

SYSTEMATIC EVIDENCE MAP (SEM) FOR TRIFLURALIN

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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CONTRIBUTORS

CHEMICAL MANAGER TEAM

Gaston Casillas, Ph.D.
Nicolette Roney, M.P.H.

Clifton Dassuncao, Sc.D., D.A.B.T.
Alessandria Schumacher, M.P.H.
Meghan Harris, B.S.
Sophia Trone, B.A.

ATSDR, Office of Innovation and Analytics,
Atlanta, GA

Eastern Research Group, Inc. (ERG),
Concord, MA

CONTENTS

1. OBJECTIVES	1
2. METHODS.....	2
2.1 LITERATURE SEARCH STRATEGY	2
2.2 LITERATURE SCREENING STRATEGY	3
2.3 HIGH-LEVEL DATA EXTRACTION FOR LITERATURE INVENTORY	4
3. RESULTS.....	6
3.1 LITERATURE SEARCH RESULTS.....	6
3.2 LITERATURE INVENTORY	8
4. REFERENCES	10
4.1 HUMAN TOXICITY	10
4.2 ANIMAL TOXICITY	11
APPENDIX A LITERATURE SEARCH STRATEGIES	A-1
APPENDIX B SUPPLEMENTAL STUDIES.....	B-1
B.1 CASE REPORTS.....	B-1
B.2 HUMAN STUDIES, NO EXPOSURE MEASURE	B-1
B.3 OTHER ROUTE TOXICITY.....	B-3
B.4 GENOTOXICITY	B-4
B.5 MECHANISTIC.....	B-6
B.6 TOXICOKINETIC (ADME/PBPK)	B-10
B.7 SECONDARY SOURCE	B-11
 Table 2-1. PECO Criteria for Screening of ATSDR SEM Literature Search Results.....	2
Table 2-2. Refined PECO Criteria for Screening of Non-Local Citations.....	4
 Figure 3-1. Literature Flow Diagram	7
Figure 3-2. Health Effects Studies for Trifluralin	9

1. OBJECTIVES

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

- Conduct literature searches to identify available studies, 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 Outcome (PECO criteria) outlined below.
- Prepare interactive literature inventory to provide overview of the evidence that meets PECO criteria.

2. METHODS

2.1 LITERATURE SEARCH STRATEGY

A literature search was conducted to identify studies examining health effects, toxicokinetics, and mechanisms of action for Trifluralin. The PECO criteria used to identify relevant studies examining the health effects of trifluralin 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., <i>Xenopus</i> 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

A non-date-limited search was conducted to capture all relevant literature. The following main databases were searched in December 2024:

- PubMed
- Scopus
- Scifinder

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for trifluralin. The query strings used for the literature search are presented in Appendix 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 statement, 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 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, which included 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 DistillerSR¹ 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 non-local (NL) retrieval items (e.g., pay-per-citation, etc.), an additional screening step was conducted based on a 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.

¹DistillerSR 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 Non-Local 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.

References that were included based on title and abstract screening advanced to full text review using the same PECO eligibility criteria. 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 [ADME/PBPK], secondary source). Additionally, studies that did not meet PECO criteria, but contained other potential profile-relevant data (i.e. data that could potentially be used in later profile development) were categorized as one of the following study types: 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, guided by the predefined PECO criteria and screening decision rules. When necessary, a senior level toxicologist was consulted to ensure consistent application of these criteria and 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 whether or not examined systems showed an exposure-related effect. Extracted data were exported into Tableau Public² for interactive data visualization.

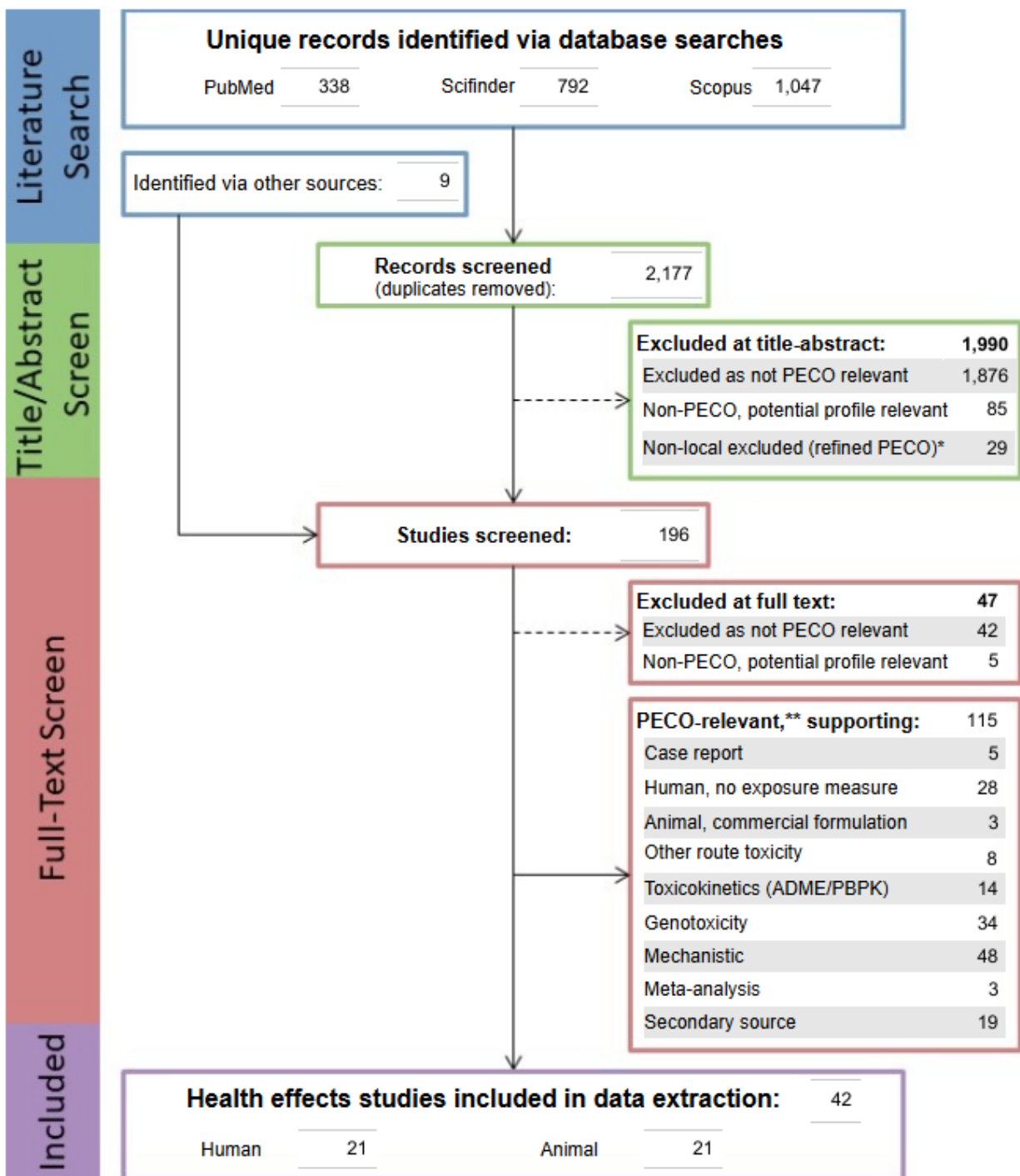
² Tableau Public is a web-based data visualization software available at <https://public.tableau.com>.

3. RESULTS

3.1 LITERATURE SEARCH RESULTS

Literature searches from all bibliographic databases yielded 2,177 unique references. Title and abstract screening identified 1,990 references as not PECO-relevant; of these, 85 were identified as non-PECO but potential profile-relevant items (i.e. considered in future profile development). An additional 29 non-local items were identified as not relevant based on refined PECO criteria. The remaining 187 items proceeded to full-text review. Gray literature search results screened outside of DistillerSR added 9 citations, bringing the total number of citations for full-text review to 196. An additional 47 references were identified as not PECO-relevant during full-text screening; of these, 5 were identified as non-PECO, potential profile-relevant items. The remaining 157 references were identified as PECO-relevant, including 42 health effects studies and 115 supporting studies. A summary of the results of the literature search and screening is presented in Figure 3-1.

Figure 3-1. Literature Flow Diagram



* Full text not locally available; excluded as not relevant based on refined PECO criteria.

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

Interactive literature flow diagram can be accessed at:

<https://public.tableau.com/app/profile/atsdr.data.viz/viz/TrifluralinSEMLitFlow2025/Dashboard>

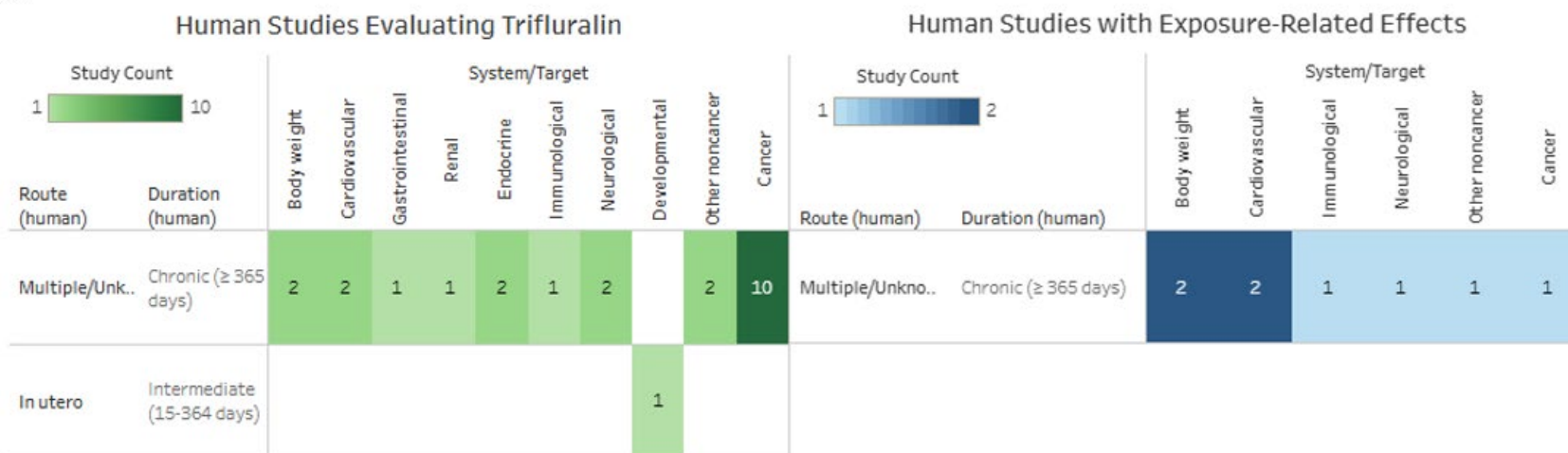
3.2 LITERATURE INVENTORY

The literature search and screen identified 21 human and 21 animal health effects studies for trifluralin. Some animal studies included multiple experiments in different species and/or of different durations.

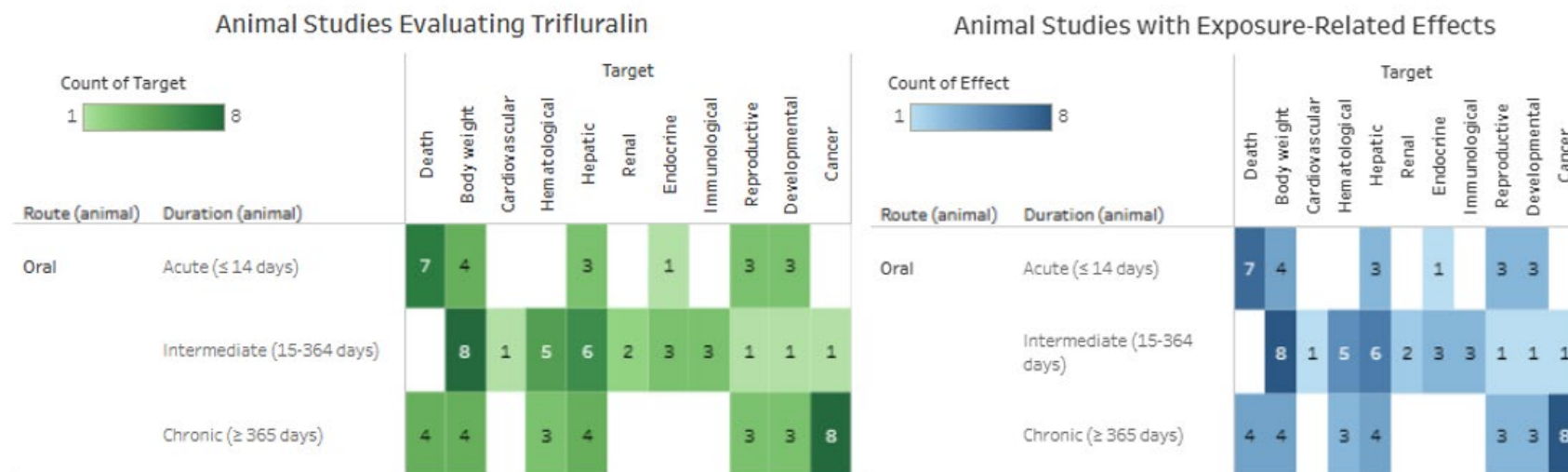
As shown in Figure 3-2A (Human Data) and Figure 3-2B (Animal Data), most human studies evaluating trifluralin exposure involved unspecified or multiple exposure routes of chronic duration (≥ 365 days). Of the 21 human studies identified, 95% (20 studies) examined trifluralin exposure via multiple or unknown routes, while 5% (1 study) involved exposure by other routes (i.e., in utero). In contrast, all 21 animal studies evaluated oral exposure, spanning acute (≤ 14 days), intermediate (15–364 days), and chronic (≥ 365 days) durations. The most frequently studied endpoints include death in animals, body weight, hematological, hepatic, and cancer. While evidence from human studies is limited, animal findings indicate that body weight, liver, the hematological system, and cancer are potential toxicity targets of trifluralin. Animal studies also reported developmental, reproductive, endocrine, and immunological effects.

Figure 3-2. Health Effects Studies for Trifluralin

A:



B:



*Interactive database can be accessed at: <https://public.tableau.com/app/profile/atsdr.data.viz/viz/TrifluralinSEMDDataViz2025/HealthEffectsOverview>

4. REFERENCES

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4.2 ANIMAL TOXICITY

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APPENDIX A LITERATURE SEARCH STRATEGIES

Table A-1. Database Query Strings

Database	
search date	Query string
PubMed	
12/2024	("Trifluralin/adverse effects"[Mesh Terms] OR "Trifluralin/antagonists and inhibitors"[Mesh Terms] OR "Trifluralin/blood"[Mesh Terms] OR "Trifluralin/cerebrospinal fluid"[Mesh Terms] OR "Trifluralin/immunology"[Mesh Terms] OR "Trifluralin/pharmacokinetics"[Mesh Terms] OR "Trifluralin/pharmacology"[Mesh Terms] OR "Trifluralin/poisoning"[Mesh Terms] OR "Trifluralin/toxicity"[Mesh Terms] OR "Trifluralin/urine"[Mesh Terms]) OR ("Trifluralin"[MeSH Terms] AND ("toxicokinetics"[MeSH Terms] OR "pharmacokinetics"[MeSH Terms] OR "Toxicological Phenomena"[Mesh])) OR ("Trifluralin"[MeSH Terms] AND ("humans"[MeSH Terms] OR "animals"[MeSH Terms])) OR (Trifluralin[MeSH Terms] AND ("environmental exposure"[MeSH Terms] OR "chemically induced"[MeSH Subheading])) OR (Trifluralin[MeSH Terms] AND ("endocrine system"[MeSH Terms] OR "hormones, hormone substitutes, and hormone antagonists"[MeSH Terms] OR "endocrine disruptors"[MeSH Terms])) OR (Trifluralin[MeSH Terms] AND ("computational biology"[MeSH Terms] OR "medical informatics"[MeSH Terms] OR genomics[MeSH Terms] OR genome[MeSH Terms] OR proteomics[MeSH Terms] OR proteome[MeSH Terms] OR metabolomics[MeSH Terms] OR metabolome[MeSH Terms] OR genes[MeSH Terms] OR "gene expression"[MeSH Terms] OR phenotype[MeSH Terms] OR genetics[MeSH Terms] OR genotype[MeSH Terms] OR transcriptome[MeSH Terms] OR ("systems biology"[MeSH Terms] AND ("environmental exposure"[MeSH Terms] OR "epidemiological monitoring"[MeSH Terms] OR analysis[sh])) OR "transcription, genetic"[MeSH Terms] OR "reverse transcription"[MeSH Terms] OR "transcriptional activation"[MeSH Terms] OR "transcription factors"[MeSH Terms] OR ("biosynthesis"[sh] AND (RNA[MeSH Terms] OR DNA[MeSH Terms])) OR "RNA, messenger"[MeSH Terms] OR "RNA, transfer"[MeSH Terms] OR "peptide biosynthesis"[MeSH Terms] OR "protein biosynthesis"[MeSH Terms] OR "reverse transcriptase polymerase chain reaction"[MeSH Terms] OR "base sequence"[MeSH Terms] OR "trans-activators"[MeSH Terms] OR "gene expression profiling"[MeSH Terms])) OR (Trifluralin[MeSH Terms] AND ("Neoplasms"[MeSH Terms] OR "Carcinogens"[MeSH Terms] OR "Lymphoproliferative disorders"[MeSH Terms] OR "Myeloproliferative disorders"[MeSH Terms] OR "Toxicity Tests"[MeSH Terms] OR (cancer*[tiab] OR carcinogen*[tiab]) OR ((risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[MeSH Terms] OR "Mutagenicity Tests"[MeSH Terms] OR "Chromosome Aberrations"[MeSH Terms] OR "DNA Damage"[MeSH Terms] OR "DNA Repair"[MeSH Terms] OR "DNA Replication/drug effects"[MeSH Terms] OR "DNA/drug effects"[MeSH Terms] OR "DNA/metabolism"[MeSH Terms] OR "Genomic Instability"[MeSH Terms] OR "Salmonella typhimurium/drug effects"[MeSH Terms] OR "Salmonella typhimurium/genetics"[MeSH Terms] OR "Sister Chromatid Exchange"[MeSH Terms] OR strand-break*[tiab])) OR (("Trifluralin"[Text Word] OR "Treflan"[Text Word] OR "1582-09-8"[Text Word]) AND ("Pesticides/adverse effects"[Mesh Terms] OR "Pesticides/antagonists and inhibitors"[Mesh Terms] OR "Pesticides/blood"[Mesh Terms] OR "Pesticides/cerebrospinal fluid"[Mesh Terms] OR "Pesticides/immunology"[Mesh Terms] OR "Pesticides/pharmacokinetics"[Mesh Terms] OR "Pesticides/pharmacology"[Mesh Terms] OR "Pesticides/poisoning"[Mesh Terms] OR

Table A-1. Database Query Strings

Database search date	Query string
	"Pesticides/toxicity"[Mesh Terms] OR "Pesticides/urine"[Mesh Terms])) OR (("Trifluralin"[Text Word] OR "Treflan"[Text Word] OR "1582-09-8"[Text Word]) NOT medline[sb])
Scopus	
12/2024	(CHEM(Trifluralin) OR TITLE-ABS-KEY(Trifluralin) OR TITLE-ABS-KEY(Treflan) OR TITLE-ABS-KEY(1582-09-8) OR TITLE-ABS-KEY ({2,6-dinitro-N,N-dipropyl-4-(trifluoromethyl)aniline}) OR TITLE-ABS-KEY (dtxsid4021395)) AND (toxicity OR death OR lethal OR fatal OR fatality OR necrosis OR lc50* OR ld50* OR {body weight} OR {weight loss} OR {weight gain} OR weight-change* OR overweight OR obesity OR inhal* OR respiratory OR {pulmonary edema} OR {pulmonary effect} OR {pulmonary system} OR {pulmonary function} OR {pulmonary organ} OR {pulmonary toxicity} 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 bronchitis OR hemothorax OR alveolar OR alveoli OR irritation OR irritant OR sensitization OR sensitizer OR cilia OR mucociliary OR cvd OR cardio OR vascular OR cardiovascular OR {circulatory system} OR {circulatory function} OR {circulatory effect} OR {circulatory organ} OR {circulatory toxicity} OR {cardiac arrest} OR {cardiac palpitation} OR {cardiac arrhythmia} OR {cardiac edema} OR {heart rate} OR {heart failure} OR {heart attack} OR {heart muscle} OR {heart beat} 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 function} OR {digestive effect} OR {digestive organ} OR {Intestinal system} OR {intestinal function} OR {intestinal microbiota} OR {intestinal effect} OR {intestinal organ} OR {gi tract} OR {gi disorder} OR abdominal OR esophagus OR stomach OR intestine 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 cyanosis 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 {joint-ache} OR {limb pain} OR {limb ache} OR hepatic OR {liver system} OR {liver function} OR {liver effect} OR {liver organ} OR {Liver enzyme} OR {liver weight} OR {liver congestion} OR {liver changes} OR {liver biochemical changes} OR {liver toxicity} OR hepatocytes OR gallbladder OR cirrhosis OR jaundice OR {hepatocellular degeneration} OR {hepatocellular hypertrophy} OR hepatomegaly OR hepatotox* OR renal OR {kidney system} OR {kidney function} OR {Kidney effect} OR {kidney toxicity} OR {urinary system} OR {urinary function} OR {urinary effect} OR {Urinary toxicity} OR {bladder system} OR {bladder effect} OR {bladder function} OR {bladder toxicity} OR {Urine volume} OR {blood urea nitrogen} OR bun OR nephropathy OR nephrotox* OR dermal OR {skin rash} OR {skin itch} OR {skin irritation} OR {skin redness} OR {skin effect} OR {skin necrosis} OR {skin exposure} OR {skin contact} OR acanthosis OR dermatitis OR psoriasis OR edema OR ulceration OR acne OR ocular OR {eye function} OR {eye effect} OR {eye irritation} OR {eye drainage} OR {eye tearing} OR blindness OR myopia OR cataracts OR endocrine OR {hormone changes} OR {hormone excess} OR {hormone deficiency} OR {hormone gland} OR {hormone secretion} OR {hormone toxicity} OR {sella turcica} OR thyroid OR adrenal OR pituitary OR immunological OR immunologic OR immune OR lymphoreticular OR lymph-

Table A-1. Database Query Strings

Database search date	Query string
	node OR spleen OR thymus OR macrophage OR leukocyte* OR white-blood-cell OR immunotox* OR neurological OR neurologic OR neurotoxic OR neurotoxicity OR neurodegenerat* OR {nervous system} OR brain OR neurotoxicant OR neurochemistry OR neurophysiology OR neuropathology OR {motor activity} OR (motor AND change*) OR behavior-change* OR behavioral-change* OR sensorychange* OR cognitive OR vertigo OR drowsiness OR headache OR ataxia OR reproductive OR {reproduction system} OR {reproduction function} OR {reproduction effect} OR {reproduction toxicity} OR fertility OR {maternal toxicity} OR developmental OR {in utero} 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 elderly OR {altered food consumption} OR {altered water consumption} OR {metabolic effect} OR {metabolic toxicity} OR fever 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 mutagenicity OR mutagenic OR {mechanism of action} OR {mechanism of absorption} OR {mechanism of distribution} OR {mechanism of excretion} OR {mechanism of metabolism} OR {mechanism of toxic effect} OR {mechanism of toxicity} OR {adverse effect} OR {adverse effects} OR {health effects} OR noncancer OR poisoning OR morbidity OR inflammation OR antagonist OR inhibitor OR metabolism OR toxicokinetics OR pharmacokinetics OR {gene expression} OR {population health} OR epidemiology OR epidemiological OR case-control* OR casereferent OR case-report OR case-series OR cohort* OR correlation-stud* OR crossectional-stud* OR ecological-studies OR ecological-study OR follow-up-stud* OR longitudinal-stud* OR metaanalyses OR metaanalysis OR meta-analysis OR prospectivestud* OR record-link* OR retrospective-stud* OR seroepidemiologic-stud* OR occupation* OR worker* OR workmen* OR workplace* OR {human health} OR {oral intake} OR {oral feed} OR {oral ingestion} OR {oral exposure} OR {oral administration} OR ingest* OR gavage* OR {drinking-water} OR {environmental exposure} OR nhanes OR {National Health and Nutrition Examination Survey} 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 flyingfox 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 long*evans 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)

Table A-1. Database Query Strings

Database search date	Query string
Scifinder	
12/2024	1582-09-8 Document Type: Journal, Review, Book, Clinical Trial, Commentary, Conference, Dissertation, Editorial, Historical, Letter, Preprint, Report Substance Role: Adverse Effect, Biological Study, Pharmacokinetics, Pharmacological Activity Publication Year: no limit CA Section: Air Pollution and Industrial Hygiene, Toxicology, Water, Waste Treatment and Disposal Database: CPlus

Table A-2. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
01/2025	1582-09-8
NTP	
01/2025	Limited to: not dated Trifluralin 1582-09-8 "2,6-dinitro-N,N-dipropyl-4-(trifluoromethyl)aniline" Treflan
NTRL	
01/2025	Limited to: titles or keywords "Trifluralin" OR 1582-09-8 OR "2,6-dinitro-N,N-dipropyl-4-(trifluoromethyl)aniline" OR "Treflan"
Regulations.gov	
01/2025	Limited to: Docket or EPA notices "Trifluralin" 1582-09-8 "2,6-dinitro-N,N-dipropyl-4-(trifluoromethyl)aniline" "Treflan"
Other	
01/2025	Identified throughout the assessment process

APPENDIX B SUPPLEMENTAL STUDIES

B.1 CASE REPORTS

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