# SYSTEMATIC EVIDENCE MAP (SEM) FOR CARBON TETRACHLORIDE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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# CONTRIBUTORS

## CHEMICAL MANAGER TEAM

Fahim Atif, Ph.D.
Gaston Casillas, Ph.D.
Franco Scinicariello, MD, MPH

ATSDR, Office of Innovation and Analytics, Toxicology Section, Atlanta, GA

Kimberly Zaccaria, Ph.D., D.A.B.T.
Claire Heit, Ph.D.
Megan Riccardi, M.S.
Megan Doldron, Ph.D.
Deborah Herber, Ph.D.
Connor McGuire, Ph.D.
Brisa Salinas, M.S.
Yasmine Sobhi, B.S.

SRC, Inc., North Syracuse, NY

# CONTENTS

# 1. OBJECTIVES

The aim and scope of the systematic evidence map (SEM) are to:

- Conduct literature searches to identify available relevant studies published since the carbon tetrachloride toxicological profile was last published in August 2005, including studies in humans, animals, *in vitro* models, or *in silico*.

- Screen literature search results using methods consistent with principles of systematic review to determine if identified studies meet the Populations, Exposures, Comparators, and Outcomes (PECO inclusion criteria) outlined below (see Section 2.1).

- Prepare an interactive literature inventory to provide an overview of the new evidence that meets PECO criteria.

- Perform high-level data review and extraction of studies identified during the updated literature search to determine if any could potentially address key data needs or impact existing minimal risk levels (MRLs) for carbon tetrachloride, as identified in the toxicological profile (ATSDR 2005).

# 2. METHODS

## 2.1 LITERATURE SEARCH STRATEGY

A literature search was conducted to identify studies examining health effects, toxicokinetics, and mechanisms of action for carbon tetrachloride. The PECO criteria used to identify relevant studies examining the health effects of carbon tetrachloride are presented in Table 2-1.

**Table 2-1. PECO Criteria for Screening of ATSDR SEM Literature Search Results**

| PECO element | Evidence |
|---|---|
| **P**opulation | Humans, laboratory mammals, and other animal models of established relevance to human health (e.g., *Xenopus* embryos); mammalian organs, tissues, and cell lines; and bacterial and eukaryote models of genetic toxicity. |
| **E**xposure | *In vivo* (all routes), *ex vivo*, and *in vitro* exposure to carbon tetrachloride, including mixtures to which carbon tetrachloride may contribute significantly to exposure or observed effects. |
| **C**omparison | Any comparison (across dose, duration, or route) or no comparison for select study types (case reports without controls, acute lethality limit tests without controls). |
| **O**utcomes | Any endpoint suggestive of a toxic effect on any bodily system, or mechanistic change associated with such effects. Any endpoint relating to toxicokinetics/ dynamics of the chemical within the body. |

ATSDR = Agency for Toxic Substances and Disease Registry; PECO = Populations, Exposures, Comparators, and Outcomes; SEM = systematic evidence map

The current literature search was intended to identify studies not included in the existing toxicological profile for carbon tetrachloride (ATSDR 2005); thus, the literature search was restricted to studies published between January 2003 to March 2024 to capture literature published since the search was conducted for the existing profile. The following main databases were searched in March 2024:

- PubMed
- Embase
- SciFinder
- Scopus

The search strategy used the chemical names, Chemical Abstracts Service Registry Numbers (CASRNs), synonyms, Medical Subject Headings (MeSH), and keywords for carbon tetrachloride. The query strings used for the literature search are presented in Appendix A (Table A-1). These query strings are designed to capture all data potentially relevant to the PECO statement as well as additional data potentially relevant to developing a toxicological profile (e.g., chemistry, production, use, environmental fate, etc.).

These additional data studies that are potentially relevant to the carbon tetrachloride toxicological profile, but do not meet the PECO criteria, will not be included in the SEM but will be tagged for potential future use in profile development.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), National Toxicology Program (NTP), National Technical Reports Library (NTRL), and Regulations.gov websites using the queries presented in Appendix A (Table A-2). Regulatory documents and review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature from these resources, including unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

## 2.2 LITERATURE SCREENING STRATEGY

Two screeners independently conducted a title and abstract screening of the search results using DistillerSR[1] to identify study references that met the PECO eligibility criteria (see Table 2-1). Additional, chemical-specific title/abstract screening criteria was implemented to indicate studies that were designed to amend (ameliorate or exacerbate) the known hepatotoxic effects of carbon tetrachloride. These studies are maintained if retrieval is warranted at a future time.

References that were included based on PECO eligibility criteria during title and abstract screen were submitted for reference retrieval. For nonlocal retrieval items (e.g., pay-per-citation, etc.), an additional screening step was conducted based on refined PECO criteria with a narrowed focus to capture only key health hazard information and studies that may fill data gaps (Table 2-2). Citations selected for full-text retrieval were limited to English-language, full-length journal articles or study reports at this stage.

[1]DistillerSR is a web-based systematic review software used to screen studies available at: https://www.evidencepartners.com/products/distillersr-systematic-review-software.

**Table 2-2. Refined PECO Criteria for Screening of Nonlocal Citations**

| PECO element | Evidence |
|---|---|
| **P**opulation | Humans or laboratory mammals. |
| **E**xposure | Inhalation, oral, or dermal exposure to carbon tetrachloride, including mixtures that contain a high percentage of carbon tetrachloride. |
| **C**omparison | Any comparison (across dose, duration, or route) or no comparison (no controls) for select study types (case reports, acute lethality limit tests). |
| **O**utcomes | Any endpoint suggestive of a toxic effect on any bodily system or containing information to address data gaps (e.g., PBPK model, toxicokinetics, toxicity or mechanistic data to inform specific effects, etc.)[a]. |

[a]Key data gaps identified in the 2005 profile for carbon tetrachloride included: occupational studies in humans; acute-duration, dose-response studies to define thresholds for hepatic and renal toxicity (<10 ppm, 5 mg/kg/day); oral chronic-duration studies to determine no-effect levels for hepatic effects, lowest dose tested was serious LOAEL at 47 mg/kg/day; dose-response studies to determine effects on other tissues and systems at doses near the thresholds for injury to the liver and kidney (<10 ppm, 5 mg/kg/day), particularly nervous, immune, reproductive, and developmental (including neurodevelopmental); oral studies with drinking water (instead of gavage) to better mimic the human exposure condition; genotoxicity studies with metabolic activation (or in metabolically competent tissues/*in vivo* systems); and studies on rates of metabolism or relevant cytochrome P450 proteins in the kidney.

LOAEL = lowest-observed-adverse-effect-level; PBPK = physiologically based pharmacokinetic; PECO = Populations, Exposures, Comparators, and Outcomes

References that were included based on title and abstract screening advanced to full-text review using the broad PECO eligibility criteria listed in Table 2-1. Full-text copies of potentially relevant references identified from title and abstract screening were retrieved, embedded in DistillerSR screening forms, and independently assessed by two screeners using DistillerSR to confirm eligibility. If studies were considered PECO-relevant based on full-text review, screeners categorized the studies as one of the following study types: primary health effects studies (human toxicity, animal toxicity) or supporting data studies. Supporting data studies include the following study types: genotoxicity, mechanistic, toxicokinetic, secondary sources, and conference abstracts. Exposure routes other than inhalation, oral, and dermal were also classified as supporting studies. An additional, chemical-specific supporting data category was developed for carbon tetrachloride called "model of toxicity" to capture studies designed to use carbon tetrachloride as a model of liver toxicity (e.g., cirrhosis models) to evaluate typical disease progression and/or therapeutic interventions. Any study designed to amend (ameliorate or exacerbate) the known hepatotoxic effects of carbon tetrachloride that was not identified at title/abstract screening was also placed into this category. These studies were not categorized as primary health effects studies (or selected for data extraction) for the following reasons: (1) the doses used were not low exposure and would not inform the MRL; (2) a single, known toxic dose was used, precluding a dose-response relationship; and (3) these study designs did not fill the data gaps identified in the existing profile. Some human toxicity studies were also classified as supporting data studies due to limited information on

quantitative dose-response metrics for carbon tetrachloride, including case reports, studies lacking quantitative exposure reporting or estimated exposure using a job-exposure matrix, and studies reporting quantitative exposure but lacking compound-specific analysis (e.g., mixed exposure analysis only). Additionally, due to integration across durations, routes, and/or species, which precluded the ability to extract data into DistillerSR forms, meta-analyses were also classified as supporting studies at full-text review. Lastly, studies that did not meet PECO criteria but contained other profile-relevant data were categorized as one of the following study types for potential use during later profile development: chemistry, biomarker, interaction, or susceptible populations.

At both the title/abstract and full-text review levels, any screening conflicts were resolved by discussion between the primary screeners, with consultation by a third screener (if needed) to resolve any remaining disagreements.

## 2.3 HIGH-LEVEL DATA EXTRACTION FOR LITERATURE INVENTORY

References that were categorized as PECO-relevant health effects studies advanced to high-level data extraction in DistillerSR. Information extracted for human toxicity studies included study population, measure of exposure, duration, route, systems evaluated, and whether examined systems showed an exposure-related effect. Information extracted for animal toxicity studies included species, strain, animal number and sex, duration, route, number of dose groups, doses/concentrations, systems evaluated, and systems showing an exposure-related effect. Extracted data were exported into Tableau Public[2] for interactive data visualization.

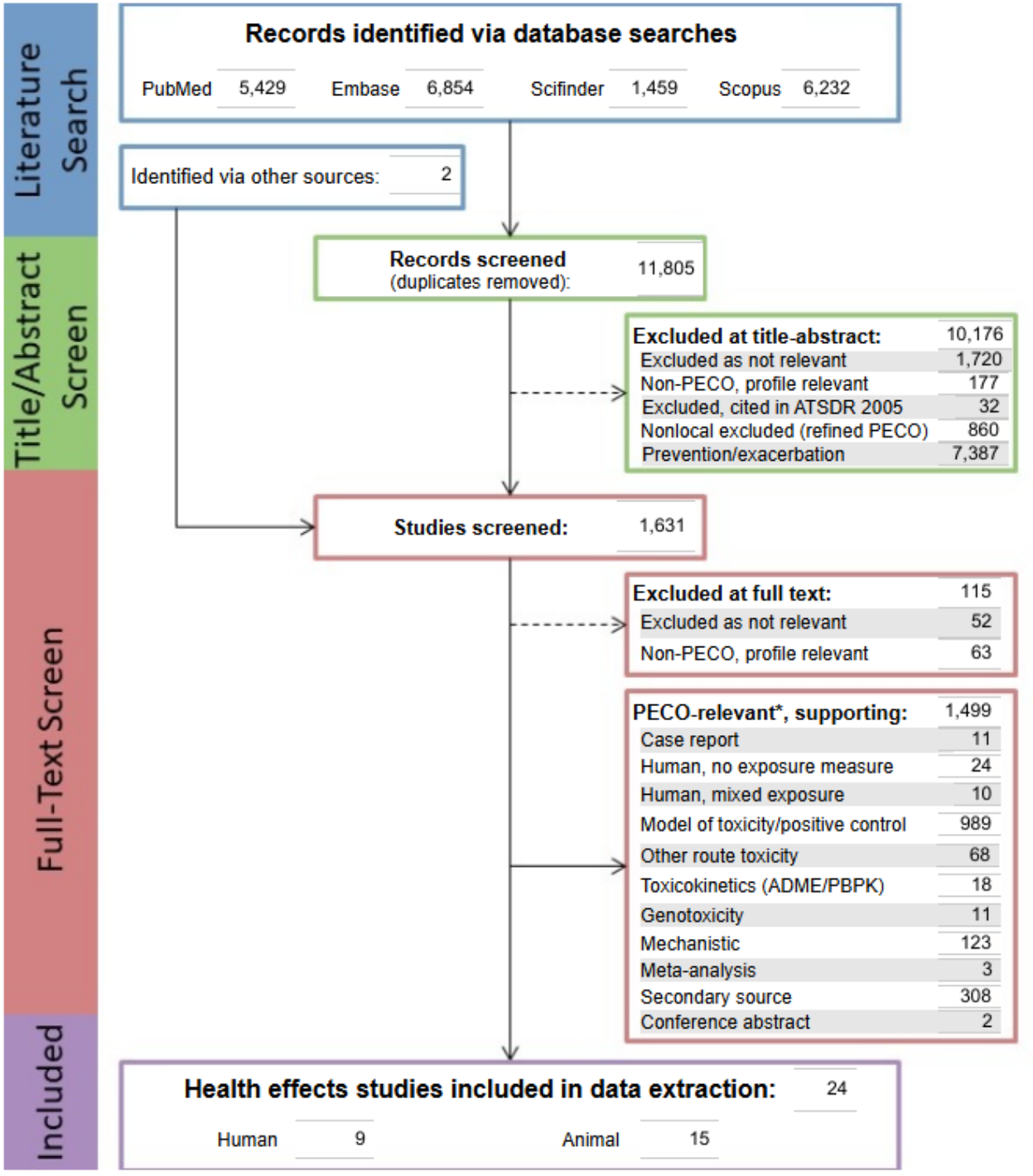
[2]Tableau Public is a web-based data visualization software available at https://public.tableau.com.

# 3. RESULTS

## 3.1 LITERATURE SEARCH RESULTS

Literature searches from all bibliographic databases yielded 11,805 unique references (after removal of duplicates). Title and abstract screening excluded 10,176 references as not relevant: 1,897 references that did not meet PECO criteria (1,720 references considered not relevant plus 177 references identified as non-PECO, profile-relevant), 32 references that were already cited in ATSDR (2005), 7,387 studies that were designed to amend (ameliorate or exacerbate) the known hepatotoxic effects of carbon tetrachloride, and 860 nonlocal references identified as not relevant based on refined PECO criteria. After removing references that did not meet PECO criteria, the remaining 1,629 items proceeded to full-text review. Grey literature search results screened outside of DistillerSR added 2 citations, bringing the total number of citations for full-text review to 1,631. An additional 115 references that did not meet PECO criteria were excluded during full-text screening; of these, 63 were identified as non-PECO, profile-relevant items. The remaining 1,516 references were identified as PECO-relevant; 16 references included health effects data, 1,491 references contained other supporting data, and 8 references contained both health effects and supporting data. A summary of the results of the literature search and screening is presented in Figure 3-1.

## Figure 3-1. Literature Flow Diagram




*Supporting studies may contain data relevant to multiple supporting categories and/or human or animal health effects data

ADME = Absorption, Distribution, Metabolism, and Excretion; PBPK = Physiologically Based Pharmacokinetic; PECO = Populations, Exposures, Comparators, and Outcomes

Interactive literature flow diagram can be accessed at: LitFlow SEM Carbon tetrachloride 2024.

## 3.2 LITERATURE INVENTORY

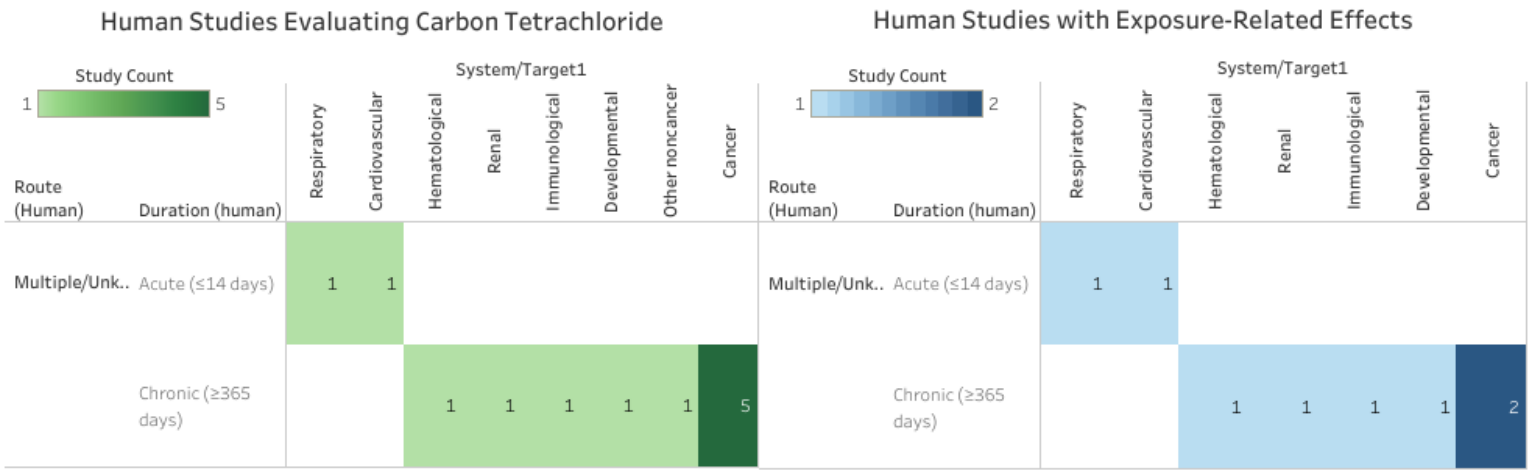
The literature search and screen identified 9 human and 15 animal health effects studies for carbon tetrachloride; some animal studies included multiple experiments in different species and/or of different durations.

As shown in the heatmaps in Figure 3-2 (A: Human Data) and (B: Animal Data), the majority of human studies were chronic-duration, and the majority of animal studies were acute-duration. For human studies, 100% of the studies evaluated exposure via biomarkers, so exposure was attributed to multiple/unknown exposure routes. The most-studied endpoint in humans was cancer. For animal studies, 49% (33) of animal studies focused on the inhalation route and 51% (34) of animal studies focused on the oral route. The most-studied endpoints in inhalation studies included death, body weight, respiratory, hepatic, and renal. In oral studies, the majority of studies focused on hepatic endpoints. Findings from human and animal studies are consistent with the existing Toxicological Profile for Carbon Tetrachloride (ATSDR 2005): (1) the hepatic system and renal system are toxicity targets of carbon tetrachloride based on human and animal data; (2) there is some evidence for respiratory effects in humans and animals; (3) animal studies generally report carbon tetrachloride-associated effects in cancer studies, but findings from human studies are mixed; and (4) evidence for effects in other organ systems are mixed (e.g., immunological, other noncancer, etc.). While the existing profile indicates that the central nervous system is a target of toxicity, no new neurological data were identified.

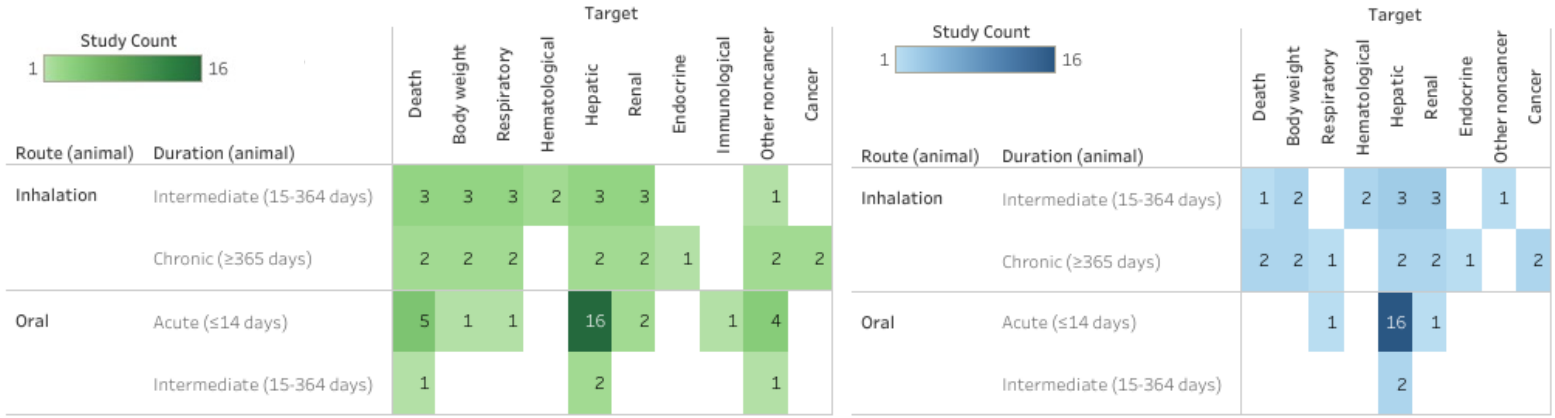
The current toxicological profile (ATSDR 2005) identified several data needs in the toxicological database for carbon tetrachloride. The number of studies identified during the updated literature search that may address these data needs is limited (see Table 3-1). However, the no-observed-adverse-effect level (NOAEL) for the intermediate-duration inhalation study by Tsujimura et al. (2008), based on author-reported hepatic effects, is 5 ppm. This value is equivalent to the point of departure for the existing intermediate-duration inhalation MRL for carbon tetrachloride based on hepatic effects (ATSDR 2005). It is noted that the study by Nagano et al. (2007) is a peer-reviewed publication of the unpublished industry report cited as Japan Bioassay Research Center (1998) in ATSDR (2005), which serves as the basis for the chronic-duration inhalation MRL.

## Figure 3-2. Health Effects Studies for Carbon Tetrachloride

**A:**




**B:**




*Interactive database can be accessed at: Interactive health effects

## Table 3-1. Data Needs Identified for Carbon Tetrachloride by ATSDR (2005)

| Exposure route | Data needs | Studies to potentially address data need |
|---|---|---|
| **Inhalation** | Additional occupational/epidemiological studies in large groups of people with better exposure estimates to better evaluate potential associations between exposure and neurological, hepatic, and renal effects | Renal study (association reported): Li et al. 2019 (cross-sectional, 499 participants in north China) |
| | Studies evaluating reproductive and developmental toxicity in humans | Association reported: Brender et al. 2014 (case-control; 60,613 birth defects, 244,927 controls) |
| | Acute-duration, dose-response studies to define thresholds for hepatic and renal toxicity (<10 ppm) | None |
| | Animal concentration-response studies to determine effects on other tissues and systems at doses near the thresholds for injury to the liver and kidney (<10 ppm), particularly nervous, immune, reproductive, and developmental (including neurodevelopmental) | None |
| **Oral** | Acute-duration, dose-response studies to define thresholds for hepatic and renal toxicity (<5 mg/kg/day) | None |
| | Studies on the time-course of changes following acute-duration exposure for sensitive parameters (liver, kidney, or central nervous system evaluated earlier than 18 hours post-exposure) | High-dose (>150 mg/kg), time-course studies: Iskusnykh et al. 2013 (hepatic, 12–125 hours); Ichi et al. 2007 (hepatic, 2–36 hours); Iida et al. 2007 (hepatic, 2–24 hours); Kikkawa et al. 2006 (hepatic, up to 24 hours); Kandori et al. 2024 (hepatic, 6 or 24 hours) Fukushima et al. 2007 (hepatic, 6 hours) |
| | Oral studies using drinking water or diet to examine intermittent consumption relative to bolus (via gavage) | None |
| | Chronic-duration studies to determine no-effect levels for hepatic effects | None |
| | Animal dose-response studies to determine effects on other tissues and systems at doses near the thresholds for injury to the liver and kidney (<5 mg/kg/day), particularly nervous, immune, reproductive, and developmental (including neurodevelopmental) | None |

ATSDR = Agency for Toxic Substances and Disease Registry; MRL = minimal risk level

# 4. REFERENCES

## 4.1 CURRENT PROFILE

ATSDR. 2005. Toxicological profile for carbon tetrachloride. Atlanta, GA: Agency for Toxic Substances and Disease Registry. https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=196&tid=35. January 15, 2025.

## 4.2 HUMAN TOXICITY

Brender, JD, Shinde, MU, Benjamin Zhan, et al. 2014. Maternal residential proximity to chlorinated solvent emissions and birth defects in offspring: A case-control study. Environmental Health: A Global Access Science Source 13(1):96. https://doi.org/10.1186/1476-069X-13-96.

Garcia, E, Hurley, S, Nelson, et al. 2015. Hazardous air pollutants and breast cancer risk in California teachers: A cohort study -No section. Environmental Health: A Global Access Science Source 14(1):14. https://doi.org/10.1186/1476-069X-14-14.

Hall, C, Heck, JE, Ritz, et al. 2019. Prenatal Exposure to Air Toxics and Malignant Germ Cell Tumors in Young Children. Journal of Occupational and Environmental Medicine 61(6):529-534. https://doi.org/10.1097/JOM.0000000000001609. http://journals.lww.com/joem.

Heck, JE, Park, AS, Qiu, et al. 2013. An exploratory study of ambient air toxics exposure in pregnancy and the risk of neuroblastoma in offspring. Environ Res 127:1-6. https://doi.org/10.1016/j.envres.2013.09.002.

Heck, JuliaE, Park, AndrewS, Qiu, et al. 2014. Risk of leukemia in relation to exposure to ambient air toxics in pregnancy and early childhood. Int. J. Hyg. Environ. Health 217(6):662-668. https://doi.org/10.1016/j.ijheh.2013.12.003.

Li, X, Guo, Y, Song, et al. 2019. A cross-sectional survey based on blood VOCs, hematological parameters and urine indicators in a population in Jilin, Northeast China. Environ Geochem Health 41(3):1599-1615. https://doi.org/10.1007/s10653-019-00241-6.

Su, LJ, Young, SG, Collins, et al. 2022. Geospatial Assessment of Pesticide Concentration in Ambient Air and Colorectal Cancer Incidence in Arkansas, 2013-2017. Int J Environ Res Public Health 19(6):3258. https://doi.org/10.3390/ijerph19063258. https://www.mdpi.com/1660-4601/19/6/3258/pdf.

Takigawa, Tomoko, Wang, Bing-Ling, Sakano, et al. 2009. A longitudinal study of environmental risk factors for subjective symptoms associated with sick building syndrome in new dwellings. Sci. Total Environ. 407(19):5223-5228. https://doi.org/10.1016/j.scitotenv.2009.06.023.

Weichenthal, S, Kulka, R, Belisle, et al. 2012. Personal exposure to specific volatile organic compounds and acute changes in lung function and heart rate variability among urban cyclists. Environ Res 118:118-123. https://doi.org/10.1016/j.envres.2012.06.005.

## 4.3 ANIMAL TOXICITY

Carroll, EE, Ippolito, DL, Permenter, et al. 2018. Utility of Serum miR-122, Liver Enzymes, and Hepatic Histopathology in Response to Hepatotoxicants in Sprague-Dawley Rats. Toxicol Pathol 46(7):835-846. https://doi.org/10.1177/0192623318795435.

Fukushima, T, Hamada, Y, Yamada, et al. 2007. Changes of micro-RNA expression in rat liver treated by acetaminophen or carbon tetrachloride--regulating role of micro-RNA for RNA expression. J Toxicol Sci 32(4):401-9. https://doi.org/10.2131/jts.32.401.

Ichi, I, Kamikawa, C, Nakagawa, et al. 2009. Neutral sphingomyelinase-induced ceramide accumulation by oxidative stress during carbon tetrachloride intoxication. Toxicology 261(1-2):33-40. https://doi.org/10.1016/j.tox.2009.04.040.

Ichi, I, Nakahara, K, Fujii, et al. 2007. Increase of ceramide in the liver and plasma after carbon tetrachloride intoxication in the rat. J Nutr Sci Vitaminol (Tokyo) 53(1):53-6. https://doi.org/10.3177/jnsv.53.53.

Iida, C, Fujii, K, Kishioka, et al. 2007. Activation of mitogen activated protein kinase (MAPK) during carbon tetrachloride intoxication in the rat liver. Arch Toxicol 81(7):489-93. https://doi.org/10.1007/s00204-007-0181-x.

Iskusnykh, IY, Popova, TN, Agarkov, et al. 2013. Expression of Glutathione Peroxidase and Glutathione Reductase and Level of Free Radical Processes under Toxic Hepatitis in Rats. J Toxicol 2013:870628. https://doi.org/10.1155/2013/870628.

Kandori, H, Aoki, M, Miyamoto, et al. 2024. Lobular distribution of enhanced expression levels of heat shock proteins using in-situ hybridization in the mouse liver treated with a single administration of CCl4. J Toxicol Pathol 37(1):29-37. https://doi.org/10.1293/tox.2023-0053. https://www.jstage.jst.go.jp/article/tox/37/1/37_2023-0053/_pdf.

Kikkawa, R, Fujikawa, M, Yamamoto, et al. 2006. In vivo hepatotoxicity study of rats in comparison with in vitro hepatotoxicity screening system. J Toxicol Sci 31(1):23-34. https://doi.org/10.2131/jts.31.23.

Nagano, K, Sasaki, T, Umeda, et al. 2007. Inhalation carcinogenicity and chronic toxicity of carbon tetrachloride in rats and mice. Inhal Toxicol 19(13):1089-103. https://doi.org/10.1080/08958370701628770.

Nagano, K, Umeda, Y, Saito, et al. 2007. Thirteen-week inhalation toxicity of carbon tetrachloride in rats and mice. J Occup Health 49(4):249-59. https://doi.org/10.1539/joh.49.249.

Omura, K, Kiyosawa, N, Uehara, et al. 2007. Gene expression profiling of rat liver treated with serum triglyceride-decreasing compounds. J Toxicol Sci 32(4):387-399. https://doi.org/10.2131/jts.32.387. http://www.jstage.jst.go.jp/article/jts/32/4/387/_pdf.

Saila Rekha, N, Murali Mohan, KV, Ananada Kumar, et al. 2012. Biochemical and histological changes in carbon tetrachloride toxicity. Indian Journal of Forensic Medicine and Toxicology 6(1):100-101. http://www.indianjournals.com/ijor.aspx?target=ijor:ijfmt&volume=6&issue=1&article=028&type=pdf.

Simpson, SA, Alexander, DJ, Reed, et al. 2005. Induction of heat shock protein 70 in rat olfactory epithelium by toxic chemicals: in vitro and in vivo studies. Arch Toxicol 79(4):224-30. https://doi.org/10.1007/s00204-004-0610-z.

Tsujimura, K, Ichinose, F, Hara, et al. 2008. The inhalation exposure of carbon tetrachloride promote rat liver carcinogenesis in a medium-term liver bioassay. Toxicol Lett 176(3):207-14. https://doi.org/10.1016/j.toxlet.2007.11.007.

Zuinen, R, Yamaji, K, Aoki, et al. 2007. Early induced, high-level interleukin-6 expression in the rat peritoneal cavity into which a hepatotoxicant carbon tetrachloride was administered. Toxicol Lett 170(1):42-8. https://doi.org/10.1016/j.toxlet.2007.02.003.

# APPENDIX A. LITERATURE SEARCH STRATEGIES

## Table A-1. Database Query Strings

| Database search date | Query string |
|---|---|
| **PubMed** | |
| 03/2024 | ((("Carbon Tetrachloride/toxicity"[mh] OR "Carbon Tetrachloride/adverse effects"[mh] OR "Carbon Tetrachloride Poisoning"[mh] OR "Carbon Tetrachloride/pharmacokinetics"[mh] OR ("Carbon Tetrachloride"[mh] AND ("environmental exposure"[mh] OR "chemically induced"[sh])) OR ("Carbon Tetrachloride"[mh] AND toxicokinetics[mh:noexp])) OR ("Carbon Tetrachloride"[mh] AND ((indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh])))) OR ("Carbon Tetrachloride/blood"[mh] OR "Carbon Tetrachloride/cerebrospinal fluid"[mh] OR "Carbon Tetrachloride/urine"[mh]) OR ("Carbon Tetrachloride"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Carbon Tetrachloride"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Carbon Tetrachloride/antagonists and inhibitors"[mh]) OR ("Carbon Tetrachloride/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Carbon Tetrachloride/pharmacology"[majr]) OR ("Carbon Tetrachloride"[mh] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab]))) OR ((("1,1,1,1-Tetrachloromethane"[tw] OR "Benzinoform"[tw] OR "Carbon chloride (CCl4)"[tw] OR "Carbon tet"[tw] OR "Carbon tetrachloride"[tw] OR "Carbona"[tw] OR "Fasciolin"[tw] OR "Flukoids"[tw] OR "Freon 10"[tw] OR "Halon 1040"[tw] OR "Methane tetrachloride"[tw] OR "Methane, tetrachloro-"[tw] OR "Necatorina"[tw] OR "Necatorine"[tw] OR "Perchloromethane"[tw] OR "Phenixin"[tw] OR "Phenoxin"[tw] OR "Tetrachlorocarbon"[tw] OR "Tetrachloromethane"[tw] OR "Tetrafinol"[tw] OR "Tetraform"[tw] OR "Tetrasol"[tw] OR "Univerm"[tw] OR "Vermoestricid"[tw]) NOT medline[sb]) AND (toxicity[ti] OR death OR lethal OR fatal OR fatality OR necrosis OR LC50* OR "LC 50" OR LD50* OR "LD 50" OR "body weight" OR "body mass index" OR "weight loss" OR "weight gain" OR weight-change* OR overweight OR obesity OR inhal* OR respiratory OR "pulmonary" OR airway OR trachea OR tracheobronchial OR lung OR lungs OR nose OR nasal OR |

**Table A-1. Database Query Strings**

| Database search date | Query string |
|---|---|
| | nasopharyngeal OR larynx OR laryngeal OR pharynx OR bronchial OR bronchi OR bronchioles OR bronchitis OR hemothorax OR alveolar OR alveoli OR irritation OR irritant OR sensitization OR sensitizer OR "asthma" OR cilia OR mucocilliary OR cardio OR vascular OR cardiovascular OR "circulatory system" OR "circulatory function" OR "circulatory effect" OR "circulatory effects" OR "circulatory toxicity" OR "cardiac" OR "coronary" OR "heart rate" OR "heart failure" OR "heart attack" OR "heart muscle" OR "heartbeat" OR "myocardial-infarction" OR "chest pain" OR artery OR arteries OR veins OR venules OR cardiotox* OR "gastro-intestinal" OR gastrointestinal OR "digestive system" OR "digestive organs" OR "digestive function" OR "digestive effect" OR "digestive effects" OR "intestinal" OR intestine* OR "gi tract" OR "gi disorder" OR abdominal OR esophagus OR esophageal OR stomach OR pancreas OR pancreatic OR diarrhea OR nausea OR vomit OR ulcer* OR constipation OR emesis OR "gut microbes" OR "gut flora" OR "gut microflora" OR anorexia OR hematological OR hematology OR hemato OR haemato OR blood OR anemia OR anaemia OR cyanosis OR "cyanotic" OR erythrocytopenia OR leukopenia OR thrombocytopenia OR hemoglobin OR erythrocyte OR hematocrit OR "bone marrow" OR reticulocyte OR methemoglobin OR red-blood-cell OR musculoskeletal OR skeletal OR muscle OR muscular OR arthritis OR "altered bone" OR "joint pain" OR "limb pain" OR hepatic OR "liver" OR hepatocytes OR gallbladder OR cirrhosis OR jaundice OR "hepatocellular degeneration" OR "hepatocellular hypertrophy" OR hepatomegaly OR hepatotox* OR renal OR "kidney" OR "kidneys" OR "urinary" OR "bladder" OR "urine" OR "blood urea nitrogen" OR bun OR nephropath* OR nephrotox* OR dermal OR "skin contact" OR "skin rash" OR "skin irritation" OR "skin redness" OR "skin effect" OR "skin effects" OR "skin exposure" OR "skin contact" OR acanthosis OR dermatitis OR psoriasis OR edema OR acne OR ocular OR "retinal" OR "eye function" OR "eye effects" OR "eye effect" OR "eye irritation" OR "blurred vision" OR blindness OR myopia OR cataracts OR "auditory system" OR ototoxic* OR endocrine OR "hormone changes" OR "hormone excess" OR "hormone deficiency" OR "hormone secretion" OR "hormone toxicity" OR "hormone levels" OR "sella turcica" OR thyroid OR adrenal OR pituitary OR immunological OR immunologic OR immune OR immunotox* OR lymphoreticular OR lymph-node OR spleen OR thymus OR macrophage OR leukocyte* OR lymphocyt* OR white-blood-cell OR immunotox* OR neurological OR neurologic OR neurotoxic OR neurotoxicity OR "neuropathy" OR neurodegenerat* OR "neurodevelopment" OR "nervous system" OR "nerve" OR brain OR "cerebrovascular" OR neurotoxicant OR neurochemistry OR neurophysiology OR neuropathology OR "motor activity" OR motor change* OR behavior-change* OR behavioral-change* OR sensory-change* OR cognitive OR "cognition" OR vertigo OR drowsiness OR headache OR ataxia OR reproductive OR "reproduction system" OR "reproduction function" OR "reproduction effect" OR "reproduction toxicity" OR "infertility" OR "maternal toxicity" OR developmental OR "in utero" OR placenta OR pregnan* OR terata* OR terato* OR embryo* OR fetus* OR foetus* OR fetal* OR foetal* OR prenatal* OR "pre-natal" OR perinatal* OR "post-natal" OR postnatal* OR neonat* OR newborn* OR zygote* OR child OR children OR infant* OR offspring OR weanling* OR elderly OR oocyte OR ovary OR ovarian OR uterus OR uterine OR testes OR testicular OR sperm OR estrogen* OR androgen* OR "human milk" OR "breast milk" OR "altered food consumption" OR "altered water consumption" OR "metabolic effect" OR "metabolic toxicity" OR Fever OR cytotox* OR cancer OR cancerous OR neoplas* OR tumor OR tumors OR tumour* OR malignan* OR carcinoma OR carcinogen OR carcinogen* OR angiosarcoma OR blastoma OR fibrosarcoma OR glioma OR leukemia OR leukaemia OR lymphoma OR melanoma OR meningioma OR mesothelioma OR myeloma OR neuroblastoma OR osteosarcoma OR sarcoma OR mutation OR mutations OR genotoxicity OR genotoxic OR "micronuclei" OR |

**Table A-1. Database Query Strings**

| Database search date | Query string |
|---|---|
| | "micronucleus" OR "chromosome aberrations" OR mutagenicity OR mutagenic OR "mechanism of action"[tiab:~0] OR "mode of action"[tiab:~0] OR "mechanism of toxicity"[tiab:~0] OR "adverse effect" OR "adverse effects" OR "health effects" OR noncancer OR poisoning OR morbidity OR inflammation OR "inflammatory response" OR antagonist OR inhibitor OR metabolism OR "environmental exposure" OR toxicokinetics OR pharmacokinetics OR "pbpk" OR "gene expression" OR "adverse outcome pathway" OR metabolom* OR proteom* OR genomic* OR transcriptom* OR epigenom* OR epigene* OR "transcription factor" OR "transcriptional activation" OR epidemiology OR epidemiological OR case-control* OR case-referent OR case-report OR case-series OR cohort* OR correlation-stud* OR cross-sectional-stud* OR ecological-studies OR ecological-study OR follow-up-stud* OR longitudinal-stud* OR metaanalyses OR metaanalysis OR meta-analysis OR prospective-stud* OR record-link* OR retrospective-stud* OR seroepidemiologic-stud* OR "population health" OR occupation* OR worker* OR workmen* OR workplace* OR "volunteers" OR "human health" OR "dietary" OR "oral intake" OR "oral exposure" OR "oral administration" OR ingest* OR gavage* OR "drinking-water" OR biomarker* OR biomonitor* OR "biological monitoring" OR "environmental fate" OR NHANES OR "Nutrition Examination Survey" OR (cvd NOT "chemical vapor deposition") OR (human AND (risk OR toxic* OR safety)) OR mammal* OR ape OR apes OR baboon* OR balb OR beagle* OR boar OR boars OR bonobo* OR bovine OR C57 OR C57bl OR callithrix OR canine OR canis OR capra OR capuchin* OR cats OR cattle OR cavia OR chicken OR chickens OR chimpanzee* OR chinchilla* OR cow OR cows OR cricetinae OR dog OR dogs OR equus OR feline OR felis OR ferret OR ferrets OR flying-fox OR Fruit-bat OR gerbil* OR gibbon* OR goat OR goats OR guinea-pig* OR guppy OR hamster OR hamsters OR horse OR horses OR jird OR jirds OR lagomorph* OR leontopithecus OR longevans OR macaque* OR marmoset* OR medaka OR merione OR meriones OR mice OR monkey OR monkeys OR mouse OR muridae OR murinae OR murine OR mustela-putorius OR nomascus OR non-human-primate* OR orangutan* OR pan-paniscus OR pan-troglodytes OR pig OR piglet* OR pigs OR polecat* OR pongopygmaeus OR quail OR rabbit OR rabbits OR rat OR rats OR rhesus OR rodent OR rodentia OR rodents OR saguinus OR sheep OR sheeps OR siamang* OR sow OR sows OR Sprague-Dawley OR swine OR swines OR symphalangus OR tamarin* OR vervet* OR wistar OR wood-mouse OR zebra-fish OR zebrafish))) AND (2004/06/01:3000[mhda] OR 2004/06/01:3000[edat] OR 2004/06/01:3000[crdt] OR 2003:3000[dp])) |
| **Embase** | |
| 03/2024 | Limits: Publication year: 2003-current; Records from: Embase<br>((carbon tetrachloride/ae, ad, cr, do, ih, it, to, po, pk, pd, pv) OR (carbon tetrachloride/ and (exp adverse drug reaction/ or exp toxicity/ or exp poisoning/ or exp death/ or exp occupational exposure/ or exp environmental exposure/ or exp drug interaction/ or exp pregnancy/ or exp pregnancy complications/ or exp fertility/ or exp infertility/ or exp reproduction/ or exp fetus/ or exp embryo/ or exp congenital disorder/ or exp child/ or exp carcinogenicity/ or exp toxicokinetics/ or exp bioinformatics/ or exp medical informatics/ or exp genomics/ or exp genome/ or exp proteomics/ or exp proteome/ or exp metabolomics/ or exp metabolome/ or exp gene/ or exp gene expression/ or exp phenotype/ or exp genetics/ or exp genotype/ or exp transcriptome/ or exp epidemiological monitoring/ or exp genetic transcription/ or exp messenger RNA/ or exp transfer RNA/ or exp protein synthesis/ or exp reverse transcriptase polymerase chain reaction/ or exp nucleotide sequence/ or exp transactivator protein/ or exp gene expression profiling/)) OR (*carbon tetrachloride/ and toxicity.ti.) OR (*carbon tetrachloride/ and (death or lethal or fatal or fatality or necrosis or LC50* or LC 50 or LD50* or LD 50 or overweight or obesity or weight loss or weight gain or weight change or weight changes or poisoning or morbidity or |

**Table A-1. Database Query Strings**

| Database search date | Query string |
|---|---|
| | inflammation or inflammatory response or irritation or irritant or sensitization or sensitizer or asthma or bronchitis or heart failure or heart attack or myocardial infarction or chest pain or circulatory function or circulatory effect or circulatory effects or circulatory toxicity or cardiotox* or digestive function or digestive effect or digestive effects or gi disorder or diarrhea or nausea or vomit* or ulcer* or constipation or emesis or anorexia or cyanosis or cyanotic or erythrocytopenia or leukopenia or thrombocytopenia or hematocrit or arthritis or altered bone or joint pain or limb pain or cirrhosis or jaundice or liver toxicity or liver lesions or liver weight or liver weights or hepatocellular degeneration or hepatocellular hypertrophy or hepatomegaly or hepatotox* or renal toxicity or kidney weights or blood urea nitrogen or bun or nephropath* or nephrotox* or skin rash or skin irritation or skin redness or skin effect or skin effects or acanthosis or dermatitis or psoriasis or eczema or edema or acne or eye function or eye effects or eye effect or eye irritation or blurred vision or blindness or myopia or cataracts or ototoxic* or hormone changes or hormone excess or hormone deficiency or hormone secretion or hormone toxicity or hormone levels or infertility or sella turcica or immunotox* or neurotoxic or neurotoxicity or neuropathy or neurodegenerat* or neurodevelopment or neurotoxicant or neuropathology or motor changes or tremor or tremors or behavior changes or sensory changes or vertigo or drowsiness or headache or ataxia or endocrine disruption or reproduction function or reproduction effect or reproduction toxicity or maternal toxicity or placenta* or terata* or terato* or embryo* or fetus* or foetus* or fetal* or foetal* or neonat* or newborn* or zygote* or child or children or infant* or offspring or elderly or weanling* or altered food consumption or altered water consumption or metabolic effect or metabolic toxicity or fever or histopathology or cytotox* or cancer or cancerous or neoplas* or tumor* or tumour* or malignan* or carcinoma* or carcinogen or carcinogen* or angiosarcoma* or blastoma* or fibrosarcoma* or glioma* or leukemia* or leukaemia* or lymphoma* or melanoma* or meningioma* or mesothelioma* or myeloma* or neuroblastoma* or osteosarcoma* or sarcoma* or mutation or mutations or genotoxicity or genotoxic or micronuclei or micronucleus or chromosomal aberrations or chromosome aberrations or mutagenicity or mutagenic or gene expression or adverse effect or adverse effects or health effects or noncancer or NHANES or Nutrition Examination Survey).ti,ab,kf.) OR (*carbon tetrachloride/ and (body weight or body mass index or respiratory or pulmonary or airway or trachea or tracheobronchial or lung or lungs or nose or nasal or nasopharyngeal or larynx or laryngeal or pharynx or bronchial or bronchi or bronchioles or hemothorax or alveolar or alveoli or cilia or mucocilliary or cardio or heart muscle or heart rate or heartbeat or circulatory system or vascular or cardiovascular or cardiac or coronary or artery or arteries or veins or venules or gastro intestinal or gastrointestinal or digestive system or digestive organs or intestinal or intestine* or gi tract or abdominal or esophag* or stomach or pancreas or pancreatic or gut microbes or gut flora or gut microflora or hematological or hematology or hemato or haemato or blood or anemia or anaemia or hemoglobin or erythrocyte* or bone marrow or reticulocyte* or methemoglobin or red blood cell or musculoskeletal or skeletal or muscle or muscular or hepatic or liver or hepatocytes or gallbladder or renal or kidney* or urinary or bladder or urine or dermal or ocular or retinal or auditory system or endocrine or thyroid or thyroxine or adrenal or pituitary or immunological or immunologic or immune or lymphoreticular or lymph node or lymph nodes or spleen or thymus or macrophage* or leukocyt* or lymphocyt* or white blood cell or white blood cells or neurological or neurologic or nervous system or nerve or brain or cerebrovascular or neurochemistry or neurophysiology or motor activity or behavioral or cognitive or cognition or reproductive or reproduction system or developmental or oocyte or ovary or ovarian or uterus or uterine or testes or testicular or sperm or estrogen* or androgen* or human milk or breast milk).ti,ab,kf.) OR (*carbon tetrachloride/ and toxic*.ti,ab,kf. and (mechanism of action or |

## Table A-1. Database Query Strings

| Database search date | Query string |
|---|---|
| | mode of action).ti,ab,kf.) OR (*carbon tetrachloride/ and (mechanism of toxicity or antagonist or inhibitor or inhibition or metabolism or toxicokinetic or toxicokinetics or pharmacokinetic or pharmacokinetics or pbpk or adverse outcome pathway or metabolom* or proteom* or genomic* or transcriptom* or epigenom* or epigene* or transcription factor or transcriptional activation or human health or exposure or exposures or exposed or inhal* or dermal exposure or dermal absorption or dermal penetration or dermal application or dermal applications or dermally applied or cutaneous application or skin contact or dietary or oral intake or oral exposure or oral administration or ingest* or gavage* or drinking water or epidemiology or epidemiological or case-control* or case-referent or case report or case reports or case series or cohort or cohorts or correlation study or correlation studies or cross-sectional study or cross-sectional studies or ecological studies or ecological study or follow-up study or follow-up studies or longitudinal study or longitudinal studies or metaanalyses or metaanalysis or meta-analysis or prospective study or prospective studies or record linked or record linkage or retrospective study or retrospective studies or seroepidemiologic study or population health or occupation* or worker* or workmen* or workplace* or volunteers or pregnan* or in utero or prenatal* or pre natal or perinatal* or post natal or postnatal* or environmental exposure or occupational exposure or biomarker* or biomonitor* or biological monitoring or environmental fate or in vitro or cell line or cell lines or cultured or 3T3 or A549 or BEAS-2B or CACO-2 or CHO cells or HELA or HepG2 or HepaRG or Jurkat or MCF-7 or mammal* or ape or Apes or baboon* or balb or beagle* or boar or boars or bonobo* or bovine or C57 or C57bl or callithrix or canine or canis or capra or capuchin* or cats or cattle or cavia or chicken or chickens or chimpanzee* or chinchilla* or cow or cows or cricetinae or dog or dogs or equus or feline or felis or ferret or ferrets or flying-fox or fruit-bat or gerbil* or gibbon* or goat or goats or guinea pig* or guppy or hamster or hamsters or horse or horses or jird or jirds or lagomorph* or leontopithecus or longevans or macaque* or marmoset* or medaka or merione or meriones or mice or monkey or monkeys or mouse or muridae or murinae or murine or mustela putorius or nomascus or non human primate* or orangutan* or pan paniscus or pan troglodytes or pig or piglet* or pigs or polecat* or pongopygmaeus or quail or rabbit or rabbits or rat or rats or rhesus or rodent or rodentia or rodents or saguinus or sheep or sheeps or siamang* or sow or sows or Sprague Dawley or swine or swines or symphalangus or tamarin* or vervet* or wistar or wood-mouse or zebra-fish or zebrafish).ti,ab,kf.)) |
| **Scifinder** | |
| 03/2024 | Advanced Search:<br>Substance: CAS Registry Number: 56-23-5<br>Publication Year: 2003 to 2024<br>Filtered By:<br>Document Type: Journal, Review, Clinical Trial, Commentary, Conference, Dissertation, Editorial, Historical, Letter, Preprint, Report<br>Substance Role: Biological Study, Adverse Effect, Pharmacokinetics, Pharmacological Activity<br>CA Section: Toxicology, Air Pollution and Industrial Hygiene, Water, Waste Treatment and Disposal<br>Database: CAplus |
| **Scopus** | |
| 03/2024 | ( TITLE-ABS ( {1,1,1,1-Tetrachloromethane} OR {Benzinoform} OR {Carbon chloride (CCl4)} OR {Carbon tet} OR {Carbon tetrachloride} OR {Carbona} OR {Fasciolin} OR {Flukoids} OR {Freon 10} OR {Halon 1040} OR {Methane tetrachloride} OR {Methane, tetrachloro-} OR {Necatorina} OR {Necatorine} OR {Perchloromethane} OR {Phenixin} OR |

**Table A-1. Database Query Strings**

| Database search date | Query string |
|---|---|
| | {Phenoxin} OR {Tetrachlorocarbon} OR {Tetrachloromethane} OR {Tetrafinol} OR {Tetraform} OR {Tetrasol} OR {Univerm} OR {Vermoestricid} ) ) AND (( INDEXTERMS ( "death" OR "lethal" OR "fatal" OR "fatality" OR "necrosis" OR lc50* OR "lc 50" OR ld50* OR "ld 50" OR "overweight" OR "obesity" OR "weight loss" OR "weight gain" OR "weight change" OR "weight changes" OR "poisoning" OR "morbidity" OR "inflammation" OR "inflammatory response" OR "irritation" OR "irritant" OR "sensitization" OR "sensitizer" OR "asthma" OR "bronchitis" OR "heart failure" OR "heart attack" OR "myocardial infarction" OR "chest pain" OR "circulatory function" OR "circulatory effect" OR "circulatory effects" OR "circulatory toxicity" OR cardiotox* OR "digestive function" OR "digestive effect" OR "digestive effects" OR "gi disorder" OR "diarrhea" OR "nausea" OR vomit* OR ulcer* OR "constipation" OR "emesis" OR "anorexia" OR "cyanosis" OR "cyanotic" OR "erythrocytopenia" OR "leukopenia" OR "thrombocytopenia" OR "hematocrit" OR "arthritis" OR "altered bone" OR "joint pain" OR "limb pain" OR "cirrhosis" OR "jaundice" OR "liver toxicity" OR "liver lesions" OR "liver weight" OR "liver weights" OR "hepatocellular degeneration" OR "hepatocellular hypertrophy" OR "hepatomegaly" OR hepatotox* OR "renal toxicity" OR "kidney weights" OR "blood urea nitrogen" OR "bun" OR nephropath* OR nephrotox* OR "skin rash" OR "skin irritation" OR "skin redness" OR "skin effect" OR "skin effects" OR "acanthosis" OR "dermatitis" OR "psoriasis" OR "eczema" OR "edema" OR "acne" OR "eye function" OR "eye effects" OR "eye effect" OR "eye irritation" OR "blurred vision" OR "blindness" OR "myopia" OR "cataracts" OR ototoxic* OR "hormone changes" OR "hormone excess" OR "hormone deficiency" OR "hormone secretion" OR "hormone toxicity" OR "hormone levels" OR "infertility" OR "sella turcica" OR immunotox* OR "neurotoxic" OR "neurotoxicity" OR "neuropathy" OR neurodegenerat* OR "neurodevelopment" OR "neurotoxicant" OR "neuropathology" OR "motor changes" OR "tremor" OR "tremors" OR "behavior changes" OR "sensory changes" OR "vertigo" OR "drowsiness" OR "headache" OR "ataxia" OR "endocrine disruption" OR "reproduction function" OR "reproduction effect" OR "reproduction toxicity" OR "maternal toxicity" OR placenta* OR terata* OR terato* OR embryo* OR fetus* OR foetus* OR fetal* OR foetal* OR neonat* OR newborn* OR zygote* OR "child" OR "children" OR infant* OR "offspring" OR "elderly" OR weanling* OR "altered food consumption" OR "altered water consumption" OR "metabolic effect" OR "metabolic toxicity" OR "fever" OR "histopathology" OR cytotox* OR "cancer" OR "cancerous" OR neoplas* OR tumor* OR tumour* OR malignan* OR carcinoma* OR "carcinogen" OR carcinogen* OR angiosarcoma* OR blastoma* OR fibrosarcoma* OR glioma* OR leukemia* OR leukaemia* OR lymphoma* OR melanoma* OR meningioma* OR mesothelioma* OR myeloma* OR neuroblastoma* OR osteosarcoma* OR sarcoma* OR "mutation" OR "mutations" OR "genotoxicity" OR "genotoxic" OR "micronuclei" OR "micronucleus" OR "chromosome aberrations" OR "mutagenicity" OR "mutagenic" OR "gene expression" OR "adverse effect" OR "adverse effects" OR "health effects" OR "noncancer" OR "nhanes" OR "nutrition examination survey" OR "body weight" OR "body mass index" OR "respiratory" OR "pulmonary" OR "airway" OR "trachea" OR "tracheobronchial" OR "lung" OR "lungs" OR "nose" OR "nasal" OR "nasopharyngeal" OR "larynx" OR "laryngeal" OR "pharynx" OR "bronchial" OR "bronchi" OR "bronchioles" OR "hemothorax" OR "alveolar" OR "alveoli" OR "cilia" OR "mucocilliary" OR "cardio" OR "heart muscle" OR "heart rate" OR "heartbeat" OR "circulatory system" OR "vascular" OR "cardiovascular" OR "cardiac" OR "coronary" OR "artery" OR "arteries" OR "veins" OR "venules" OR "gastro intestinal" OR "gastrointestinal" OR "digestive system" OR "digestive organs" OR "intestinal" OR intestine* OR "gi tract" OR "abdominal" OR esophag* OR "stomach" OR "pancreas" OR "pancreatic" OR "gut microbes" OR "gut flora" OR "gut microflora" OR "hematological" OR "hematology" OR "hemato" OR "haemato" OR "blood" OR "anemia" OR "anaemia" OR |

## Table A-1. Database Query Strings

| Database search date | Query string |
|---|---|
| | "hemoglobin" OR erythrocyte* OR "bone marrow" OR reticulocyte* OR "methemoglobin" OR "red blood cell" OR "musculoskeletal" OR "skeletal" OR "muscle" OR "muscular" OR "hepatic" OR "liver" OR "hepatocytes" OR "gallbladder" OR "renal" OR kidney* OR "urinary" OR "bladder" OR "urine" OR "dermal" OR "ocular" OR "retinal" OR "auditory system" OR "endocrine" OR "thyroid" OR "thyroxine" OR "adrenal" OR "pituitary" OR "immunological" OR "immunologic" OR "immune" OR "lymphoreticular" OR "lymph node" OR "lymph nodes" OR "spleen" OR "thymus" OR macrophage* OR leukocyt* OR lymphocyt* OR "white blood cell" OR "white blood cells" OR "neurological" OR "neurologic" OR "nervous system" OR "nerve" OR "brain" OR "cerebrovascular" OR "neurochemistry" OR "neurophysiology" OR "motor activity" OR "behavioral" OR "cognitive" OR "cognition" OR "reproductive" OR "reproduction system" OR "developmental" OR "oocyte" OR "ovary" OR "ovarian" OR "uterus" OR "uterine" OR "testes" OR "testicular" OR "sperm" OR estrogen* OR androgen* OR "human milk" OR "breast milk" OR (toxic* AND "mechanism of action" ) OR ( toxic* AND "mode of action" ) OR "mechanism of toxicity" OR "antagonist" OR "inhibitor" OR "inhibition" OR "metabolism" OR "toxicokinetic" OR "toxicokinetics" OR "pharmacokinetic" OR "pharmacokinetics" OR "pbpk" OR "adverse outcome pathway" OR metabolom* OR proteom* OR genomic* OR transcriptom* OR epigenom* OR epigene* OR "transcription factor" OR "bioinformatics" OR "medical informatics" OR "genomics" OR "genome" OR "proteomics" OR "proteome" OR "metabolomics" OR "metabolome" OR "genes" OR "gene expression" OR "phenotype" OR "genetics" OR "genotype" OR "transcriptome" OR "epidemiological monitoring" OR "genetic transcription" OR "messenger rna" OR "transfer rna" OR "protein synthesis" OR "reverse transcriptase polymerase chain reaction" OR "nucleotide sequence" OR "transactivator protein" OR "gene expression profiling" ) ) ) AND PUBYEAR > 2002 AND PUBYEAR < 2025 AND ( LIMIT-TO ( SUBJAREA,"ENVI" ) OR LIMIT-TO ( SUBJAREA,"MEDI" ) OR LIMIT-TO ( SUBJAREA,"BIOC" ) OR LIMIT-TO ( SUBJAREA,"PHAR" ) OR LIMIT-TO ( SUBJAREA,"AGRI" ) OR LIMIT-TO ( SUBJAREA,"IMMU" ) OR LIMIT-TO ( SUBJAREA,"EART" ) OR LIMIT-TO ( SUBJAREA,"NEUR" ) OR LIMIT-TO ( SUBJAREA,"HEAL" ) OR LIMIT-TO ( SUBJAREA,"VETE" ) OR LIMIT-TO ( SUBJAREA,"PSYC" ) OR LIMIT-TO ( SUBJAREA,"NURS" ) OR LIMIT-TO ( SUBJAREA,"DENT" ) ) |

**Table A-2. Strategies to Augment the Literature Search**

| Source | Query and number screened when available |
|---|---|
| **TSCATS via ChemView** | |
| 03/2024 | 56-23-5 |
| **NTP** | |
| 03/2024 | Limited to 2000 to present or not dated<br>"56-23-5" "Carbon tetrachloride" "Tetrachloromethane" "Carbon tet"<br>"Fasciolin" "Methane, tetrachloro-"<br>"1,1,1,1-Tetrachloromethane" "Benzinoform" "Carbon chloride (CCl4)" "Carbona"<br>"Flukoids" "Freon 10" "Halon 1040" "Methane tetrachloride"<br>"Necatorina" "Necatorine" "Perchloromethane" "Phenixin"<br>"Phenoxin" "Tetrachlorocarbon" "Tetrafinol" "Tetraform"<br>"Tetrasol" "Univerm" "Vermoestricid" |
| **NTRL** | |
| 03/2024 | Limited to 2003 to present, terms appearing in title or keyword<br>"Carbon tetrachloride" OR "Tetrachloromethane" OR "Carbon tet" OR "Fasciolin" OR "Methane, tetrachloro-" OR "1,1,1,1-Tetrachloromethane" OR "Benzinoform" OR "Carbon chloride (CCl4)" OR "Carbona" OR "Flukoids" OR "Freon 10" OR "Halon 1040" OR "Methane tetrachloride" OR "Necatorina" OR "Necatorine" OR "Perchloromethane" OR "Phenixin" OR "Phenoxin" OR "Tetrachlorocarbon" OR "Tetrafinol" OR "Tetraform" OR "Tetrasol" OR "Univerm" OR "Vermoestricid" |
| **Regulations.gov** | |
| 03/2024 | Limited to 2004 to present by Posted date<br>"56-23-5"<br>"Carbon tetrachloride"<br>"Tetrachloromethane"<br>"Carbon tet" |
| **Other** | Identified throughout the assessment process |

# APPENDIX B. SUPPLEMENTAL STUDIES

## B.1. HUMAN STUDIES, MIXED EXPOSURE ONLY

Gao, Yu, Zhang, Yan, Kamijima, et al. 2014. Quantitative assessments of indoor air pollution and the risk of childhood acute leukemia in Shanghai. Environ. Pollut. (Oxford, U. K.) 187:81-89. https://doi.org/10.1016/j.envpol.2013.12.029.

Garcia-Perez, Javier, Morales-Piga, Antonio, Gomez-Barroso, et al. 2017. Risk of bone tumors in children and residential proximity to industrial and urban areas: New findings from a case-control study. Sci. Total Environ. 579:1333-1342. https://doi.org/10.1016/j.scitotenv.2016.11.131.

Guajardo, OlgaA, Oyana, TonnyJ. 2009. A critical assessment of geographic clusters of breast and lung cancer incidences among residents living near the Tittabawassee and Saginaw Rivers, Michigan, USA. J. Environ. Public Health https://doi.org/10.1155/2009/316249.

Gutierrez, MariadelosA, Palmieri, MonicaA, Giuliani, et al. 2020. Monitoring human genotoxicity risk associated to urban and industrial Buenos Aires air pollution exposure. Environ. Sci. Pollut. Res. 27(12):13995-14006. https://doi.org/10.1007/s11356-020-07863-9.

Hoppin, JA, Umbach, DM, London, et al. 2009. Pesticide use and adult-onset asthma among male farmers in the Agricultural Health Study. Eur Respir J 34(6):1296-303. https://doi.org/10.1183/09031936.00005509.

Huijbregts, MarkAJ, Rombouts, LindaJA, Ragas, et al. 2005. Human toxicological effect and damage factors of carcinogenic and noncarcinogenic chemicals for life cycle impact assessment. Integr. Environ. Assess. Manage. 1(3):181-244. https://doi.org/10.1897/2004-007r.1.

Infante-Rivard, Claire, Siemiatycki, Jack, Lakhani, et al. 2005. Maternal exposure to occupational solvents and childhood leukemia. Environ. Health Perspect. 113(6):787-792. https://doi.org/10.1289/ehp.7707.

Koutros, Stella, Andreotti, Gabriella, Berndt, et al. 2011. Xenobiotic-metabolizing gene variants, pesticide use, and the risk of prostate cancer. Pharmacogenet. Genomics 21(10):615-623. https://doi.org/10.1097/fpc.0b013e3283493a57.

Malek, AngelaM, Barchowsky, Aaron, Bowser, et al. 2015. Exposure to hazardous air pollutants and the risk of amyotrophic lateral sclerosis. Environ. Pollut. (Oxford, U. K.) 197:181-186. https://doi.org/10.1016/j.envpol.2014.12.010.

Takeda, Makoto, Saijo, Yasuaki, Yuasa, et al. 2009. Relationship between sick building syndrome and indoor environmental factors in newly built Japanese dwellings. Int. Arch. Occup. Environ. Health 82(5):583-593. https://doi.org/10.1007/s00420-009-0395-8.

## B.2. HUMAN, NO EXPOSURE MEASURE OR ESTIMATED EXPOSURE ONLY (BASED ON JOB HISTORY/JOB-EXPOSURE MATRIX)

Barry, KH, Zhang, Y, Lan, et al. 2011. Genetic variation in metabolic genes, occupational solvent exposure, and risk of non-hodgkin lymphoma. Am J Epidemiol 173(4):404-13. https://doi.org/10.1093/aje/kwq360.

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## B.10. CONFERENCE ABSTRACT

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## B.11. META-ANALYSIS

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