April 27, 2020

Comments from Academics, Scientists and Clinicians on the Draft Risk Evaluation for Trichloroethylene

Submitted online via *Regulations.gov* to docket EPA-HQ-OPPT-2019-0500

These comments are submitted on behalf of the undersigned academics, scientists, and clinicians. We declare collectively that we have no direct or indirect financial or fiduciary interest in any chemical or product that is the subject of these comments. The co-signers' institutional affiliations are included for identification purposes only and do not imply institutional endorsement or support, unless indicated otherwise.

We appreciate the opportunity to provide written comments on the draft risk evaluation for Trichloroethylene, issued under EPA's Toxic Substances Control Act (TSCA), as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act ("amended TSCA"). [1] Trichloroethylene is a solvent with both industrial and consumer uses, as a vapor degreaser, lubricant, adhesive, and as a spot cleaner. According to the draft risk evaluation, an estimated 83.6% of TCE's annual production volume is used as an intermediate in the manufacture of the hydrofluorocarbon, HFC-134a, an alternative to the refrigerant chlorofluorocarbon, CFC-12. [2] Several epidemiological studies of Trichloroethylene have consistently reported an increased incidence of birth defects in exposed populations, such as in Camp Lejune, North Carolina, where individuals were exposed to drinking water which had been primarily contaminated with Trichloroethylene. [3,4]

We have previously commented on EPA's inadequate scientific methods that have been implemented in the completed draft risk evaluations, and many of these continue to be present in this evaluation.[5,6,7] We again identify multiple flaws in EPA's systematic review methodology, including; its incomplete and non-transparent literature review practice; its unvalidated, non-empirically based scoring system used in the evaluation of data quality, which excludes a study based on only one 'unacceptable' metric; and its development of a new post hoc weight of evidence analysis employed against a single endpoint which EPA appears to single out throughout the draft risk evaluation. The Science Advisory Committee on Chemicals (SACC) has repeatedly provided comments and recommendations needed to improve the risk

[1] US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Available: EPA Document #740R18008

[2] Id. Page 28.

[3] Ruckart, P. Z., Bove, F. J., & Maslia, M. (2013). Evaluation of exposure to contaminated drinking water and specific birth defects and childhood cancers at Marine Corps Base Camp Lejeune, North Carolina: a case–control study. *Environmental Health*, *12*(1). doi: 10.1186/1476-069x-12-104

[4] Ruckart, P. Z., Bove, F. J., & Maslia, M. (2014). Evaluation of contaminated drinking water and preterm birth, small for gestational age, and birth weight at Marine Corps Base Camp Lejeune, North Carolina: a cross-sectional study. *Environmental Health*, *13*(1). doi: 10.1186/1476-069x-13-99

[5] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1-Bromopropane. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0053

[6] US EPA. (2019). Draft Toxic Substances Control Act (TSCA) Risk Evaluations and TSCA Science Advisory Committee on Chemicals (SACC) Meetings; Cyclic Aliphatic Bromide Cluster (HBCD) and 1,4-Dioxane; Notice of Availability and Public Meetings. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0059 and https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0056

[7] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Methylene Chloride. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, University of California, San Francisco (UCSF PRHE) et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0437-0069

evaluation process that echo the concerns we have raised in our previous comments, but the Trichloroethylene draft risk evaluation fails to reflect the SACC's recommended changes.[8, 9, 10] Therefore, EPA should incorporate the SACC recommendations and other scientifically based changes to comprehensively assess risks as required by law before finalizing the Trichloroethylene evaluation.

EPA also finds Trichloroethylene presents risks of concern for many conditions of use across workers, occupational non-users (ONUs), consumers, and bystanders.[11] However, we assert that critical scientific flaws in EPA's risk assessment approach led to underestimation of risk; the actual risks are of greater magnitude than that stated by EPA and additional conditions of use present unreasonable risks.

Our comments address the following main points:

1. **EPA's literature review step incorporates select best practices, but also falls short of, or is unclear about, many other best practices for conducting a systematic and transparent literature review.**
2. **EPA's scoring method wrongly downgrades or excludes a study based on a reporting deficiency, conflating how well a study is reported with how well the underlying research was conducted.**
3. **EPA's scoring method inappropriately excludes a study based on a "serious flaw," or one single reporting / methodological limitation.**
4. **EPA has employed a post hoc weight of evidence analysis against one single endpoint only.**
5. **EPA's rationale for changing the representative acute non cancer endpoint is unclear and inconsistent within the draft risk evaluation.**
6. **EPA's choice of a representative acute non cancer endpoint is less sensitive, less protective of vulnerable populations, nor consistent with best practices in scientific evaluation and use.**

We appreciate the opportunity to provide public input. Please do not hesitate to contact us with any questions regarding these comments.

Sincerely,

Swati Rayasam, MSc
Science Associate
Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Nicholas Chartres, PhD
Associate Research Scientist
Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

[8] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1-Bromopropane. 1-BP TSCA SACC Meeting Minutes Final Report. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

[9] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1, 4 Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD); SACC July 2019 Meeting Minutes and Final Report Docket. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0063

[10] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Methylene Chloride; MeCl Meeting Minutes Final Report 03/02/2020. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0437-0080

[11] US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 374. Available: EPA Document #740R18008

Tracey Woodruff, PhD, MPH
Director
Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

DETAILED COMMENTS

1. EPA's literature review step incorporates select best practices, but also falls short of, or is unclear about, many other best practices for conducting a systematic and transparent literature review.

We extensively commented before on the issues with the literature review step issues present in EPA's draft risk evaluation for Carbon Tetrachloride,[12] and these same issues carry through in both similar and different ways in the draft risk evaluation for Trichloroethylene. For example, in section 1.5.2 Data Evaluation in the Trichloroethylene Draft Risk Evaluation, EPA states:

"During the data evaluation stage, the EPA assesses the quality of the methods and reporting of results of the individual studies identified during problem formulation using the evaluation strategies described in Application of Systematic Review in TSCA Risk Evaluations (U.S. EPA, 2018b). ***The EPA evaluated the quality of the on-topic TCE study reports identified in [Trichloroethylene (CASRN 79-01-6) Bibliography: Supplemental File for the TSCA Scope Document; (U.S. EPA, 2017i)], and gave all studies an overall high, medium, low or unacceptable confidence rating during data evaluation****."*[13] (emphasis ours)

This indicates that the Agency evaluated **ALL** 'on topic' study reports in the cited bibliography. Looking to the Trichloroethylene Bibliography: Supplemental File for the TSCA Scope Document,[14] the document contains 49 pages of 'on topic' study reports for Human Health Hazards, with approximately 25 citations per page, totaling **approximately >1200 'on topic' study reports.**

However, in Figure 1-9 Literature Flow Diagram for Human Health Hazard in the draft risk evaluation shown below, [15] **EPA indicates that only 180 studies go through Data Evaluation, leaving over >1000 'on-topic' Trichloroethylene studies which have not been evaluated or accounted for by EPA.**

[12] US EPA. (2020). Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0499-0041

[13] US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 66. Available: EPA Document #740R18008

[14] US EPA. (2017). Trichloroethylene (CASRN 79-01-6) Bibliography: Supplemental File for the TSCA Scope Document; Available: https://www.epa.gov/sites/production/files/2017-06/documents/tce_comp_bib.pdf

[15] US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 66. Available: EPA Document #740R18008

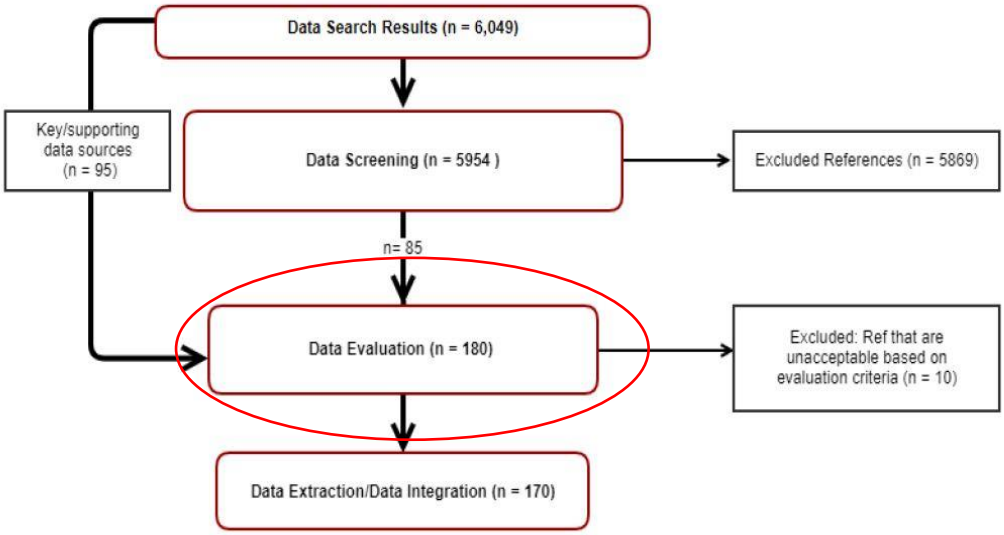

Figure 1-9. Literature Flow Diagram for Human Health Hazard

Of further concern, is the significant and problematic inconsistency between the number of studies included in the data evaluation step as recorded in the data evaluation supplemental files and those shown in the Flow Diagram 1-9 for Human Health Hazards above.

EPA states in the Trichloroethylene Draft Risk Evaluation that:

"Supplemental files also provide details of the data evaluations including individual metric scores and the overall study score for each data source (Docket: EPA-HQ-OPPT-2019-0500)."[16]

EPA goes on reference in a footnote to "See Appendix B for the list of all supplemental files."

In Appendix B EPA cites the following files for reference:

- Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies – Animal and Mechanistic Data [17] and
- Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies – Epidemiological Data[18]

According to EPA these files contain ALL of the included studies EPA evaluated for Human Health Hazards. However, there are 97 animal and 22 mechanistic (total-119) studies which go through Data Quality Evaluation in the first file,[19] and 96 Epidemiological studies that go through Data Quality

[16]US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 66. Available: EPA Document #740R18008

[17]US EPA. (2020). Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies – Animal and Mechanistic Data. Available: https://www.epa.gov/sites/production/files/2020-02/documents/14_tce-data_quality_evaluation_of_human_health_hazard_studies_-_animal_and_mechanistic_data.pdf

[18]US EPA. (2020). Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies – Epidemiological Data Available: ttps://www.epa.gov/sites/production/files/2020-02/documents/15_tce-data_quality_evaluation_of_human_health_hazard_studies_-_epidemiological_data.pdf

[19]US EPA. (2020). Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies – Animal and Mechanistic Data. Available: https://www.epa.gov/sites/production/files/2020-02/documents/14_tce-data_quality_evaluation_of_human_health_hazard_studies_-_animal_and_mechanistic_data.pdf

Evaluation in the second file. [20] This equals **215 studies** that EPA evaluated for quality in assessing Human Health Hazards, which is inconsistent with Figure 1-9 that shows 180 studies go through data evaluation.

Therefore, the above two cited files in Appendix B are missing almost 1000 'on-topic' study reports from the supplemental bibliography from the Trichloroethylene scoping document, and there are an additional 35 studies which go missing between the 215 study reports in the cited supplemental bibliographies for the draft risk evaluation, and the 180 studies referenced in Figure 1-9. Such inconsistencies are deeply concerning and threaten the validity of the draft risk evaluations.

Further, EPA's method to account for included studies in each step of the Literature Flow Diagram for Human Health Hazards above is inconsistent with its method on the previous page for Environmental Health Hazards as shown by the Literature Flow Diagram in Figure 1-8 below.

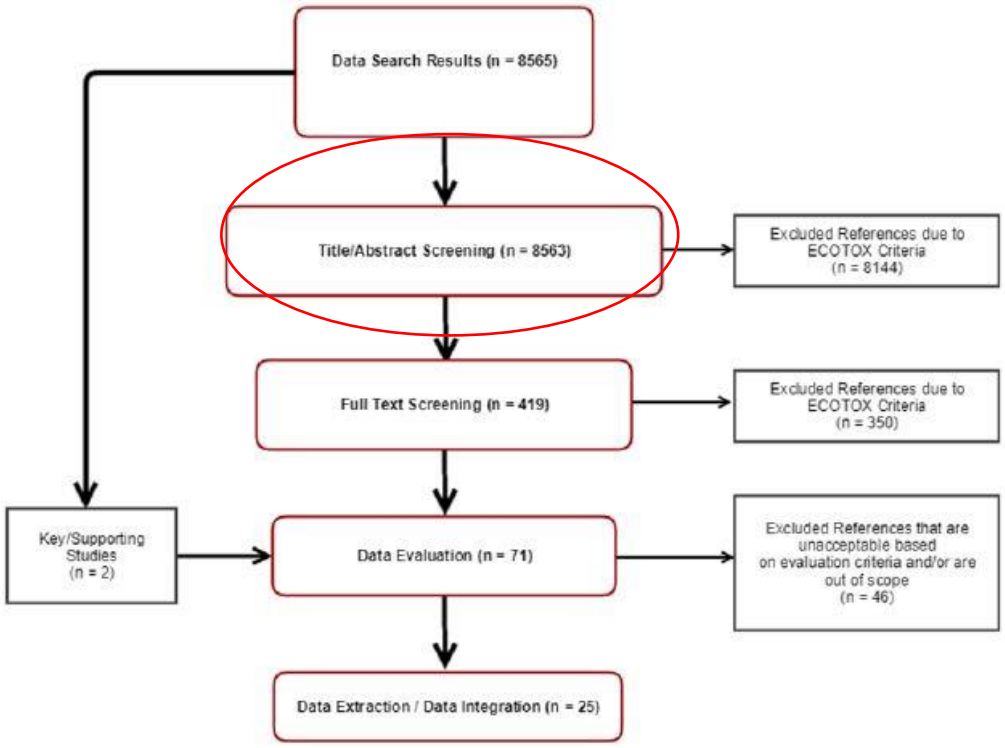

Figure 1-8. Literature Flow Diagram for Environmental Hazard

In Figure 1-8 EPA includes the **appropriate** additional step of reporting the number of studies screened at the 'Title/Abstract' stage and the number at the 'Full Text Screening' stage while Figure 1-9 (just one page below this figure) does not.[21] It is deeply concerning that, within the Trichloroethylene Draft Risk Evaluation, EPA uses two different approaches to report how included and excluded studies were

[20] US EPA. (2020). Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies – Epidemiological Data Available: ttps://www.epa.gov/sites/production/files/2020-02/documents/15_tce-data_quality_evaluation_of_human_health_hazard_studies_-_epidemiological_data.pdf

[21] US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 65. Available: EPA Document #740R18008

evaluated not only within a single evaluation, as shown by the Human Health Hazard example, but also between evaluations, as shown by the Environmental Health Hazard examples.

As we stated above, these issues are not restricted to the Trichloroethylene draft risk evaluation alone; these inconsistencies have been highlighted by EPA's own Peer Reviewers. The SACC Peer Review report of 1-BP commented that:

*"The Committee expected all of the quality sources identified in the SR would be used in the DRE and if not, that the general public would be able to follow the rationale as to why they were not used. The Committee generally concluded that it was difficult at best to determine exactly what was done during the SR…..**Committee members expressed that they experienced challenges in trying to follow the actions taken in the SR**, and how the results of the SR were used in the draft risk assessment."* [22] (emphasis ours)

Additionally, the SACC Peer Review report of 1, 4 Dioxane commented:

"The Evaluation flow charts suggest a full systematic review was performed, but the text describes a more limited review."[23]

2. EPA's scoring method wrongly downgrades or excludes a study based on a reporting deficiency, conflating how well a study is reported with how well the underlying research was conducted.

Studies can be scored as "low quality," and even excluded from EPA's review, based solely on a deficiency in reporting, irrespective of the quality of the underlying research. Study reporting addresses how well research findings are written up, i.e., whether there is a complete and transparent description of what was planned, what was done, what was found, and what the results mean. Guidelines and checklists such as the "Strengthening of Reporting of Observational Studies in Epidemiology" or "STROBE" Initiative have been developed for authors to help ensure all information pertinent to assessing the quality and meaning of research is included in the report.[24]

Although EPA has posted its "Updates to the Data Quality Criteria for Epidemiological Studies,"[25] the Agency's TSCA method still uses reporting measures in its scoring of the quality of human studies; this includes incorporating reporting guidelines into the rationales for scoring studies "low quality" (Metrics 1 and 15) or "unacceptable for use" (Metrics 3, 4, 6, 7). **EPA's TSCA method acknowledges that reporting is not the same as an underlying flaw in study methodology**, "The challenge, in many cases, is to distinguish a deficit in reporting from a problem in the underlying methodological quality of the

[22] US EPA. (2019). Peer Review for the United States Environmental Protection Agency (EPA) Draft Risk Evaluation for 1-Bromopropane (1-BP). Page. 22. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

[23] US EPA. (2019). Peer Review for EPA Draft Risk Evaluations for 1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD). Page. 32 Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0064

[24] See Strobe statement at: https://www.strobe-statement.org/index.php?id=strobe-aims

[25] US EPA. (2020). Risk Evaluation for Trichloroethylene Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies CASRN: 79-01-6. Available: https://www.epa.gov/sites/production/files/2020-02/documents/16_tce-updates_to_the_data_quality_criteria_for_epidemiological_studies.pdf

data/information source"[26] but then proceeds to ignore this distinction and use [27]OBJ

EPA's TSCA method also conflates reporting with quality by using metrics in the STROBE reporting guidelines to score individual studies in the TCE assessment. This is contrary to the recommendations given by the authors of the STROBE guidelines, who specifically note that the guidelines are not a measure of the quality of the underlying research. [28] Moreover, the Agency's inclusion of numerous reporting items irrelevant to bias in a quality scoring rule (e.g., an indicator of whether power calculations were reported), will disproportionately reduce some of the resulting scores and erroneously undervalue the study quality.[29]

3. EPA's scoring method inappropriately excludes a study based on a "serious flaw," or one single reporting / methodological limitation.

The use of a scoring system that excludes a study based on only one criterion/metric directly contradicts widely accepted empirically-based systematic review methodological approaches, such as the National Toxicology Programs's of Health Assessment and Translation (NTP OHAT) and the University of California, San Francisco Navigation Guide method, and it will almost certainly result in flawed conclusions and threaten the protection of the public's health. This approach is also inconsistent with TSCA mandates to use the "best available science" and "reasonably available information", while discussing its "strengths and limitations."[30]

Furthermore, there is no empirical evidence demonstrating how each ROB domain should be weighted[31] and the exclusion of studies based on an arbitrary rating of the evidence is not supported. It has also been empirically demonstrated overall "quality scores" are unable to distinguish between studies with a high or low ROB in meta-analyses.[32] [33]Thus, including only "high" quality studies may lead to a biased evaluation of the evidence, as there is no scientific justification for the use of overall quality scoring measures. If studies are to be excluded from a body of evidence, it is more appropriate to evaluate their influence on the overall effect estimates quantitatively using meta-analysis. Strategies including conducting sensitivity analyses which calculate overall effect estimates among high quality studies only or stratifying results based on overall study quality. Researchers may also choose to present all studies and qualitatively discuss the ROB using structured approaches, similar to OHAT and GRADE.[34]

In the "serious flaw" component of EPA's TSCA method scoring system, for each type of evidence stream, i.e., epidemiologic, animal, *in vitro*, etc., EPA created an arbitrary list of metrics, wherein if studies score poorly according to EPA on any single metric, they will "unacceptable for use in the hazard assessment," stating:

[26] EPA (2018) Application of Systematic Review in TSCA Risk Evaluations. Page 31.
[27] Id.
[28] Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M, Initiative. S. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg. 2014;12(12):1500-24. doi: 10.1016/j.ijsu.2014.07.014.
[29] Greenland S, O'Rourke K. On the bias produced by quality scores in meta-analysis, and a hierarchical view of proposed solutions. Biostatistics. 2001;2(4):463-71.
[30] 40 CFR 702.33
[31] Higgins JPT, Green S, Cochrane C. Cochrane handbook for systematic reviews of interventions. Chichester, England; Hoboken, NJ: Wiley-Blackwell; 2008.
[32] Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *Jama.* 1999;282(11):1054-1060.
[33] Jüni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. BMJ. 2001;323(7303):42-46.
[34] NTP. (2015). Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration. U.S. Dept. of Health and Human Services, National Toxicology Program.

> "*EPA/OPPT plans to use data with an overall quality level of High, Medium, or Low confidence to quantitatively or qualitatively support the risk evaluations, but does not plan to use data rated as Unacceptable.* ***Studies with any single metric scored as 4 will be automatically assigned an overall quality score of Unacceptable and further evaluation of the remaining metrics is not necessary****. An Unacceptable score means that* ***serious flaws*** *are noted in the domain metric that consequently make the data unusable (or invalid).*[35] (emphasis added)

There is no empirical basis for EPA's selected list of "serious flaws".

Illustrative of this "serious flaw" aspect of EPA' scoring system, for human epidemiologic studies in the TSCA Method (See Section H.5, Table H-8).[36] EPA lists six domains of study quality:

1. Study Participation;
2. Exposure Characterization;
3. Outcome Assessment;
4. Potential Confounding/Variable Control;
5. Analysis; and
6. Other Considerations for Biomarker Selection and Measurement.

In addition, it lists 22 metrics to assess the six domains. A study that has even one of the **19** "serious flaws" metrics is considered to be "unacceptable for use." However, EPA has since amended the number of metrics that can be rated as "unacceptable for use" with now 14 metrics, as shown in the "Updates to the Data Quality Criteria for Epidemiological Studies", in the draft risk evaluation for Trichloroethylene.[37] We strongly urge EPA removes the option to rate a study "Unacceptable" from every metric as the underlying assumptions of EPA's "serious flaws" metrics are not evidence-based, specifically:

- **EPA's list of "serious flaws" are not all equal indicators of study quality**:
    - For example, among human observational studies, any one of the 14 metrics listed in "Updates to the Data Quality Criteria for Epidemiological Studies", in the Draft Risk Evaluation for Trichloroethylene [38] can eliminate a study from consideration as EPA considers all of these "flaws" to be of equal importance.
- **EPA's list of "serious flaws" are not all related to real flaws in the underlying research**:
    - **Reporting** guidelines are wrongly equated with "serious flaws" in study quality.

      For example, in scoring the quality of human studies, 4 of 14 "serious flaw" metrics (Metrics 3, 4, 6, 7) are STROBE reporting guidelines (STROBE checklist items # 6, 7, 8, 15). **A study would be scored as "unacceptable for use" by EPA based on any one of these STROBE reporting guidelines.** As described above in Point 2, the STROBE guideline developers

[35] EPA (2018) Application of Systematic Review in TSCA Risk Evaluations. Page. 227.
[36] Id. Page 231.
[37] US EPA. (2020). Risk Evaluation for Trichloroethylene Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies CASRN: 79-01-6. Available: https://www.epa.gov/sites/production/files/2020-02/documents/16_tce-updates_to_the_data_quality_criteria_for_epidemiological_studies.pdf
[38] Id.

explicitly state this is neither the intended nor a scientifically valid use of these guidelines. [39] Given the historical and present-day deficiencies in how studies are reported in the peer-reviewed literature, and because EPA's scoring system rates as 'unacceptable for use' any human study that does not report even one of four reporting metrics, EPA's method could exclude an important portion of the existing body of knowledge on the impact of environmental chemicals on human health.

- **Analysis** is equated with a "serious flaw" in study quality, but statistical power[40] is not a valid measure of study quality and should not be used to disqualify studies from consideration.

  For example, as shown below in Metric 13 from "Risk Evaluation for Trichloroethylene Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies CASRN: 79-01-6", EPA's framework excludes cohort and cross-sectional studies if " The number of participants is inadequate to detect an effect in the exposed population and/or subgroups of the total population" or if the reported statistical power is not high enough (≥ 80%) to detect an effect in the exposure population and/or subgroups of the total population. [41]

EPA Metric 13. Excerpted from Risk Evaluation for Trichloroethylene Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies CASRN: 79-01-6

[39] Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M, Initiative. S. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg. 2014;12(12):1500-24. doi: 10.1016/j.ijsu.2014.07.014.

[40] A power calculation is an estimate of the size of the study population needed to detect an effect of a given size.

[41] US EPA. (2020). Risk Evaluation for Trichloroethylene Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies CASRN: 79-01-6. Available: https://www.epa.gov/sites/production/files/2020-02/documents/16_tce-updates_to_the_data_quality_criteria_for_epidemiological_studies.pdf

Metric 13. Statistical power (sensitivity)	
High (score = 1)	Do not select for this metric
Medium (score = 2)	• ***For cohort and cross-sectional studies:*** The number of participants are adequate to detect an effect in the exposed population and/or subgroups of the total population. **OR** • The paper reported statistical power high enough (≥ 80%) to detect an effect in the exposure population and/or subgroups of the total population. • ***For case-control studies:*** The number of cases and controls are adequate to detect an effect in the exposed population and/or subgroups of the total population. **OR** • The paper reported statistical power was high (≥ 80%) to detect an effect in the exposure population and/or subgroups of the total population.
Low (score =3)	• Do not select for this metric.
Unacceptable (score = 4)	• ***For cohort and cross-sectional studies:*** The number of participants are inadequate to detect an effect in the exposed population and/or subgroups of the total population. • ***For case-control studies:*** The number of cases and controls are inadequate to detect an effect in the exposed population and/or subgroups of the total population.
Not rated/applicable	• *Do not select for this metric*

EPA's Metric 13 statistical power/sensitivity confuses bias with imprecision. Individual studies that are "underpowered" (for example, because in the real world the exposed population may not be large enough for statistical purposes even if they are health-impacted) can still be potentially valuable to evidence-based decision-making. For example a small study may be imprecise but that should not be confused with whether it is biased;[42] a small study can be imprecise but at the same time less biased than a larger study.[43] Small "underpowered" studies can also be combined in a meta-analysis that increases the statistical power of the body of evidence to reflect the relationship between an exposure and a health impact. Additionally, "underpowered" studies that find a health effect to be present may be indicative of a larger effect size than anticipated; **omitting or downgrading such studies due to being underpowered would severely bias the conclusions of the review.**

EPA's own peer-review reports likewise recommend against this use of a "serious flaw" multiple times. The SACC Peer Review report of 1-BP commented that *"Several Committee members discussed in depth that it was not appropriate to determine an "unacceptable" rating during data quality evaluation based solely on one criterion."*[44] Additionally the SACC Peer Review report of 1, 4 Dioxane recommended that EPA *"…not be overly stringent and exclude studies based on a single criterion."*[45]

[42] Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [Updated March 2011]: The Cochrane Collaboration. Available from http://www.cochrane-handbook.org.; 2011.

[43] National Research Council. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: National Academies Press; 2014.

[44] US EPA. (2019). Peer Review for the United States Environmental Protection Agency (EPA) Draft Risk Evaluation for 1-Bromopropane (1-BP). Page. 21. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

[45] US EPA. (2019). Peer Review for EPA Draft Risk Evaluations for 1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD). Page. 38. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0064

We likewise recommend against EPA's use of a quantitative scoring method to assess quality in individual studies. The Agency should not be conflating study reporting with study quality; and it should not exclude otherwise quality research based on a single reporting or methodological limitationas recommended by its own SACC Peer Reviewers.

4. EPA has employed a post hoc weight of evidence analysis against one single endpoint only.

We have commented numerous times before that EPA has employed new methodologies in its draft risk evaluations, which have not been subject to peer-review nor public comment; specifically, the newly introduced Hierarchy of Preferences.[46,47,48, 49,50] In the draft risk evaluation for Trichloroethylene, EPA has continued this pattern and implemented an entirely new method (a weight of evidence analysis) to assess the human hazards of only one specific end point, congenital heart defects, which was identified as the most sensitive endpoint in the EPA TSCA Work Plan Chemical Risk Assessment. [51]

However, in the Hazards Section (Chapter 3) of the Draft Risk Evaluation, EPA states that:

> *"In previous assessments EPA concluded that the weight of evidence supports TCE exposure posing a potential hazard for congenital malformations, including cardiac defects in offspring (Makris et al., 2016; U.S. EPA, 2014b, 2011e). Given both the conflicting results and the publication of newer animal, epidemiological, and in vitro studies since the completion of the 2014 TCE Risk Evaluation, EPA re-evaluated the weight of evidence for congenital heart defects (see Section 3.2.4.1.6 and Appendix G)[52] …..After reviewing a sampling of recent literature on systematic approaches to performing weight-of-evidence evaluation, EPA adopted the methodology described in [Weight of Evidence in Ecological Assessment. Risk Assessment Forum. EPA/100/R16/00. (U.S. EPA, 2016i)], which advocates presenting evidence on a semiqualitative scale on the basis of three evidence areas: reliability, outcome/strength, and relevance (see Appendix G.2.1 for more details on selection of approach and methodological details)."*[53]

While we commend EPA for attempting to use a more transparent and detailed approach to first evaluate the quality of the evidence for each evidence stream and then integrate it, the post hoc

[46] US EPA. (2019). Draft Toxic Substances Control Act (TSCA) Risk Evaluations and TSCA Science Advisory Committee on Chemicals (SACC) Meetings; Cyclic Aliphatic Bromide Cluster (HBCD) and 1,4-Dioxane; Notice of Availability and Public Meetings. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0059 and https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0056

[47] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1-Bromopropane. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0053

[48] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Methylene Chloride. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, University of California, San Francisco (UCSF PRHE) et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0437-0069

[49] US EPA. (2020). Comment submitted by Veena Singla, Associate Director, Program on Reproductive Health and the Environment, School of Medicine, University of California, San Francisco. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0236-0040

[50] US EPA. (2020). Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0499-0041

[51] US EPA. (2014). TSCA Work Plan Chemical Risk Assessment Trichloroethylene: Degreasing, Spot Cleaning and Arts & Crafts Uses. Page 97. Available: https://www.epa.gov/sites/production/files/2014-11/documents/tce_opptworkplanchemra_final_062414.pdf

[52] US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page. 217. Available: EPA Document #740R18008

[53] Id. Page 223.

method chosen by EPA is unvalidated, not empirically based, has not been subject to peer review nor public comment, and falls short of the best practice methods in systematic review methods – which is the codified approach that EPA must take for risk evaluations.

For example, for the metric of 'reliability,' which EPA defines as "inherent properties that make evidence convincing…this refers primarily to aspects of study design, execution, and transparency," instead of looking at the overall study quality evaluations already completed by EPA for Trichloroethylene, as would be normal practice when assessing the influence of risk of bias on the quality/certainty of a body of evidence, EPA states that:

> "*In contrast to the study quality evaluations performed in Distiller, which included >20 specific quality criteria for each study, here each study was given only a single overall grade. We considered the same issues, but we did not formally go through and assign grades on each one individually. Instead, focus was on key attributes. Noteworthy deficiencies were recorded and grades were assigned based on the number and nature of the specific deficiencies identified."* [54]

This is inconsistent with how the quality of the evidence should be evaluated based on the overall risk of bias of the included studies (or study quality in the case of the draft risk evaluations conducted under TSCA by EPA). Additionally, EPA is not clear in its definition of these referenced 'key attributes' which lead to a higher score for metrics such as reliability. [55]

Further, there is no empirical basis for the "grades assigned based on the number and nature of the specific deficiencies identified." Despite its attempt to be more rigorous and transparent, EPA has continued its pattern of creating a method that is incompatible with best practice, post hoc. In its attempt to identify this new method for the data integration step for congenital heart defects in the Trichloroethylene Draft Risk Evaluation, EPA states that:

> "EPA identified, collected and reviewed a sampling of recent literature on systematic approaches to performing weight-of-evidence evaluation. Relevant articles were identified by simple Google searches and by tree searching references listed in these publications. References included the following" [56]

References included the 'NTP 2015 Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration (NTP, 2015).' [57] However, despite identifying this method, EPA chose not to use it, opting instead for an adapted ecological assessment over the OHAT Approach, a validated method recommended by its own SACC peer reviewers[58] and the NAS.[59]

[54]US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 612. Available: EPA Document #740R18008

[55]Id. Page 615.

[56]US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page. 610 Available: EPA Document #740R18008

[57]Id.

[58] US EPA. (2019). Peer Review for EPA Draft Risk Evaluations for 1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD). Page 150. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0064

[59] National Research Council. (2014). Review of EPA's Integrated Risk Information System (IRIS) Process. Page 105. Washington, DC: The National Academies Press; 2014.

EPA has not rated the confidence in the body of evidence in any of the draft risk evaluations it has completed to date, nor has it implemented a predefined evidence integration step to come to its final conclusion on whether the chemical being assessed poses an unreasonable risk for certain conditions of use. Therefore, how EPA translates the available evidence into its final conclusion is unclear and unjustified by the Agency. We strongly recommend that EPA use the validated, peer review method of NTP OHAT, which they have cited in the Trichloroethylene Draft Risk Evaluation and is consistent with best practice, for the evidence integration step in all risk evaluations it conducts. This method will allow EPA to transparently demonstrate the process for how the conclusions are reached in assessing human health hazards for each end point it assesses.

5. EPA's rationale for changing the representative acute non cancer endpoint is unclear and inconsistent within the draft risk evaluation.

Throughout the draft risk evaluation for Trichloroethylene, we found scientifically unsupported, unclear, and internally inconsistent statements around the evidence base for fetal cardiac defects and EPA's choice of representative acute non cancer endpoint.

In the both the IRIS Assessment for Trichloroethylene and the 2014 TSCA Work Plan Chemical Risk Assessment, fetal cardiac defects observed after developmental Trichloroethylene exposure in animal studies was identified as the most sensitive acute developmental toxicity endpoint, [60,61] bolstered by the Johnson (2003) study and subsequent communications. Chapter 3 of the draft risk evaluation for Trichloroethylene also itself identifies this endpoint as important stating that *"based on the hazard findings from reviewing the reasonably available literature for **this assessment**, which conclude that developmental toxicity is among the most sensitive acute health effects associated with TCE exposure."* [62] (emphasis ours) Chapter 3 of the draft risk evaluation also names the Johnson (2003) and Dawson (1993) studies in particular as "key" animal studies for the fetal cardiac defects endpoint in addition to multiple key epidemiological studies which have "identified statistically significant increased risk of developmental cardiac defects following TCE exposure," [63] and mechanistic studies which have "identified an association between TCE exposures and cardiac defects in the developing embryo and/or fetus (U.S. EPA, 2011e)," [64] and "provided strong and consistent supporting information for effects of TCE and metabolites on cardiac development and precursor effects." [65]

However, EPA writes in its risk determination (Chapter 5) that the evidence base provided by the Johnson et al. (2003) study and additional animal, epidemiological and mechanistic data, contains uncertainties which decrease EPA's confidence in the endpoint of fetal cardiac defects. However, this is not consistent with previous authoritative evaluations of the scientific evidence which determined that fetal cardiac defects are the most sensitive endpoint for risk assessment, nor is it consistent with the hazards section (Chapter 3) of EPA's own draft risk evaluation for Trichloroethylene. [66] These rationales

[60] US EPA. (2014). TSCA Work Plan Chemical Risk Assessment Trichloroethylene: Degreasing, Spot Cleaning and Arts & Crafts Uses. Page 97. Available: https://www.epa.gov/sites/production/files/2014-11/documents/tce_opptworkplanchemra_final_062414.pdf

[61] US EPA. (2011). TOXICOLOGICAL REVIEW OF TRICHLOROETHYLENE (CAS No. 79-01-6), In Support of Summary Information on the Integrated Risk Information System (IRIS). Page xliii. Available: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0199tr/0199tr.pdf

[62] US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 234. Available: EPA Document #740R18008

[63] Id. Page 216.

[64] Id.

[65] Id. Page 223.

[66] Id. Page 377.

are unclear and there are clear inconsistencies between the summary statements and the body of the evaluation.

EPA's previous claims in its IRIS Assessment and TSCA Work Plan, and current claims in Chapter 3 of the Draft Risk Evaluation (Hazards), find that the fetal cardiac defects endpoint was the most sensitive (thus should be chosen as the representative non cancer endpoint), and the support of animal, epidemiological and mechanistic data. However, Chapter 5 of the Draft Risk Evaluation (Risk Determination) rewrites the scientific evaluation of fetal cardiac defects, claiming that there are uncertainties which decrease EPA's confidence in this endpoint. [67] This internal inconsistency and rewrite of the scientific evaluation suggests that there may have been some type of interference in this document. [68]

Not only is Chapter 3 (Hazards) in conflict with Chapter 5 (Risk Determination), it is also in conflict with itself *within Chapter 3* of the Draft Risk Evaluation for Trichloroethylene.

On page 257, regarding the developmental endpoints presented by Johnson, EPA states that *"Confidence is reduced from a high due to the data quality scores, the wide range of PODs, and controversy over the most sensitive POD, from (Johnson et al., 2003). For developmental endpoints, there is some uncertainty extrapolating from chronic developmental toxicity studies to acute exposure, especially in assuming a consistent dose-response…Confidence is raised from the robust WOE analysis performed on the congenital heart defects endpoint (see Appendix G), the presence of a variety of endpoints including a study using acute TCE administration, and reduced uncertainty factors due to the use of a PBPK model or allometric scaling."* [69]

However, **in the next line**, EPA chooses the immunosuppression endpoint proposed by Selgrade and Glimour 2010, without justification for why the fetal cardiac defects endpoint was insufficient to serve as the representative endpoint despite just stating that " confidence is *raised from the robust WOE analysis performed on the congenital heart defects endpoint"*

The Agency asserts in the Trichloroethylene draft risk evaluation that the data for fetal cardiac defects is not robust enough to represent acute non cancer endpoints and instead chooses immunosuppression as the sensitive endpoint for acute inhalation and dermal exposures as it is "…considered to be the most robust and best representative POD for acute non cancer scenarios." [70] Although EPA indicates that the endpoint of fetal cardiac defects was not sufficiently robust and thus not a good candidate as the noncancer endpoint for Trichloroethylene, this is inconsistent with its IRIS Assessment which found that regarding fetal cardiac defects, "[t]here is high confidence in these noncancer reference values, as they are supported by moderate-to-high confidence estimates for multiple effects from multiple studies."[71] and the fact that EPA itself states " confidence is *raised from the robust WOE analysis performed on the congenital heart defects endpoint"* There is also no definition of 'robust'. Further, individual studies

[67] US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 377. Available: EPA Document #740R18008

[68] Shogren, E., & Center for Investigative Reporting. (2020, February 29). EPA scientists found a toxic chemical damages fetal hearts. The Trump White House rewrote their assessment. Retrieved from https://www.revealnews.org/article/epa-scientists-found-a-toxic-chemical-damages-fetal-hearts-the-trump-white-house-rewrote-their-assessment/

[69] US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 257. Available: EPA Document #740R18008

[70] Id.

[71] US EPA. (2011). TOXICOLOGICAL REVIEW OF TRICHLOROETHYLENE (CAS No. 79-01-6), In Support of Summary Information on the Integrated Risk Information System (IRIS). Page xliii. Available: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0199tr/0199tr.pdf

should be carried forward to and evaluated in the context of the other streams of evidence, in this case human and mechanistic evidence. Further, the Johnson study is rated Medium quality, making it credible for further evaluation in the risk evaluation. (Point 6)

On page 215 of the draft risk evaluation, in reference to its literature search, EPA indicated that "*For congenital heart defects, EPA evaluated more recent epidemiological studies, mechanistic studies, and a single experimental animal study that provide conflicting evidence for this endpoint."* [72] However, when looking to the newly added information on fetal cardiac defects, the draft risk evaluation seems to rely heavily on an analysis focused on data quality reliability through a Risk of Bias Assessment (Wikoff, 2018), and the experimental animal study by Charles River Laboratories (2019).

Wikoff et al. (2018)

With regard to the Wikoff study, EPA itself notes that the study "*did not evaluate any mechanistic data, which may explain the different overall conclusions between that study and this analysis."* [73] This is troubling for two reasons.

First, Wikoff's lack of consideration of mechanistic studies removes from its evidence base " *In vivo* animal studies in rats and chicks [which] have identified an association between TCE exposures and 1016 cardiac defects in the developing embryo and/or fetus (U.S. EPA, 2011e)" [74] and "provided strong and consistent supporting information for effects of TCE and metabolites on cardiac development and precursor effects." [75] This indicates that the study conclusions for Wikoff likely underestimates risk by excluding this key base of evidence.

Second, in the draft risk evaluation EPA indicates that this lack of mechanistic data may "explain the different overall conclusions between that study and this analysis," which seems to imply that the analysis for the draft risk evaluation showed a positive association between Trichloroethylene and fetal cardiac defects in comparison to Wikoff's negative association, which is contrary to the summary statements regarding this endpoint. [76] This rationale is internally inconsistent, may be a result of interference,[77] and as we outline in Point 1, threatens the validity of the draft risk evaluation.

Fisher et al. (2001) and Charles River Laboratories (2019)

Regarding animal studies, the draft risk evaluation outlines that *"scientific literature also has examples of relatively well-conducted studies in rats and mice that did not observe an increase in TCE-induced cardiac malformations,"* [78] citing Fisher et al (2001) and Carney et al (2006) and referencing the new study (Charles River Laboratories, 2019).

[72]US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 215. Available: EPA Document #740R18008

[73]Id. Page 223.

[74]Id. Page 216.

[75]US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 223. Available: EPA Document #740R18008

[76]Id. Page 377.

[77] Shogren, E., & Center for Investigative Reporting. (2020, February 29). EPA scientists found a toxic chemical damages fetal hearts. The Trump White House rewrote their assessment. Retrieved from https://www.revealnews.org/article/epa-scientists-found-a-toxic-chemical-damages-fetal-hearts-the-trump-white-house-rewrote-their-assessment/

[78]US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 216. Available: EPA Document #740R18008

However, the Agency goes on to note that while Fisher et al (2001) *"did not report statistically-significant increases in combined cardiac and cardiovascular effects, there was a very high background incidence of cardiovascular defects in soybean oil-control rats and the authors did observe a 19% increase in cardiac-specific defects (per-1033 litter, significance not calculated) following TCE treatment compared to controls."* [79] This is troubling for a few reasons. EPA's specific language that the Fisher et al. study did not find a *statistically significant* risk is correct. The study did however find **an elevated risk**, reporting that "[t]he rate of heart malformations ranged from 3% to 5% across the TCE, TCA, and DCA dose groups…on a per fetus basis. On a per litter basis, the rate of heart malformations for TCE, TCA, and DCA ranged from 42% to 60%."[80] The risk for fetal cardiac defects may not have been statistically significant, however that is not the same as finding no elevated risk. Second, the high background incidence in the soybean oil control, as identified by both the study authors and again by EPA in this draft risk evaluation, likely resulted in less statistical power to detect the risk which would lead to an underestimation of risk. Third, EPA cites that Fisher et al.. *"did not identify a statistically significant increase in cardiac defects following TCE administration at a high dose via gavage, [it] identified a significant number of additional defects that match those identified in (Johnson et al., 2003) and (Dawson et al., 1993) (including atrial septal and valve defects),"* [81] indicating that while the study may not have been entirely consistent with previous studies on the particular endpoint of fetal cardiac defects, it was in agreement on other defects, meaning it was not as contrary to the Johnson et al (2003) study as certain parts of the draft risk evaluation indicated.

With regard to the Charles River Laboratories (2019) study, EPA found that despite being the only additional animal study in the updated literature search, the "methodology was likely of reduced sensitivity" [82] and it *"was not considered a close enough replication to (Johnson et al., 2003) to sway the weight of evidence for the endpoint on it's own,"* [83] and *"insufficiently replicates the methodology of (Johnson et al., 2003)."* [84] This led EPA to conclude that the results of the Charles River Laboratories (2019) study do not entirely contradict the conclusions of Johnson et al. (2003). Thus, the Agency incorporated it along with other studies into a post hoc weight of evidence analysis methodology. (Point 4)

Despite the above evidence, and EPA's statement that the Charles River Laboratories (2019) study did not sway the weight of evidence for the endpoint on its own, it is unclear how exactly EPA arrived at its conclusion to discard the previously established endpoint of fetal cardiac defects. We recommend that EPA base its decisions on its previous assessments for Trichloroethylene, as would be normal practice rather than this new unvalidated post hoc method. [85,86]

[79] US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 217. Available: EPA Document #740R18008

[80] Fisher, J. W., Channel, S. R., Eggers, J. S., Johnson, P. D., Macmahon, K. L., Goodyear, C. D., … Graeter, L. J. (2001). Trichloroethylene, Trichloroacetic Acid, and Dichloroacetic Acid: Do They Affect Fetal Rat Heart Development? *International Journal of Toxicology*, *20*(5), 257–267. doi: 10.1080/109158101753252992

[81] US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 223. Available: EPA Document #740R18008

[82] Id. Page 222.

[83] Id. Page 223.

[84] Id.

[85] US EPA. (2014). TSCA Work Plan Chemical Risk Assessment Trichloroethylene: Degreasing, Spot Cleaning and Arts & Crafts Uses. Page 97. Available: https://www.epa.gov/sites/production/files/2014-11/documents/tce_opptworkplanchemra_final_062414.pdf

[86] US EPA. (2011). TOXICOLOGICAL REVIEW OF TRICHLOROETHYLENE (CAS No. 79-01-6), In Support of Summary Information on the Integrated Risk Information System (IRIS). Page xliii. Available: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0199tr/0199tr.pdf

Yauck et al. (2004)

EPA is inconsistent with its reporting of study conclusions throughout the draft risk evaluation; one example in particular is the Yauck et al. (2004) study.

On page 215, EPA outlines that "Yauck et al. (2004) observed a **strong relative risk estimate** for cardiac malformations in infants from Milwaukee, Wisconsin born to TCE-exposed mothers aged 38 years or older. In addition to older age, increased risk was also independently associated with other confounders including alcohol use, hypertension, and diabetes," however on the next page, EPA indicates that the Yauck conclusions are "equivocal." [87] (emphasis ours)

Later in the weight of evidence analysis, it calls the Yauck conclusions ambiguous, because it *"reported a positive association between congenital heart defects and TCE exposure **only** in older mothers, while younger mothers and the overall population had a null association."* [88] (emphasis ours) First, this interpretation of the conclusions do not take into account that Yauck et al. (2004) also found independent associations with other risk factors though, like alcohol use, hypertension, and diabetes. Second, earlier in the draft risk evaluation, EPA noted that:

"*Among life stages, the most susceptible is likely to be pregnant women and their developing fetus based on the hazard findings from reviewing the reasonably available literature for this assessment, which conclude that developmental toxicity is among the most sensitive acute health effects associated with TCE exposure. Among pregnant women, older women may be especially susceptible to TCE-induced cardiac defects in their offspring. Maternal age is known to have a large influence on the incidence of congenital heart defects,"* [89]

These inconsistencies threaten the validity of the draft risk evaluation and appear to incorrectly downplay the strength of the fetal cardiac defect endpoint in support of an immunosuppression endpoint whose POD is orders of magnitude less protective.

6. EPA's choice of a representative acute non cancer endpoint is less sensitive, less protective of vulnerable populations, nor consistent with best practices in scientific evaluation and use.

In the Draft Risk Evaluation, EPA chose to rely upon immunosuppression for acute inhalation and dermal exposures as the "…the POD for mortality due to immunosuppression from (Selgrade and Gilmour, 2010) is considered to be the most robust and best representative POD for acute non cancer scenarios," [90] however it fails to sufficiently detail what makes this choice of endpoint more robust and best representative.

As we previously stated, this choice of acute noncancer endpoint is also in contrast to EPA's IRIS Assessment for Trichloroethylene, which outlined its "…RfD for noncancer effects of 0.0005 mg/kg/day is based on the critical effects of heart malformations… There is high confidence in these noncancer

[87] US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 217. Available: EPA Document #740R18008
[88] Id. Page 614.
[89] Id. Page 234.
[90] Id. Page 257.

reference values, as they are supported by moderate-to-high confidence estimates for multiple effects from multiple studies."[91]

Table 3-7 in the draft risk evaluation below places the two studies of interest side by side, outlining the dose-response analysis for acute exposure scenarios. [92]

2030 **Table 3-7: Dose-response analysis of selected studies considered for acute exposure scenarios**

Target Organ/ System	Species	Duration	POD Type [1] (applied dose)	Effect	Dose Metric	HEC_{50} (ppm)	HEC_{99} (ppm)	HED_{50} (mg/kg)	HED_{99} (mg/kg)	Uncertainty Factors (UFs) [2]	Reference	Data Quality [3]
Develop-mental Effects	Rat (female)	Gestational days 6 to 15	$BMDL_{01}$= 32.2 mg/kg-bw/day	Increased resorptions	TotMetab BW34	57	23	29	28	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; Total UF=10	(Narotsky et al., 1995)	High (1.3)
	Rat (female)	22 days throughout gestation (gestational days 0 to 22)	$BMDL_{01}$ = 0.0207 mg/kg-bw/day	Congenital heart defects	TotOx Metab BW34	0.012	0.0037	0.0058	0.0052	UF_S=1; UF_A= 3; UF_H=3; UF_L=1; Total UF=10	(Johnson et al., 2003)	Medium (1.9)
	Rat (male pups)	Postnatal days 10 to 16	LOAEL = 50 mg/kg-bw/day	Decreased rearing activity	TotMetab BW34	8	3	4.2	4.1	UF_S=1; UF_A= 3; UF_H=3; UF_L=10; Total UF=100	(Fredriksson et al., 1993)	Medium (1.7)
Immune System	Rat (female)	3hr/day, single dose; followed by respiratory infection	$BMDL_{01}$ = 13.9 ppm	Immuno-suppression	N/A[4]	N/A[4]	1.74[4]	N/A[4]	2.74[4,5]	UF_S=1; UF_A= 3; UF_H=10; UF_L=1; *Total UF=30*	(Selgrade and Gilmour, 2010)	High (1.6)

[1] POD type can be NOAEL, LOAEL, or BMDL. EPA adjusted all values to continuous exposure.
[2] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF.
[3] See [*Data Quality Evaluation of Human Health Hazard Studies. Docket: EPA-HQ-OPPT-2019-0500]* for full evaluation by metric.
[4] Data from Selgrade and Gilmour, 2010) was not subject to PBPK modeling due to uncertainty concerning the most appropriate dose metric. The BMDL value adjusted for a 24hr exposure will be used as the POD for occupational risk estimates, while the 3hr value will be used for consumer risk estimates. This value is presented in the HEC_{99} column but does not represent any particular percentile since it was not PBPK-modeled.
[5] A dermal HED was obtained through route-to-route extrapolation using breathing rate and body weight data on male CD-1 mice (insufficient female data was reasonably available) from (U.S. EPA, 1988) and allometric scaling based on (U.S. EPA, 2011d) using a dosimetric adjustment factor of 0.14 for mice.

As shown by the Table, the POD for the chosen endpoint from the Selgrade and Glimour (2010) study is 13.9ppm after a single exposure of 3hr/day, in comparison to the much lower POD from the Johnson (2003) study of 0.0207 mg/kg-bw/day administered throughout the early gestational period. Additionally, in reference to the Data Quality Scores, there is **only 0.3 difference** in the score between the Selgrade and Glimour study (1.6) and the Johnson study (1.9). While we find these scores to be arbitrary and capricious (Point 2 and 3), EPA has failed to justify why it is unable to use the POD for fetal cardiac defects, which is orders of magnitude more protective than the immunosuppression endpoint, as its representative acute non cancer endpoint.

If EPA were to pursue the representative endpoint of immunosuppression, the Agency would be allowing acute exposures that are significantly greater than the POD for fetal cardiac defects. Especially considering the Johnson (2003) study "*reported a statistically and biologically significant increase in the formation of heart defects at the 0.048 mg/kg-bw/day and higher dose levels (concentrations of 0, 0.00045, 0.048, 0.218 or 129 mg/kg-bw/day) measured on both an individual fetus basis and a litter basis."*[93] While the Agency still concluded that Trichloroethylene presented an unreasonable risk for

[91] US EPA. (2011). TOXICOLOGICAL REVIEW OF TRICHLOROETHYLENE (CAS No. 79-01-6), In Support of Summary Information on the Integrated Risk Information System (IRIS). Page xliii. Available: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0199tr/0199tr.pdf
[92] US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 238. Available: EPA Document #740R18008
[93] US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 236. Available: EPA Document #740R18008

many conditions of use, if it were to employ the more sensitive endpoint it would have resulted in more protective unreasonable risk determinations for workers, occupational non-users, consumers and bystanders.

Choosing an immune endpoint would also fail to account for the particular sensitivity represented by developmental endpoints, as "…*certain developmental effects may result from* ***a single exposure during a critical window of development*** *(Davis et al., 2009; Van Raaij et al., 2003). This is consistent with EPA's Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996) and Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991), which state that repeated exposure is not a necessary prerequisite for the manifestation of developmental toxicity.* ***This is a health protective assumption****."*[94] (emphasis ours)

Choosing to use the immunosuppression endpoint in comparison to the fetal cardiac defect endpoint means discarding a more sensitive endpoint that has evidence of hazard to human health and which accounts for potentially exposure to susceptible subpopulations, such as fetuses, pregnant women, infants, and children. Considering the disparities between PODs for the two endpoints and the potential human health ramifications due to this inadequately representative non cancer endpoint for Trichloroethylene, the Agency should use fetal cardiac defects as the basis of the noncancer acute health effects and the subsequent risk assessment.

EPA needs to give deference to the nature of this endpoint, and the sensitive nature in particular as it impacts a vulnerable developmental period (fetuses and pregnant women). This is particularly relevant as EPA's has a mandate under TSCA to ensure the protection of vulnerable populations such as these from unreasonable risks.[95]

[94]US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 257. Available: EPA Document #740R18008

[95] TSCA§ 6(b)(4)