 mg AI/L	Not reported	Static, Measured	Mortality	( <a href="#">Brooke, 1987</a> )	High
Fathead minnow ( <i>Pimephales promelas</i> )	Fresh	96-hour	LC <sub>50</sub> = 41.4 mg AI/L	Not reported	Flow-through, Measured	Mortality	( <a href="#">Brooke, 1987</a> )	High
Fathead minnow ( <i>Pimephales promelas</i> )	Fresh	5-day	LC <sub>100</sub> = 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	( <a href="#">Black et al., 1982</a> )	High
Fathead minnow ( <i>Pimephales promelas</i> )	Fresh	9-day	LC <sub>100</sub> = 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	( <a href="#">Black et al., 1982</a> )	High
Fathead minnow ( <i>Pimephales promelas</i> )	Fresh	5-day	LC <sub>50</sub> = 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	( <a href="#">Black et al., 1982</a> )	High
Fathead minnow ( <i>Pimephales promelas</i> )	Fresh	9-day	LC <sub>50</sub> = 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	( <a href="#">Black et al., 1982</a> )	High
Japanese medaka ( <i>Oryzias latipes</i> )	Fresh	10-day	LC <sub>50</sub> = 96 mg AI/L	0, 58, 70, 84, 101, 121, 145 mg/L	Renewal, Nominal	Mortality	( <a href="#">Schell, 1987</a> )	High
Japanese medaka ( <i>Oryzias latipes</i> )	Fresh	10-day	LC <sub>100</sub> = 145 mg AI/L	0, 58, 70, 84, 101, 121, 145 mg/L	Renewal, Nominal	Mortality	( <a href="#">Schell, 1987</a> )	High
Japanese medaka ( <i>Oryzias latipes</i> )	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	( <a href="#">Schell, 1987</a> )	High

Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Mozambique tilapia ( <i>Oreochromis mossambicus</i> )	Fresh	24-hour	LOAEL = 9 mg/L	0, 9 mg/L	Static, Nominal	Malondialdehyde content in liver	( <a href="#">de Vera and Pocsidio, 1998</a> )	High
Mozambique tilapia ( <i>Oreochromis mossambicus</i> )	Fresh	48-hour	NOAEL = 9 mg/L	0, 9 mg/L	Static, Nominal	Malondialdehyde content in liver	( <a href="#">de Vera and Pocsidio, 1998</a> )	High
Mozambique tilapia ( <i>Oreochromis mossambicus</i> )	Fresh	72-hour	NOAEL = 9 mg/L	0, 9 mg/L	Static, Nominal	Malondialdehyde content in liver	( <a href="#">de Vera and Pocsidio, 1998</a> )	High
Mozambique tilapia ( <i>Oreochromis mossambicus</i> )	Fresh	96-hour	LOAEL = 9 mg/L	0, 9 mg/L	Static, Nominal	Malondialdehyde content in liver	( <a href="#">de Vera and Pocsidio, 1998</a> )	High
Mozambique tilapia ( <i>Oreochromis mossambicus</i> )	Fresh	168-hour	LOAEL = 9 mg/L	0, 9 mg/L	Static, Nominal	Malondialdehyde content in liver	( <a href="#">de Vera and Pocsidio, 1998</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	Fresh	42-44-hour	LOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intra-peritoneal, Nominal	Hematocrit	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	Fresh	42-44-hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intra-peritoneal, Nominal	Muscle water content	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High

Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High

Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	Fresh	42-44- hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intra- peritoneal, Nominal	Anion gap	( <a href="#">Chen et al., 2004</a> )	High

Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Nile tilapia ( <i>Oreochromis niloticus</i> )	Fresh	42-44- hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intra- peritoneal, Nominal	Total protein	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	Fresh	42-44- hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intra- peritoneal, Nominal	Glucose	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	Fresh	42-44- hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intra- peritoneal, Nominal	Cholesterol	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	Fresh	42-44- hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intra- peritoneal, Nominal	Bilirubin	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	Fresh	42-44- hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intra- peritoneal, Nominal	Alanine transaminase activity	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	Fresh	42-44- hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intra- peritoneal, Nominal	Aspartate aminotransfer ase activity	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	Fresh	42-44- hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intra- peritoneal, Nominal	Alkaline phosphatase activity	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	Fresh	42-44- hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intra- peritoneal, Nominal	Creatine kinase activity	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High

Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	Fresh	42-44- hour	NOAEL = 1.12 mL/kg body weight	0, 1.12 mL/kg body weight	Intra- peritoneal, Nominal	Body weight	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High



Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Nile tilapia ( <i>Oreochromis niloticus</i> )	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	( <a href="#">Chen et al., 2004</a> )	High
Tidewater silversides ( <i>Menidia beryllina</i> )	Salt	96-hour	LC <sub>50</sub> = 150 mg/L	0, 75, 100, 125, 200, 320 mg/L	Static, Nominal, Solvent: Not specified	Mortality	( <a href="#">Dawson et al., 1977</a> )	Medium
Bluegill ( <i>Lepomis macrochirus</i> )	Fresh	96-hour	LC <sub>50</sub> = 125 mg/L	0, 75, 100, 125, 200, 320 mg/L	Static, Nominal, Solvent: Not specified	Mortality	( <a href="#">Dawson et al., 1977</a> )	Medium

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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 <sub>50</sub> = 38 mg AI/L	Not reported	Static, Measured	Mortality	(Freitag et al., 1994)	High
<i>Aquatic Invertebrates</i>								
Water flea ( <i>Daphnia magna</i> )	Fresh	24-hour	LC <sub>50</sub> = 35 mg AI/L	Not reported	Static, Nominal, Solvent: Unknown	Mortality	(LeBlanc, 1980)	High
Water flea ( <i>Daphnia magna</i> )	Fresh	48-hour	LC <sub>50</sub> = 35 mg AI/L	Not reported	Static, Nominal, Solvent: Unknown	Mortality	(LeBlanc, 1980)	High
Water flea ( <i>Daphnia magna</i> )	Fresh	48-hour	NOEC = 7.7 mg AI/L	Not reported	Static, Nominal, Solvent: Unknown	Mortality	(LeBlanc, 1980)	High
Water flea ( <i>Daphnia magna</i> )	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 ( <i>Daphnia magna</i> )	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 ( <i>Daphnia magna</i> )	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 ( <i>Daphnia magna</i> )	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 ( <i>Daphnia magna</i> )	Fresh	3.5-hour	LC <sub>0</sub> = 75 mg AI/L	0, 75 mg/L	Static, Nominal	Mortality	(Martins et al., 2007b)	High
Water flea ( <i>Daphnia magna</i> )	Fresh	3.5-hour	NOAEL = 75 mg AI/L	0, 75 mg/L	Static, Nominal	Oxygen consumption	(Martins et al., 2007b)	High
Water flea ( <i>Daphnia magna</i> )	Fresh	15-minute	NOAEL = 75 mg AI/L	0, 75 mg/L	Static, Nominal	Oxygen consumption	(Martins et al., 2007b)	High
Water flea ( <i>Daphnia magna</i> )	Fresh	24-hour	EC <sub>50</sub> = 20 mg AI/L	Not reported	Static, Measured	Immobilization	(Freitag et al., 1994)	High

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Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Scud ( <i>Gammarus pseudolimnaeus</i> )	Fresh	96-hour	LC <sub>50</sub> = 11.1 mg AI/L	Not reported	Flow- through, Measured	Mortality	( <a href="#">Brooke, 1987</a> )	High
Ostracod ( <i>Cypris subglobosa</i> )	Fresh	24-hour	EC <sub>50</sub> = 301 mg AI/L	Not reported	Renewal, Nominal	Immobilizatio n	( <a href="#">Khangarot and Das, 2009</a> )	High
Ostracod ( <i>Cypris subglobosa</i> )	Fresh	48-hour	EC <sub>50</sub> = 181 mg AI/L	Not reported	Renewal, Nominal	Immobilizatio n	( <a href="#">Khangarot and Das, 2009</a> )	High
Flatworm ( <i>Dugesia japonica</i> )	Fresh	7-day	LC <sub>50</sub> = 0.2 mg AI/L	Not reported	Renewal, Nominal	Mortality	( <a href="#">Yoshioka et al., 1986</a> )	Unacceptable
Flatworm ( <i>Dugesia japonica</i> )	Fresh	7-day	EC <sub>50</sub> = 1.5 mg AI/L	Not reported	Renewal, Nominal	Abnormal regeneration	( <a href="#">Yoshioka et al., 1986</a> )	Unacceptable
Ciliate ( <i>Tetrahymena pyriformis</i> )	Fresh	24-hour	EC <sub>50</sub> = 830 mg AI/L	Not reported	Static, Nominal, Solvent: unknown	Population growth rate	( <a href="#">Yoshioka et al., 1985</a> )	Unacceptable
Midge ( <i>Chironomus tentans</i> )	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	( <a href="#">Lee et al., 2006</a> )	High
Midge ( <i>Chironomus tentans</i> )	Fresh	48-hour	NOAEL = 2 mg AI/L	0, 0.02, 0.2, 2 mg/L	Static, Nominal, Solvent: acetone	Body fresh weight	( <a href="#">Lee et al., 2006</a> )	High
Midge ( <i>Chironomus tentans</i> )	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	( <a href="#">Lee et al., 2006</a> )	High
Yellow fever mosquito ( <i>Aedes aegypti</i> )	Fresh	24-hour	LC <sub>50</sub> = 224 mg AI/L	Not reported	Static, Nominal	Mortality	( <a href="#">Richie et al., 1984</a> )	High
Yellow fever mosquito ( <i>Aedes aegypti</i> )	Fresh	0.5-hour	LC <sub>50</sub> = 467 mg AI/L	Not reported	Static, Nominal	Mortality	( <a href="#">Richie et al., 1984</a> )	High
Yellow fever mosquito ( <i>Aedes aegypti</i> )	Fresh	1-hour	LC <sub>50</sub> = 375 mg AI/L	Not reported	Static, Nominal	Mortality	( <a href="#">Richie et al., 1984</a> )	High
<i>Algae</i>								
Green algae ( <i>Chlamydomon as reinhardtii</i> )	Fresh	72-hour	EC <sub>50</sub> = 0.25 mg AI/L	Not reported	Static, Measured	Biomass	( <a href="#">Brack and Rottler, 1994</a> )	High
Green algae ( <i>Chlamydomon as reinhardtii</i> )	Fresh	72-hour	EC <sub>10</sub> = 0.07 mg AI/L	Not reported	Static, Measured	Biomass	( <a href="#">Brack and Rottler, 1994</a> )	High

Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Green algae ( <i>Pseudokirchneriella subcapitata</i> )	Fresh	48-hour	EC <sub>50</sub> = 23.59 mg AI/L	Not reported	Static, Nominal	Growth	( <a href="#">Tsai and Chen, 2007</a> )	High
Algae ( <i>Desmodesmus subspicatus</i> )	Fresh	72-hour	EC <sub>50</sub> = 21 mg/L	Not reported	Static, Measured	Inhibition	( <a href="#">Freitag et al., 1994</a> )	High
Marine bacterium ( <i>Photobacterium phosphoreum</i> )	Salt	15-minute	EC <sub>50</sub> = 5 mg/L	Not reported	Static, Measured	Bioluminescence	( <a href="#">Freitag et al., 1994</a> )	Medium
Activated sludge microorganisms	Fresh	5-day	EC <sub>50</sub> > 1000 mg/L	Not reported	Static, Measured	O <sub>2</sub> consumption	( <a href="#">Freitag et al., 1994</a> )	High
<i>Amphibians</i>								
Bullfrog ( <i>Rana catesbeiana</i> )	Fresh	4-day	LC <sub>50</sub> = 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	( <a href="#">Birge et al., 1980</a> )	High
Bullfrog ( <i>Rana catesbeiana</i> )	Fresh	8-day	LC <sub>50</sub> = 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	( <a href="#">Birge et al., 1980</a> )	High
Bullfrog ( <i>Rana catesbeiana</i> )	Fresh	4-day	LC <sub>100</sub> = 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	( <a href="#">Birge et al., 1980</a> )	High
Bullfrog ( <i>Rana catesbeiana</i> )	Fresh	8-day	LC <sub>100</sub> = 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	( <a href="#">Birge et al., 1980</a> )	High
Pickereel frog ( <i>Lithobates palustris</i> )	Fresh	4-day	LC <sub>50</sub> = 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	( <a href="#">Birge et al., 1980</a> )	High
Pickereel frog ( <i>Lithobates palustris</i> )	Fresh	8-day	LC <sub>50</sub> = 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	( <a href="#">Birge et al., 1980</a> )	High
Fowler's toad ( <i>Anaxyrus bufo</i> )	Fresh	3-day	LC <sub>50</sub> > 92 mg AI/L	0, 0.020, 0.032, 0.69, 4.98, 92.5 mg/L	Flow-through, Measured	Teratogenesis Leading to Mortality	( <a href="#">Birge et al., 1980</a> )	High
Fowler's toad ( <i>Anaxyrus bufo</i> )	Fresh	7-day	LC <sub>50</sub> = 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	( <a href="#">Birge et al., 1980</a> )	High
Bullfrog ( <i>Rana catesbeiana</i> )	Fresh	8-day	LC <sub>10</sub> = 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	( <a href="#">Birge et al., 1980</a> )	High
Bullfrog ( <i>Rana catesbeiana</i> )	Fresh	8-day	LC <sub>01</sub> = 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	( <a href="#">Birge et al., 1980</a> )	High
Pickereel frog ( <i>Lithobates palustris</i> )	Fresh	8-day	LC <sub>10</sub> = 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	( <a href="#">Birge et al., 1980</a> )	High
Pickereel frog ( <i>Lithobates palustris</i> )	Fresh	8-day	LC <sub>01</sub> = 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	( <a href="#">Birge et al., 1980</a> )	High

Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Pickereel frog ( <i>Lithobates palustris</i> )	Fresh	4-day	LC <sub>100</sub> = 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	( <a href="#">Birge et al., 1980</a> )	High
Pickereel frog ( <i>Lithobates palustris</i> )	Fresh	8-day	LC <sub>100</sub> = 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	( <a href="#">Birge et al., 1980</a> )	High
Fowler's toad ( <i>Anaxyrus bufo</i> )	Fresh	7-day	LC <sub>100</sub> = 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	( <a href="#">Birge et al., 1980</a> )	High
Bullfrog ( <i>Rana catesbeiana</i> )	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	( <a href="#">Birge et al., 1980</a> )	High
Pickereel frog ( <i>Lithobates palustris</i> )	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	( <a href="#">Birge et al., 1980</a> )	High
Fowler's toad ( <i>Anaxyrus bufo</i> )	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	( <a href="#">Birge et al., 1980</a> )	High
Pickereel frog ( <i>Lithobates palustris</i> )	Fresh	4.5-day	LC <sub>50</sub> = 3.62 mg AI/L	Not reported	Flow- through, Measured	Teratogenesis Leading to Mortality	( <a href="#">Black et al., 1982</a> )	High
Pickereel frog ( <i>Lithobates palustris</i> )	Fresh	8.5-day	LC <sub>50</sub> = 2.37 mg AI/L	Not reported	Flow- through, Measured	Teratogenesis Leading to Mortality	( <a href="#">Black et al., 1982</a> )	High
Fowler's toad ( <i>Anaxyrus bufo</i> )	Fresh	3-day	LC <sub>50</sub> > 92 mg AI/L	Not reported	Flow- through, Measured	Teratogenesis Leading to Mortality	( <a href="#">Black et al., 1982</a> )	High
Fowler's toad ( <i>Anaxyrus bufo</i> )	Fresh	7-day	LC <sub>50</sub> = 2.83 mg AI/L	Not reported	Flow- through, Measured	Teratogenesis Leading to Mortality	( <a href="#">Black et al., 1982</a> )	High
European common frog ( <i>Rana temporaria</i> )	Fresh	9-day	LC <sub>50</sub> = 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	( <a href="#">Black et al., 1982</a> )	High
European common frog ( <i>Rana temporaria</i> )	Fresh	9-day	LC <sub>100</sub> = 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	( <a href="#">Black et al., 1982</a> )	High
European common frog ( <i>Rana temporaria</i> )	Fresh	9-day	LC <sub>10</sub> = 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	( <a href="#">Black et al., 1982</a> )	High
European common frog ( <i>Rana temporaria</i> )	Fresh	9-day	LC <sub>01</sub> = 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	( <a href="#">Black et al., 1982</a> )	High
European common frog ( <i>Rana temporaria</i> )	Fresh	5-day	LC <sub>50</sub> = 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	( <a href="#">Black et al., 1982</a> )	High

Test Species	Fresh/ Salt Water	Duration	End- point	Concentration(s)	Test Analysis	Effect(s)	References	Data Quality Evaluation
Leopard frog ( <i>Lithobates pipiens</i> )	Fresh	9-day	LC <sub>50</sub> = 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	( <a href="#">Black et al., 1982</a> )	High
Leopard frog ( <i>Lithobates pipiens</i> )	Fresh	9-day	LC <sub>10</sub> = 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	( <a href="#">Black et al., 1982</a> )	High
Leopard frog ( <i>Lithobates pipiens</i> )	Fresh	9-day	LC <sub>01</sub> = 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	( <a href="#">Black et al., 1982</a> )	High
Leopard frog ( <i>Lithobates pipiens</i> )	Fresh	5-day	LC <sub>50</sub> = 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	( <a href="#">Black et al., 1982</a> )	High
Northwestern salamander ( <i>Ambystoma gracile</i> )	Fresh	5.5-day	LC <sub>50</sub> = 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	( <a href="#">Black et al., 1982</a> )	High
Northwestern salamander ( <i>Ambystoma gracile</i> )	Fresh	9.5-day	LC <sub>50</sub> = 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	( <a href="#">Black et al., 1982</a> )	High
African clawed frog ( <i>Xenopus laevis</i> )	Fresh	2-day	LC <sub>50</sub> > 27 mg AI/L	0, 0.004, 0.073, 0.60, 10.5, 27.2 mg/L	Flow- through, Measured	Teratogenesis Leading to Mortality	( <a href="#">Black et al., 1982</a> )	High
African clawed frog ( <i>Xenopus laevis</i> )	Fresh	6-day	LC <sub>50</sub> = 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	( <a href="#">Black et al., 1982</a> )	High

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## 6907 G.2 Hazard Identification- Aquatic

6908 Relevant data from the screened literature are summarized below (Table\_Apx G-2) as ranges  
6909 (min-max). Studies with data quality evaluation results of ‘medium’ to ‘high’ were used to  
6910 characterize the environmental hazards of carbon tetrachloride. Table\_Apx G-2 provides the  
6911 species, media, duration, endpoint, effects, etc. for the acceptable acute toxicity studies that were  
6912 evaluated.

### 6913 Toxicity to Aquatic Organisms

6914 For the aquatic environment, the hazard endpoint for fish, from acute exposure durations (24-  
6915 96-h LC<sub>50</sub>) to carbon tetrachloride, ranges from 10.4 - 150 mg/L (data quality evaluation scores  
6916 for each citation are in the parenthesis) ([Freitag et al., 1994](#)) (high); ([Schell, 1987](#)) (high);  
6917 ([Brooke, 1987](#)) (high); ([Kimball, 1978](#)) (high); ([Geiger et al., 1990](#)) (high); ([Buccafusco et al.,](#)  
6918 [1981](#)) (medium); and ([Dawson et al., 1977](#)) (medium). The hazard endpoint for aquatic  
6919 invertebrates, from acute exposure durations (24-48-h L/EC50) to carbon tetrachloride, ranges  
6920 from 11.1 - 181 mg/L ([LeBlanc, 1980](#)) (high); ([Freitag et al., 1994](#)) (high); ([Brooke, 1987](#))  
6921 (high); ([Khargarot and Das, 2009](#)) (high); and ([Richie et al., 1984](#)) (high). The hazard endpoint  
6922 for aquatic plants, from acute exposure durations (72-hr EC50) to carbon tetrachloride, ranges  
6923 from 0.25 – 23.59 mg/L ([Brack and Rottler, 1994](#)) (high); ([Freitag et al., 1994](#)) (high); and  
6924 ([Tsai and Chen, 2007](#)) (high).  
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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<sub>10</sub>). The LC<sub>10</sub> 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<sub>50</sub>) 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<sub>10</sub>) 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 <sup>a</sup>	Units	Effect Endpoint	References <sup>b</sup>
Acute	Fish	LC <sub>50</sub>	10.40 – 150.0	mg/L	Mortality	( <a href="#">Brooke, 1987</a> ) (high); ( <a href="#">Freitag et al., 1994</a> ) (high); ( <a href="#">Schell, 1987</a> ) (high); ( <a href="#">Kimball, 1978</a> ) (high); ( <a href="#">Geiger et al., 1990</a> ) (high); ( <a href="#">Buccafusco et al., 1981</a> ) (medium); ( <a href="#">Dawson et al., 1977</a> ) (medium)
	Aquatic invertebrates	L/EC <sub>50</sub>	11.10 – 224.0	mg/L	Mortality/ immobilization	( <a href="#">Brooke, 1987</a> ) (high); ( <a href="#">LeBlanc, 1980</a> ) (high); ( <a href="#">Freitag et al., 1994</a> ) (high); ( <a href="#">Khangarot and Das, 2009</a> ) (high); ( <a href="#">Richie et al., 1984</a> ) (high)
	Amphibians	LC <sub>50</sub>	<b>0.900</b> – 22.42	mg/L	Teratogenesis Leading to Mortality <sup>c</sup>	( <a href="#">Birge et al., 1980</a> ) (high); ( <a href="#">Black et al., 1982</a> ) (high)
	Acute COC		0.09	mg/L		

Exposure Duration	Test organism	Endpoint	Hazard value <sup>a</sup>	Units	Effect Endpoint	References <sup>b</sup>
Chronic	Fish	LC <sub>50</sub>	1.970	mg/L	Mortality	( <a href="#">Black et al., 1982</a> ) (high)
	Aquatic invertebrates	Chronic value	1.100 (ACR10)	mg/L	Growth and reproduction	( <a href="#">Brooke, 1987</a> ) (high)
	Amphibians	LC <sub>10</sub>	<b>0.025-0.436</b>	mg/L	Teratogenesis Leading to Mortality	( <a href="#">Birge et al., 1980</a> ) (high); ( <a href="#">Black et al., 1982</a> ) (high)
	Chronic COC	0.003		mg/L		
Algae		EC <sub>10</sub>	<b>0.070</b>	mg/L	Biomass	( <a href="#">Brack and Rottler, 1994</a> ) (high)
		EC <sub>50</sub>	0.250 – 23.59	mg/L	Biomass/growth rate	( <a href="#">Brack and Rottler, 1994</a> ) (high); ( <a href="#">Freitag et al., 1994</a> ) (high); ( <a href="#">Tsai and Chen, 2007</a> ) (high)
	Algae COC	0.007		mg/L		
<sup>a</sup> Values in <b>bold</b> were used to derive the COC. <sup>b</sup> Data quality evaluation scores for each citation are in the parenthesis. <sup>c</sup> The study authors defined embryo-larval teratogenesis as the percent of survivors with gross and debilitating abnormalities likely to result in eventual mortality.						

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### 6948 *Toxicity to Sediment and Terrestrial Organisms*

6949 The limited number of environmental toxicity studies for carbon tetrachloride on sediment and  
6950 terrestrial organisms were determined to contain data or information not relevant (off-topic) for  
6951 the risk evaluation. No relevant (on-topic) toxicity data were available for carbon tetrachloride to  
6952 birds. Hazard studies for sediment and terrestrial organisms are not likely to be conducted  
6953 because exposure to carbon tetrachloride by these organisms is not expected due to the physical,  
6954 chemical, and fate properties of the chemical.

### 6955 G.3 Weight of Evidence

6956 During the data integration stage of systematic review, EPA analyzed, synthesized, and  
6957 integrated the data/information. This involved weighing scientific evidence for quality and  
6958 relevance, using a Weight of Evidence (WoE) approach ([U.S. EPA, 2018a](#)).

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6960 During data evaluation, studies were rated high, medium, low, or unacceptable for quality based  
6961 on the TSCA criteria described in the *Application of Systematic Review in TSCA Risk*  
6962 *Evaluations* ([U.S. EPA, 2018a](#)). Only data/information rated as high, medium, or low for quality  
6963 was used for the environmental risk assessment (unless otherwise noted). Any information rated  
6964 as unacceptable was not used. While integrating environmental hazard data for carbon  
6965 tetrachloride, EPA gave more weight to relevant data/information rated high or medium for  
6966 quality. The ecological risk assessor decided if data/information were relevant based on whether  
6967 it has biological, physical/chemical, and environmental relevance ([U.S. EPA, 1998](#)):



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- 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](#)).

6974 This WoE approach was used to assess hazard data (Appendix H.2) and develop COCs as  
6975 described in Appendix H.4. Where high or medium quality studies were available for a  
6976 taxonomic group, low quality studies were not used to derive COCs. Additionally, where  
6977 multiple toxicity values were reported within a study for the same species (e.g., multiple EC<sub>50</sub>s  
6978 with different durations), they were summarized as ranges (min-max) in the Appendix Table H-2  
6979 and the higher quality or more relevant citation was used. If quality and relevance were equal,  
6980 the lowest toxicity endpoint value for acute and chronic exposures were used to derive acute and  
6981 chronic COCs.

6982

6983 Certain environmental studies on carbon tetrachloride were of high quality but were not  
6984 biologically relevant for purposes of environmental hazard assessment due to the reported  
6985 endpoints (e.g., glutamic pyruvic transaminase activity, serum total protein, catalase activity,  
6986 sodium concentration in blood, whole body residue). These studies ([Chen et al., 2004](#)); ([de Vera  
6987 and Pocsidio, 1998](#)); ([Barrows et al., 1980](#)); ([Liu et al., 2015](#)); ([Jia et al., 2013](#)); ([Kotsanis and  
6988 Metcalfe, 1988](#)); ([Weber et al., 1979](#)); ([Koskinen et al., 2004](#)); ([Bauder et al., 2005](#)); ([Martins et  
6989 al., 2007a](#)); ([Lee et al., 2006](#))) are contained within the on-topic data evaluation section of  
6990 Appendix H.2, but were not used within the risk evaluation process. During risk evaluation, EPA  
6991 made refinements to the conceptual models resulting in the elimination of the terrestrial exposure  
6992 pathway and studies that are not biologically relevant from further analysis. Thus, environmental  
6993 hazard data sources on terrestrial organisms and on metabolic endpoints were considered out of  
6994 scope and excluded from data quality evaluation.

6995

6996 Environmental test data are reported from the Japanese Ministry of the Environment (MOE).  
6997 EPA obtained the Japanese MOE test data in Japanese (not English). Since studies in a foreign  
6998 language are generally excluded from evaluation (although there are exceptions on a case-by-  
6999 case basis) and the Japanese test data are not driving the environmental assessment, EPA decided  
7000 not to translate the Japanese test data into English or use the test data in this risk evaluation. EPA  
7001 acknowledges the studies exist and are included in carbon tetrachloride's docket.

7002

7003 To assess aquatic toxicity from acute exposures, data for four taxonomic groups were available:  
7004 amphibians, fish, aquatic invertebrates, and algae. For each taxonomic group, data were available  
7005 for multiple species, and were summarized in Appendix Table G-2 as ranges (min-max).

7006

7007 There were no chronic studies that encompassed amphibian metamorphoses and adult  
7008 reproductive stages of the amphibian life-cycle. However, amphibian embryo and larvae were  
7009 the most sensitive life stages to sub-chronic exposures of carbon tetrachloride in the aquatic  
7010 environment. In two sub-chronic studies that EPA assigned an overall quality level of high,  
7011 amphibian embryos and larvae were exposed to carbon tetrachloride for 2 to 9 days under flow-  
7012 through conditions ([Black et al., 1982](#); [Birge et al., 1980](#)). The study authors combined embryo-

7013 larval lethality and teratogenesis effect concentrations to establish a 10% impairment value  
7014 (LC<sub>10</sub>) in *Lithobates palustris* (Birge et al., 1980) and *Rana temporaria* and *Lithobates pipiens*  
7015 (Black et al., 1982), at carbon tetrachloride concentrations ranging from 0.010 – 92.5 mg/L.  
7016

7017 EPA considered the sub-chronic hazard LC<sub>50</sub>s and LC<sub>10</sub>s for amphibians for teratogenicity  
7018 leading to mortality to estimate acute and chronic hazard values for amphibians, respectively. To  
7019 assess aquatic toxicity from acute and chronic exposures, EPA used and rounded the lowest LC<sub>50</sub>  
7020 to 0.09 mg/L and LC<sub>10</sub> to 0.03 mg/L, respectively, from two high quality 9-days amphibian  
7021 studies (Black et al., 1982; Birge et al., 1980). When comparing these values to the other acute  
7022 and chronic data from fish and aquatic invertebrates, amphibians were again the most sensitive  
7023 taxonomic group. Therefore, the amphibian 9-day lowest LC<sub>50</sub> of 0.09 mg/L and LC<sub>10</sub> of 0.03  
7024 mg/L were used to derive an acute COC in Appendix Section G.5 and chronic COC in Appendix  
7025 Section G.6. These values were from two scientific articles that EPA assigned an overall quality  
7026 level of high and represents three species of amphibians.  
7027

7028 The 72-hour algal EC<sub>10</sub> of 0.0717 mg/L represented the most sensitive toxicity value derived  
7029 from the available algal toxicity data to carbon tetrachloride and this value was used to derive an  
7030 algal COC as described in Appendix Section 7G.7. This value is from one algal study that EPA  
7031 assigned an overall quality of high.  
7032

#### 7033 **G.4 Concentrations of Concern**

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7034 EPA calculated screening-level acute and chronic COCs for aquatic species based on the  
7035 environmental hazard data for carbon tetrachloride, using EPA methods (U.S. EPA, 2012b);  
7036 (U.S. EPA, 2013b). While there was data representing amphibians, fish, aquatic invertebrates,  
7037 and aquatic plants, the data were not robust enough to conduct a more detailed species sensitivity  
7038 distribution analysis. Therefore, EPA chose to establish the COC as protective cut-off standards  
7039 above which exposures to carbon tetrachloride are expected to cause effects for each taxonomic  
7040 group in the aquatic environment. The acute, chronic, and algal COCs for carbon tetrachloride  
7041 are based on the lowest toxicity value in the dataset. For the aquatic environment, EPA derived  
7042 acute and a chronic COCs for amphibians as well as a COC for algae to serve as representative  
7043 COCs for all aquatic taxa.  
7044

7045 After weighing the scientific evidence and selecting the appropriate toxicity values from the  
7046 integrated data to calculate COCs, EPA applied an assessment factor (AF) according to EPA  
7047 methods (U.S. EPA, 2012b); (U.S. EPA, 2013b), when possible. The application of AFs provides  
7048 a lower bound effect level that would likely encompass more sensitive species not represented by  
7049 the available experimental data. AFs also account for differences in inter- and intra-species  
7050 variability, as well as laboratory-to-field variability. These assessment factors are dependent  
7051 upon the availability of datasets that can be used to characterize relative sensitivities across  
7052 multiple species within a given taxa or species group. The assessment factors are standardized in  
7053 risk assessments conducted under TSCA, since the data available for most industrial chemicals  
7054 are limited. For fish and aquatic invertebrates (e.g., *Daphnia sp.*), the acute hazard values were  
7055 divided by an AF of 5 and the chronic hazard values were divided by an AF of 10. For algal  
7056 species, the hazard values were divided by an AF of 10. For amphibians, EPA does not have a  
7057 standardized AF. The greater level of uncertainty (i.e., unknown inter-species variability)

7058 associated with the sub-chronic endpoints in the amphibian studies necessitates the use of a more  
7059 protective AF of 10. As such, for the acute and chronic COCs derived from amphibian data, an  
7060 AF of 10 is used ([U.S. EPA, 2013b](#), [2012b](#)).

## 7061 **G.5 Hazard Estimation for Acute Exposure Durations**

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7062 The lowest acute toxicity value for aquatic organisms (i.e., most sensitive species) for carbon  
7063 tetrachloride is from a 9-day amphibian toxicity study where the LC<sub>50</sub> is 0.9 mg/L ([Black et al.,](#)  
7064 [1982](#); [Birge et al., 1980](#)). The lowest value was then divided by the AF of 10.

7065  
7066 *Acute COC*

7067 The acute COC = (0.9 mg/L) / (AF of 10) = 0.09 mg/L x 1,000 = 90 µg/L or 90 ppb

7068  
7069 The acute COC of 90 µg/L, derived from experimental amphibian endpoint, is used as the  
7070 conservative (screening-level) hazard level in this risk evaluation for carbon tetrachloride.

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## 7072 **G.6 Hazard Estimation for Chronic Exposure Durations**

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7073 The lowest chronic toxicity value for aquatic organisms (i.e., most sensitive species) for carbon  
7074 tetrachloride is from a 9-day amphibian toxicity study where the LC<sub>10</sub> is 0.03 mg/L ([Black et al.,](#)  
7075 [1982](#)). The chronic COC was derived from the lowest chronic toxicity value from the amphibian  
7076 LC<sub>10</sub> (for developmental effects and mortality in frogs). Throughout the systematic review  
7077 process, these two studies were both assigned a quality level of high ([Black et al., 1982](#); [Birge et](#)  
7078 [al., 1980](#)). The LC<sub>10</sub> was then divided by an assessment factor of 10, and then multiplied by  
7079 1,000 to convert from mg/L to µg/L, or ppb.

7080  
7081 *Chronic COC*

7082 The chronic COC = (0.03 mg/L) / (AF of 10) = 0.003 mg/L x 1,000 = 3 µg/L or ppb

7083  
7084 The amphibian chronic COC for carbon tetrachloride is 3 µg/L is used as the lower bound hazard  
7085 level in this risk evaluation for carbon tetrachloride.

7086

## 7087 **G.7 Hazard Estimation for Algal Toxicity**

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7088  
7089 Given that the hazard endpoints for aquatic plants (72-hr EC<sub>10</sub>/NOEC)) exposed to carbon  
7090 tetrachloride ranges from ranges from 0.0717 - 2.2 mg/L ([Brack and Rottler, 1994](#)), the chronic  
7091 COC is derived by dividing the 72-hr algal EC<sub>10</sub> of 0.0717 mg/L (the lowest chronic value in the  
7092 dataset) by an assessment factor of 10:

7093  
7094 *Algal Toxicity COC*

7095 The 72-hr algal toxicity value = (0.0717 mg/L) / AF of 10 = 0.007 mg/L or 7 µg/L.

7096  
7097 The chronic COC of 7 µg/L, derived from experimental algal endpoint, is used as the lower  
7098 bound hazard level for algal toxicity in this risk evaluation for carbon tetrachloride.

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**G.8 Summary of Environmental Hazard Assessment**

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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](#)).

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7130 **Appendix H HUMAN HEALTH HAZARDS**

7131 This appendix provides a high-level summary of the human health animal and in vitro (genotoxicity) studies that were evaluated in the  
 7132 systematic review process. The appendix summarizes and presents study findings in Tables.  
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7134 **Table\_Apx H-1. Summary of Reviewed Human Health Animal Studies for Carbon Tetrachloride**  
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Target Organ/System <sup>1</sup>	Study Type	Species/Strain/Sex (Number/group) <sup>2</sup>	Exposure Route	Doses/Concentrations <sup>3</sup>	Duration <sup>4</sup>	Effect Dose or Concentration (Sex)	Effect <sup>6</sup>	Reference	Data Quality Evaluation <sup>8</sup>
Mortality	Chronic	Mouse, Crj:BDF1 (SPF), M/ F (n=100/group)	Inhalation, vapor, whole body	0, 32, 160, 801 mg/m <sup>3</sup> (0, 5, 25, 125 ppm)	6 hours/day, 5 days/week for 104 weeks	NOAEL=32 mg/m <sup>3</sup> (F), LOAEL=160 mg/m <sup>3</sup> (F)	Reduced survival late in study (because of liver tumors)	( <a href="#">Nagano et al., 2007a</a> )	High
Mortality	Short-term (1-30 days)	Rat, Wistar, M (n=10/group)	Inhalation	0, 63,80 mg/kg-bw/day	6 hours/day, 5 days/week for 4 weeks	NOAEL= 80 mg/m <sup>3</sup>	No effect on general condition of rats; no significant effects on body weight that were considered treatment-related.	( <a href="#">Civo Institute Tno, 1985</a> )	High
Mortality	Other	Guinea pig (n=20)	Dermal	0.5 or 2.0 mL (260 mg/ cm <sup>3</sup> )	Once; contact for 5 days	LOAEL= 260 mg/ cm <sup>3</sup> <sup>i</sup>	5 of 20 animals died	( <a href="#">Wahlberg and Boman, 1979</a> )	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	( <a href="#">Roudabus h et al., 1965</a> )	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 <sup>iii</sup>	Reduced survival	( <a href="#">Roudabus h et al., 1965</a> )	Unacceptable

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Target Organ/System <sup>1</sup>	Study Type	Species/Strain/Sex (Number/group) <sup>2</sup>	Exposure Route	Doses/Concentrations <sup>3</sup>	Duration <sup>4</sup>	Effect Dose or Concentration (Sex)	Effect <sup>6</sup>	Reference	Data Quality Evaluation <sup>8</sup>
Hepatic	Chronic	Mouse, Crj:BDF1 (SPF), M/ F (n=100/group)	Inhalation, vapor, whole body	0, 32, 160, 801 mg/m <sup>3</sup> (0, 5, 25, 125 ppm)	6 hours/day, 5 days/week for 104 weeks	NOAEL= 32 mg/m <sup>3</sup> , LOAEL= 160 mg/m <sup>3</sup>	Incidence of hepatocellular adenoma or carcinoma	( <a href="#">Nagano et al., 2007a</a> )	High
Hepatic	Chronic	Rat, F344/DuCrj (SPF), M/ F (n=100/group)	Inhalation, vapor, whole body	0, 32, 160, 801 mg/m <sup>3</sup> (0, 5, 25, 125 ppm)	6 hours/day, 5 days/week for 104 weeks	NOAEL= 160 mg/m <sup>3</sup> , LOAEL= 125 ppm	Incidence of hepatocellular adenoma or carcinoma	( <a href="#">Nagano et al., 2007a</a> )	High
Hepatic	Chronic	Rat, F344/DuCrj (SPF), M/ F (n=100/group)	Inhalation, vapor, whole body	0, 31, 157 or 786 mg/m <sup>3</sup> (0, 5, 25 or 125 ppm)	6 hours/day, 5 days/week for 104 weeks	NOAEL= 31 mg/m <sup>3</sup> , LOAEL= 157 mg/m <sup>3</sup>	Increased AST, ALT, LDH, GPT, BUN, CPK; lesions in the liver (fatty changes, fibrosis)	( <a href="#">Nagano et al., 2007a</a> )	High
Hepatic	Chronic	Mouse, Crj:BDF1 (SPF), M/F (n= 100/group)	Inhalation, vapor, whole body	0, 31, 157 or 786 mg/m <sup>3</sup> (0, 5, 25 or 125 ppm)	6 hours/day, 5 days/week for 104 weeks	LOAEL=31 mg/m <sup>3</sup> (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)	( <a href="#">Nagano et al., 2007a</a> )	High

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Target Organ/System <sup>1</sup>	Study Type	Species/ Strain/Sex (Number/group) <sup>2</sup>	Exposure Route	Doses/ Concentrations <sup>3</sup>	Duration <sup>4</sup>	Effect Dose or Concentration (Sex)	Effect <sup>6</sup>	Reference	Data Quality Evaluation <sup>8</sup>
Hepatic	Chronic	Mouse, BDF1, M/ F (n=20/ group)	Inhalation, vapor, whole body	0, 63, 189, 566, 1699, or 5096 mg/m <sup>3</sup> (0, 10, 30, 90, 270, or 810 ppm)	6 hours/ day, 5 days/ week for 13 weeks	LOAEL= 63 mg/m <sup>3</sup>	Slight cytological alterations in the liver; Cytoplasmic globules	( <a href="#">Nagano et al., 2007b</a> )	High
Hepatic	Chronic	Rat, F344, M/ F (n=20/ group)	Inhalation, vapor, whole body	0, 63, 189, 566, 1699, 5096 mg/m <sup>3</sup> (0, 10, 30, 90, 270, 810 ppm)	6 hours/ day, 5 days/ week for 13 weeks	NOAEL= 63 mg/m <sup>3</sup> (F), LOAEL=189 mg/m <sup>3</sup> (F)	Increased liver weight; Large droplet fatty change in liver	( <a href="#">Nagano et al., 2007b</a> )	High
Hepatic	Chronic	Rat, F344, M/ F (n=20/ group)	Inhalation, vapor, whole body	0, 63, 189, 566, 1699, or 5096 mg/m <sup>3</sup> (0, 10, 30, 90, 270, or 810 ppm)	6 hours/ day, 5 days/ week for 13 weeks	LOAEL= 63 mg/m <sup>3</sup>	Increased liver weight; fatty change in liver	( <a href="#">Nagano et al., 2007b</a> )	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 <sup>3</sup> (0, 5, 10, 25, 50, 100, 200 or 400 ppm)	7 hours/ day, 5 days/ week for 6 months	NOAEL= 31 mg/m <sup>3</sup> , LOAEL= 63 mg/m <sup>3</sup>	Increased liver weight; fatty degeneration in liver	( <a href="#">Adams et al., 1952</a> )	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 <sup>3</sup> (0, 5, 10, 25, 50, 100, 200 or 400 ppm)	7 hours/ day, 5 days/ week for 6 months	NOAEL= 31 mg/m <sup>3</sup> , LOAEL= 63 mg/m <sup>3</sup>	Increased liver weight; fatty degeneration in liver	( <a href="#">Adams et al., 1952</a> )	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 <sup>3</sup> (0, 5, 10, 25, 50, 100, 200 or 400 ppm)	7 hours/ day, 5 days/ week for 6 months	NOAEL= 63 mg/m <sup>3</sup> , LOAEL= 157 mg/m <sup>3</sup>	Increased liver weight; fatty degeneration and slight cirrhosis in liver	( <a href="#">Adams et al., 1952</a> )	Low

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Target Organ/System <sup>1</sup>	Study Type	Species/Strain/Sex (Number/group) <sup>2</sup>	Exposure Route	Doses/Concentrations <sup>3</sup>	Duration <sup>4</sup>	Effect Dose or Concentration (Sex)	Effect <sup>6</sup>	Reference	Data Quality Evaluation <sup>8</sup>
Hepatic	Chronic	Monkey, rhesus, M/ F (n=2-4/ group)	Inhalation, vapor, whole body	0, 31, 63, 157, 315 or 630 mg/m <sup>3</sup> (0, 5, 20, 25, 50 or 100 ppm)	7 hours/ day, 5 days/ week for 6 months	NOAEL= 315 mg/m <sup>3</sup> , LOAEL= 629 mg/m <sup>3</sup>	Slight fatty degeneration and increased lipid content in liver	( <a href="#">Adams et al., 1952</a> )	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, hepatocytomegaly, necrosis, and hepatitis	( <a href="#">Hayes et al., 1986</a> )	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, hepatocytomegaly, necrosis, and hepatitis	( <a href="#">Hayes et al., 1986</a> )	Medium
Hepatic	Subchronic	Rat, F344/ Crl, M (n=10/ group)	Inhalation, whole body	0, 31, 126, or 629 mg/m <sup>3</sup> (0, 5, 20 or 100 ppm)	6 hours/ day, 5 days/ week for 12 weeks	NOAEL= 126 mg/m <sup>3</sup> (M), LOAEL= 629 mg/m <sup>3</sup> (M)	Increased ALT, SDH; necrosis in liver	( <a href="#">Benson and Springer, 1999</a> )	High
Hepatic	Subchronic	Mouse, B6C3F1, M (n=10/ group)	Inhalation, whole body	0, 31, 126, or 629 mg/m <sup>3</sup> (0, 5, 20 or 100 ppm)	6 hours/ day, 5 days/ week for 12 weeks	NOAEL= 31 mg/m <sup>3</sup> (M), LOAEL= 126 mg/m <sup>3</sup> (M)	Increased ALT, SDH; necrosis and cell proliferation in liver	( <a href="#">Benson and Springer, 1999</a> )	High



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Target Organ/System <sup>1</sup>	Study Type	Species/ Strain/Sex (Number/group) <sup>2</sup>	Exposure Route	Doses/ Concentrations <sup>3</sup>	Duration <sup>4</sup>	Effect Dose or Concentration (Sex)	Effect <sup>6</sup>	Reference	Data Quality Evaluation <sup>8</sup>
Hepatic	Subchronic	Hamster, Syrian, M (n=10/ group)	Inhalation, whole body	0, 31, 127 or 636 mg/m <sup>3</sup> (0, 5, 20 or 100 ppm)	6 hours/ day, 5 days/ week for 12 weeks	NOAEL= 126 mg/m <sup>3</sup> (M), LOAEL= 629 mg/m <sup>3</sup> (M)	Increased ALT, SDH; necrosis and cell proliferation in liver	( <a href="#">Benson and Springer, 1999</a> )	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	( <a href="#">Bruckner et al., 1986</a> )	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	( <a href="#">Allis et al., 1990</a> )	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 (hepatocytomegaly, necrosis, inflammation)	( <a href="#">Condie et al., 1986</a> )	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	( <a href="#">Sun et al., 2014</a> )	High

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Target Organ/System <sup>1</sup>	Study Type	Species/ Strain/Sex (Number/group) <sup>2</sup>	Exposure Route	Doses/ Concentrations <sup>3</sup>	Duration <sup>4</sup>	Effect Dose or Concentration (Sex)	Effect <sup>6</sup>	Reference	Data Quality Evaluation <sup>8</sup>
Hepatic	Acute	Guinea pig, albino (n=20)	Dermal	513 mg/ cm <sup>2</sup>	15 minutes to 16 hours	LOAEL= 513 mg/ cm <sup>2</sup> (ATSDR)	Hydropic changes, slight necrosis	( <a href="#">Kronevi et al., 1979</a> )	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	( <a href="#">Sun et al., 2014</a> )	High
Renal	Chronic	Rat, F344, M/ F (n=20/ group)	Inhalation, vapor, whole body	0, 63, 189, 566, 1699, 5096 mg/m <sup>3</sup> (0, 10, 30, 90, 270, 810 ppm)	6 hours/ day, 5 days/ week for 13 weeks	NOAEL=1699 mg/m <sup>3</sup> , LOAEL=5096 mg/m <sup>3</sup>	Histopathological lesions, kidney glomerulosclerosis	( <a href="#">Nagano et al., 2007b</a> )	High
Renal	Chronic	Rat, F344/DuCrj (SPF), M/ F (n=100/ group)	Inhalation, vapor, whole body	0, 31, 157 or 786 mg/m <sup>3</sup> (0, 5, 25 or 125 ppm)	6 hours/ day, 5 days/ week for 104 weeks	NOAEL= 31 mg/m <sup>3</sup> LOAEL= 157 mg/m <sup>3</sup>	Lesions in the kidney (progressive glomerulonephrosis)	( <a href="#">Nagano et al., 2007a</a> )	High

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Target Organ/System <sup>1</sup>	Study Type	Species/ Strain/Sex (Number/group) <sup>2</sup>	Exposure Route	Doses/ Concentrations <sup>3</sup>	Duration <sup>4</sup>	Effect Dose or Concentration (Sex)	Effect <sup>6</sup>	Reference	Data Quality Evaluation <sup>8</sup>
Renal	Chronic	Mouse, Crj:BDF1 (SPF), M/ F (n=100/group)	Inhalation, vapor, whole body	0, 31, 157 or 786 mg/m <sup>3</sup> (0, 5, 25 or 125 ppm)	6 hours/day, 5 days/week for 104 weeks	NOAEL= 31 mg/m <sup>3</sup> , LOAEL= 157 mg/m <sup>3</sup>	Increased ALT, AST, LDH, ALP, protein, total bilirubin, and BUN; lesions in the kidney (protein casts); benign pheochromocytoma (males)	( <a href="#">Nagano et al., 2007a</a> )	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	( <a href="#">Sun et al., 2014</a> )	High
Skin	Other	Guinea pig, albino (n=20)	Dermal	513 mg/ cm <sup>2</sup>	15 minutes to 16 hours	LOAEL= 513 mg/ cm <sup>2</sup>	Karyopynosis, spongiosis, perinuclear edema	( <a href="#">Kronevi et al., 1979</a> )	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	( <a href="#">Roudabus h et al., 1965</a> )	Unacceptable

PEER REVIEW DRAFT, DO NOT CITE OR QUOTE

Target Organ/System <sup>1</sup>	Study Type	Species/ Strain/Sex (Number/group) <sup>2</sup>	Exposure Route	Doses/ Concentrations <sup>3</sup>	Duration <sup>4</sup>	Effect Dose or Concentration (Sex)	Effect <sup>6</sup>	Reference	Data Quality Evaluation <sup>8</sup>
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	( <a href="#">Roudabush et al., 1965</a> )	Unacceptable
Developmental 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	( <a href="#">Narotsky et al., 1997</a> )	High
Developmental 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	( <a href="#">Narotsky et al., 1997</a> )	High
Body weight	Chronic	Rat, F344/DuCrj (SPF), M/ F (n=100/group)	Inhalation, vapor, whole body	0, 32, 160, 801 mg/m <sup>3</sup> (0, 5, 25, 125 ppm)	6 hours/ day, 5 days/ week for 104 weeks	NOAEL= 32 mg/m <sup>3</sup> , LOAEL=160 mg/m <sup>3</sup>	Reduced body weight gain	( <a href="#">Nagano et al., 2007a</a> )	High
Body weight	Chronic	Mouse, Crj:BDF1 (SPF), M/F (n=100/group)	Inhalation, vapor, whole body	0, 32, 160, 801 mg/m <sup>3</sup> (0, 5, 25, 125 ppm)	6 hours/ day, 5 days/ week for 104 weeks	NOAEL= 32 mg/m <sup>3</sup> , LOAEL=160 mg/m <sup>3</sup>	Reduced body weight gain	( <a href="#">Nagano et al., 2007a</a> )	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	( <a href="#">Sun et al., 2014</a> )	High

Target Organ/System <sup>1</sup>	Study Type	Species/ Strain/Sex (Number/group) <sup>2</sup>	Exposure Route	Doses/ Concentrations <sup>3</sup>	Duration <sup>4</sup>	Effect Dose or Concentration (Sex)	Effect <sup>6</sup>	Reference	Data Quality Evaluation <sup>8</sup>
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 <sup>3</sup>	No effect on general condition of rats; no significant effects on body weight that were considered treatment-related.	( <a href="#">Civo Institute Tno, 1985</a> )	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	( <a href="#">Sun et al., 2014</a> )	High
Immune	Chronic	Mouse, Crj:BDF1 (SPF), M/F (n= 100/group)	Inhalation, vapor, whole body	0, 32, 160, 801 mg/m <sup>3</sup> (0, 5, 25, 125 ppm)	6 hours/day, 5 days/week for 104 weeks	NOAEL= 160 mg/m <sup>3</sup> , LOAEL= 801 mg/m <sup>3</sup>	Lesions in the spleen (extra medullary hemato-poiesis)	( <a href="#">Nagano et al., 2007a</a> )	High

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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	<i>In vitro</i>	0, 4.38, 6.55, 8.76 mmol/L (+S9)	3 hours	Positive at 6.55 and 8.76 mmol/L <sup>a</sup> (at relative toxicities of 6% and 16%, respectively)	Alkaline unwinding of DNA (ratio of ssDNA and dsDNA); cell viability	( <a href="#">Garberg et al., 1988</a> )	Unacceptable
Genotoxicity	Acute	<i>Salmonella typhimurium</i> strains TA 98, TA 100, TA 1535, TA 1537 <3 replicates /group	<i>In vitro</i>	0, 0.005, 0.01, 0.05, 0.1, 0.2, 0.5, 1, 2, 5% ( $\pm$ S9) <sup>b</sup>	24 hours	Weakly positive <sup>c</sup> in TA 98 (-S9) at $\geq$ 1%; negative in TA 98 (+S9); negative in TA 100, TA 1535, and TA 1537 ( $\pm$ S9)	Reverse mutation (gas exposure method)	( <a href="#">Araki et al., 2004</a> )	High
Genotoxicity	Acute	<i>Escherichia coli</i> strains WP2/ <i>uvrA</i> /pKM101, WP2/pKM101 <3 replicates /group	<i>In vitro</i>	0, 0.005, 0.01, 0.05, 0.1, 0.2, 0.5, 1, 2, 5% ( $\pm$ S9) <sup>b</sup>	24 hours	Weakly positive <sup>c</sup> at 2% in WP2/ <i>uvrA</i> /pKM101 ( $\pm$ S9); positive at $\geq$ 0.1% (-S9) and $\geq$ 0.2% (+S9) in WP2/pKM101 <sup>d</sup>	Reverse mutation (gas exposure method)	( <a href="#">Araki et al., 2004</a> )	High

<sup>a</sup>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.

<sup>b</sup>Tests were also conducted with glutathione-supplemented S9 mix.

<sup>c</sup>A result was considered positive if a two-fold increase in the number of revertants was observed.

<sup>d</sup>Data for *E.coli* strain WP2/pKM101 were based on < 3 measurements (statistical analyses were not performed).

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## 7145 **Appendix I GENOTOXICITY**

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7146 The *in vitro* and *in vivo* genotoxicity databases for carbon tetrachloride, including their  
7147 limitations are described below.

### 7148 **I.1 In vitro Genotoxicity and Mutation**

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7149 The *in vitro* genotoxicity database for carbon tetrachloride, while large in number of studies, it is  
7150 not diverse in the type of assays contained to examine carbon tetrachloride's genotoxicity  
7151 potential. The studies identified below, while not definitive provide indications of mutational or  
7152 chromosomal changes that may be relevant to the mode of action of carbon tetrachloride  
7153 carcinogenesis.

7154 *Bacterial mutagenicity with reference to strains more capable to detect oxidative damage.*  
7155 Many experiments have tested carbon tetrachloride for mutagenesis in standard salmonella  
7156 reverts mutation assays. Eastmond (2008) observes: "While carbon tetrachloride has consistently  
7157 been negative in studies using Salmonella and certain strains of E. coli, at high exposure  
7158 concentrations, it has been reported to produce differential DNA repair and mutations in the  
7159 WP2 strain of E. coli, a strain that is particularly sensitive to oxidative mutagens (Araki et al.,  
7160 2004; De Flora et al., 1984) EPA IRIS (U.S. EPA, 2010) further notes that because the WP2  
7161 strains of E. coli have an AT base pair at the critical mutation site within the trpE gene, they have  
7162 been recommended for screening oxidizing mutagens (Martínez et al., 2000; Gatehouse et al.,  
7163 1994). "In contrast, using E. coli strains that are more sensitive to oxidative mutagens, increases  
7164 in DNA repair were reported by De Flora (1984) and increases in reverse mutation were reported  
7165 by Araki (2004) and Norpoth (1980). In the De Flora (1984) study, carbon tetrachloride was  
7166 more toxic to the E. coli strain CM871 (uvrA- recA- lexA-) than it was to the isogenic repair-  
7167 proficient WP2 strain or WP67 (uvrA- polA-). Although a similar pattern was seen in the  
7168 presence of metabolic activation, carbon tetrachloride was more active in the absence of  
7169 activation.

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7171 *Bacterial test strains*

7172 Although carbon tetrachloride has been evaluated many times in the standard Salmonella test  
7173 strains, it has not been tested in either TA102 or TA104 and only a few times in the E. coli WP2  
7174 strains, the strains that would be the most sensitive to the oxidative DNA damage likely to be  
7175 generated during carbon tetrachloride toxicity.

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7177 Based on OECD relevant guidance as to selection of bacterial strains, standard Salmonella test  
7178 strains "may not detect certain oxidizing mutagens, cross-linking agents, and hydrazines. Such  
7179 substances may be detected by E.coli WP2 strains or S. typhimurium TA102..." OECD's  
7180 recommended combination of strains includes E. coli WP2 strains or S. typhimurium TA102.  
7181 (OECD Guideline for Testing of Chemicals. Bacterial Reverse Mutation Test. Report 471,  
7182 adopted 21 July 1997.) Additionally, a statistically significant but well less than a twofold  
7183 increase for E. coli WP2uvrA was reported by Norpoth (1980) at high levels (about 25,000 ppm)  
7184 in another gas-phase exposure study."

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7188 *In vitro* genotoxicity studies for carbon tetrachloride in mammalian cells

7189 As discussed below, *in vitro* studies of carbon tetrachloride genotoxic effects in metabolically  
7190 competent liver cells will be of most importance. Studies in lung and kidney cells may provide  
7191 supplemental information, while studies in other cell types may not allow for metabolism  
7192 believed to be necessary for carbon tetrachloride toxicity/carcinogenicity.

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7194 *Metabolism induction*

7195 According to EPA IRIS Assessment ([U.S. EPA, 2010](#)), “when standard inducing procedures  
7196 (Arochlor 1254 or the combination of phenobarbitone and beta-naphthoflavone) have been used,  
7197 the levels of CYP2E1 in the rat liver are markedly suppressed ([Burke et al., 1994](#)). This would  
7198 lead to a decrease in CYP2E1 in the S9 used for the test and could potentially contribute to the  
7199 observed negative results.” However, mammalian cell test strains using lymphocytes, ovary  
7200 cells, lung cells, or kidney cells may not closely resemble liver cells in the ability to metabolize  
7201 carbon tetrachloride. The kidney and lung do have P450 metabolic capability that has been  
7202 evaluated for carbon tetrachloride and this has been used in the development of PBPK models.  
7203 Using *in vitro* measurements with p-nitrophenol as a reference compound, ([Yoon et al., 2007](#))  
7204 has estimated CYP2E1 activity (V<sub>max</sub> – nmole/min/g) in the lung and kidney as approximately  
7205 6% and 5% of that in the liver. Accordingly, cells from these other tissues may not be similar to  
7206 liver cells in the metabolism of carbon tetrachloride.

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7208 *Mammalian cell mutagenesis tests*

7209 There are no mutagenesis tests identified in mammalian liver, kidney or lung cells *in vitro*.  
7210 OECD now recommends *in vitro* mammalian cell gene mutation tests using the hprt or xprt  
7211 genes (OECD TG 476). The OECD cited tests include lung cell lines (V79 and CHL) that could  
7212 be examined for CYP2E1 competence.

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7214 *Chromosomal changes*

7215 In the absence of mutation studies, the current review focuses on chromosomal aberration and  
7216 micronucleus studies in mammalian cells *in vitro* – using cells from (1) liver, (2) kidney, or lung  
7217 which also show some CYP2E1 activity, or (3) cells with CYP2E1 capability is added. These are  
7218 extracted from EPA IRIS Assessment ([U.S. EPA, 2010](#)) below.



7219 **Table\_Apx I-1.** Bacterial mutagenesis data in systems believed relevant to detection of oxidative damage to DNA – excerpted from  
 7220 EPA IRIS Assessment

Test system	Endpoint	Test conditions	Results with metabolic activation	Results without metabolic activation		Reference
<i>Escherichia coli</i> WP2uvrA/pKM101	Reverse mutation	Gas phase exposure in a gas sampling bag for 24 hrs	±	±	10,000 ppm	( <a href="#">Araki et al., 2004</a> )
<i>EE. coli</i> WP2/pKM101	Reverse mutation	Gas phase exposure in a gas sampling bag for 24 hrs	+	+ <sup>e</sup>	5,000 ppm	( <a href="#">Araki et al., 2004</a> )
<i>E. coli</i> WP2uvrA	Reverse mutation	Gas phase exposure in a desiccator	ND	±	25,000 ppm	( <a href="#">Norpoth et al., 1980</a> )

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 7222 +: positive results; - : negative results; ± : equivocal or weakly positive; T: Toxicity; ND: No Data

7223 <sup>e</sup>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.

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7243 **Table\_Apx I-2.** Chromosomal changes in *in vitro* studies mammalian cells from liver, kidney or lung; or cells with CYP2E1 genetic  
7244 capability added – excerpted from EPA IRIS Assessment

Test system	Endpoint	Test conditions	Results with metabolic activation	Results without metabolic activation		Reference
RL <sub>1</sub> cultured cell line derived from rat liver	Chromosomal aberrations	Assay conducted in sealed flasks	-	ND	0.02 µg/mL in DMSO <sup>d</sup>	( <a href="#">Dean and Hodson-Walker, 1979</a> )
V79 Chinese hamster lung cell line	Aneuploidy	3-Hr incubation	+	ND	246 µg/mL	( <a href="#">Onfelt, 1987</a> )
V79 Chinese hamster lung cell line	c-Mitosis (spindle disturbance)	30-Min incubation	± (T)	ND	492 µg/mL	( <a href="#">Onfelt, 1987</a> )
h2E1 cell line (cDNA for CYP2E1)	Micronucleus formation	Immunofluorescent labeling of kinetochore proteins	+ <sup>e</sup> (T)	ND	308 µg/mL	( <a href="#">Doherty et al., 1996</a> )
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	+ <sup>e</sup> (T)	ND	308 µg/mL	( <a href="#">Doherty et al., 1996</a> )
See comment above						

7245 positive results; - : negative results; ± : equivocal or weakly positive; T: Toxicity; ND: No Data

7246 <sup>e</sup> 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.

7247 <sup>d</sup> 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.<sup>24</sup> 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.

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<sup>24</sup> Yoon (2007) has estimated CYP2E1 activity (V<sub>max</sub> – 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  
7293 Assessment

Test system	Endpoint	Test conditions	DNA adducts IRIS (2010) descriptor <sup>a</sup>	Dose <sup>b</sup>	Reference
Mouse (B6C3F <sub>1</sub> , <i>lacI</i> transgenic; Big Blue™, male)	Mutations in <i>lacI</i> transgene in liver	The target <i>lacI</i> 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)	( <a href="#">Mirsalis et al., 1994</a> )
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 <i>in vivo</i> experiments. The sensitivity of this experiment could have been strengthened if CT were administered for a longer period.					
Mouse (CD2F <sub>1</sub> <i>lacZ</i> transgenic, Mutamouse™, male)	Mutations in the <i>lacZ</i> transgene in liver	The target <i>lacZ</i> 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	( <a href="#">Tombolan et al., 1999</a> )
Comment: The carbon tetrachloride data was generated as an adjunct of a study with a different research focus, and were thus limited in scope. CT mutation frequency exceeded controls by 60% which was not indicated as significant. Use of only a single test administration limits the sensitivity of these results. This study should not be judged as a specifically negative finding.					
Mouse (CD2F <sub>1</sub> <i>lacZ</i> transgenic, Mutamouse™, male)	Mutations in the <i>lacZ</i> transgene in liver	The target <i>lacZ</i> 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	( <a href="#">Hachiya and Motohashi, 2000</a> )
Comment: Increases in mutation frequency, some more than 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 degraded 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	( <a href="#">Curtis and Tilley, 1968</a> )
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	( <a href="#">Sawada et al., 1991</a> )

Test system	Endpoint	Test conditions	DNA adducts IRIS (2010) descriptor <sup>a</sup>	Dose <sup>b</sup>	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	( <a href="#">Sawada et al., 1991</a> )
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	( <a href="#">Van Goethem et al., 1993</a> )
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) <sup>g</sup>	3,200 mg/kg by oral gavage in corn oil	( <a href="#">Van Goethem et al., 1995</a> )
Mouse (CBAC575BL/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	( <a href="#">Uryvaeva and Delone, 1995</a> )

<sup>a</sup>+ = positive, ± = equivocal or weakly positive, – = negative, (T) = toxicity

<sup>b</sup> i.m. = intramuscular, i.p. intraperitoneal, i.g. = intragastric gavage, s.c. = subcutaneous.

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7301 **Appendix J EVIDENCE ON LINEARITY OF THE PBPK MODEL**

7302 The appendix table below presents the external:internal dose ratios for the human PBPK model over a  
 7303 span of concentrations, using the model assumptions adopted by the IRIS assessment (model parameter  
 7304  $V_{maxC} = 1.49 \text{ mg/hr/kg BW}^{0.70}$ , continuous 24 hour/day, 7 days/week exposure), including PBPK  
 7305 model results for the MCA (mean arterial concentration) internal dose metric and results for the  
 7306 MRAMKL (mean rate of metabolism in the liver) internal dose metric. This appendix table is a  
 7307 modification of Tables C-6 and C-10 in the IRIS assessment.

7309 **Table\_Apx J-1. Table Summarizing PBPK Model results in the IRIS Assessment Tables C-6 and**  
 7310 **C-10**

EC (ppm)	EC (mg/m <sup>3</sup> )	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

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### 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.

7355 The submission cites the following experimental data as supporting qualitative evaluation of the  
7356 proposed MOA (paraphrased for succinctness):

- 7357 (1) Metabolism of carbon tetrachloride has been demonstrated to produce free radicals including  
7358  $CCl_3\bullet$ , which has been detected in spin trapping studies with the liver in vivo, isolated liver  
7359 cells, and microsomal preparations.
- 7360 (2) Studies using a variety of methodologies show that carbon tetrachloride exposures can cause  
7361 lipid peroxidation in the liver.
- 7362 (3) A study in CYP2E1 knockout mice found that these animals avoided liver toxicity. Other  
7363 studies using CYP450 inhibitors indicate that prevention of carbon tetrachloride metabolism  
7364 also prevents liver toxicity. Studies with co-administration of free radical scavengers with  
7365 carbon tetrachloride have reduced liver toxicity. Conversely, there is increased carbon  
7366 tetrachloride cytotoxicity in hepatocyte cell lines that over express P450.
- 7367 (4) Studies using free radical scavengers or antioxidants in conjunction with carbon tetrachloride  
7368 administration have shown reduced liver toxicity or lipid peroxidation. Co-administration of  
7369 antioxidants (vitamin E) with carbon tetrachloride have reduced liver peroxidation.
- 7370 (5) Cytosolic calcium levels have been strongly increased by carbon tetrachloride treatment.
- 7371 (6) CT administration increases cell replication in liver tissue. A 1x administration of 40 mg/kg  
7372 carbon tetrachloride increased BrdU uptake by cells in the peri-portal zone at within one day,  
7373 plateauing at 3 days.
- 7374 (7) Altered hepatic foci [of the GST-P form that are believed to be indicative of carcinogenic  
7375 processes] were increased by 12 weeks carbon tetrachloride treatment. [Such foci are  
7376 observed at the 25 ppm and 125 ppm inhalation exposures in Tsujimura (2008), but not  
7377 significantly elevated at 5 ppm or 1 ppm.]
- 7378 (8) “Hepatocellular carcinomas appear only at the high dose in rats and mid and high doses in  
7379 mice, with an all or none response.”

7380  
7381 However, while these study findings inform our understanding of carbon tetrachloride  
7382 carcinogenesis, much uncertainty also remains.

- 7383 (1) Metabolism of carbon tetrachloride to free radicals, at least substantially by CYP2E1, is  
7384 responsible for observed lipid peroxidation and liver toxicity of this compound but this does  
7385 not establish relative role of cytotoxicity or genotoxicity in a cancer MOA – both processes  
7386 could be driven by carbon tetrachloride metabolites and/or peroxidation products.
- 7387 (2) These results suggest a hypothesis that lipid peroxidation is a specific cause of observed liver  
7388 toxicity, but it is not apparent that this hypothesis has been specifically challenged. Direct  
7389 liver toxicity from carbon tetrachloride metabolites is also possible. Also, importantly, a  
7390 recently discovered process termed ferroptosis describes cell death elicited by lipid  
7391 peroxidation as being “genetically, biochemically, and morphologically distinct from other  
7392 cell death modalities, including apoptosis, unregulated necrosis, and necroptosis” (Yang and  
7393 Stockwell, 2016, Ferroptosis: Death by Lipid Peroxidation. Trends Cell Biol. 26(3):165-176).  
7394 As carbon tetrachloride toxicity studies have identified liver “necrosis”, the above suggests  
7395 that this necrosis may be distinct from a lipid driven process. On the other hand, if ferroptosis  
7396 plays a role in (some) observed CT cell death, the effects of such cell death may not fit with a  
7397 regenerative hyperplasia (necrosis) driven MOA for cancer. A study by Siegers et al (1988)  
7398 provides substantial evidence that an iron mediated lipid peroxidation process is involved in



7399 carbon tetrachloride liver toxicity. Pretreatment of rodents with the iron binding agent  
7400 deferoxamine before carbon tetrachloride administration reduced both the liver toxicity  
7401 (indicated by plasma GPT and SDH activity levels) and reduced lipid peroxidation (as  
7402 indicated by exhaled ethane levels) ([Siegers et al., 1988](#)). The CT analogue  
7403 bromotrichloromethane showed the same pattern of results, while several other hepatotoxic  
7404 agents did not show a reduction of liver toxicity or lipid peroxidation following  
7405 deferoxamine treatment. This suggests that the response observed was specifically relevant  
7406 to carbon tetrachloride's toxic mode of action.

- 7407 (3) The submission proposes that lipid peroxidation-induced cell death drives cellular  
7408 proliferation-induced liver cancer. This conclusion ignores the carcinogenic potential of steps  
7409 leading up to lipid peroxidation, including oxygen and lipid based radical reactions resulting  
7410 from carbon tetrachloride metabolism, derangement of cellular calcium levels, potential  
7411 enhanced cellular iron availability to catalyze oxygen-radical induced lipid peroxidation, and  
7412 depletion of cellular glutathione and consequent inhibition of enzymes responsible for repair  
7413 of lipid peroxides.
- 7414 (4) Changes in cytosolic calcium levels occur during carbon tetrachloride toxicity, but it is not  
7415 apparent that the hypothesis that elevation of cellular calcium concentrations *causes* toxicity  
7416 has been experimentally challenged.
- 7417 (5) Cell replication is increased early, but not immediately, in the process of carbon tetrachloride  
7418 toxicity (i.e., at two days). Such proliferation is proposed to be due to tissue regeneration,  
7419 however other processes might also be involved.
- 7420 (6) Cytotoxic processes (considered holistically) or increased cell replication specifically can be  
7421 proposed as causes of carbon tetrachloride carcinogenicity. However, these hypotheses are  
7422 proposed based on broader biological considerations and not directly supported or tested by  
7423 data on carbon tetrachloride.
- 7424 (7) The observed tumorigenicity data have mostly shown steep dose response patterns that are  
7425 interpreted in the submission as indicative of thresholds. However, the study authors of the  
7426 inhalation cancer bioassay ([Nagano et al., 2007a](#)) and EPA's IRIS assessment provide a more  
7427 nuanced characterization of the tumor data as being indicative of responses at some of the  
7428 lower dose levels.<sup>25</sup>
- 7429 (8) Data on carbon tetrachloride increased GST-P liver foci in male rats are observed in  
7430 intermediate term experiments in male rats and follow a dose response pattern similar to, but  
7431 distinct from, the tumor dose response seen in male rats. (Foci were statistically elevated at  
7432 an inhaled concentration of 25 ppm, while a tumor response was not observed at that dose.)  
7433 In other studies, this GST-P foci protocol has been suggested as a practical indicator for  
7434 carcinogenicity by either genotoxic or non-genotoxic pathways. Thus, the observation of

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<sup>25</sup> 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.

7435 these foci thus provides qualitative supporting evidence for carbon tetrachloride  
7436 carcinogenicity and also support for an upward curving (but not necessarily threshold) dose  
7437 response relationship in male rats. The role of this data in supporting a cytotoxic versus an  
7438 alternative MOA for carbon tetrachloride is not apparent. The occurrence of liver foci after  
7439 carbon tetrachloride treatment – without prior treatment by an initiating agent or use of a  
7440 partial hepatectomy may be interpreted to indicate that carbon tetrachloride is a “complete  
7441 carcinogen” (i.e., a compound that contributes to both tumor induction and promotion.)

7442 The “Essentiality” criterion is scored in the submission as maximally high for all steps in their  
7443 proposed MOA. The resulting score contributes strongly to the highly positive ranking they assign to  
7444 the cytotoxicity MOA for tumors. However, a scoring problem is present in this methodology.  
7445 Specifically, the “essentiality” score for each proposed key event in a pathway is assigned “the  
7446 highest score achieved by any one of the unique Key Events in the pathway”. This is a problematic  
7447 approach because a MOA may (and usually does) involve varied events with different degrees of  
7448 experimental support. Assigning the maximum score to all such events over states the available  
7449 evidence. In the case of the carbon tetrachloride, this numeric process leads to strongly over-scoring  
7450 the degree of experimental evidence for the cytotoxic MOA.

#### 7451 B. Dose-response concordance

7452 The submission states: “Because the earlier key events are demonstrated via *in vitro* assays, the  
7453 concentrations do not align with the longer term *in vivo* studies. It is clear, however, that the doses  
7454 for the earlier key events are lower than those needed to elicit liver tumors ... for dose concordance  
7455 the precursor key events must occur earlier and at lower doses than the tumorigenic dose.”  
7456

7457 This quote does not provide a strong argument in favor of a cytotoxicity MOA. First, it is not clear to  
7458 the reader that doses at which early events have been demonstrated are lower than the experimental  
7459 tumorigenic doses. While it is difficult to compare *in vitro* and *in vivo* systems, with the available  
7460 PK predictions, the authors could have undertaken some comparisons between molar concentrations  
7461 of carbon tetrachloride in liver tissue and those used in the *in vitro* experiments they are referring to.  
7462 It is logically correct that precursor key events (if measured with sufficient sensitivity) must occur  
7463 doses at least as low as tumorigenic doses. Violation of this pattern can be strong evidence *against* a  
7464 MOA proposal. Such an example is presented in EPA (2010): namely tumors were observed in the  
7465 female mouse inhalation bioassay at a lower concentration (25 ppm) than where substantial toxicity  
7466 was observed. This provides evidence against cytotoxic effects alone providing an explanation for  
7467 observed tumors.  
7468

7469 Secondly, a showing that precursor events occur at lower doses than tumors sets a rather low bar for  
7470 evaluating this dose response concordance. A range of diverse biological responses may occur at  
7471 doses below those that cause frank toxicity. Knowing that a given effect occurs at a subtoxic dose is  
7472 not in itself evidence that the two are related. Stronger evidence for a MOA would come from  
7473 demonstrating a reasonable quantitative functional relationship between increasing levels of the  
7474 proposed precursor response and increased incidence of apical toxic response<sup>26</sup>. The ACC materials  
7475 do not present such an analysis.  
7476  
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<sup>26</sup> 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.

7478 The submitted example case scored dose response concordance as providing “moderate” support  
7479 most of the proposed key events in the cytotoxicity MOA. In my evaluation, the evidence is  
7480 somewhat weaker. The data as assembled do not reveal unambiguous relationships between  
7481 increasing cytotoxicity and increasing tumorigenicity. EPA (2010) has also judged that the  
7482 inhalation study tumor response in the low dose (5 ppm) female mice occurred in the absence of  
7483 substantial observed toxicity.  
7484

### 7485 C. Temporal concordance

7486 Temporal relationships can provide important evidence for causal relationships, as reflected in  
7487 Bradford Hill’s criterion: “The effect has to occur after the cause (and if there is an expected delay  
7488 between the cause and expected effect, then the effect must occur after that delay).” However, in  
7489 evaluating mechanistic data, it is also true that an agent can cause a variety of biological  
7490 perturbations resulting from short term exposure. That is many biological effects may occur much in  
7491 advance of chronic apical effects such as cancer. The observation that a proposed precursor occurs  
7492 rapidly (or even at subchronic duration) does not in itself provide much evidence for a causal  
7493 relationship between the two. Specific to carbon tetrachloride, ACC’s concordance table shows  
7494 metabolism of carbon tetrachloride to reactive radicals, lipid peroxidation, loss of calcium  
7495 homeostasis, and initial cytotoxicity all occurring within 24 hours; cellular proliferation is observed  
7496 after two days, and liver tumors are observed at 2 years. This pattern of shorter term versus longer  
7497 term findings may simply reflect the expected time scales for (1) prompt events of metabolism and  
7498 initial chemical tissue interactions, (2) acute toxicological changes, and (3) chronic toxicity. This  
7499 pattern in itself doesn’t provide much information to support a MOA.  
7500

7501 The submitted example case cites Cabre et al., (2000) as showing liver fibrosis, changes in  
7502 glutathione pathways, and observation of products of lipid peroxidation at time periods before the  
7503 occurrence of cirrhosis. These earlier events may have a role in carbon tetrachloride carcinogenesis,  
7504 however, this study doesn’t seem to provide evidence of a cancer MOA.  
7505

7506 The MOA scoring process attributed maximum scores for “temporal concordance” for all five  
7507 hypothesized key events in the cytotoxicity pathway, contributing heavily to high overall score  
7508 assigned to the MOA. However, we believe the cited data on temporal patterns for carbon  
7509 tetrachloride effects provides only marginal insight for evaluating the MOA for this compound.  
7510

## 7511 *II. ACC evaluation of a mutagenicity MOA*

7512 This MOA as constructed calls for direct mutagenicity by carbon tetrachloride metabolites to account for  
7513 the observed cancer findings. As noted above, this inference does not agree with the conclusions about a  
7514 carbon tetrachloride MOA as described by EPA (2010). The IRIS assessment suggested a multi-step  
7515 MOA that may involve both mutagenicity and promotion by cytotoxic effects. Such mutagenic effects of  
7516 carbon tetrachloride need not be direct (in the sense of a direct metabolite of carbon tetrachloride  
7517 binding to DNA). A multistep MOA may involve oxidative DNA adducts derived through lipid  
7518 peroxidation resulting from carbon tetrachloride metabolism. Such effects need not be limited to  
7519 situations with carbon tetrachloride toxicity, as chemical interactions leading to ROS formation may  
7520 occur in the absence of toxicity. The presence of cytotoxicity may quantitatively alter the dose response  
7521 for production of DNA oxidation, however the specific effects of toxicity processes is unknown. High  
7522 doses of carbon tetrachloride may not produce maximal adduct response, as: (1) High carbon  
7523 tetrachloride doses can impair CYP2E1 metabolism to species causing lipid peroxidation (2) cell killing  
7524 at high doses will cause birth of cells not exposed to initial carbon tetrachloride doses – or prior  
7525 background conditions. While there are positive studies showing increased oxidative binding following

7526 carbon tetrachloride exposure, this database is complex and sometimes inconsistent. However, with the  
7527 present state of knowledge, carbon tetrachloride induced oxidative adducts may be an important  
7528 contributor to carbon tetrachloride's MOA for cancer. Feasible, studies using modern methods and  
7529 quality assurance procedures could substantially resolve these questions.

7530

7531 The submitted example case statement of a mutagenicity MOA is specific and calls for proof at several  
7532 stages for mutagenic processes:

7533 (1) Metabolism of carbon tetrachloride to a reactive intermediate that leads to the formation of  
7534 carbon tetrachloride - induced pro-mutagenic DNA adducts

7535 (2) Insufficient or mis- repair of carbon tetrachloride -induced DNA Adducts

7536 (3) Early Mutations induced in cancer critical genes

7537 (4) Clonal Expansion/Cell Proliferation to form Pre-neoplastic AHF

7538 (5) Progression and late mutations

7539 (6) Hepatocellular Carcinoma

7540 Given the current lack of resolution on the potential for carbon tetrachloride mutagenicity at bioassay  
7541 and human relevant exposure levels (see below) the resultant scoring for this MOA was low. However,  
7542 the score derived by ACC was driven by the choice of steps included above. Note that step (1) includes  
7543 both metabolism and production of pro-mutagenic DNA adducts. This compound step would demand  
7544 much evidence to satisfy. This contrasts with the accompanying hypothesized cytotoxicity MOA where  
7545 step 1 was purely metabolic: "Metabolism via CYP2E1 and formation of trichloromethyl peroxy  
7546 radical". Requiring that both metabolism and DNA lesions be established in a first step for the  
7547 mutagenic MOA reduces the scoring for this MOA. The decision to separately include step (2) -  
7548 establishing that DNA repair is inadequate - seems both experimentally challenging and somewhat  
7549 beside the point as step (3) calls for specific data on completed mutations. Note also that step (3)  
7550 specifically addresses mutations in cancer critical genes, data that is rarely available from chemical  
7551 mutagenesis studies.

7552

7553 The practical challenge for evaluating a mutagenic MOA (or a role for mutation in a multi-step MOA) is  
7554 assessing the available data on mutagenesis. The attachments to this paper excerpt key data from EPA  
7555 (2010) for *in vivo* and *in vitro* genotoxicity toxicity studies. These tables seek to show that while there is  
7556 a large database of genotoxicity studies on carbon tetrachloride, there are also major limitations in the  
7557 database. In particular there are very limited *in vitro* data that applicable to oxidative damage to DNA by  
7558 carbon tetrachloride (i.e., positive but limited findings in E coli strains) and very limited *in vivo*  
7559 mutagenesis data for carbon tetrachloride metabolizing tissues. The submitted example case has judged  
7560 the carbon tetrachloride database as essentially demonstrating lack of a mutagenic effect. By comparison  
7561 EPA (2010) emphasized the available data do not allow characterization of the genotoxicity at low  
7562 carbon tetrachloride exposure levels or the role of such genotoxicity in a cancer MOA.

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7565

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	<i>In vitro</i>	0, 4.38, 6.55, 8.76 mmol/L (+S9)	3 hours	Positive at 6.55 and 8.76 mmol/L <sup>a</sup> (at relative toxicities of 6% and 16%, respectively)	Alkaline unwinding of DNA (ratio of ssDNA and dsDNA); cell viability	( <a href="#">Garberg et al., 1988</a> )	Unacceptable
Genotoxicity	Acute	<i>Salmonella typhimurium</i> strains TA 98, TA 100, TA 1535, TA 1537 <3 replicates /group	<i>In vitro</i>	0, 0.005, 0.01, 0.05, 0.1, 0.2, 0.5, 1, 2, 5% ( $\pm$ S9) <sup>b</sup>	24 hours	Weakly positive <sup>c</sup> in TA 98 (-S9) at $\geq$ 1%; negative in TA 98 (+S9); negative in TA 100, TA 1535, and TA 1537 ( $\pm$ S9)	Reverse mutation (gas exposure method)	( <a href="#">Araki et al., 2004</a> )	High
Genotoxicity	Acute	<i>Escherichia coli</i> strains WP2/ <i>uvrA</i> /pKM101, WP2/pKM101 <3 replicates /group	<i>In vitro</i>	0, 0.005, 0.01, 0.05, 0.1, 0.2, 0.5, 1, 2, 5% ( $\pm$ S9) <sup>b</sup>	24 hours	Weakly positive <sup>c</sup> at 2% in WP2/ <i>uvrA</i> /pKM101 ( $\pm$ S9); positive at $\geq$ 0.1% (-S9) and $\geq$ 0.2% (+S9) in WP2/pKM101 <sup>d</sup>	Reverse mutation (gas exposure method)	( <a href="#">Araki et al., 2004</a> )	High

<sup>a</sup>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.

<sup>b</sup>Tests were also conducted with glutathione-supplemented S9 mix.

<sup>c</sup>A result was considered positive if a two-fold increase in the number of revertants was observed.

<sup>d</sup>Data for *E.coli* strain WP2/pKM101 were based on < 3 measurements (statistical analyses were not performed).

7566