SYSTEMATIC EVIDENCE MAP (SEM) FOR METHYLENE CHLORIDE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Agency for Toxic Substances and Disease Registry

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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 methylene chloride toxicological profile was last published in September 2000, 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 methylene chloride, as identified in the toxicological profile (ATSDR 2000).

2. METHODS

2.1 LITERATURE SEARCH STRATEGY

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

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

PECO element	Evidence
Population	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.
Exposure	*In vivo* (all routes), *ex vivo*, and *in vitro* exposure to the chemical of interest, including mixtures to which the chemical of interest may contribute significantly to exposure or observed effects.
Comparison	Any comparison (across dose, duration, or route) or no comparison for select study types (case reports without controls, acute lethality limit tests without controls).
Outcomes	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 methylene chloride (ATSDR 2000); thus, the literature search was restricted to studies published between January 1998 to July 2022 to capture literature published since the search was conducted for the existing profile. The following main databases were searched in July 2022:

- PubMed
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for methylene chloride. 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, 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).

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
Population	Humans or laboratory mammals.
Exposure	Inhalation, oral, or dermal exposure to the chemical of interest, including mixtures that contain a high percentage of the chemical of interest.
Comparison	Any comparison (across dose, duration, or route) or no comparison for select study types (case reports without controls, acute lethality limit tests without controls).
Outcomes	Any endpoint suggestive of a toxic effect on any bodily system or containing information to address data gaps (e.g., PBPK model, toxicokinetics, mechanisms of action, etc.)[a].

[a]Data gaps identified in the 2000 toxicological profile for methylene chloride included genotoxicity studies in mammalian cells for which the expression of GSTT1 and/or CYP2E1 isoenzymes are identified, toxicokinetic data for oral and dermal exposures, excretion parameters as functions of concentration, and impact of differences in species sensitivity to specific internal doses by different routes of exposure.

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: health effects studies (human toxicity, animal toxicity) or supporting studies (genotoxicity, mechanistic, toxicokinetic, secondary source). Additionally, 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 or not 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.

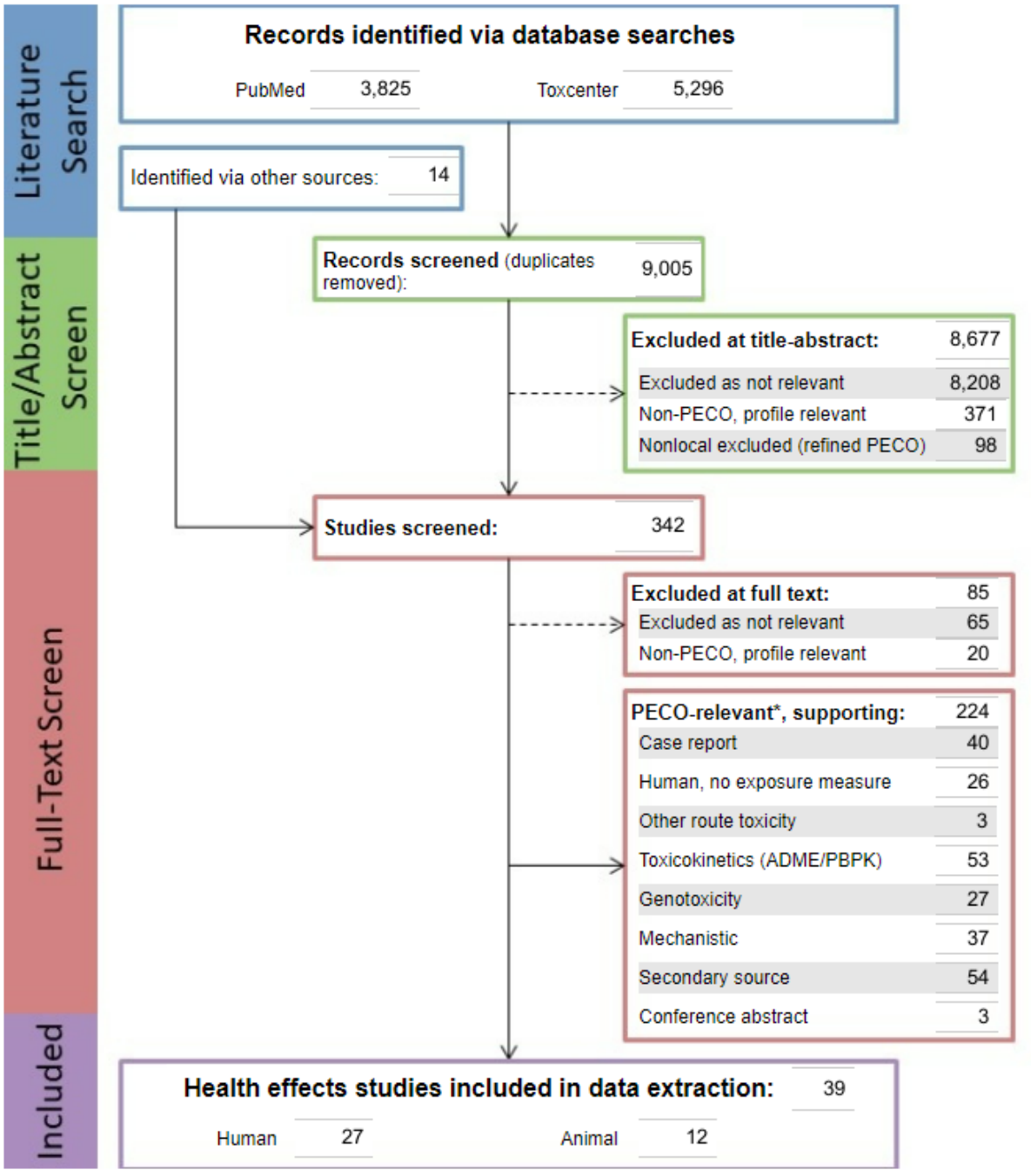
[2]Tableau Public is a web-based data visualization software available at https://public.tableau.com.

3. RESULTS

3.1 LITERATURE SEARCH RESULTS

Literature searches from all bibliographic databases yielded 9,005 unique references (after removal of duplicates). Title and abstract screening identified 8,677 references as not PECO-relevant; of these, 371 were identified as non-PECO profile-relevant items and 48 were nonlocal items identified as not relevant based on refined PECO criteria. After removing not PECO-relevant references, the remaining 328 items proceeded to full-text review. Gray literature search results screened outside of DistillerSR added 14 citations, bringing the total number of citations for full-text review to 342. An additional 85 references were identified as not PECO-relevant during full-text screening; of these, 20 were identified as non-PECO profile-relevant items. The remaining 257 references were identified as PECO-relevant; 33 references included health effects data, 218 references contained other supporting data, and 6 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 = adsorption, distribution, metabolism, and excretion; PBPK = physiologically based pharmacokinetic; PECO = Populations, Exposures, Comparators, and Outcomes

Interactive literature flow diagram can be accessed at:
https://public.tableau.com/app/profile/eha.tableau.team/viz/LitFlowDiagram-MethyleneChloride2022/Dashboard

3.2 LITERATURE INVENTORY

The literature search and screen identified 27 human and 12 animal health effects studies for methylene chloride; some animal studies included multiple experiments in different species and/or of different durations.

As shown in Figure 3-2 (A: Human Data) and (B: Animal Data), the majority of newly identified studies with toxicity data examined exposure via the inhalation route, with a few oral route studies in animals. 100% (25) of human data gathered focused on the inhalation route, 54% (7) of animal studies focused on the inhalation route, and 46% (6) of animal studies focused on the oral route. The most-studied endpoints include body weight, hepatic, neurological, and cancer. While evidence from human studies is mixed, findings from animal studies are consistent with the existing toxicological profile for methylene chloride (ATSDR 2000), indicating that the nervous system, liver, and kidney are potential toxicity targets of methylene chloride. Additional studies in animals also reported carcinogenic effects.

The current toxicological profile (ATSDR 2000) identified several data needs in the toxicological database for methylene chloride. Very few of the studies identified during the updated literature search address these data needs (see Table 3-1). None of the identified studies are expected to impact the existing inhalation or oral MRLs.

Figure 3-2. Health Effects Studies for Methylene Chloride

A:

Human Studies Evaluating Methylene Chloride

Exposure Route	Exposure Duration	Death	Respiratory	Cardiovascular	Neurological	Developmental	Cancer
		System/Target					
Inhalation	Acute (≤14 days)		1	1			
	Intermediate (15-364 days)		2			4	
	Chronic (≥365 days)	2		1	4	1	15

Human Studies with Exposure-Related Effects

Exposure Route	Exposure Duration	Neurological	Developmental	Cancer
		System/Target		
Inhalation	Intermediate (15-364 days)		2	
	Chronic (≥365 days)	3	1	6

B:

Animal Studies Evaluating Methylene Chloride

Administration Route	Study Duration	Death	Body weight	Respiratory	Cardiovascular	Hematological	Hepatic	Renal	Immunological	Neurological	Cancer
		Target									
Inhalation	Acute (≤14 days)		5	4			5			4	
	Intermediate (15-364 days)	3	3	2	1	2	4	1	1	3	
	Chronic (≥365 days)	2	2	1			2				2
Oral	Acute (≤14 days)		3	1			3	3		1	
	Intermediate (15-364 days)	1	1				1	1			
	Chronic (≥365 days)	1	1								1

Animal Studies with Exposure-Related Effects

Administration Route	Study Duration	Death	Body weight	Respiratory	Cardiovascular	Hematological	Hepatic	Renal	Neurological	Cancer
		Target								
Inhalation	Acute (≤14 days)			1			4		4	
	Intermediate (15-364 days)		2		1	1	4		3	
	Chronic (≥365 days)	2	1	1			2			2
Oral	Acute (≤14 days)						2	2	1	
	Chronic (≥365 days)	1								1

*Interactive database can be accessed at:
https://public.tableau.com/app/profile/eha.tableau.team/viz/DRAFTSEMDataVisualizationforMethyleneChloride/HealthEffectsOverview

Table 3-1. Data Needs Identified for Methylene Chloride by ATSDR (2000)

Exposure route	Data needs	Studies to potentially address data need
Inhalation	Low-concentration, acute-duration studies evaluating neurological function in animals	None
	Studies evaluating immunological function in animals	Warbrick et al. 2003 (no adverse immunological effects)
Oral	Additional low-dose, acute-duration studies in animals	Owumi et al. 2019 and Kim et al. 2011; examined respiratory, hepatic, and/or renal endpoints at ≥150 mg/kg/day
	Low-dose, intermediate-duration studies in animals to provide dose-response data, especially a NOAEL (below the lowest LAOEL of 166 mg/kg-day)	None
	Studies evaluating immunological function in animals	None
	Studies evaluating neurological function in animals	None
	Studies evaluating reproduction and development in animals	None
	Studies evaluating carcinogenicity in animals	NTP 1994 (*Note: the primary purpose of the study was to evaluate the impact of different gavage vehicles on tumor development)*
Dermal	Acute, intermediate, and chronic (including carcinogenicity) studies in animals	None

ATSDR = Agency for Toxic Substances and Disease Registry; LOAEL = lowest-observed-adverse effect level; NOAEL = no-observed-adverse-effect level

4. REFERENCES

4.1 CURRENT PROFILE

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4.2 HUMAN TOXICITY

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4.3 ANIMAL TOXICITY

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APPENDIX A. LITERATURE SEARCH STRATEGIES

Table A-1. Database Query Strings

Database search date	Query string
PubMed	
07/2022	((75-09-2[rn] AND (1998:3000[mhda] OR 1998:3000[crdt] OR 1998:3000[edat])) AND (("methylene chloride/toxicity"[mh] OR "methylene chloride/adverse effects"[mh] OR "methylene chloride/poisoning"[mh] OR "methylene chloride/pharmacokinetics"[mh] OR "methylene chloride/antagonists and inhibitors"[mh] OR "methylene chloride/pharmacology"[majr] OR "methylene chloride/blood"[mh] OR "methylene chloride/cerebrospinal fluid"[mh] OR "methylene chloride/urine"[mh]) OR ("methylene chloride"[mh] AND toxicokinetics[mh:noexp]) OR ("methylene chloride/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("methylene chloride"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("methylene chloride"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("methylene chloride"[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 ("methylene chloride"[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 ((("Dichloromethane"[tw] OR "Dichoromethane"[tw] OR "Methane dichloride"[tw] OR "Methylene bichloride"[tw] OR "Methylene chloride"[tw] OR "Methylene dichloride"[tw] OR "Aerothene MM"[tw] OR "Dichlormethan"[tw] OR "F 30 (chlorocarbon)"[tw] OR "Freon 30"[tw] OR "Khladon 30"[tw] OR "Metaclen"[tw] OR "Methaclean U"[tw] OR "Methane, dichloro-"[tw] OR "Narkotil"[tw] OR "R 30 (refrigerant)"[tw] OR "R30 (refrigerant)"[tw] OR "Solaesthin"[tw] OR "Soleana VDA"[tw] OR "Solmethine"[tw]) AND (1998:3000[crdt] OR 1998:3000[edat] OR 1998:3000[dp])) NOT medline[sb])
Toxcenter	
07/2022	FILE 'TOXCENTER' ENTERED AT 10:09:37 ON 06 JUL 2022 CHARGED TO COST=EH038.16.02.LB.04 L1 28571 SEA FILE=TOXCENTER 75-09-2 L2 28134 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 19133 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 4342 SEA FILE=TOXCENTER L3 AND PY>=2018 L5 13808 SEA FILE=TOXCENTER L3 AND PY>=1998 ACT TOXQUERY/Q

Table A-1. Database Query Strings

Database search date	Query string

	L6 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L7 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L8 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L9 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L10 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L11 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L12 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L13 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L14 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L15 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L16 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L17 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L18 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L19 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L20 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L21 QUE (ENDOCRIN? AND DISRUPT?)
	L22 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L23 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L24 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L25 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L26 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L27 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L28 QUE (NEPHROTOX? OR HEPATOTOX?)
	L29 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L30 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L31 QUE L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30

Table A-1. Database Query Strings

Database search date	Query string
	L32 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L33 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L34 QUE L31 OR L32 OR L33 L35 QUE (NONHUMAN MAMMALS)/ORGN L36 QUE L34 OR L35 L37 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L38 QUE L36 OR L37 --------- L39 6866 SEA FILE=TOXCENTER L5 AND L38 L40 6104 SEA FILE=TOXCENTER L5 AND L31 L41 379 SEA FILE=TOXCENTER L40 AND MEDLINE/FS L42 759 SEA FILE=TOXCENTER L40 AND BIOSIS/FS L43 4942 SEA FILE=TOXCENTER L40 AND CAPLUS/FS L44 24 SEA FILE=TOXCENTER L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L45 5697 DUP REM L41 L42 L44 L43 (407 DUPLICATES REMOVED) L*** DEL 379 S L40 AND MEDLINE/FS L*** DEL 379 S L40 AND MEDLINE/FS L46 379 SEA FILE=TOXCENTER L45 L*** DEL 759 S L40 AND BIOSIS/FS L*** DEL 759 S L40 AND BIOSIS/FS L47 644 SEA FILE=TOXCENTER L45 L*** DEL 4942 S L40 AND CAPLUS/FS L*** DEL 4942 S L40 AND CAPLUS/FS L48 4657 SEA FILE=TOXCENTER L45 L*** DEL 24 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 24 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L49 17 SEA FILE=TOXCENTER L45 L50 5318 SEA FILE=TOXCENTER (L46 OR L47 OR L48 OR L49) NOT MEDLINE/FS L51 661 SEA FILE=TOXCENTER L50 NOT CAPLUS/FS D SCAN L51 L52 4657 SEA FILE=TOXCENTER L50 AND CAPLUS/FS D SCAN L52

Table A-2. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
07/2022	75-09-2

Table A-2. Strategies to Augment the Literature Search

Source	Query and number screened when available
NTP	
07/2022	Limited to: 1990-present, and not dated "Methylene chloride" "Dichloromethane" "75-09-2" "Methylene dichloride" "Dichoromethane" "Methane dichloride" "Methylene bichloride" "Methane, dichloro-" "Dichlormethan" "Aerothene MM" "F 30 (chlorocarbon)" "Freon 30" "Khladon 30" "Metaclen" "Methaclean U" "Narkotil" "R 30 (refrigerant)" "R30 (refrigerant)" "Solaesthin" "Soleana VDA" "Solmethine"
NTRL	
07/2022	Limited to: titles or keywords and 1998-present "Methylene chloride" OR "Dichloromethane" OR "Dichlormethan" OR "Methylene dichloride" OR "Dichoromethane" OR "Methane dichloride" OR "Methylene bichloride" OR "Methane, dichloro-" OR "Aerothene MM" OR "F 30 (chlorocarbon)" OR "Freon 30" OR "Khladon 30" OR "Metaclen" OR "Methaclean U" OR "Narkotil" OR "R 30 (refrigerant)" OR "R30 (refrigerant)" OR "Solaesthin" OR "Soleana VDA" OR "Solmethine"
Regulations.gov	
07/2022	Limited to: Docket or EPA notices "Methylene chloride" 75-09-2 "Dichloromethane" "Methylene dichloride" "Methane dichloride" "Dichoromethane"
Other	Identified throughout the assessment process

APPENDIX B. SUPPLEMENTAL STUDIES

B.1. CASE REPORTS

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