TARGETED SYSTEMATIC EVIDENCE MAP (SEM) AND RAPID SYSTEMATIC REVIEW FOR TRICHLOROETHYLENE AND DEVELOPMENTAL CARDIOTOXICITY

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

April 2025

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CHAPTER 1. OBJECTIVES

Trichloroethylene is a colorless, volatile liquid that evaporates quickly into the air (ATSDR 2019). Its primary uses are as a solvent (e.g., to remove grease from metal parts) and in the production of other chemicals (e.g., refrigerants such as HFC-134a) (ATSDR 2019). The current chronic-duration inhalation and oral minimal risk levels (MRLs) for trichloroethylene are based on co-critical studies/effects including immunotoxicity and fetal heart malformations (ATSDR 2019). This approach is consistent with the U.S. Environmental Protection Agency (EPA) oral reference dose (RfD) (EPA 2011e). However, inclusion of developmental cardiotoxicity as a co-critical effect for toxicity values has been controversial, with some evaluations concluding that the database is insufficient to support developmental cardiotoxicity as a toxicity target for trichloroethylene in humans (Bukowski et al. 2014; EPA 2014b; Wikoff et al. 2018) and others concluding that overall evidence indicates that exposure to trichloroethylene may result in congenital heart defects (EPA 2020). Therefore, the Agency for Toxic Substances and Disease Registry (ATSDR) elected to conduct an independent rapid systematic review of the available data evaluating potential associations between developmental exposure to trichloroethylene and cardiotoxicity.

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

- Conduct literature searches to identify available studies evaluating developmental cardiotoxicity following exposure to trichloroethylene published after the trichloroethylene toxicological profile was last published in June 2019 through August 2023. This includes studies in humans, animals, *in vitro* models, or *in silico*.

- Screen results of literature searches and the reference list of the 2019 toxicological profile using systematic review methods to determine if identified studies meet the Populations, Exposures, Comparators, and Outcome (PECO) criteria outlined in Section 2.1.

- Prepare an interactive literature inventory (SEM) with high-level data review and extraction to provide an overview of evidence that meets PECO criteria for developmental cardiovascular endpoints, including newly identified literature through August 2023 as well as literature included in the 2019 toxicological profile.

- Perform rapid systematic review for human and animal studies evaluating developmental cardiotoxicity to evaluate the confidence in the body of evidence in order to make a hazard determination.

CHAPTER 2. METHODS

2.1 LITERATURE SEARCH STRATEGY

A literature search was conducted to identify studies examining toxic effects on the cardiovascular system following exposure to trichloroethylene as well as relevant mechanisms of action. The PECO criteria used to identify relevant studies are presented in Table 2-1. While the focus of the targeted SEM is developmental cardiotoxicity, the literature search strategy was designed to capture all studies relevant to cardiotoxicity (including non-developmental exposures) in order to be comprehensive at the title/abstract screening stage. Non-developmental studies, along with mechanistic studies, were retained as supporting studies during full-text screening, while only developmental studies were carried forward to the literature inventory (see Section 2.2).

Table 2-1. Populations, Exposures, Comparators, and Outcome (PECO) Criteria for Screening of Literature Search Results for Targeted Systematic Evidence Map (SEM) on Trichloroethylene Cardiotoxicity

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.
Exposure	*In vivo* (all routes, all durations), *ex vivo*, and *in vitro* exposure to trichloroethylene, including mixtures to which trichloroethylene may contribute significantly to exposure or observed effects.
Comparison	Any comparison (across dose, duration, or route) or no comparison.
Outcomes	Any endpoint suggestive of a toxic effect on the cardiovascular system following adult or developmental exposure, or mechanistic change associated with such effects.

The current literature search was intended to identify studies that were not included in the existing toxicological profile for trichloroethylene (ATSDR 2019); thus, the literature search was restricted to studies published between January 2017 to August 2023 to capture literature published since the search was conducted for the existing profile. The following main databases were searched in August 2023:

- PubMed
- Scientific and Technical Information Network's TOXCENTER

These two databases are typically used by ATSDR for toxicological profiles. The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for trichloroethylene. The query strings used for the literature search are presented in Appendix A (Table A-1). These query strings were designed to capture all cardiotoxicity

data potentially relevant to the PECO statement. Synonyms, found in the query strings, were gathered from the EPA's CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard) and the American Chemical Society's Common Chemistry (https://commonchemistry.cas.org/) databases.

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, 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 (summarized in 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.), citations selected for full-text retrieval were limited to English-language, full-length journal articles, and study reports.

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: developmental cardiotoxicity health effects studies (human or animal toxicity; inhalation or oral exposure) or related information (adult cardiotoxicity, other route cardiotoxicity, mechanistic, secondary source, conference abstract, commentaries, letters, or erratum).

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

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 developmental cardiotoxicity 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.

2.4 RISK OF BIAS ASSESSMENT FOR INDIVIDUAL STUDIES

The risk of bias of individual studies evaluating developmental cardiotoxicity following exposure to trichloroethylene was assessed using the Office of Health Assessment and Translation (OHAT) Risk of Bias Tool (NTP 2015) by a toxicologist, with quality assurance review by a senior toxicologist. The risk of bias questions for observational epidemiology studies and animal experimental studies are presented in Tables 2-2 and 2-3, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

Table 2-2. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?

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

Table 2-2. Risk of Bias Questionnaire for Observational Epidemiology Studies

Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table 2-3. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used. If the information was insufficient to answer the question or not reported, "probably high risk of bias" was selected unless it was deemed that deviations from low risk-of-bias practices for the evaluated criteria would not appreciably bias results (e.g., lack of reporting for blinding for purely quantitative endpoints). In those cases, "probably low risk of bias" was selected.

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risks of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on all the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for all the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

2.5 RATING THE CONFIDENCE IN THE BODY OF EVIDENCE

The confidence in the body of evidence for an association or no association between exposure to trichloroethylene and developmental cardiotoxicity was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, cohort, ecological, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

Initial Confidence Rating. In ATSDR's modification to the National Toxicology Program (NTP) OHAT approach, the body of evidence for an association (or no association) between exposure to trichloroethylene and developmental cardiotoxicity was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology

(cohort, ecological, and case-control) studies and experimental animal studies are presented in Tables 2-4 and 2-5, respectively. The confidence for each individual study was determined based on the number of key features present in the study design:

- **High Confidence:** Studies in which the responses to the four questions were "yes"
- **Moderate Confidence:** Studies in which the responses to only three of the questions were "yes"
- **Low Confidence:** Studies in which the responses to only two of the questions were "yes"
- **Very Low Confidence:** Studies in which the response to one or none of the questions was "yes"

After all studies were evaluated, initial confidence ratings were assigned across human and animal studies grouped by route and duration based on the highest identified individual study confidence. For example, if confidence ratings available for acute-duration oral animal studies included one low, three moderate, and one high confidence study, the initial confidence rating for acute-duration oral animal studies would be "high." Similarly, if the initial confidence ratings for acute-, intermediate-, and chronic-duration oral studies in animals were high, moderate, and high, respectively, the initial confidence rating for the entire animal oral database would be considered "high."

Table 2-4. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table 2-5. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Adjustment of Confidence Rating. The initial confidence rating determined for each species and route was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below.

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (see Tables 3-1 and 3-2). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
  - No downgrade if most studies are in the risk of bias first tier
  - Downgrade one confidence level if most studies are in the risk of bias second tier
  - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
  - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
  - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
  - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
  - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
  - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
  - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
  - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
  - No downgrade if none of the factors are considered indirect
  - Downgrade one confidence level if one of the factors is considered indirect
  - Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure

scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
- Upgrade one confidence level if there is a high degree of consistency in the database

2.6 TRANSLATING THE CONFIDENCE RATING INTO LEVEL OF EVIDENCE

In the next step of the systematic review of the developmental cardiotoxicity for trichloroethylene, the confidence in the body of evidence was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

2.7 INTEGRATING THE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

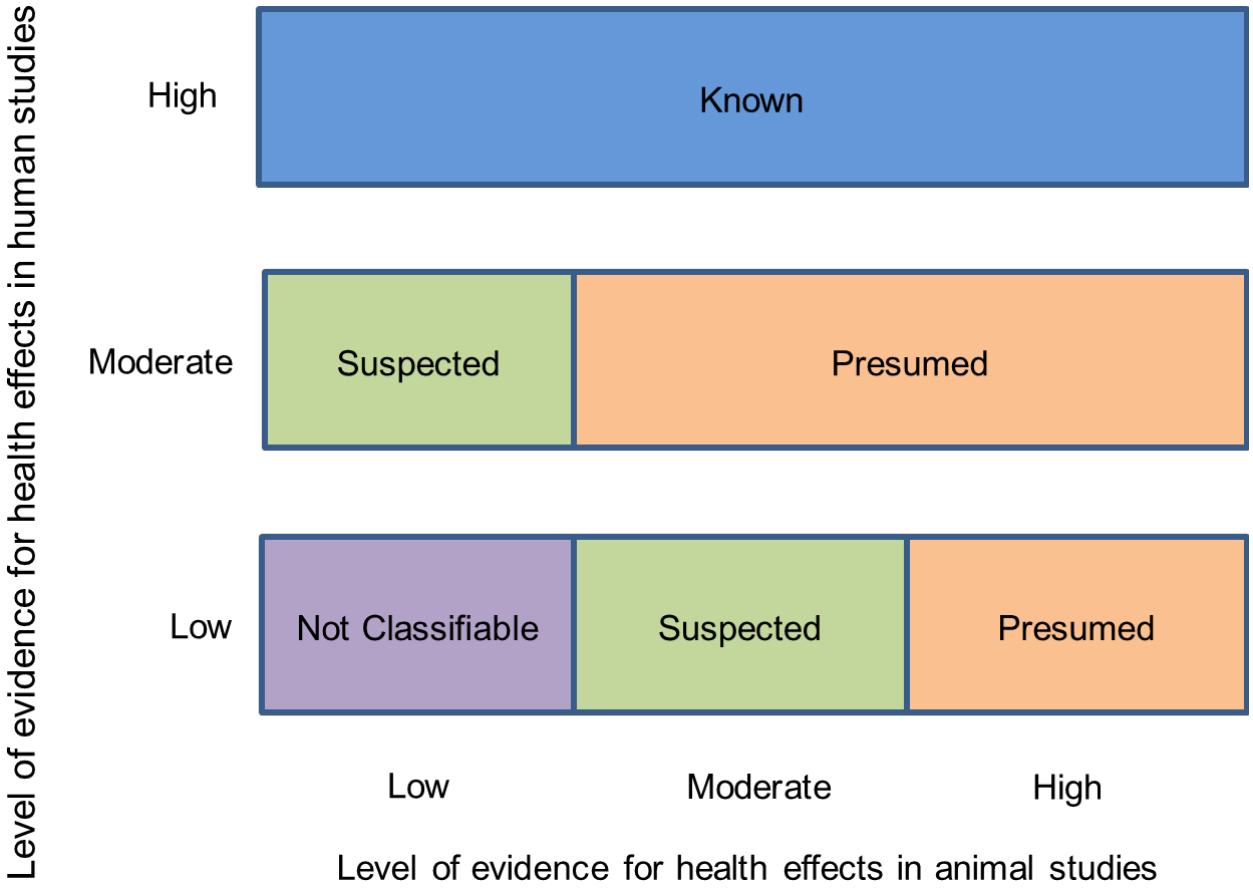
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure 2-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** any level of evidence in animal studies (including no evidence).
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence (or no evidence) in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence (or no evidence) in animal studies **OR**
  - Low level of evidence (or no evidence) in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence (or no evidence) in human studies **AND** low level of evidence (or no evidence) in animal studies

Figure 2-1. Hazard Identification Scheme



Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

CHAPTER 3. RESULTS

3.1 LITERATURE SEARCH RESULTS

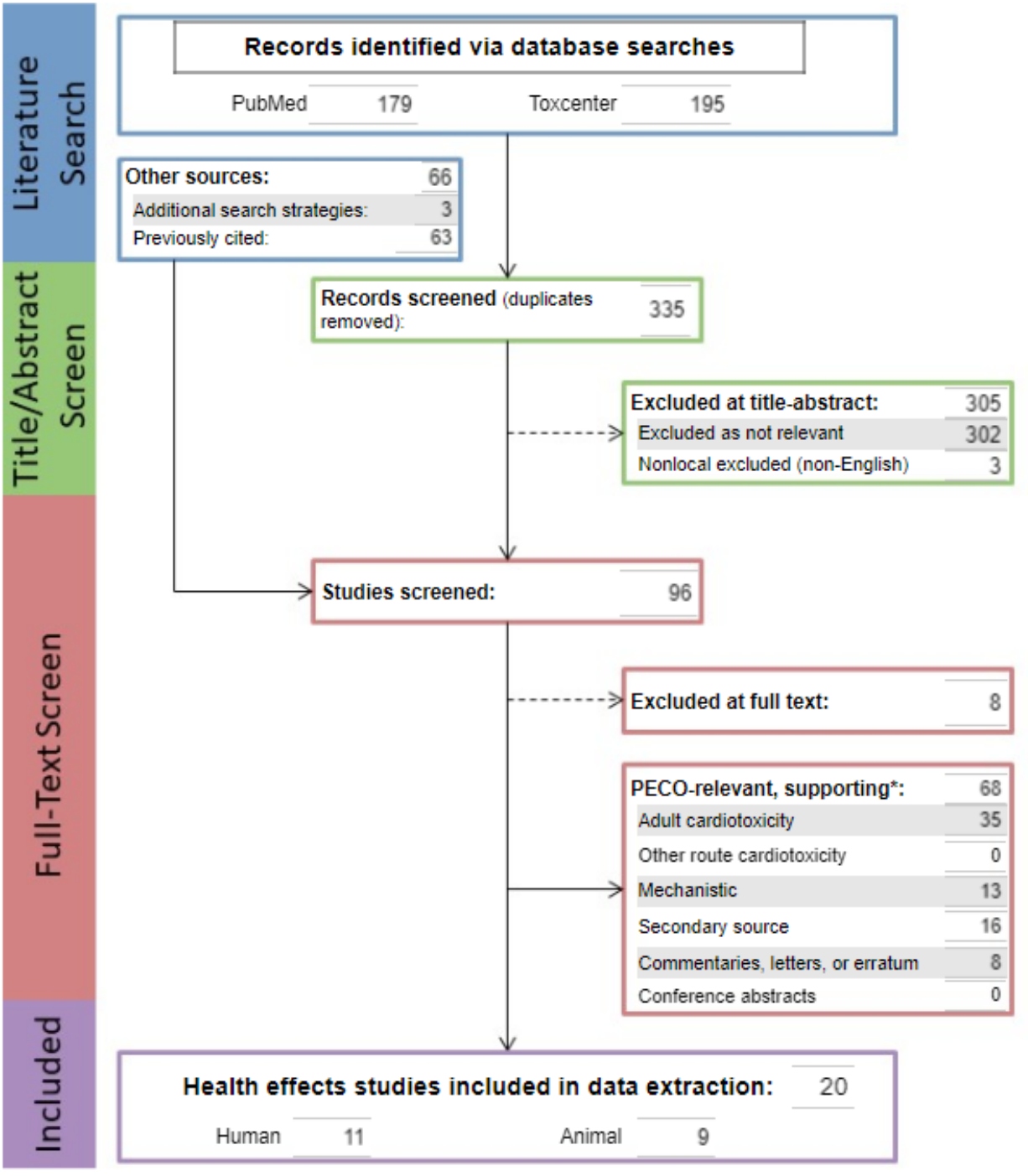
Literature searches from all bibliographic databases yielded 335 unique references. Title and abstract screening identified 302 references as not PECO-relevant. An additional three nonlocal items were excluded at title and abstract screening (foreign language). The remaining 30 items identified as PECO-relevant during title/abstract screening proceeded to full-text review. Items added to full-text review included 3 citations identified from the gray literature search results screened outside of DistillerSR and 63 citations identified from the 2019 toxicological profile, bringing the total number of citations for full-text review to 96. An additional 8 references were identified as not PECO-relevant during full-text screening. The remaining 88 references were identified as PECO-relevant, including 20 studies evaluating developmental cardiotoxicity and 68 supporting studies. A summary of the results of the literature search and screening is presented in Figure 3-1.

3.2 LITERATURE INVENTORY

The targeted literature search and screen identified 11 human studies and 9 animal studies (containing 21 animal experiments) evaluating developmental cardiotoxicity following exposure to trichloroethylene. Of these studies, only two studies (one human, one animal) were published between August 2023 and the literature search conducted for the 2019 toxicological profile (DeSesso et al. 2019; Liu et al. 2021).

As shown in the SEM in Figure 3-2, developmental cardiovascular toxicity has been evaluated in both humans and animals, with more studies conducted in animals than humans. In humans, the numbers of inhalation and oral studies are similar. However, it is acknowledged that while ingestion is the predominant exposure route for humans exposed via domestic water sources, multi-route exposure is expected with potential inhalation and dermal exposure (e.g., via cooking, showering, and bathing activities). In animals, inhalation studies are more numerous, and are available in three species (rat, mouse, rabbit), while available oral studies are restricted to rats. Human studies were a mixture of intermediate- and chronic-duration studies, while animal studies were primarily intermediate-duration with a few acute-duration gestation-only studies.

Figure 3-1. Literature Flow Diagram



*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: Trichloroethylene Developmental Cardiotoxicity Interactive Literature Flow Diagram

Figure 3-2. Studies Evaluating Cardiovascular Effects Following Developmental Exposure to Trichloroethylene

Human

Route - human	Duration - human	Adverse effect in humans? Yes	No
Inhalation	Intermediate (15-364 days)		1
	Chronic (≥365 days)	3	1
Oral	Intermediate (15-364 days)	2	2
	Chronic (≥365 days)		1
Multiple/Unknown	Chronic (≥365 days)		1

Animal

Route - animal	Duration - animal	Adverse effect in animals? Yes	No
Inhalation	Acute (≤14 days)		4
	Intermediate (15-364 days)		10
Oral	Acute (≤14 days)		2
	Intermediate (15-364 days)	4	1

Interactive database can be accessed at: Trichloroethylene Developmental Cardiotoxicity SEM

3.3 RAPID SYSTEMATIC REVIEW

The results of the risk of bias assessment for the studies evaluating developmental cardiotoxicity following exposure to trichloroethylene (observational epidemiology and animal experimental studies) are presented in Tables 3-1 and 3-2, respectively. All human studies were rated as second tier studies. In animals, inhalation studies were all rated as first tier studies; however, oral studies were a mixture of first, second, and third tier studies.

Table 3-1. Summary of Risk of Bias Assessment for Trichloroethylene—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — Did the study design or analysis account for important confounding and modifying variables?*	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?*	Detection bias — Is there confidence in the outcome assessment?*	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Outcome: Developmental cardiotoxicity							
Cohort studies							
Bove et al. 1995	+	–	+	+	++	++	Second
Lagakos et al. 1986	+	–	–	–	–	++	Second
MDPH 1996	+	+	+	–	+	++	Second
MDPH 1988	+	+	+	–	+	++	Second
Tola et al. 1980	+	–	+	–	–	+	Second
Case-control							
Brender et al. 2014	+	–	++	–	++	++	Second
Gilboa et al. 2012	+	–	++	– –	++	++	Second
Liu et al. 2021	+	+	++	–	++	++	Second
Yauck et al. 2004	+	–	++	–	++	++	Second

Table 3-1. Summary of Risk of Bias Assessment for Trichloroethylene—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?*	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?*	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Ecological study							
ATSDR 2006, 2008; Forand et al. 2012[a]	+	+	+	–	+	+	Second
Goldberg et al. 1990	+	+	+	–	+	+	Second

[a]ATSDR (2006, 2008) are comprehensive reports by ATSDR associated with the published report by Forand et al. (2012). Data contained in these reports were utilized to answer risk of bias questions.

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias

*Key question used to assign risk of bias tier.

Table 3-2. Summary of Risk of Bias Assessment for Trichloroethylene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition / exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Outcome: Developmental cardiotoxicity									
Inhalation acute exposure									
Dorfmueller et al. 1979 (rat, premating)	+	+	+	+	+	++	+	+	First
NIOSH 1980 (rat, GDs 6–18)	+	++	–	++	++	++	+	++	First
Schwetz et al. 1975 (rat, gestation)	–	+	+	+	–	++	+	+	First
Schwetz et al. 1975 (mouse, gestation)	–	+	+	+	–	++	+	+	First
Inhalation intermediate exposure									
Carney et al. 2006 (rat)	+	++	++	++	++	++	+	++	First
Dorfmueller et al. 1979 (rat, gestation)	+	+	+	+	+	++	+	+	First
Dorfmueller et al. 1979 (rat, premating, and gestation)	+	+	+	+	+	++	+	+	First
NIOSH 1980 (rat, GDs 0–18)	+	++	+	++	++	++	+	++	First
NIOSH 1980 (rat, premating, and GDs 6–18)	+	++	–	++	++	++	+	++	First

Table 3-2. Summary of Risk of Bias Assessment for Trichloroethylene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition / exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
NIOSH 1980 (rat, premating, and GDs 0–18)	+	++	–	++	++	++	+	++	First
NIOSH 1980 (rabbit, GDs 7–21)	+	++	–	++	++	++	+	++	First
NIOSH 1980 (rabbit, GDs 0-21)	+	++	–	++	++	++	+	++	First
NIOSH 1980 (rabbit, premating, and GDs 7–21)	+	++	–	++	++	++	+	++	First
NIOSH 1980 (rabbit, premating, and GDs 0–21)	+	++	–	++	++	++	+	++	First
Oral acute exposure									
Fisher et al. 2001 (rat, GDs 6–15)	++	++	+	++	+	+	++	++	First
Narotsky et al. 1995 (rat)	+	+	++	+	+	–	+	+	First
Oral intermediate exposure									
Dawson et al. 1993 (rat, premating)	–	+	– –	+	–	–	–	–	Third
Dawson et al. 1993 (rat, gestation)	–	+	– –	+	–	–	–	–	Third
Dawson et al. 1993 (rat, premating, and gestation)	–	+	– –	+	–	–	–	–	Third

Table 3-2. Summary of Risk of Bias Assessment for Trichloroethylene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
DeSesso et al. 2019 (rat, one-generation study)	++	++	+	++	++	++	++	++	First
Johnson et al 2003, 2004[a] (rat, gestation)	–	+	– –	+	–	+	–	+	Second

[a]Johnson et al. (2004) is an editorial response containing additional methodological details for Johnson et al. (2003), particularly pertaining to non-concurrent nature of study groups, that was utilized to answer risk of bias questions.

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; GD = gestation day

*Key question used to assign risk of bias tier.

The presence or absence of the key features and the resulting confidence levels for studies examining developmental cardiotoxicity observed in the observational epidemiology, and animal experimental studies are presented in Tables 3-3 and 3-4, respectively. Confidence in the studies for evaluation of developmental cardiotoxicity was moderate for the majority of human studies and animal inhalation studies and low for the majority of animal oral studies.

Table 3-3. Presence of Key Features of Study Design for Trichloroethylene—Observational Epidemiology Studies

Reference	Key features				Study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Developmental cardiotoxicity					
Cohort studies					
Bove et al. 1995	No	Yes	Yes	Yes	Moderate
Lagakos et al. 1986	No	Yes	Yes	Yes	Moderate
MDPH 1996	No	Yes	Yes	Yes	Moderate
MDPH 1988	No	Yes	Yes	Yes	Moderate
Tola et al. 1980	No	Yes	Yes	Yes	Moderate
Case-control					
Brender et al. 2014	No	Yes	Yes	Yes	Moderate
Gilboa et al. 2012	No	Yes	Yes	Yes	Moderate
Liu et al. 2021	No	No	Yes	Yes	Low
Yauck et al. 2004	No	Yes	Yes	Yes	Moderate
Ecological study					
ATSDR 2006, 2008; Forand et al. 2012	No	Yes	Yes	Yes	Moderate
Goldberg et al. 1990	No	Yes	Yes	Yes	Moderate

Table 3-4. Presence of Key Features of Study Design for Trichloroethylene—Experimental Animal Studies

Reference	Key features				Study confidence
	Concurrent control group	Sufficient number of subjects	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Outcome: Developmental cardiotoxicity					
Inhalation acute exposure					
Dorfmueller et al. 1979 (rat, premating)	Yes	No	Yes	Yes	Moderate
NIOSH 1980 (rat, GDs 6–18)	Yes	Yes	Yes	No	Moderate
Schwetz et al. 1975 (rat, gestation)	Yes	No	Yes	Yes	Moderate
Schwetz et al. 1975 (mouse, gestation)	Yes	No	Yes	Yes	Moderate
Inhalation intermediate exposure					
Carney et al. 2006 (rat)	Yes	Yes	Yes	Yes	High
Dorfmueller et al. 1979 (rat, gestation)	Yes	No	Yes	Yes	Moderate
Dorfmueller et al. 1979 (rat, premating, and gestation)	Yes	No	Yes	Yes	Moderate
NIOSH 1980 (rat, GDs 0–18)	Yes	Yes	Yes	No	Moderate
NIOSH 1980 (rat, premating, and GDs 6–18)	Yes	Yes	Yes	No	Moderate
NIOSH 1980 (rat, premating, and GDs 0–18)	Yes	Yes	Yes	No	Moderate
NIOSH 1980 (rabbit, GDs 7–21)	Yes	Yes	Yes	No	Moderate
NIOSH 1980 (rabbit, GDs 0–21)	Yes	Yes	Yes	No	Moderate
NIOSH 1980 (rabbit, premating, and GDs 7–21)	Yes	Yes	Yes	No	Moderate
NIOSH 1980 (rabbit, premating, and GDs 0–21)	Yes	Yes	Yes	No	Moderate
Oral acute exposure					
Fisher et al. 2001 (rat, GDs 6–15)	Yes	Yes	Yes	Yes	High
Narotsky et al. 1995 (rat)	Yes	Yes	Yes	No	Moderate
Oral intermediate exposure					
Dawson et al. 1993 (rat, premating)	No	No	Yes	Yes	Low
Dawson et al. 1993 (rat, gestation)	No	No	Yes	Yes	Low
Dawson et al. 1993 (rat, premating, and gestation)	No	No	Yes	Yes	Low
DeSesso et al. 2019 (rat, one-generation study)	Yes	Yes	Yes	Yes	High
Johnson et al 2003 (rat, gestation)	No	No	Yes	Yes	Low

GD = gestation day

A summary of the initial confidence ratings for each outcome is presented in Table 3-5. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence.

Table 3-5. Initial Confidence Rating for Trichloroethylene Health Effects Studies

	Study confidence	Initial confidence rating
Outcome: Developmental cardiotoxicity		
Inhalation acute exposure		
Animal studies		
Dorfmueller et al. 1979 (rat, premating)	Moderate	Moderate
NIOSH 1980 (rat, GDs 6–18)	Moderate	
Schwetz et al. 1975 (rat, gestation)	Moderate	
Schwetz et al. 1975 (mouse, gestation)	Moderate	
Inhalation intermediate exposure		
Human studies		
Gilboa et al. 2012	Moderate	Moderate
Animal studies		
Carney et al. 2006 (rat)	High	High
Dorfmueller et al. 1979 (rat, gestation)	Moderate	
Dorfmueller et al. 1979 (rat, premating, and gestation)	Moderate	
NIOSH 1980 (rat, GDs 0–18)	Moderate	
NIOSH 1980 (rat, premating, and GDs 6–18)	Moderate	
NIOSH 1980 (rat, premating, and GDs 0–18)	Moderate	
NIOSH 1980 (rabbit, GDs 7–21)	Moderate	
NIOSH 1980 (rabbit, GDs 0–21)	Moderate	
NIOSH 1980 (rabbit, premating, and GDs 7–21)	Moderate	
NIOSH 1980 (rabbit, premating, and GDs 0–21)	Moderate	
Inhalation chronic exposure		
Human studies		
Brender et al. 2014	Moderate	Moderate
ATSDR 2006, 2008; Forand et al. 2012	Moderate	
Tola et al. 1980	Moderate	
Yauck et al. 2004	Moderate	
Oral acute exposure		
Animal studies		
Fisher et al. 2001 (rat, GDs 6–15)	High	High
Narotsky et al. 1995 (rat)	Moderate	

Table 3-5. Initial Confidence Rating for Trichloroethylene Health Effects Studies

	Study confidence	Initial confidence rating
Oral intermediate exposure		
Human studies		
Bove et al. 1995	Moderate	Moderate
Goldberg et al. 1990	Moderate	
MDPH 1988	Moderate	
MDPH 1996	Moderate	
Animal studies		
Dawson et al. 1993 (rat, premating)	Low	High
Dawson et al. 1993 (rat, gestation)	Low	
Dawson et al. 1993 (rat, premating, and gestation)	Low	
DeSesso et al. 2019 (rat, one-generation study)	High	
Johnson et al 2003 (rat, gestation)	Low	
Oral chronic exposure		
Human studies		
Lagakos et al. 1986	Moderate	Moderate
Multiple/unknown chronic exposure		
Human studies		
Liu et al. 2021	Low	Low

GD = gestation day

The initial confidence ratings presented in Table 3-5 were adjusted based on whether there were substantial issues that would decrease or increase confidence in the body of evidence, as shown in Table 3-6.

Table 3-6. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating[a]	Final confidence
Outcome: Developmental cardiotoxicity following inhalation exposure			
Human studies	Moderate	-1 Risk of Bias	Low
Animal studies	High	-1 Imprecision	Moderate
Outcome: Developmental cardiotoxicity following oral exposure			
Human studies	Moderate	-1 Risk of Bias -1 Unexplained inconsistency	Very low
Animal studies	High	-1 Risk of Bias -1 Unexplained inconsistency	Low

[a]Details regarding adjustments discussed in bullets below Table 3-7.

The final confidence, combined with the observed direction of health effect, was translated into a level of evidence for developmental cardiotoxicity for trichloroethylene, as shown in Table 3-7.

Table 3-7. Level of Evidence for Developmental Cardiotoxicity for Trichloroethylene

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Inhalation exposure	Low	Adverse effect	Low
Oral exposure	Very low	Adverse effect	Inadequate evidence
Animal studies			
Inhalation exposure	Moderate	No adverse effect	Inadequate evidence
Oral exposure	Low	Adverse effect	Low

Based on findings presented in Table 3-7, and the hazard identification scheme shown in Figure 2-1, **developmental cardiotoxicity is not classifiable as a health effect in humans following inhalation or oral exposure to trichloroethylene.** Key information supporting this hazard classification is reviewed below.

- Inhalation exposure
  - There is a low level of evidence from general population studies reporting increased risk of developmental cardiotoxicity following maternal exposure to chlorinated solvents, including trichloroethylene, via emissions (Brender et al. 2014; Yauck et al. 2004) or vapor intrusion (Forand et al. 2012). Two studies did not identify increased risk of developmental cardiotoxicity following maternal occupational exposure to trichloroethylene (Gilboa et al. 2012; Tola et al. 1980).
  - There is a moderate level of evidence indicating no cardiac malformations or variations in fetal visceral examinations following maternal inhalation exposure prior to and/or during gestation in rats (Carney et al. 2006; Dorfmueller et al. 1979; NIOSH 1980; Schwetz et al. 1975), mice (Schwetz et al. 1975), or rabbits (NIOSH 1980).
    - ***Imprecision:*** Most inhalation studies lacked targeted cardiac assessments.

- Oral exposure
  - There is a very low level of evidence for an association between increased risk of developmental cardiotoxicity following maternal exposure to trichloroethylene via drinking water. Interpretation of studies are often confounded by co-exposure to other water contaminants, including other chlorinated solvents.
    - ***Unexplained inconsistency***: Increased risks are reported in some studies (Bove et al. 1995; Goldberg et al. 1990) but not others (Lagakos et al. 1986; MDPH 1988, 1996).
  - There is a low level of evidence for cardiac malformations in rats following maternal exposure to trichloroethylene during gestation. Oral studies reporting effects (Dawson et al.

1993; Johnson et al. 2003) have critical study design flaws, including use of non-concurrent controls and exposure groups (Hardin et al. 2004; Johnson et al. 2004).

- ***Unexplained inconsistency***: Other studies in rats have not reported cardiac malformations following maternal exposure to trichloroethylene during gestation (DeSesso et al. 2019; Fisher et al. 2001). While exposure duration was shorter in the study by Fisher et al. (2001), exposure (gestational days 6–15) was inclusive of the cardiac developmental period in fetal rats (Wikoff et al. 2018).

- Mechanistic data
  - While not systematically reviewed for this assessment, a systematic evaluation of mechanistic data by Urban et al. (2020) concluded that available mechanistic studies did not support an association between congenital heart defects and exposure to trichloroethylene. This study further concluded that there was no biological plausibility for congenital heart defects based on a putative adverse outcome pathway for valvular-septal cardiac defects.
  - Several studies in zebrafish have been published since Urban et al. (2020) conducted their systematic review. These studies report heart defects in zebrafish embryos exposed to trichloroethylene, attributed to reactive oxygen species and unchecked cell proliferation (Huang et al. 2020, 2021; Jin et al. 2020). A transcriptomic network study in zebrafish by Li et al. (2020) also predicts that trichloroethylene is cardiotoxic. However, these findings are unlikely to alter the conclusions made by Urban et al. (2020), as that report indicated that the zebrafish model has limitations with regards to its ability to evaluate developmental cardiotoxicity in humans due to differences in fish versus mammalian heart structure as well as the exposure paradigm (direct embryo-environment exposure interface).
  - Mechanistic studies in mammalian cells published since Urban et al. (2020) are limited to targeted analyses of altered expression of a specific transcription factor (hepatocyte Nuclear Factor 4 alpha) or protein (connexin 43) following exposure to trichloroethylene (Chen et al. 2020; Teng et al. 2023; Xi et al. 2022). Findings from these studies are considered too narrow in scope to alter the conclusions made by Urban et al. (2020).

CHAPTER 4. CONCLUSIONS

Based on a rapid systematic review of available data through August 2023, developmental cardiotoxicity is not classifiable as a health effect in humans following exposure to trichloroethylene via the inhalation or oral exposure routes. In humans, the evidence for an association between trichloroethylene and developmental cardiotoxicity in the general population is low following inhalation exposure and very low following oral exposure. In animals, there is moderate evidence indicating a lack of developmental cardiotoxicity following inhalation exposure and a low level of evidence suggesting an association following oral exposure. Available mechanistic data are inadequate to support an association between exposure to trichloroethylene and developmental cardiotoxicity.

CHAPTER 5. REFERENCES

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APPENDIX A. LITERATURE SEARCH STRATEGIES

Table A-1. Database Query Strings

Database search date	Query string
PubMed 08/2023	("Trichloroethylene"[mh] OR "1,1-Dichloro-2-chloroethylene"[tw] OR "1-Chloro-2,2-dichloroethylene"[tw] OR "Acetylene trichloride"[tw] OR "Algylen"[tw] OR "Anamenth"[tw] OR "Benzinol"[tw] OR "Blacosolv"[tw] OR "Blancosolv"[tw] OR "Cecolene"[tw] OR "Chlorilen"[tw] OR "Chlorylea"[tw] OR "Chlorylen"[tw] OR "Chorylen"[tw] OR "Circosolv"[tw] OR "Crawhaspol"[tw] OR "Densinfluat"[tw] OR "Dow-tri"[tw] OR "Dukeron"[tw] OR "Ethene, 1,1,2-trichloro-"[tw] OR "Ethene, trichloro-"[tw] OR "Ethinyl trichloride"[tw] OR "Ethylene trichloride"[tw] OR "Ethylene, trichloro-"[tw] OR "Fleck-flip"[tw] OR "Flock FLIP"[tw] OR "Fluate"[tw] OR "Germalgene"[tw] OR "Lanadin"[tw] OR "Lethurin"[tw] OR "Narcogen"[tw] OR "Narkosoid"[tw] OR "Nialk"[tw] OR "Per-A-Clor"[tw] OR "Perm-A-chlor"[tw] OR "Petzinol"[tw] OR "Philex"[tw] OR "Threthylen"[tw] OR "Threthylene"[tw] OR "Trethylene"[tw] OR "Triasol"[tw] OR "Trichloraethylenum"[tw] OR "Trichloran"[tw] OR "Trichloren"[tw] OR "Trichlorethylene"[tw] OR "Trichlorethylenum"[tw] OR "Trichloroethene"[tw] OR "Trichloroethylene"[tw] OR "Tri-clene"[tw] OR "Trielene"[tw] OR "Trielin"[tw] OR "Trielina"[tw] OR "Trieline"[tw] OR "Triklone N"[tw] OR "Trilen"[tw] OR "Trilene"[tw] OR "Trimar"[tw] OR "Tri-plus"[tw] OR "Vestrol"[tw] OR "Vitran"[tw] OR "Westrosol"[tw] OR "1,1,2-Trichloroethene"[tw] OR "1,1,2-Trichloroethylene"[tw] OR "HCO 1120"[tw] OR "LPS HDX Heavy Duty Degreaser"[tw] OR "TCE (chlorohydrocarbon)"[tw] OR "TRICHLORAETHYLEN"[tw] OR "Trichlorethylen"[tw] OR "Triclene"[tw]) AND (2018/02/01:3000[mhda] OR 2018/02/01:3000[edat] OR 2018/02/01:3000[crdat]) AND (("Cardiotoxicity"[mh] OR "Cardiovascular Diseases"[mh] OR "Heart Function Tests"[mh] OR "Cardiovascular Physiological Phenomena"[mh] OR "Heart Disease Risk Factors"[mh] OR "aortic valve"[tw] OR "aortic valves"[tw] OR arrhythmi*[tw] OR "atria"[tw] OR "atrial"[tw] OR "atrioventricular"[tw] OR "atrium"[tw] OR "bradycardia"[tw] OR "bradycardias"[tw] OR "cardiac"[tw] OR cardial*[tw] OR cardio*[tw] OR "chest pain"[tw] OR "coronaries"[tw] OR "coronary"[tw] OR diastol*[tw] OR echocardiogram*[tw] OR "echocardiography"[tw] OR "ejection fraction"[tw] OR electrocardiogram*[tw] OR "electrocardiography"[tw] OR endocardi*[tw] OR endomyocardi*[tw] OR extrasystol*[tw] OR "fibrillation"[tw] OR "flutter"[tw] OR "heart"[tw] OR "heart ventricles"[tw] OR "hearts"[tw] OR "interatrial"[tw] OR "interventricular"[tw] OR ischaemi*[tw] OR ischemi*[tw] OR "mitral"[tw] OR myocardi*[tw] OR palpitation*[tw] OR pericardi*[tw] OR "pulmonary valve"[tw] OR "pulmonary valves"[tw] OR "SA node"[tw] OR "SA nodes"[tw] OR "sinoatrial"[tw] OR "sinus node"[tw] OR "sinus nodes"[tw] OR "sinus rhythm"[tw] OR "sinus rhythms"[tw] OR "stroke volume"[tw] OR "systole"[tw] OR "systoles"[tw] OR "systolic"[tw] OR "tachycardia"[tw] OR "tachycardias"[tw] OR "tricuspid valve"[tw] OR "tricuspid valves"[tw] OR "veno-occlusive"[tw] OR ventricle*[tw] OR "ventricular"[tw] OR "22q11 deletion syndrome"[tw] OR "adams-stokes syndrome"[tw] OR "alagille syndrome"[tw] OR "andersen syndrome"[tw] OR "aortic coarctation"[tw] OR "aortico-ventricular tunnel"[tw] OR "aortopulmonary septal defect"[tw] OR "aortopulmonary window"[tw] OR "barth syndrome"[tw] OR "bicuspid aortic valve disease"[tw] OR "brugada syndrome"[tw] OR "bundle-branch block"[tw] OR "carney complex"[tw] OR "cor triatriatum"[tw] OR "dextrocardia"[tw] OR "ebstein anomaly"[tw] OR "ebstein's anomaly"[tw] OR "ectopia cordis"[tw] OR "eisenmenger complex"[tw] OR "eisenmenger syndrome"[tw] OR "glycogen storage disease"[tw] OR "heterotaxy syndrome"[tw] OR "jervell-lange nielsen syndrome"[tw] OR "kartagener syndrome"[tw] OR "kearns-sayre syndrome"[tw] OR "leopard syndrome"[tw] OR "levocardia"[tw] OR "long qt"[tw] OR "lown-ganong-levine"[tw] OR "marfan syndrome"[tw] OR "noonan syndrome"[tw] OR "papillary fibroelastoma"[tw] OR "parasystol*"[tw] OR "patent ductus"[tw] OR "pneumopericardium"[tw] OR "pre-excitation"[tw] OR "preexcitation"[tw]

Table A-1. Database Query Strings

Database search date	Query string
	OR "premature contractions"[tw] OR "romano-ward syndrome"[tw] OR "sarcoglycanopathy"[tw] OR "sick sinus syndrome"[tw] OR "tetralogy of fallot"[tw] OR "transposition of great vessels"[tw] OR "transposition of the great vessels"[tw] OR "tricuspid atresia"[tw] OR "trilogy of fallot"[tw] OR "trisomy 13 syndrome"[tw] OR "trisomy 18 syndrome"[tw] OR "turner syndrome"[tw] OR "univentricular"[tw] OR "wolff-parkinson-white syndrome"[tw]) OR ("abnormalities"[sh] OR "congenital"[sh] OR "embryology"[sh] OR (Animals[mh] AND "growth and development"[sh]) OR "Congenital, Hereditary, and Neonatal Diseases and Abnormalities"[mh] OR "Embryonic and Fetal Development"[mh] OR "Embryonic Structures"[mh] OR "Maternal Exposure"[mh] OR "Paternal Exposure"[mh] OR "Prenatal Exposure Delayed Effects"[mh] OR "Teratogens"[mh] OR "Teratogenesis"[mh] OR "Child Development"[mh] OR "Adolescent Development"[mh] OR "Young Adult"[mh] OR "Adolescent"[mh] OR "Child"[mh] OR "Infant"[mh] OR "Pregnancy"[mh] OR "Pregnancy Complications"[mh] OR "Pregnancy Outcome"[mh] OR "Placenta"[mh] OR "Cell Proliferation"[mh] OR "Cell Differentiation"[mh] OR "Stem Cells"[mh] OR "Gene Expression Regulation, Developmental"[mh] OR "Epigenesis, Genetic"[mh] OR "Neurodevelopmental Disorders"[mh] OR "Neurologic Manifestations"[mh] OR "Growth Disorders"[mh] OR abnormalit*[tw] OR abort*[tw] OR adolescen*[tw] OR "birth"[tw] OR "child"[tw] OR "children"[tw] OR cleft*[tw] OR congenital*[tw] OR "defect"[tw] OR "defects"[tw] OR "development"[tw] OR developmental*[tw] OR embryo*[tw] OR fertil*[tw] OR fetal*[tw] OR fetus*[tw] OR foetal*[tw] OR foetus*[tw] OR infant*[tw] OR juvenile*[tw] OR malform*[tw] OR "maternal"[tw] OR neonat*[tw] OR newborn*[tw] OR "offspring"[tw] OR "paternal"[tw] OR perinatal*[tw] OR postnatal*[tw] OR pregnan*[tw] OR prenatal*[tw] OR steril*[tw] OR stillbirth*[tw] OR teratogen*[tw] OR wean*[tw] OR zygote*[tw] OR "cell proliferation"[tw] OR "cell differentiation"[tw] OR "stem cells"[tw] OR "gene expression"[tw]))
Toxcenter 8/2023	FILE 'TOXCENTER' ENTERED AT 16:19:08 ON 23 AUG 2023 L1 24408 SEA FILE=TOXCENTER 79-01-6 NOT PATENT/DT L2 2133 SEA FILE=TOXCENTER L1 AND ED>=20180201 L3 QUE "AORTIC VALVE" OR "AORTIC VALVES" OR ARRHYTHMI? OR "ATRIA" OR "ATRIAL" OR "ATRIOVENTRICULAR" OR "ATRIUM" OR "BRADYCARDIA" OR "BRADYCARDIAS" OR "CARDIAC" OR CARDIAL? OR CARDIO? L4 QUE "CHEST PAIN" OR "CORONARIES" OR "CORONARY" OR DIASTOL? OR ECHOCARDIOGRAM? OR "ECHOCARDIOGRAPHY" OR "EJECTION FRACTION" OR ELECTROCARDIOGRAM? OR "ELECTROCARDIOGRAPHY" L5 QUE ENDOCARDI? OR ENDOMYOCARDI? OR EXTRASYSTOL? OR "FIBRILLATIO N" OR "FLUTTER" OR "HEART" OR "HEART VENTRICLES" OR "HEARTS" OR "INTERATRIAL" OR "INTERVENTRICULAR" OR ISCHAEMI? OR ISCHEMI? OR "MITRAL" L6 QUE MYOCARDI? OR PALPITATION? OR PERICARDI? OR "PULMONARY VALVE" OR "PULMONARY VALVES" OR "SA NODE" OR "SA NODES" OR "SINOATRIAL" OR "SINUS NODE" OR "SINUS NODES" OR "SINUS RHYTHM" L7 QUE "SINUS RHYTHMS" OR "STROKE VOLUME" OR "SYSTOLE" OR "SYSTOLES" OR "SYSTOLIC" OR "TACHYCARDIA" OR "TACHYCARDIAS" OR

Table A-1. Database Query Strings

Database search date	Query string
	"TRICUSPID VALVE" OR "TRICUSPID VALVES" OR "VENO-OCCLUSIVE" OR VENTRICLE?
	L8 QUE "VENTRICULAR" OR "22Q11 DELETION SYNDROME" OR "ADAMS-STOKES SYNDROME" OR "ALAGILLE SYNDROME" OR "ANDERSEN SYNDROME" OR "AORTIC COARCTATION" OR "AORTICO-VENTRICULAR TUNNEL"\
	L9 QUE "VENTRICULAR" OR "22Q11 DELETION SYNDROME" OR "ADAMS-STOKES SYNDROME" OR "ALAGILLE SYNDROME" OR "ANDERSEN SYNDROME" OR "AORTIC COARCTATION" OR "AORTICO-VENTRICULAR TUNNEL"
	L10 QUE "AORTOPULMONARY SEPTAL DEFECT" OR "AORTOPULMONARY WINDOW" OR "BARTH SYNDROME" OR "BICUSPID AORTIC VALVE DISEASE" OR "BRUGADA SYNDROME" OR "BUNDLE-BRANCH BLOCK" OR "CARNEY COMPLEX"
	L11 QUE "COR TRIATRIATUM" OR "DEXTROCARDIA" OR "EBSTEIN ANOMALY" OR "EBSTEIN'S ANOMALY" OR "ECTOPIA CORDIS" OR "EISENMENGER COMPLEX" OR "EISENMENGER SYNDROME" OR "GLYCOGEN STORAGE DISEASE"
	L12 QUE "HETEROTAXY SYNDROME" OR "JERVELL-LANGE NIELSEN SYNDROME" OR "KARTAGENER SYNDROME" OR "KEARNS-SAYRE SYNDROME" OR "LEOPARD SYNDROME" OR "LEVOCARDIA" OR "LONG QT" OR "LOWN-GANONG -LEVINE"
	L13 QUE "MARFAN SYNDROME" OR "NOONAN SYNDROME" OR "PAPILLARY FIBROELASTOMA" OR "PARASYSTOL?" OR "PATENT DUCTUS" OR "PNEUMOPE RICARDIUM" OR "PRE-EXCITATION" OR "PREEXCITATION"
	L14 QUE "PREMATURE CONTRACTIONS" OR "ROMANO-WARD SYNDROME" OR "SARCOGLYCANOPATHY" OR "SICK SINUS SYNDROME" OR "TETRALOGY OF FALLOT" OR "TRANSPOSITION OF GREAT VESSELS" OR "TRANSPOSITION OF THE GREAT VESSELS"
	L15 QUE "TRICUSPID ATRESIA" OR "TRILOGY OF FALLOT" OR "TRISOMY 13 SYNDROME" OR "TRISOMY 18 SYNDROME" OR "TURNER SYNDROME" OR "UNIVENTRICULAR" OR "WOLFF-PARKINSON-WHITE SYNDROME" OR ABNORMALIT?
	L16 QUE ABORT? OR ADOLESCEN? OR "BIRTH" OR "CHILD" OR "CHILDREN"

Table A-1. Database Query Strings

Database search date	Query string
	OR CLEFT? OR CONGENITAL? OR "DEFECT" OR "DEFECTS" OR "DEVELOPME NT" OR DEVELOPMENTAL? OR EMBRYO? OR FERTIL? OR FETAL? OR FETUS? OR FOETAL?
	L17 QUE FOETUS? OR INFANT? OR JUVENILE? OR MALFORM? OR "MATERNAL" OR NEONAT? OR NEWBORN? OR "OFFSPRING" OR "PATERNAL" OR PERINATAL? OR POSTNATAL? OR PREGNAN? OR PRENATAL? OR STERIL?
	L18 QUE STILLBIRTH? OR TERATOGEN? OR WEAN? OR ZYGOTE? OR "CELL PROLIFERATION" OR "CELL DIFFERENTIATION" OR "STEM CELLS" OR "GENE EXPRESSION"
	L19 QUE L3 OR L4 OR L5 OR L6 OR L7 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18
	DIS COST
	L20 409 SEA FILE=TOXCENTER L2 AND L19
	L21 107 SEA FILE=TOXCENTER L20 AND MEDLINE/FS
	L22 302 SEA FILE=TOXCENTER L20 NOT MEDLINE/FS
	L23 199 DUP REM L22 L21 (103 DUPLICATES REMOVED)
	L*** DEL 107 S L25 AND MEDLINE/FS
	L*** DEL 107 S L25 AND MEDLINE/FS
	L24 107 SEA FILE=TOXCENTER L23
	L*** DEL 302 S L25 NOT MEDLINE/FS
	L*** DEL 302 S L25 NOT MEDLINE/FS
	L25 199 SEA FILE=TOXCENTER L23
	L26 199 SEA FILE=TOXCENTER (L24 OR L25) NOT MEDLINE/FS
	D SCAN L26

Table A-2. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView 8/2023	Compound searched: 79-01-6
NTP 8/2023	79-01-6 "Trichlorethylene" "Trichloroethene" "Trichloroethylene" "1,1-Dichloro-2-chloroethylene" "Acetylene trichloride" "Ethinyl trichloride" "Ethylene trichloride"
NTRL 8/2023	"1,1-Dichloro-2-chloroethylene" OR "1-Chloro-2,2-dichloroethylene" OR "Acetylene trichloride" OR "Algylen" OR "Anamenth" OR "Benzinol" OR "Blacosolv" OR "Blancosolv" OR "Cecolene" OR "Chlorilen" OR "Chlorylea" OR "Chlorylen" OR "Chorylen" OR "Circosolv" OR "Crawhaspol" OR "Densinfluat" OR "Dow-tri" OR "Dukeron" OR "Ethene, 1,1,2-trichloro-" OR "Ethene, trichloro-" OR "Ethinyl trichloride" OR "Ethylene trichloride" OR "Ethylene, trichloro-" OR "Fleck-flip" OR "Flock FLIP" OR "Fluate" OR "Germalgene" OR "Lanadin" OR "Lethurin" OR "Narcogen" OR "Narkosoid" OR "Nialk" OR "Per-A-Clor" OR

Table A-2. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"Perm-A-chlor" OR "Petzinol" OR "Philex" OR "Threthylen" OR "Threthylene" OR "Trethylene" OR "Triasol" OR "Trichloraethylenum" OR "Trichloran" OR "Trichloren" OR "Trichlorethylene" OR "Trichlorethylenum" OR "Trichloroethene" OR "Trichloroethylene" OR "Tri-clene" OR "Trielene" OR "Trielin" OR "Trielina" OR "Trieline" OR "Triklone N" OR "Trilen" OR "Trilene" OR "Trimar" OR "Tri-plus" OR "Vestrol" OR "Vitran" OR "Westrosol" OR "1,1,2-Trichloroethene" OR "1,1,2-Trichloroethylene" OR "HCO 1120" OR "LPS HDX Heavy Duty Degreaser" OR "TCE (chlorohydrocarbon)" OR "TRICHLORAETHYLEN" OR "Trichlorethylen" OR "Triclene"
Regulations.gov 8/2023	79-01-6 trichloroethylene trichloroethene
NIH RePORTER 8/2023	Search Criteria Fiscal Year: Active ProjectsText Search: "1,1-Dichloro-2-chloroethylene" OR "1-Chloro-2,2-dichloroethylene" OR "Acetylene trichloride" OR "Algylen" OR "Anamenth" OR "Benzinol" OR "Blacosolv" OR "Blancosolv" OR "Cecolene" OR "Chlorilen" OR "Chlorylea" OR "Chlorylen" OR "Chorylen" OR "Circosolv" OR "Crawhaspol" OR "Densinfluat" OR "Dow-tri" OR "Dukeron" OR "Ethene, 1,1,2-trichloro-" OR "Ethene, trichloro-" OR "Ethinyl trichloride" OR "Ethylene trichloride" OR "Ethylene, trichloro-" OR "Fleck-flip" OR "Flock FLIP" OR "Fluate" OR "Germalgene" OR "Lanadin" OR "Lethurin" OR "Narcogen" OR "Narkosoid" OR "Nialk" OR "Per-A-Clor" OR "Perm-A-chlor" OR "Petzinol" OR "Philex" OR "Threthylen" OR "Threthylene" OR "Trethylene" OR "Triasol" OR "Trichloraethylenum" OR "Trichloran" OR "Trichloren" OR "Trichlorethylene" OR "Trichlorethylenum" OR "Trichloroethene" OR "Trichloroethylene" OR "Tri-clene" OR "Trielene" OR "Trielin" OR "Trielina" OR "Trieline" OR "Triklone N" OR "Trilen" OR "Trilene" OR "Trimar" OR "Tri-plus" OR "Vestrol" OR "Vitran" OR "Westrosol" OR "1,1,2-Trichloroethene" OR "1,1,2-Trichloroethylene" OR "HCO 1120" OR "LPS HDX Heavy Duty Degreaser" OR "TCE (chlorohydrocarbon)" OR "TRICHLORAETHYLEN" OR "Trichlorethylen" OR "Triclene" (advanced)Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

APPENDIX B. SUPPLEMENTAL STUDIES

B.1 ADULT CARDIOTOXICITY

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B.2 OTHER ROUTE CARDIOTOXICITY

No studies matched this criterion.

B.3 MECHANISTIC

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B.4 SECONDARY SOURCE

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B.5 CONFERENCE ABSTRACT

No studies matched this criterion.

B.6 COMMENTARIES, LETTERS, OR ERRATUM

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