SYSTEMATIC EVIDENCE MAP (SEM) FOR ETHYLBENZENE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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DISCLAIMER

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CONTENTS

1. OBJECTIVES

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

- Conduct literature searches to identify available studies published since the ethylbenzene toxicological profile was last published in November 2010, 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 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 ethylbenzene, as identified in the toxicological profile (ATSDR 2010).

2. METHODS

2.1 LITERATURE SEARCH STRATEGY

A literature search was conducted to identify studies examining health effects, toxicokinetics, and mechanisms of action for ethylbenzene. The PECO criteria used to identify relevant studies examining the health effects of ethylbenzene 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 ethylbenzene (ATSDR 2010); thus, the literature search was restricted to studies published between January 2008 to December 2024 to capture literature published since the search was conducted for the existing profile. The following main databases were searched in 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 ethylbenzene. 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 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 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.

[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 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 or containing information to address data gaps (e.g., PBPK model, toxicokinetics, mechanisms of action, etc.)[a].

[a] Data gaps identified in the 2010 toxicological profile for ethylbenzene included genotoxicity studies in mammalian systems, the mechanism of action by which ethylbenzene elicits ototoxicity, studies on hearing and ear physiology in rodents to evaluate which species is most similar to humans, biomarkers of exposure specific to ethylbenzene, biomarkers of effect, toxicokinetic data for oral and dermal exposures.

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 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 Public[2] for interactive data visualization.

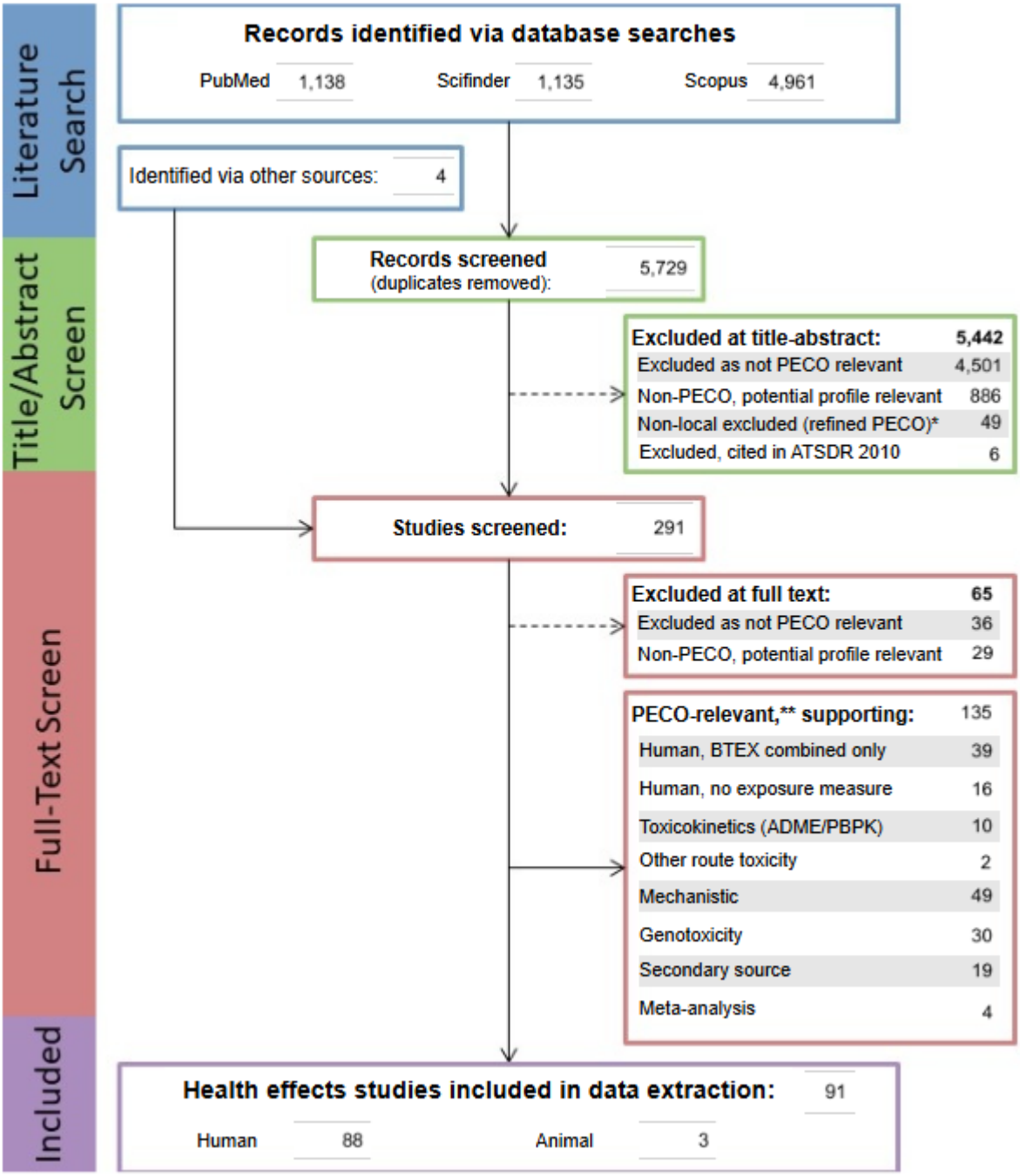
[2] Tableau Public is a web-based data visualization software available at https://public.tableau.com.

3. RESULTS

3.1 LITERATURE SEARCH RESULTS

Literature searches from all bibliographic databases yielded 5,720 unique references. Title and abstract screening identified 5,442 references as not PECO-relevant; of these, 886 were identified as non-PECO but potential profile-relevant items (i.e. considered in future profile development). An additional 49 non-local items were identified as not relevant based on refined PECO criteria, and 6 items were previously cited in the current toxicological profile (ATSDR 2010). The remaining 4,501 items proceeded to full-text review. Gray literature search results screened outside of DistillerSR added 4 citations, bringing the total number of citations for full-text review to 291. An additional 65 references were identified as not PECO-relevant during full-text screening; of these, 29 were identified as non-PECO, potential profile-relevant items. The remaining 226 references were identified as PECO-relevant, including 91 health effects studies and 135 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.visualizations/viz/EthylbenzeneSEMLiteratureFlowDiagram2025/Dashboard

3.2 LITERATURE INVENTORY

The literature search and screen identified 88 human and 3 animal health effects studies for ethylbenzene. One animal study included multiple experiments with different routes of exposure.

As shown in Figure 3-2A (Human Data) and Figure 3-2B (Animal Data), most human studies evaluating ethylbenzene exposure involved exposure via inhalation, in utero, or unspecified/multiple exposure routes of chronic duration (≥365 days). Of the 88 human studies identified, 42% (37 studies) examined ethylbenzene exposure by inhalation, 43% (38 studies) by multiple or unknown exposure routes, and 16% (14 studies) involved in utero exposures. In contrast, all 3 animal studies evaluated inhalation exposures of intermediate (15–364 days) duration, and 1 also evaluated oral exposure. The most frequently studied endpoints include respiratory, cardiovascular, neurological, hepatic, developmental, and cancer. Human studies indicate that respiratory, cardiovascular, and cancer are potential toxicity targets of ethylbenzene. While evidence from animal studies is limited, they also report effects on body weight and other noncancer effects.

The current toxicological profile (ATSDR 2010) identified several data needs in the toxicological database for ethylbenzene. One of the studies identified during the updated literature search potentially addresses these data needs (see Table 3). None of the identified studies are expected to impact the existing inhalation or oral MRLs.

Table 3. Data Needs Identified for ethylbenzene by ATSDR (2010)

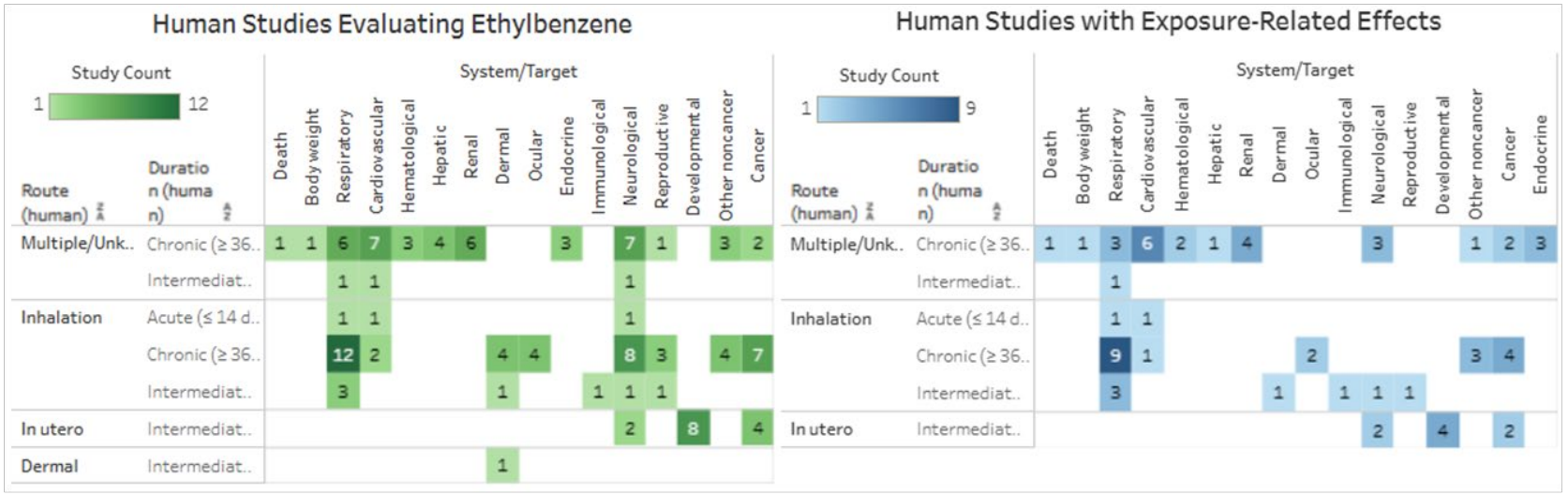
Exposure route	Data needs	Studies to potentially address data need
Inhalation	Additional studies to establish an intermediate-duration NOAEL (below the LOAEL of 10 ppm) for ototoxic effects	Zhang et al. 2023
Oral	Acute duration studies in animals	None
	Chronic (including carcinogenicity) studies in animal	None
	Additional studies evaluating reproductive effects in animals	None

Table 3. Data Needs Identified for ethylbenzene by ATSDR (2010)

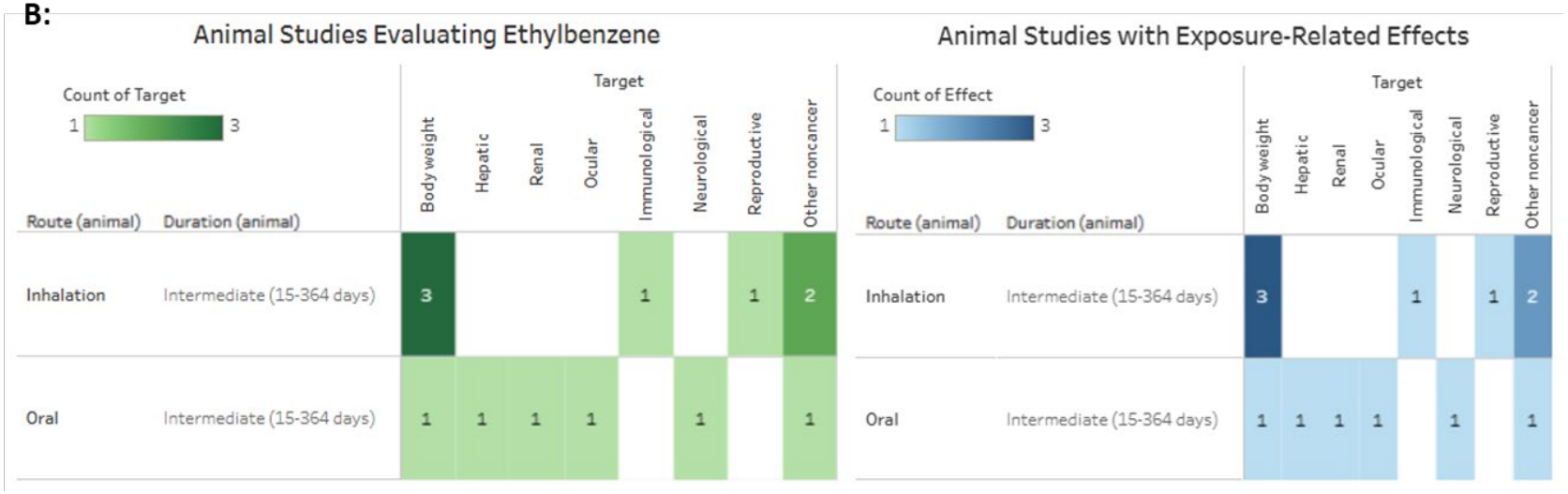
Exposure route	Data needs	Studies to potentially address data need
	Developmental studies in animals	None
	Additional studies to characterize the concentration-response pattern for ototoxicity after acute- and intermediate-duration exposures	None
Dermal	Acute, intermediate, and chronic (including carcinogenicity) studies in animals	None

Figure 3-2. Health Effects Studies for Ethylbenzene

A:



B:



**Interactive database can be accessed at:*
https://public.tableau.com/app/profile/atsdr.visualizations/viz/EthylbenzeneSEMDataVisualization2025/HealthEffectsOverview

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4.1 CURRENT PROFILE

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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 01/2025	((Ethylbenzene[Supplementary Concept] OR 100-41-4[rn] OR ethylbenzene[tw]) AND 2008:3000[dp] AND ("Benzene Derivatives/adverse effects"[MeSH Terms] OR "Benzene Derivatives/antagonists and inhibitors"[MeSH Terms] OR "Benzene Derivatives/blood"[MeSH Terms] OR "Benzene Derivatives/cerebrospinal fluid"[MeSH Terms] OR "Benzene Derivatives/immunology"[Mesh Terms] OR "Benzene Derivatives/pharmacokinetics"[Mesh Terms] OR "Benzene Derivatives/pharmacology"[Mesh Terms] OR "Benzene Derivatives/poisoning"[MeSH Terms] OR "Benzene Derivatives/toxicity"[MeSH Terms] OR "Benzene Derivatives/urine"[MeSH Terms] OR toxicokinetics[MeSH Terms] OR "pharmacokinetics"[MeSH Terms] OR "pharmacology"[MeSH Terms] OR "Toxicological Phenomena"[MeSH Terms] OR "humans"[MeSH Terms] OR "animals"[MeSH Terms] OR “Chemically induced”[sh] OR "environmental exposure"[MeSH Terms] OR "endocrine system"[MeSH Terms] OR "hormones, hormone substitutes, and hormone antagonists"[MeSH Terms] OR "endocrine disruptors"[MeSH Terms] OR "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 "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]) AND (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 "occupational diseases"[MeSH Terms] OR "epidemiologic studies"[MeSH Terms])) OR (("Ethylbenzene"[tw] OR “ethyl benzene”[tw] OR “Ethylbenzol”[tw] OR “phenylethane”[tw] OR “Benzene, ethyl-“[tw] OR “Aethylbenzol”[tw] OR “etilbenzene”[tw] OR “ethylbenzene”[tw] OR “aethylbenzo”[tw] OR “etylobenzen”[tw] OR “Etilbenzene”[tw]) AND 2008:3000[dp] NOT medline[sb] AND (toxicity[ti] 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

Table A-1. Database Query Strings

Database search date	Query string
	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 mucocilliary 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-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 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

Table A-1. Database Query Strings

Database search date	Query string
	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"[tiab:~0] OR "mechanism of absorption"[tiab:~0] OR "mechanism of distribution"[tiab:~0] OR "mechanism of excretion"[tiab:~0] OR "mechanism of metabolism"[tiab:~0] OR "mechanism of toxic effect"[tiab:~0] 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 "environmental exposure" 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 crosssectional-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 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 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))
Scopus 01/2025	(CHEM(ethylbenzene) OR TITLE-ABS-KEY(ethylbenzene) OR TITLE-ABS-KEY({ethyl benzene}) OR TITLE-ABS-KEY({benzene, ethyl-}) OR TITLE-ABS-KEY(ethylbenzol) OR TITLE-ABS-KEY(phenylethane) OR TITLE-ABS-KEY(etilbenzene) OR TITLE-ABS-KEY(aethylbenzo) OR TITLE-ABS-KEY(etylobenzen) OR TITLE-ABS-KEY(etilbenzene)) AND (PUBYEAR > 2007 AND PUBYEAR < 2026) 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

Table A-1. Database Query Strings

Database search date	Query string
	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-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

Table A-1. Database Query Strings

Database search date	Query string
	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 crosssectional-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)
Scifinder	
01/2025	100-41-4 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: 2008 to 2025 CA Section: Air Pollution and Industrial Hygiene, Toxicology, Water, Waste Treatment and Disposal Database: CAplus

Table A-2. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
01/2025	100-41-4 2008 to Present
NTP	
01/2025	Limited to: 2008 – Present or Not Dated Match exact word or phrase: 100-41-4 Ethylbenzene “ethyl benzene” Content types: Reports & Publications, Systematic Review
NTRL	
01/2025	Limited to: titles or keywords Limited to: 2008 – Present “Ethylbenzene” OR “ethyl benzene” OR 100-41-4
Regulations.gov	
01/2025	Limited to: Docket Documents Limited to: 2008 – Present “Ethylbenzene” “ethyl benzene” 100-41-4

APPENDIX B SUPPLEMENTAL STUDIES

B.1 HUMAN, BTEX COMBINED ONLY

Abduljalel ME, et al. 2022. Toxicopathological Effect of Benzene, Toluene, Ethylbenzene, and Xylenes (BTEX) As A Mixture and the Protective Effect of Citicoline in Male Rats Followings 90-Day Oral Exposure. Revista Electronica de Veterinaria 23(3):399.

Aguilera I, Garcia-Esteban R, et al. 2010. Prenatal exposure to traffic-related air pollution and ultrasound measures of fetal growth in the INMA Sabadell cohort.. Environ Health Perspect 118(5):705-11. https://doi.org/10.1289/ehp.0901228.

Aguilera I, Guxens M, et al. 2009. Association between GIS-based exposure to urban air pollution during pregnancy and birth weight in the INMA Sabadell Cohort.. Environ Health Perspect 117(8):1322-7. https://doi.org/10.1289/ehp.0800256.

Al-Harbi M, et al. 2020. Health symptoms associated with occupational exposure of gasoline station workers to BTEX compounds. Atmos Environ 241. https://doi.org/10.1016/j.atmosenv.2020.117847.

Bulog A, Karaconji IB, et al. 2011. Immunomodulation of cell-mediated cytotoxicity after chronic exposure to vapors.. Coll Antropol 35 Suppl 2:61-4.

Cassidy-Bushrow AE, Burmeister C, et al. 2020. Prenatal airshed pollutants and preterm birth in an observational birth cohort study in Detroit, Michigan, USA. Environ Res 189:109845. https://doi.org/10.1016/j.envres.2020.109845.

Cassidy-Bushrow AE, Burmeister C, et al. 2021. Ambient BTEX exposure and mid-pregnancy inflammatory biomarkers in pregnant African American women. J Reprod Immunol 145:103305. https://doi.org/10.1016/j.jri.2021.103305.

Chen L, Hu G, et al. 2018. Association of PAHs and BTEX exposure with lung function and respiratory symptoms among a nonoccupational population near the coal chemical industry in Northern China. Environ Int 120:480-488. https://doi.org/10.1016/j.envint.2018.08.004.

da Rosa JC, Fiegenbaum M, et al. 2013. Cytogenetic evaluation and the association with polymorphisms of the CPY1A1 and NR1I3 genes in individuals exposed to BTEX.. Environ Monit Assess 185(7):5883-90. https://doi.org/10.1007/s10661-012-2992-3

Dai K, et al. 2023. Expression level and function analysis of serum miRNAs in workers with occupational exposure to benzene series. Chemosphere 313. https://doi.org/10.1016/j.chemosphere.2022.137460.

Felzenszwalb I, et al. 2018. Indoor air pollution: BTEX in occupational environments. WIT Transactions on Ecology and the Environment 230:279. https://doi.org/10.2495/AIR180261.

Feng X, Qiu F, et al. 2024. Exposure to volatile organic compounds and mortality in US adults: A population-based prospective cohort study. Sci Total Environ 928:172512. https://doi.org/10.1016/j.scitotenv.2024.172512.

Ghahri A, Seydi P, et al. 2024. Evaluation of exposure to volatile organic compounds (BTEX) and Polycyclic Aromatic Hydrocarbons (PAHs) in gas station workers and oxidative stress assessment in Karaj city.. Toxicology reports 13:101767. https://doi.org/10.1016/j.toxrep.2024.101767.

Gordian ME, Stewart AW, et al. 2010. Evaporative gasoline emissions and asthma symptoms.. Int J Environ Res Public Health 7(8):3051-62. https://doi.org/10.3390/ijerph7083051.

Guo Y, et al. 2023. Benchmark dose estimation based on oxidative damage in Chinese workers exposed to benzene series compounds. Environ Toxicol Pharmacol 100. https://doi.org/10.1016/j.etap.2023.104150.

Harati B, Shahtaheri SJ, et al. 2018. Evaluation of Respiratory Symptoms among Workers in an Automobile Manufacturing Factory, Iran. Iran J Public Health 47(2):237-245.

Kasemy ZA, Kamel GM, et al. 2019. Environmental and Health Effects of Benzene Exposure among Egyptian Taxi Drivers. J Environ Public Health 2019:7078024. https://doi.org/10.1155/2019/7078024.

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