December 15, 2023

Comments from Scientists, Academics, and Clinicians on the Trichloroethylene Rulemaking under TSCA section 6(a)

Submitted online via Regulations.gov to docket EPA-HQ-OPPT-2020-0642

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 proposed risk management rule ("Proposed Rule") for trichloroethylene ("TCE"),[1] issued under EPA's Toxic Substances Control Act ("TSCA"). TCE is a solvent with both industrial and consumer uses, as a vapor degreaser, lubricant, adhesive, and as a spot cleaner. An estimated 83.6% of TCE's annual production volume is used as an intermediate in the manufacture of the hydrofluorocarbon refrigerant HFC-134a.[2] Hazards of TCE include cancer, immune effects, reproductive and developmental effects, kidney toxicity, liver toxicity, and neurotoxicity. Epidemiological studies of TCE have consistently reported an increased incidence of birth defects in exposed populations, such as in Camp Lejeune, North Carolina, where individuals were exposed to drinking water contaminated with TCE.[3,4]

EPA previously found that TCE presents unreasonable risks to human health due to high exposures to workers and consumers from a broad range of TCE conditions of use,[5] and is therefore required under TSCA section 6(a)to issue a rule applying requirements "so that the chemical…no longer presents such risk."[6] EPA has now proposed to prohibit all manufacture, importation, processing and distribution in commerce of TCE, including for consumer uses, as well as a prohibition on all industrial and commercial uses. For many conditions of use, prohibitions would be effective in one year, while specified industrial and commercial uses may continue for several years, subject to implementation of a Workplace Chemical Protection Program ("WCPP"). EPA states that the WCPP would not be sufficient to eliminate unreasonable risk and that prohibition of all uses is necessary to meet the requirements of TSCA. Although worker protections are proposed for those uses subject to extended phaseout periods, EPA has not proposed any measures to protect residents of fenceline communities located adjacent to TCE-emitting facilities from elevated risks.

[1] Trichloroethylene (TCE); Regulation Under the Toxic Substances Control Act (TSCA), Proposed rule, October 31, 2023. 88 FR 74712.
[2] Trichloroethylene (TCE); Regulation Under the Toxic Substances Control Act (TSCA), Proposed rule, October 31, 2023. 88 FR 74712, p. 74718.
[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. (2022). Final Revised Unreasonable Risk Determination for Trichloroethylene, December 2022. https://www.epa.gov/system/files/documents/2023-01/TCE_Final%20Revised%20RD_12-21-22-FINAL-v2.pdf.
[6] 15 U.S.C. § 2605(a).

Our comments address the following main points:

1. **EPA should promptly issue a final rule with a complete prohibition of TCE manufacture, import, processing, distribution in commerce, industrial and commercial use, consumer use, and disposal.**
2. **EPA should make full use of data on fetal cardiac malformations and all other sensitive non-cancer TCE endpoints in setting the workplace inhalation exposure standard.**
3. **EPA can and should quantify reduced risks of fetal cardiac malformations from chronic TCE exposures using available World Health Organization probabilistic methods.**
4. **A TCE workplace inhalation exposure standard lower than the level proposed by EPA is necessary to eliminate unreasonable risk to workers.**
5. **EPA's final TCE rule should incorporate additional risk management measures to protect fenceline communities from unreasonable risk.**

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

Sincerely,

Daniel Axelrad, MPP
Independent Consultant
Washington, DC

Jessica Trowbridge, PhD
Associate Research Scientist
Program on Reproductive Health and the Environment
University of California, San Francisco

Nicholas Chartres, PhD
Senior Research Fellow,
Faculty of Medicine & Health
The University of Sydney

Rashmi Joglekar, PhD
Associate Director, Science, Policy and Engagement
Program on Reproductive Health and the Environment
University of California, San Francisco

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

Phil Brown, PhD
University Distinguished Professor of Sociology and Health Sciences
Northeastern University

Thomas A. Burke, PhD, MPH
Professor Emeritus
Johns Hopkins University

Courtney Carignan, PhD
Assistant Professor
Michigan State University

Jeanne Conry, MD, PhD
President
The Environmental Health Leadership Foundation

Mary Martin Gant, MS
Government Liaison
Kids for Saving Earth*

Carly Hyland, PhD, MS
Assistant Professor
Environmental Health Sciences
University of California, Berkeley School of Public Health

Ronnie Levin
Instructor
Harvard T.H. Chan School of Public Health

Ted Schettler, MD, MPH
Science Director
Science and Environmental Health Network*

Patrice Sutton, MPH
Research Collaborator
Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Julia Varshavsky, PhD, MPH
Assistant Professor
Northeastern University

Ronald H. White, MST
Principal
RHWhite Consulting

DETAILED COMMENTS

1. **EPA should promptly issue a final rule with a complete prohibition of TCE manufacture, import, processing, distribution in commerce, industrial and commercial use, consumer use, and disposal.**

EPA's risk evaluation found that exposures to TCE occur at levels that pose significant risks to human health for a broad range of serious health endpoints. The only action sufficient to eliminate unreasonable risks from TCE is a complete prohibition, as proposed by EPA. Any continued uses of TCE will mean continued unreasonable risks to workers, consumers, the general population, and susceptible subpopulations, including fence line communities. In the Proposed Rule, EPA has acknowledged that the proposed Workplace Chemical Protection Program ("WCPP") is not sufficient to eliminate unreasonable risk to workers, and that therefore prohibition of all industrial and commercial uses is necessary to eliminate unreasonable risk as required by TSCA. And yet, EPA has also proposed to allow continued specified industrial and commercial uses of TCE to continue for several years, subject to implementation of a WCPP. In addition, the Proposed Rule does not provide protection to residents of fenceline communities who are at unreasonable risk from TCE emissions and releases. For these reasons, any uses that EPA allows to continue must be subject to prohibition at the earliest date possible. As long as any uses of TCE continue, there will be continuing unreasonable risks.

It is particularly critical that any continued uses are of minimum duration because the WCPP proposed for TCE would not prohibit workplace exposures above the level of the proposed existing chemical exposure limit ("ECEL"), but instead require employers only to avoid such exposures "to the extent possible."[7] This stands in contrast to other TSCA risk management proposed rules that prohibit worker exposures above the level of the ECEL. EPA does not provide clear indication of how a "to the extent possible" standard would be enforced, but this novel approach makes clear that workplace exposures well above the level of the ECEL are expected to occur. Full attainment of the proposed ECEL itself would not be sufficient to eliminate unreasonable risk (see comment 4 below), and continued exposures above the ECEL would only increase the risks to workers. Therefore, the proposed duration of continued industrial and commercial uses subject to the WCPP must be minimized in order to protect worker health.

EPA has requested comment on an alternate WCPP approach that would set an "interim" workplace exposure standard of 0.036 ppm, or 30-fold greater than the proposed ECEL of 0.0011 ppm. The interim level would be based on the limit of detection for available measurement methods. EPA should not promulgate an interim workplace exposure standard or any other measure that sets a workplace exposure standard that is not health-protective. It is unlikely that any great technical advances in measurement technologies or exposure protections will occur within the timeframe of most of the proposed phaseouts (ten years or less), so any "interim" level that EPA might adopt would likely become the actual standard for the full duration of continued use for the vast majority of workers and would represent an abandonment of efforts by EPA to reduce the unreasonable risk to the greatest extent possible.

EPA has proposed a scheduled phasedown of the use of TCE as an intermediate in manufacture of the refrigerant HFC-134a for 8.5 years. For production of HFC-134a, the amount of TCE used would be reduced by 25% after 2.5 years, 50% after 4.5 years, 75% after 6.5 years, and 100% after 8.5 years. This approach of a declining volume of TCE allowed should be applied to all other continuing industrial and commercial uses, in order to minimize ongoing unreasonable risks to workers and fenceline communities to the greatest extent possible.

[7] Trichloroethylene (TCE); Regulation Under the Toxic Substances Control Act (TSCA), Proposed rule, October 31,2023. 88 FR 74712, p. 74735.

2. EPA should make full use of data on fetal cardiac malformations and all other sensitive non-cancer TCE endpoints in setting the workplace inhalation exposure standard.

EPA's proposed ECEL is based on the endpoint of fetal cardiac malformations, which was identified as the most sensitive health endpoint in the TCE risk evaluation. EPA has also computed an alternative workplace standard based on the autoimmunity endpoint, which is also a sensitive health endpoint and a significant concern for worker health. EPA based its risk determination for TCE on autoimmunity rather than fetal cardiac malformations. As has been documented elsewhere, this decision was made by political appointees in the prior presidential administration[8] and reversed the conclusions of a previous EPA peer reviewed TCE assessment.[9] This decision was a violation of scientific integrity principles and should have no bearing on determination of the ECEL.

As part of the final TCE risk evaluation, EPA reviewed all available evidence for fetal cardiac malformations from TCE exposure, including mechanistic evidence and studies of TCE metabolites, and concluded that there is

> positive overall evidence that TCE exposure may result in congenital heart defects in humans (based on positive evidence from epidemiology studies, mixed evidence from animal toxicity studies, and stronger positive evidence from mechanistic studies)…Overall, an association between increased congenital cardiac defects and TCE exposure is supported by the weight of evidence…epidemiological data indicates that TCE is strongly associated with CHDs in older mothers.[10]
>
> Overall, the database is both reliable and relevant and provides positive overall evidence that TCE may produce cardiac defects in humans.[11]

These conclusions of the EPA TSCA risk evaluation indicate that there is no scientific basis for disregarding the evidence of fetal cardiac malformations in selecting risk management measures for TCE.

3. EPA can and should quantify reduced risks of fetal cardiac malformations from chronic TCE exposures using available World Health Organization probabilistic methods.

EPA estimates that nearly 1,000 pregnant women may be exposed to TCE in the workplace annually, indicating that reduced risks of fetal cardiac malformations may be a significant benefit of the Proposed Rule. EPA, however, has not quantified the risk and thus it has not been included in the estimated monetized benefits of the proposal. EPA has solicited input on this topic in the preamble to the Proposed Rule:

> EPA requests comment on information that would allow EPA to quantify the magnitude of avoided risk of fetal cardiac defects due to reductions in TCE exposure under the proposed rulemaking.[12]

The International Programme on Chemical Safety ("IPCS"), part of the World Health Organization

[8] Elizabeth Shogren, EPA scientists found a toxic chemical damages fetal hearts. The Trump White House rewrote their assessment, Reveal/The Center for Investigative Reporting, February 28, 2020. https://revealnews.org/article/epa-scientists-found-a-toxic-chemical-damages-fetal-hearts-the-trump-white-house-rewrote-their-assessment/.
[9] US EPA. (2011), Toxicological Review of Trichloroethylene.
[10] US EPA. (2020), Risk Evaluation for Trichloroethylene, pp. 249-250.
[11] US EPA. (2020), Risk Evaluation for Trichloroethylene, p. 654.
[12] Trichloroethylene (TCE); Regulation Under the Toxic Substances Control Act (TSCA), Proposed rule, October 31,2023. 88 FR 74712, p. 74775.

("WHO"), has published a methodology for risk quantification that can be directly applied to fetal cardiac defects and other non-cancer effects of TCE and represents the "best available science."[13] This methodology, which was co-authored by an EPA scientist, built on an extensive literature regarding probabilistic dose-response methods (with many of these articles authored by EPA scientists or funded by EPA[14,15]) and recommendations by the National Academy of Sciences in the 2009 EPA-funded report *Science and Decisions*.[16] EPA has been at the forefront of development of these methods for three decades, and there is now a substantial foundation for use of the WHO/IPCS approach to support EPA rulemaking.

The Technical Appendix to these comments presents an application of the WHO/IPCS probabilistic dose-response assessment method for fetal cardiac defects, immune effects and kidney effects of TCE. These analyses are conducted entirely using data and methods available from EPA's TCE assessments – the 2020 TSCA risk evaluation and the 2011 IRIS Toxicological Review – the IPCS report on the methodology, and related journal articles on the IPCS methodology. The Technical Appendix demonstrates how EPA can quantify the relationship between exposure concentrations of TCE and risks of fetal cardiac defects. For example, at a TCE dose of 0.0005 ppm the risk of fetal cardiac defects is as high as 0.1% (1-in-1000). These dose-response estimates can be used along with EPA's data on baseline TCE exposure concentrations and the number of people exposed to quantify avoided risks of fetal cardiac defects under the proposed risk management action. EPA should apply the WHO/IPCS probabilistic dose-response assessment methods to estimate the risk of fetal cardiac defects and other non-cancer health effects of TCE.

4. A TCE workplace inhalation exposure standard lower than the level proposed by EPA is necessary to eliminate unreasonable risk to workers.

We recognize the proposed ECEL is much lower than existing workplace standards, difficult to achieve, and that measurement of such low levels of TCE in air is difficult. However, existing standards set by OSHA and other agencies are based on outdated science and are not designed to eliminate unreasonable risk. TSCA requires EPA to eliminate unreasonable risk, and application of the WHO/IPCS probabilistic methodology indicates that risks of non-cancer effects are very high at the proposed ECEL of 0.0011 ppm (8-hour time weighted average) – such that even with full attainment of the proposed ECEL, unreasonable risks to worker health would remain.

Specifically, as detailed in the Technical Appendix, at the level of the proposed ECEL the risk of non-cancer effects can be as high as >1% (1-in-100) for decreased thymus weight, about 0.1% (1-in-1000) for autoimmunity, about 0.05% (1-in-2000) for fetal heart malformations, and about 0.05% (1-in-2000) for kidney effects (based on NTP study). These risks are far greater than the target range of protection for carcinogenic risks typically applied by EPA of 1-in-10,000 (10^{-4}) to 1-in-1,000,000 (10^{-6}).[17] To eliminate unreasonable occupational risk, the ECEL should be set to protect workers from an upper bound risk for any health effect of no more than 1-in-100,000, and preferably at the 1-in-1,000,000 risk level. EPA should set a health-protective level, and then consider how to address issues related to measurement and compliance, rather than promulgating a standard that is not health-protective. As noted above, problems with attaining the proposed ECEL or a lower, more health-protective ECEL can best be addressed by minimizing the duration of continued TCE use to the greatest extent possible.

[13] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition.
[14] Hattis D, Baird S, Goble R. A straw man proposal for a quantitative definition of the RfD. Drug Chem Toxicol 2002; 25:403-436.
[15] Swartout, J.C.; Price, P.S.; Dourson, M.L.; Carlson-Lynch, H.L.; Keenan, R.E. A Probabilistic Framework for the Reference Dose (Probabilistic RfD). Risk Analysis 1998, 18, 271–282.
[16] National Research Council. (2009). Science and decisions: Advancing risk assessment. Washington, DC: National Academies Press; 2009.
[17] Methylene Chloride; Regulation Under the Toxic Substances Control Act (TSCA), Proposed rule, May 3, 2023. 88 Fed. Reg. 28284, p. 28326.

5. EPA's final TCE rule should incorporate additional risk management measures to protect fenceline communities from unreasonable risk.

We support EPA's decision to consider impacts to fenceline communities when regulating TCE under the Proposed Rule, which is needed to comply with TSCA. We also support EPA's decision to consider multiple years of TRI-reported chemical releases to support this analysis, which underscored the "year-to-year variability that exists in the release data and illustrates the potential impact of considering multiple years of TRI data on exposure and risk estimates."[18] However, as currently drafted, the Proposed Rule fails to comprehensively account for the ways that fenceline communities are exposed to and harmed by TCE, and thus understates the harm that fenceline residents face from TCE exposures.

EPA failed to consider all relevant exposure pathways, aggregate exposures, cumulative risks, non-chemical stressors, and reasonably available chemical release data when evaluating risk to fenceline communities in the Proposed Rule, which was recommended by EPA's Scientific Advisory Committee on Chemicals ("SACC").[19] Together, these critical omissions result in an underestimation of risk to fenceline community residents.

EPA found that certain TCE conditions of use pose high cancer risk to fenceline communities that constitutes unreasonable risk, even without appropriately accounting for all exposures and risks. For example, in its Fenceline Technical Support Analysis for the air pathway, EPA found that TCE ambient air exposures resulting from 6-year average releases reported to the TRI for 133 facilities were associated with cancer risk (more than 1×10^{-6}) to fenceline residents for 23 conditions of use, some of which have proposed exemptions or will undergo a longer phase out period under the Proposed Rule.[20] EPA failed to propose adequate measures to mitigate these risks. Instead, EPA concluded that the proposed WCPP requirements for those conditions of use with exemptions or longer phase out periods "may reduce exposures to the general population for facilities identified in the fenceline analysis with expected exposures to fenceline communities."[21] While EPA highlighted that "[u]nder the proposed WCPP requirements, facilities would need to monitor indoor TCE air concentrations, which would allow facilities to better understand and manage the total releases of TCE,"[22] EPA also requested comment on whether these controls could actually result in "increased releases of TCE to outdoor air associated with the implementation of the WCPP."[23] In doing so, EPA is acknowledging that WCPP mitigation strategies could potentially *increase* facility releases, putting fenceline communities at higher risk of harm from TCE exposures during proposed phase-out windows. EPA should promptly issue prohibition on all TCE conditions of use to ensure that the chemical no longer presents unreasonable risk to fenceline communities.

[18] US EPA. (2022). Trichloroethylene (TCE): Fenceline Technical Support—Ambient Air Pathway. https://www.regulations.gov/document/EPA-HQ-OPPT-2020-0642-0091.
[19] US EPA. (2022). Final Report on Draft TSCA Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities Version 1.0 pp 49. https://www.epa.gov/system/files/documents/2022-01/draft-fenceline-report_sacc.pdf.
[20] US EPA. (2022). Trichloroethylene (TCE): Fenceline Technical Support—Ambient Air Pathway. https://www.regulations.gov/document/EPA-HQ-OPPT-2020-0642-0091.
[21] Trichloroethylene (TCE); Regulation Under the Toxic Substances Control Act (TSCA), Proposed rule, October 31,2023. 88 FR 74712, p. 74769.
[22] Trichloroethylene (TCE); Regulation Under the Toxic Substances Control Act (TSCA), Proposed rule, October 31,2023. 88 FR 74712, p. 74770.
[23] Trichloroethylene (TCE); Regulation Under the Toxic Substances Control Act (TSCA), Proposed rule, October 31,2023. 88 FR 74712, p. 74740.

Technical Appendix: Analysis of trichloroethylene non-cancer effects risk using WHO/IPCS methodology

In the TSCA risk evaluation of trichloroethylene (TCE), EPA selected autoimmunity from a study of mice as the "best overall chronic non-cancer endpoint"[24] for estimation of risks from chronic inhalation exposures and for making determinations regarding unreasonable risk. The TSCA risk evaluation also presented risk estimates for several other endpoints, including liver, kidney, neurological, reproductive and developmental effects.

For risk characterization of non-cancer health effects, the TSCA risk evaluation calculates a "margin of exposure" (MOE) for each exposure scenario, which is the ratio of the point of departure (POD) to the exposure level. EPA's approach to risk characterization does not actually estimate risks of adverse effects in the population with chronic exposure to TCE, but instead simply applies a "bright line" judgment of whether or not the MOE "was interpreted as human health risk" or "indicated negligible concerns for adverse human health effects."[25] A more informative approach for both risk characterization and risk management would be to apply the probabilistic dose-response assessment methods of the International Programme on Chemical Safety (IPCS),[26] part of the World Health Organization (WHO), to estimate the risk of adverse effects at various levels of exposure. The IPCS methodology has previously been described and applied in several peer-reviewed journal articles.[27,28,29,30,31]

We applied the IPCS approach for "quantal-deterministic" endpoints and "approximate probabilistic" calculation (see IPCS report Fig. 3.5, panel C)[32] to estimate risks of several non-cancer endpoints of TCE using data previously analyzed by EPA.

---

[24] US EPA. (2020), Risk Evaluation for Trichloroethylene, p. 281.

[25] US EPA. (2020), Risk Evaluation for Trichloroethylene, p. 303.

[26] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition. https://www.who.int/publications/i/item/9789241513548.

[27] Chiu WA, Slob W. A Unified Probabilistic Framework for Dose–Response Assessment of Human Health Effects. Environmental Health Perspectives, 2015 December;123(12): 1241–1254. doi:10.1289/ehp.1409385.

[28] Nielsen GH, Heiger-Bernays WJ, Levy JI, White RF, Axelrad DA, Lam J, Chartres N, Abrahamsson D.P, Rayasam SDG, Shaffer RM, Zeise, L, Woodruff TJ, Ginsberg GL. (2023). Application of probabilistic methods to address variability and uncertainty in estimating risks for non-cancer health effects. Environ Health, 21(Suppl 1), 129. https://doi.org/10.1186/s12940-022-00918-z.

[29] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. doi:10.1289/EHP3368.

[30] Blessinger T, Davis A, Chiu WA, Stanek J, Woodall GM, Gift J, Thayer KA, Bussard D. Application of a unified probabilistic framework to the dose-response assessment of acrolein. Environment International, 2020 October;143:105953. doi: 10.1016/j.envint.2020.105953.

[31] Chiu WA, Paoli GM. Recent Advances in Probabilistic Dose–Response Assessment to Inform Risk-Based Decision Making. Risk Analysis, 2021 April;41(4):596-609. doi: 10.1111/risa.13595.

[32] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition.

The TSCA risk evaluation made use of the hazard assessment and quantitative analysis from the previous EPA Integrated Risk Information System (IRIS) assessment of TCE for identifying hazards, selecting endpoints, and determining the point of departure (POD) for each endpoint. However, there are important differences between the IRIS assessment and TSCA assessment regarding the selection of critical endpoints. In the IRIS assessment, decreased thymus weight in mice (Keil et al. 2009) and fetal heart malformations in rats (Johnson et al. 2003) were designated as co-critical endpoints (IRIS Table 5-28), and toxic nephropathy in rats (NTP 1988) was identified as a supporting endpoint (IRIS Table 5-29). The TSCA risk evaluation used a different immunotoxicity endpoint (autoimmunity) from the Keil et al. study for risk characterization and for determination of unreasonable risk, and did not include the thymus weight endpoint. The TSCA evaluation included the Johnson et al. study of fetal heart malformations in its risk characterization, but then did not consider these results in making the unreasonable risk determinations, instead using only the less-sensitive autoimmunity endpoint. The TSCA evaluation did not use the kidney effects from the NTP study for risk characterization, instead using kidney effects from a different study (Maltoni et al. 1986) with a higher POD. The TSCA risk evaluation, therefore, did not use the three study/endpoint combinations most important in the IRIS assessment for determining unreasonable risk of TCE.

Because of these important differences between the TSCA risk evaluation and the IRIS assessment, our analysis of non-cancer risks of TCE using the IPCS methodology considered five endpoints: thymus weight and autoimmunity from Keil et al., fetal heart malformations from Johnson et al., and kidney effects from the studies by NTP and Maltoni et al. These endpoints and their use in the two EPA assessments are summarized in the following table.

Key non-cancer endpoints in EPA's IRIS and TSCA assessments of TCE chronic inhalation exposure					
Endpoint (study)	**Role in EPA analyses**	**POD type**	**HEC_{50} (ppm)**	**HEC_{99} (ppm)**	**Comments**
Autoimmunity (Keil et al. 2009)	TSCA "best overall chronic non-cancer endpoint."[a] Only chronic endpoint used for determining unreasonable risk.[b]	LOAEL	0.092[c]	0.033[c]	Selected as preferred to decreased thymus weight and fetal heart malformations in TSCA risk evaluation. IRIS and TSCA assessments used UF_L=3 for this endpoint.[c]
Decreased thymus weight (Keil et al. 2009)	IRIS co-critical effect.[d]	LOAEL	0.092[e]	0.033[e]	Not used in TSCA risk evaluation, with assertion that "this effect is insufficiently adverse compared to the other endpoints and the effects are inconsistent with the indications of autoimmunity,"[f] but EPA reached a different conclusion in the IRIS assessment.[d] IRIS assessment used UF_L=10 for this endpoint.[d]
Fetal heart malformations (Johnson et al. 2003	IRIS co-critical effect.[d]	$BMDL_{01}$	0.012[c]	0.0037[c]	Included in TSCA risk characterization; not used in TSCA risk determination with assertion that "there is lower confidence in the dose-response and extrapolation of results,"[g] but EPA reached a different conclusion in the IRIS assessment.[d]
Toxic nephropathy (NTP 1988)	IRIS supporting effect.[h]	$BMDL_{05}$	0.042[i]	0.0056[i]	Not used in TSCA risk evaluation with assertion that asserted "elevated doses in (NTP, 1988) resulted in massive nephrotoxicity and introduce large uncertainty in BMD modeling the effects at low doses well below the tested doses with a BMR well below the observed effect incidence in the study. Therefore, the BMDL and resulting HEC/HED from (Maltoni et al., 1986) was considered more reliable,"[j] but EPA reached a different conclusion in the IRIS assessment.[h]

Pathology changes in renal tubule (Maltoni et al. 1986)	TSCA preferred kidney study for risk characterization.[c]	$BMDL_{10}$	0.19[c]	0.025[c]	Study selected as preferred to NTP 1988 for TSCA risk evaluation - see comments above.

Abbreviations: BMDL – benchmark dose, lower confidence limit; BMR – benchmark response; HEC – human equivalent concentration; LOAEL – lowest-observed adverse effect level; NTP – National Toxicology Program; POD – point of departure; UF_L – uncertainty factor, LOAEL-to-NOAEL adjustment.

Studies:

Johnson, P; Goldberg, S; Mays, M; Dawson, B. (2003). Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. Environ Health Perspect 111: 289-292.

Keil, D; Peden-Adams, M; Wallace, S; Ruiz, P; Gilkeson, G. (2009). Assessment of trichloroethylene (TCE) exposure in murine strains genetically-prone and non-prone to develop autoimmune disease. J Environ Sci Health A Tox Hazard Subst Environ Eng 44: 443-453.

Maltoni, C; Lefemine, G; Cotti, G. (1986). Experimental research on trichloroethylene carcinogenesis (Vol. 5). Princeton, NJ: Princeton Scientific Publishing.

NTP. (National Toxicology Program). (1988). Toxicology and carcinogenesis studies of trichloroethylene (CAS No. 79-01-6) in four strains of rats (ACI, August, Marshall, Osborne-Mendel) (gavage studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health.

Notes:

[a] US EPA. (2020), Risk Evaluation for Trichloroethylene, p. 281.
[b] US EPA. (2020), Risk Evaluation for Trichloroethylene, pp. 409-410.
[c] US EPA. (2020), Risk Evaluation for Trichloroethylene, Table 3-14.
[d] US EPA. (2011), Toxicological Review of Trichloroethylene, Table 5-28.
[e] US EPA. (2011), Toxicological Review of Trichloroethylene, Table 5-16.
[f] US EPA. (2020), Risk Evaluation for Trichloroethylene, p. 272.
[g] US EPA. (2020), Risk Evaluation for Trichloroethylene, p. 280.
[h] US EPA. (2011), Toxicological Review of Trichloroethylene, Table 5-29.
[i] US EPA. (2011), Toxicological Review of Trichloroethylene, Table 5-14.
[j] US EPA. (2020), Risk Evaluation for Trichloroethylene, p. 268.

The analysis involved the following steps for each of the five endpoints:

1. Derivation of IPCS POD and corresponding uncertainty adjustments
2. Application of interspecies adjustments
3. Application of intraspecies adjustments
4. Calculation of HD_M^I - the human dose (HD) of TCE associated with a particular magnitude of effect (M) at a particular population incidence (I).

For each aspect of the analysis, including the values used to derive the IPCS POD and the adjustment factors applied to derive the HD_M^I, the IPCS methodology uses a 50^{th} percentile value (P50) as a central estimate and the ratio of 95^{th} percentile to 50^{th} percentile (P95/P50) as a measure of uncertainty. All POD and HD_M^I values presented in this analysis are for continuous exposures.

STEP 1: Derivation of IPCS POD and corresponding uncertainty adjustments

The IPCS methodology requires the use of an ED_{50} (median effective dose) value as the POD for quantal-deterministic endpoints. Since an ED_{50} is not available from the EPA risk evaluation, we began with EPA's median human equivalent concentration (HEC_{50}) POD values and applied adjustments provided by the IPCS methodology. At the same time, we incorporated quantitative uncertainties as recommended by IPCS for each of these adjustments. We use the HEC_{50} for the POD rather than 99th percentile (HEC_{99}) because the latter value incorporates toxicokinetic variability. Following the IPCS methodology, we apply toxicokinetic variability, as represented by the difference between the HEC_{50} and HEC_{99}, in step 3 below.

EPA's HEC_{50} POD values are derived from a lowest-observed-effect-level (LOAEL) for the Keil et al. study of immune-related effects, and from benchmark dose (BMD) modeling for the other three endpoints. The IPCS methodology for deriving an ED_{50} differs between LOAELs and BMDs, so we discuss these adjustments separately.

a. Derivation of IPCS POD from the Keil et al. LOAEL (HEC_{50})

For both the autoimmunity and decreased thymus weight endpoints, the HEC_{50} for the Keil et al. study is based on a LOAEL value of 0.092 ppm. The first adjustment to derive an ED_{50}, as required by the IPCS methodology, is to apply a factor to convert the LOAEL to a NOAEL. For this adjustment, Chiu et al. 2018 recommends applying as a central estimate (P50) the traditional LOAEL-to-NOAEL uncertainty factor reported in the existing EPA assessments (which are 3 for autoimmunity and 10 for decreased thymus weight), and the P95/P50 ratio representing uncertainty equal to 3.[33]

The second adjustment is to then apply a factor to convert the NOAEL to an ED_{50}. For quantal-deterministic endpoints, the IPCS recommends a central estimate (P50) of 2/9 and a P95/P50 ratio representing uncertainty equal to 5.[34]

The median (P50) estimate of the ED_{50} is then derived by dividing the LOAEL (HEC_{50}) by the two adjustment factors (P50). The uncertainty adjustments (P95/P50) for each POD aspect are combined into a composite P95/P50 value. In the IPCS approximate probabilistic calculation template, those values are entered as follows:

[33] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. Figure 4. doi:10.1289/EHP3368.

[34] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.1

Determination of point of departure (POD) and its uncertainty[a] for probabilistic dose-response analysis of chronic TCE inhalation: immune-related effects (Keil et al. 2009)				
	Autoimmunity		Decreased thymus weight	
Aspect	P50	P95/P50	P50	P95/P50
LOAEL(HEC_{50})	0.092 ppm	1	0.092 ppm	1
$AF_{LOAEL\text{-}to\text{-}NOAEL}$[b]	3	3	10	3
$AF_{NOAEL\text{-}to\text{-}ED50}$[c]	0.22	5	0.22	5
IPCS POD = $ED_{50}(HEC_{50})$	**0.14 ppm**	**7.02[d]**	**0.04 ppm**	**7.02[d]**

[a] Uncertainty is expressed as the ratio of the 95th percentile (P95) to the 50th percentile (P50).
[b] The IRIS and TSCA assessments of TCE both applied a LOAEL-to-NOAEL adjustment factor of 3 for autoimmunity. The IRIS assessment applied a factor of 10 for decreased thymus weight (not addressed in TSCA assessment).
[c] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.1
[d] (Composite P95/P50) = $10^{[(\log 1)^2 + (\log 3)^2 + (\log 5)^2]^{0.5}} = 7.02$

b. Derivation of IPCS PODs from the BMD (HEC_{50}) values for fetal heart malformations and kidney effects

For the studies of fetal heart malformations and kidney effects, the HEC_{50} values used as the PODs in the IRIS and TSCA assessments are based on lower confidence limits from benchmark dose modeling (BMDLs). The first POD adjustment in the IPCS methodology is to convert each BMDL value to a BMD (i.e., the central estimate of the benchmark dose) as follows:

- BMD = BMDL x (BMD / BMDL)

This adjustment requires the BMD / BMDL ratio for each endpoint, which were obtained from the IRIS assessment of TCE.[35] In the IPCS methodology, uncertainty in the BMD is represented by the ratio of 95th percentile to 50th percentile (P95/P50), which is equal to the same ratio of BMD / BMDL.

The second POD adjustment is to convert from the BMD to an ED_{50}. The ED_{50} and its uncertainty are determined by applying the following conversion from Chiu et al. 2018: "if

[35] US EPA. (2020), Risk Evaluation for Trichloroethylene, Table F-13.

ED50 not reported: BMD at the reported BMR is multiplied by an additional factor of 3.0; additional uncertainty through adding 1.5^2 to $(P95/P50)^2$."[36]

The median (P50) estimate of the ED_{50} is then derived by multiplying the BMDL(HEC_{50}) by the two adjustment factors (P50). The uncertainty adjustments (P95/P50) for each POD aspect are combined into a composite P95/P50 value. In the IPCS approximate probabilistic calculation template, those values are entered as follows:

Determination of point of departure (POD) and its uncertainty[a] for probabilistic dose-response analysis of chronic TCE inhalation: fetal heart malformations and kidney effects						
	Fetal Heart Malformations		Kidney Effects (NTP)		Kidney Effects (Maltoni et al.)	
Aspect	**P50**	**P95/P50**	**P50**	**P95/P50**	**P50**	**P95/P50**
BMDL(HEC_{50})	0.012 ppm	1	0.042 ppm	1	0.19 ppm	1
BMD/BMDL ratio[b]	3.12	3.12	1.45	1.45	1.60	1.60
BMD-to-ED_{50} adjustment[c]	3	1.5	3	1.5	3	1.5
IPCS POD = $ED_{50}(HEC_{50})$	**0.11 ppm**	**3.35[d]**	**0.18 ppm**	**1.73[e]**	**0.9 ppm**	**1.86[f]**

[a] Uncertainty is expressed as the ratio of the 95th percentile (P95) to the 50th percentile (P50)
[b] US EPA. (2020), Risk Evaluation for Trichloroethylene, Table F-13
[c] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. Figure 4. doi:10.1289/EHP3368
[d] (Composite P95/P50) = $10^{[(\log 1)^2 + (\log 3.12)^2 + (\log 1.5)^2]^{0.5}} = 3.35$
[e] (Composite P95/P50) = $10^{[(\log 1)^2 + (\log 1.45)^2 + (\log 1.5)^2]^{0.5}} = 1.73$
[f] (Composite P95/P50) = $10^{[(\log 1)^2 + (\log 1.60)^2 + (\log 1.5)^2]^{0.5}} = 1.86$

STEP 2: Application of interspecies adjustments

For interspecies (animal-to-human) adjustments, the IPCS methodology first considers a factor for body-size scaling, and then a factor for remaining toxicokinetic (TK) and toxicodynamic (TD) differences. Since the determination of the EPA BMDL values incorporated dosimetric adjustments, no further adjustment for body size is necessary (P50 = 1). The uncertainty in the bodyweight scaling is not quantified in this analysis (P95/P50 = 1).

[36] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. Figure 4. doi:10.1289/EHP3368.

For the TK/TD differences remaining after bodyweight scaling, the IPCS report recommends a central estimate (P50) of 1 (i.e., no additional interspecies differences) and representing uncertainty with a P95/P50 factor of 3.[37] We incorporated these IPCS recommendations. The adjustments are the same for all five chronic endpoints in this analysis. The interspecies adjustments are entered In the IPCS approximate probabilistic calculation template as follows:

Interspecies adjustments for probabilistic dose-response analysis of chronic TCE inhalation		
Aspect	**P50**	**P95/P50**
$AF_{Interspecies\text{-}BS}$	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3

STEP 3: Application of intraspecies adjustments - incorporating TCE-specific toxicokinetic data

In the IPCS methodology, the value of the human variability adjustment factor ($AF_{intraspecies}$) varies depending on the incidence of the adverse effect in the exposed population – with a larger adjustment factor necessary to extrapolate to lower levels of incidence. The IPCS report provides default $AF_{intraspecies}$ for several incidence (I) values. As with the POD, the IPCS methodology uses the P50 as a central estimate and the P95/P50 as a measure of uncertainty for each value of I.

As noted above in Step 1, the HEC distribution estimated by EPA represents human toxicokinetic variability in the air concentration producing the internal dose BMDL, and the EPA IRIS assessment reports the median and 99th percentile (HEC_{50} and HEC_{99}) of the HEC distribution.

In accordance with the IPCS methodology, we removed the human TK variability from the POD in Step 1 by using the HEC_{50} rather than the HEC_{99} as our starting point in deriving the IPCS POD. We now incorporate human TCE TK variability into the adjustment factor for combined human TK and TD variability. Specifically, we combine TCE-specific TK variability (which varies across endpoints, due to differences in EPA's preferred dose metrics) and the IPCS default distribution for TD variability.

In the standard application of the IPCS methodology, there are no chemical-specific data on human variability for the chemical being assessed. The IPCS default distributions for human TK

[37] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.3.

and TD variability are based on data from chemicals that do have chemical-specific data. The available data sets display a range of TK and TD variability across chemicals – that is, the extent of TK or TD variability (represented statistically by the geometric standard deviation, GSD) is narrower for some chemicals and broader for other chemicals. The IPCS approach assumes that the range of observed variability in TK or TD response across chemicals (i.e., the distribution of GSDs) represents a range of possible values for any individual chemical being assessed that lacks chemical-specific data. Since chemical-specific data are not available, the human TK/TD variability of the target chemical is (conceptually) estimated probabilistically by sampling from the distribution of observed GSDs for the chemicals that do have data.

The IPCS default distributions are presented in the IPCS report Table 4.4, which provides values for toxicokinetic variability as $\log(GSD_{H\text{-}TK})$, toxicodynamic variability as $\log(GSD_{H\text{-}TD})$ and combined TK/TD variability as $\log(GSD_H)$. For each of these three human variability parameters (TK, TD, and combined) the table summarizes a distribution of values with a central estimate or median (P50) and the ratio of the 95th percentile to the median (P95/P50). The P50 value represents a central estimate across chemicals of the extent of variability (i.e. the GSD); so half of chemicals have a GSD representing more human variability than the P50 value and half of chemicals have a GSD representing less human variability than the P50 value. The P95/P50 ratios represents uncertainty in the GSD for any given chemical being assessed that lacks TK and/or TD data.

The standard application of the IPCS "approximate probabilistic" method uses the $\log(GSD_H)$ for TK-TD combined variability from IPCS Table 4.4 as an input. For application of the IPCS method to TCE, we performed a series of calculations to replace the Table 4.4 values with values that incorporate the chemical-specific TK data.

A. Calculate TCE-specific and endpoint-specific $\log(GSD_{H\text{-}TK})$.

For each TCE endpoint of interest, EPA reports an HEC_{50} and HEC_{99}. The difference between these two values is a representation of human variability – the HEC_{50} is the concentration of TCE in air producing the internal dose POD for the median individual, and the HEC_{99} is the air concentration producing the same internal dose POD for the 99th percentile individual. The 99th percentile individual converts more of a given air concentration of TCE into internal dose TCE, thus at the 99th percentile a lower air concentration is needed to produce the same internal dose and the HEC_{99} is lower than the HEC_{50}. For use in the IPCS methodology, the variability in conversion of air TCE to internal dose TCE represented by the HEC_{50} and HEC_{99} needs to be statistically expressed as a $\log(GSD_{H\text{-}TK})$. We fit a lognormal distribution to the HEC_{50} and HEC_{99} for each of the endpoints of interest to produce the following estimates of $\log(GSD_{H\text{-}TK})$:

Estimates of Log($GSD_{H\text{-}TK}$) for TCE non-cancer endpoints of interest[a]				
Endpoint/Study	**HEC_{50}**	**HEC_{99}**	**$GSD_{H\text{-}TK}$**	**Log($GSD_{H\text{-}TK}$)**
Immune/Keil[b]	0.092	0.0330	1.56	0.192
Malformations/Johnson	0.012	0.0037	1.66	0.220
Kidney/NTP	0.042	0.0056	2.38	0.377
Kidney/Maltoni	0.190	0.0250	2.40	0.380

[a] Estimated by UCSF by fitting a lognormal distribution to the EPA-reported HEC_{50} and HEC_{99} for each endpoint/study combination.
[b] Both the HEC_{50} and HEC_{99} are the same for thymus weight and autoimmunity.

As previously mentioned, the default values in IPCS Table 4.4 for log($GSD_{H\text{-}TK}$) represent a distribution of values for human TK variability across chemicals, summarized with a P50 and a P95/P50 value. In the current application, since we have data for human TK variability for the chemical of interest, there is no distribution across chemicals; rather we have a single value for TCE TK variability for each endpoint. The uncertainty in the TCE TK values is uncharacterized because no confidence intervals or standard errors are provided for EPA's HEC values.

B. Re-compute the log(GSD_H) distribution using the point estimate of log($GSD_{H\text{-}TK}$) for each TCE endpoint and the default distribution of log($GSD_{H\text{-}TD}$) from IPCS Table 4.4.

The default log(GSD_H) distribution in IPCS Table 4.4 was originally calculated by "Monte Carlo simulation combining log($GSD_{H\text{-}TK}$) and log($GSD_{H\text{-}TD}$) assuming independent lognormal distributions."[38] The same Monte Carlo simulation approach was applied, now with the TCE-specific log($GSD_{H\text{-}TK}$) value for each endpoint (shown in the table above) and with the default log($GSD_{H\text{-}TD}$) distribution (see Attachment for code and outputs). The resulting values of log(GSD_H) for TK and TD variability combined are as follows:

Estimates of Log(GSD_H) for TCE non-cancer endpoints of interest incorporating chemical-specific and endpoint-specific estimates of Log($GSD_{H\text{-}TK}$)		
Endpoint/Study	**P50**	**P95/P50**
Immune/Keil[a]	0.369	1.784

[38] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.4.

Malformations/Johnson	0.395	1.691
Kidney/NTP	0.532	1.381
Kidney/Maltoni	0.534	1.378
[a] Values are same for thymus weight and autoimmunity endpoints.		

C. Calculate $AF_{Intraspecies}$ for various values of incidence (I) for each TCE endpoint.

For the "approximate probabilistic" application of the IPCS methodology with default adjustment factors, IPCS converted the values of the log(GSD_H) distribution into P50 and P95/P50 values of the intraspecies adjustment factor ($AF_{Intraspecies}$) for various levels of incidence (I), shown in IPCS Table 4.5. We applied formulas embedded in IPCS APROBA spreadsheet[39] to derive the lognormal approximation TCE-specific $AF_{Intraspecies}$ values using the log(GSD_H) P50 and P95/P50 values derived in step B. Results are shown in the following table.

$AF_{Intraspecies}$ values for chronic TCE inhalation incorporating TCE-specific human toxicokinetic variability								
Incidence (I)	Immune Effects		Fetal Heart Malformations		Kidney Effects (NTP)		Kidney Effects (Maltoni et al.)	
	P50	P95/P50	P50	P95/P50	P50	P95/P50	P50	P95/P50
5%	5.15	2.35	5.51	2.28	8.33	1.94	8.39	1.93
1%	10.17	3.36	11.18	3.20	20.06	2.55	20.26	2.54
0.5%	13.04	3.82	14.48	3.63	27.67	2.82	27.98	2.81
0.1%	21.78	4.99	24.69	4.69	53.71	3.47	54.42	3.45
0.05%	26.59	5.54	30.39	5.18	69.53	3.76	70.51	3.74
0.01%	40.76	6.93	47.41	6.42	120.80	4.47	122.73	4.45

As seen in the table, the median (P50) values of $AF_{Intraspecies}$ are much larger for kidney effects than for the other endpoints. This difference is consistent with greater ratios of HEC_{99} to HEC_{50} for kidney effects, which indicate greater human toxicokinetic variability in air concentrations that produce the internal dose POD for these outcomes. These TCE-specific values of $AF_{Intraspecies}$ generally result is smaller overall intraspecies adjustments than the IPCS defaults (shown in IPCS Table 4.5) for the immune effects and

[39] Available at: https://www.who.int/publications/i/item/9789241513548.

fetal heart malformations, and larger overall intraspecies adjustments than the IPCS defaults for kidney effects.

STEP 4: Calculation of HD_M^I

The output of the IPCS methodology is generically described as an HD_M^I value – the human dose (HD) associated with a particular magnitude of effect (M) at a particular population incidence (I). For the HD_M^I analyses of TCE, the "M" represents the endpoints of immune effects, fetal heart malformations, and kidney effects.

We used IPCS Fig 3.5, panel C[40] as a template for a spreadsheet used to compute HD_M^I values for TCE using the inputs described above in Steps 1-3. The following tables present the results for I = 5%, 1%, 0.5%, 0.1%, 0.05% and 0.01% for each endpoint, using the POD, $AF_{Interspecies}$ and $AF_{Intraspecies}$ values shown above. The IPCS approach is a probabilistic method, so the HD_M^I is a distribution; selected values from that distribution are presented as follows:

- P05: 5th percentile estimate (lower confidence limit) of HD_M^I (this value is shown in **bold**)
- P50: 50th percentile estimate (median) of HD_M^I
- P95: 95th percentile estimate (upper confidence limit) of HD_M^I.

The only difference between the tables for each endpoint are the varying values for $AF_{Intraspecies}$, which change as I is changed, and the subsequent HD_M^I. Differences across endpoints result from both the POD and the $AF_{Intraspecies}$.

[40] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition.

Calculation of HD_M^I from chronic TCE inhalation exposure: Immune-related effects (Incidence = 5%)				
	Autoimmunity		Decreased thymus weight	
Aspect	**P50**	**P95/P50**	**P50**	**P95/P50**
LOAEL(HEC_{50})	0.092 ppm	1	0.092 ppm	1
$AF_{LOAEL\text{-}to\text{-}NOAEL}$	3	3	10	3
$AF_{NOAEL\text{-}to\text{-}ED50}$	0.22	5	0.22	5
IPCS POD = ED_{50}(HEC_{50})	**0.14 ppm**	**7.02**	**0.04 ppm**	**7.02**
$AF_{Interspecies\text{-}BS}$	1	1	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3	1	3
$AF_{Intraspecies\ (I=5\%)}$	5.15	2.35	5.15	2.35
HD_M^I	0.027 ppm[a]	11.0[b]	0.008[a] ppm	11.0[b]
	P05	**P95**	**P05**	**P95**
$HD_M^{I\ (c)}$	**0.002 ppm**	0.29 ppm	**0.0007 ppm**	0.09 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b](Composite P95/P50) = $10^{[(\log 7.02)^2 + (\log 1)^2 + (\log 3)^2 + (\log 2.35)^2]^{0.5}} = 11.0$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic TCE inhalation exposure: Immune-related effects (Incidence = 1%)				
	Autoimmunity		Decreased thymus weight	
Aspect	**P50**	**P95/P50**	**P50**	**P95/P50**
LOAEL(HEC_{50})	0.092 ppm	1	0.092 ppm	1
$AF_{LOAEL\text{-}to\text{-}NOAEL}$	3	3	10	3
$AF_{NOAEL\text{-}to\text{-}ED50}$	0.22	5	0.22	5
IPCS POD = ED_{50}(HEC_{50})	**0.14 ppm**	**7.02**	**0.04 ppm**	**7.02**
$AF_{Interspecies\text{-}BS}$	1	1	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3	1	3

$AF_{Intraspecies\ (I=1\%)}$	10.17	3.36	10.17	3.36
HD_M^I	0.014 ppm[a]	12.73[b]	0.004[a] ppm	12.73[b]
	P05	**P95**	**P05**	**P95**
$HD_M^{I\ (c)}$	**0.0011 ppm**	0.17 ppm	**0.0003 ppm**	0.05 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b](Composite P95/P50) = $10^{[(\log 7.02)^2 + (\log 1)^2 + (\log 3)^2 + (\log 3.36)^2]^{0.5}} = 12.73$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic TCE inhalation exposure: Immune-related effects (Incidence = 0.5%)

	Autoimmunity		Decreased thymus weight	
Aspect	**P50**	**P95/P50**	**P50**	**P95/P50**
LOAEL(HEC_{50})	0.092 ppm	1	0.092 ppm	1
$AF_{LOAEL\text{-}to\text{-}NOAEL}$	3	3	10	3
$AF_{NOAEL\text{-}to\text{-}ED50}$	0.22	5	0.22	5
IPCS POD = ED_{50}(HEC_{50})	**0.14 ppm**	**7.02**	**0.04 ppm**	**7.02**
$AF_{Interspecies\text{-}BS}$	1	1	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3	1	3
$AF_{Intraspecies\ (I=0.5\%)}$	13.04	3.82	13.04	3.82
HD_M^I	0.011 ppm[a]	13.57[b]	0.003[a] ppm	13.57[b]
	P05	**P95**	**P05**	**P95**
$HD_M^{I\ (c)}$	**0.0008 ppm**	0.14 ppm	**0.0002 ppm**	0.04 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b](Composite P95/P50) = $10^{[(\log 7.02)^2 + (\log 1)^2 + (\log 3)^2 + (\log 3.82)^2]^{0.5}} = 13.57$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic TCE inhalation exposure: Immune-related effects (Incidence = 0.1%)				
	Autoimmunity		Decreased thymus weight	
Aspect	P50	P95/P50	P50	P95/P50
LOAEL(HEC_{50})	0.092 ppm	1	0.092 ppm	1
$AF_{LOAEL\text{-}to\text{-}NOAEL}$	3	3	10	3
$AF_{NOAEL\text{-}to\text{-}ED50}$	0.22	5	0.22	5
IPCS POD = ED_{50}(HEC_{50})	**0.14 ppm**	**7.02**	**0.04 ppm**	**7.02**
$AF_{Interspecies\text{-}BS}$	1	1	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3	1	3
$AF_{Intraspecies\ (I=0.1\%)}$	21.78	4.99	21.78	4.99
HD_M^I	0.006 ppm[a]	15.72[b]	0.002 ppm[a]	15.72[b]
	P05	P95	P05	P95
$HD_M^{I\ (c)}$	**0.0004 ppm**	0.10 ppm	**0.0001 ppm**	0.030 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b](Composite P95/P50) = $10^{[(\log 7.02)^2 + (\log 1)^2 + (\log 3)^2 + (\log 4.99)^2]^{0.5}} = 15.72$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic TCE inhalation exposure: Immune-related effects (Incidence = 0.05%)				
	Autoimmunity		Decreased thymus weight	
Aspect	P50	P95/P50	P50	P95/P50
LOAEL(HEC_{50})	0.092 ppm	1	0.092 ppm	1
$AF_{LOAEL\text{-}to\text{-}NOAEL}$	3	3	10	3
$AF_{NOAEL\text{-}to\text{-}ED50}$	0.22	5	0.22	5
IPCS POD = ED_{50}(HEC_{50})	**0.14 ppm**	**7.02**	**0.04 ppm**	**7.02**
$AF_{Interspecies\text{-}BS}$	1	1	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3	1	3

$AF_{Intraspecies\ (I=0.05\%)}$	26.59	5.54	26.59	5.54
HD_M^I	0.005 ppm[a]	16.73[b]	0.002 ppm[a]	16.73[b]
	P05	**P95**	**P05**	**P95**
$HD_M^{I\ (c)}$	**0.0003 ppm**	0.09 ppm	**0.0001 ppm**	0.026 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b](Composite P95/P50) = $10^{[(\log 7.02)^2 + (\log 1)^2 + (\log 3)^2 + (\log 5.54)^2]^{0.5}} = 16.73$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic TCE inhalation exposure: Immune-related effects (Incidence = 0.01%)

	Autoimmunity		Decreased thymus weight	
Aspect	**P50**	**P95/P50**	**P50**	**P95/P50**
LOAEL(HEC_{50})	0.092 ppm	1	0.092 ppm	1
$AF_{LOAEL\text{-}to\text{-}NOAEL}$	3	3	10	3
$AF_{NOAEL\text{-}to\text{-}ED50}$	0.22	5	0.22	5
IPCS POD = ED_{50}(HEC_{50})	**0.14 ppm**	**7.02**	**0.04 ppm**	**7.02**
$AF_{Interspecies\text{-}BS}$	1	1	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3	1	3
$AF_{Intraspecies\ (I=0.01\%)}$	40.76	6.93	40.76	6.93
HD_M^I	0.003 ppm[a]	19.26[b]	0.001 ppm[a]	19.26[b]
	P05	**P95**	**P05**	**P95**
$HD_M^{I\ (c)}$	**0.0002 ppm**	0.06 ppm	**0.00005 ppm**	0.020 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b](Composite P95/P50) = $10^{[(\log 7.02)^2 + (\log 1)^2 + (\log 3)^2 + (\log 6.93)^2]^{0.5}} = 19.26$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic TCE inhalation exposure: Fetal heart malformations and kidney effects (Incidence = 5%)

Aspect	Fetal Heart Malformations		Kidney Effects (NTP)		Kidney Effects (Maltoni et al.)	
	P50	**P95/P50**	**P50**	**P95/P50**	**P50**	**P95/P50**
BMDL(HEC_{50})	0.012 ppm	1	0.042 ppm	1	0.19 ppm	1
BMD/BMDL ratio	3.12	3.12	1.45	1.45	1.60	1.60
BMD-to-ED_{50} adjustment	3	1.5	3	1.5	3	1.5
IPCS POD = ED_{50}(HEC_{50})	**0.11 ppm**	**3.35**	**0.18 ppm**	**1.73**	**0.9 ppm**	**1.86**
$AF_{Interspecies\text{-}BS}$	1	1	1	1	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3	1	3	1	3
$AF_{Intraspecies\ (I=5\%)}$	5.51	2.28	8.33	1.94	8.39	1.93
HD_M^I	0.020 ppm[a]	6.23[b]	0.022 ppm[a]	4.04[c]	0.109 ppm[a]	4.15[d]
	P05	**P95**	**P05**	**P95**	**P05**	**P95**
HD_M^I [(e)]	**0.003 ppm**	0.13 ppm	**0.005 ppm**	0.09 ppm	**0.026 ppm**	0.45 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b](Composite P95/P50) = $10^{[(\log 3.35)^2 + (\log 1)^2 + (\log 3)^2 + (\log 2{,}28)^2]^{0.5}} = 6.23$
[c](Composite P95/P50) = $10^{[(\log 1.73)^2 + (\log 1)^2 + (\log 3)^2 + (\log 1.94)^2]^{0.5}} = 4.04$
[d](Composite P95/P50) = $10^{[(\log 1.86)^2 + (\log 1)^2 + (\log 3)^2 + (\log 1.93)^2]^{0.5}} = 4.15$
[e] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic TCE inhalation exposure: Fetal heart malformations and kidney effects (Incidence = 1%)						
	Fetal Heart Malformations		Kidney Effects (NTP)		Kidney Effects (Maltoni et al.)	
Aspect	P50	P95/P50	P50	P95/P50	P50	P95/P50
BMDL(HEC_{50})	0.012 ppm	1	0.042 ppm	1	0.19 ppm	1
BMD/BMDL ratio	3.12	3.12	1.45	1.45	1.60	1.60
BMD-to-ED_{50} adjustment	3	1.5	3	1.5	3	1.5
IPCS POD = ED_{50}(HEC_{50})	**0.11 ppm**	**3.35**	**0.18 ppm**	**1.73**	**0.9 ppm**	**1.86**
$AF_{Interspecies\text{-}BS}$	1	1	1	1	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3	1	3	1	3
$AF_{Intraspecies\ (I=1\%)}$	11.18	3.20	20.06	2.55	20.26	2.54
HD_M^I	0.010 ppm[a]	7.43[b]	0.009 ppm[a]	4.68[c]	0.045 ppm[a]	4.80[d]
	P05	P95	P05	P95	P05	P95
HD_M^I [(e)]	**0.0014 ppm**	0.07 ppm	**0.002 ppm**	0.04 ppm	**0.009 ppm**	0.22 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b](Composite P95/P50) = $10^{[(\log 3.35)^2 + (\log 1)^2 + (\log 3)^2 + (\log 3.20)^2]^{0.5}} = 7.43$
[c](Composite P95/P50) = $10^{[(\log 1.73)^2 + (\log 1)^2 + (\log 3)^2 + (\log 2.55)^2]^{0.5}} = 4.68$
[d](Composite P95/P50) = $10^{[(\log 1.86)^2 + (\log 1)^2 + (\log 3)^2 + (\log 2.54)^2]^{0.5}} = 4.80$
[e] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic TCE inhalation exposure: Fetal heart malformations and kidney effects (Incidence = 0.5%)						
	Fetal Heart Malformations		Kidney Effects (NTP)		Kidney Effects (Maltoni et al.)	
Aspect	**P50**	**P95/P50**	**P50**	**P95/P50**	**P50**	**P95/P50**
BMDL(HEC_{50})	0.012 ppm	1	0.042 ppm	1	0.19 ppm	1
BMD/BMDL ratio	3.12	3.12	1.45	1.45	1.60	1.60
BMD-to-ED_{50} adjustment	3	1.5	3	1.5	3	1.5
IPCS POD = $ED_{50}(HEC_{50})$	**0.11 ppm**	**3.35**	**0.18 ppm**	**1.73**	**0.9 ppm**	**1.86**
$AF_{Interspecies\text{-}BS}$	1	1	1	1	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3	1	3	1	3
$AF_{Intraspecies\ (I=0.5\%)}$	14.48	3.63	27.67	2.82	27.98	2.81
HD_M^I	0.008 ppm[a]	8.01[b]	0.007 ppm[a]	4.99[c]	0.033 ppm[a]	5.11[d]
	P05	**P95**	**P05**	**P95**	**P05**	**P95**
HD_M^I [(e)]	**0.0010 ppm**	0.06 ppm	**0.0013 ppm**	0.03 ppm	**0.006 ppm**	0.17 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b](Composite P95/P50) = $10^{[(\log 3.35)^2 + (\log 1)^2 + (\log 3)^2 + (\log 3.63)^2]^{0.5}} = 8.01$
[c](Composite P95/P50) = $10^{[(\log 1.73)^2 + (\log 1)^2 + (\log 3)^2 + (\log 2.82)^2]^{0.5}} = 4.99$
[d](Composite P95/P50) = $10^{[(\log 1.86)^2 + (\log 1)^2 + (\log 3)^2 + (\log 2.81)^2]^{0.5}} = 5.11$
[e] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic TCE inhalation exposure: Fetal heart malformations and kidney effects (Incidence = 0.1%)						
	Fetal Heart Malformations		Kidney Effects (NTP)		Kidney Effects (Maltoni et al.)	
Aspect	**P50**	**P95/P50**	**P50**	**P95/P50**	**P50**	**P95/P50**
BMDL(HEC_{50})	0.012 ppm	1	0.042 ppm	1	0.19 ppm	1
BMD/BMDL ratio	3.12	3.12	1.45	1.45	1.60	1.60
BMD-to-ED_{50} adjustment	3	1.5	3	1.5	3	1.5
IPCS POD = $ED_{50}(HEC_{50})$	**0.11 ppm**	**3.35**	**0.18 ppm**	**1.73**	**0.9 ppm**	**1.86**
$AF_{Interspecies-BS}$	1	1	1	1	1	1
$AF_{Interspecies-TK/TD}$	1	3	1	3	1	3
$AF_{Intraspecies\ (I=0.1\%)}$	24.69	4.69	53.71	3.47	54.42	3.45
HD_M^I	0.005 ppm[a]	9.47[b]	0.003 ppm[a]	5.74[c]	0.017 ppm[a]	5.86[d]
	P05	**P95**	**P05**	**P95**	**P05**	**P95**
HD_M^I [(e)]	**0.0005 ppm**	0.04 ppm	**0.0006 ppm**	0.02 ppm	**0.003 ppm**	0.10 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b](Composite P95/P50) = $10^{[(\log 3.35)^2 + (\log 1)^2 + (\log 3)^2 + (\log 4.69)^2]^{0.5}} = 9.47$
[c](Composite P95/P50) = $10^{[(\log 1.73)^2 + (\log 1)^2 + (\log 3)^2 + (\log 3.47)^2]^{0.5}} = 5.74$
[d](Composite P95/P50) = $10^{[(\log 1.86)^2 + (\log 1)^2 + (\log 3)^2 + (\log 3.45)^2]^{0.5}} = 5.86$
[e] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic TCE inhalation exposure: Fetal heart malformations and kidney effects (Incidence = 0.05%)						
	Fetal Heart Malformations		Kidney Effects (NTP)		Kidney Effects (Maltoni et al.)	
Aspect	**P50**	**P95/P50**	**P50**	**P95/P50**	**P50**	**P95/P50**
BMDL(HEC_{50})	0.012 ppm	1	0.042 ppm	1	0.19 ppm	1
BMD/BMDL ratio	3.12	3.12	1.45	1.45	1.60	1.60
BMD-to-ED_{50} adjustment	3	1.5	3	1.5	3	1.5
IPCS POD = $ED_{50}(HEC_{50})$	**0.11 ppm**	**3.35**	**0.18 ppm**	**1.73**	**0.9 ppm**	**1.86**
$AF_{Interspecies\text{-}BS}$	1	1	1	1	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3	1	3	1	3
$AF_{Intraspecies\ (I=0.05\%)}$	30.39	5.18	69.53	3.76	70.51	3.74
HD_M^I	0.004 ppm[a]	10.16[b]	0.003 ppm[a]	6.09[c]	0.013 ppm[a]	6.21[d]
	P05	**P95**	**P05**	**P95**	**P05**	**P95**
HD_M^I [(e)]	**0.0004 ppm**	0.04 ppm	**0.0004 ppm**	0.02 ppm	**0.002 ppm**	0.08 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b](Composite P95/P50) = $10^{[(\log 3.35)^2 + (\log 1)^2 + (\log 3)^2 + (\log 5.18)^2]^{0.5}} = 10.16$
[c](Composite P95/P50) = $10^{[(\log 1.73)^2 + (\log 1)^2 + (\log 3)^2 + (\log 3.76)^2]^{0.5}} = 6.09$
[d](Composite P95/P50) = $10^{[(\log 1.86)^2 + (\log 1)^2 + (\log 3)^2 + (\log 3.74)^2]^{0.5}} = 6.21$
[e] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic TCE inhalation exposure: Fetal heart malformations and kidney effects (Incidence = 0.01%)						
	Fetal Heart Malformations		Kidney Effects (NTP)		Kidney Effects (Maltoni et al.)	
Aspect	**P50**	**P95/P50**	**P50**	**P95/P50**	**P50**	**P95/P50**
BMDL(HEC_{50})	0.012 ppm	1	0.042 ppm	1	0.19 ppm	1
BMD/BMDL ratio	3.12	3.12	1.45	1.45	1.60	1.60
BMD-to-ED_{50} adjustment	3	1.5	3	1.5	3	1.5
IPCS POD = $ED_{50}(HEC_{50})$	**0.11 ppm**	**3.35**	**0.18 ppm**	**1.73**	**0.9 ppm**	**1.86**
$AF_{Interspecies\text{-}BS}$	1	1	1	1	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3	1	3	1	3
$AF_{Intraspecies\ (I=0.01\%)}$	47.41	6.42	120.80	4.47	122.73	4.45
HD_M^I	0.002 ppm[a]	11.88[b]	0.0015 ppm[a]	6.93[c]	0.007 ppm[a]	7.06[d]
	P05	**P95**	**P05**	**P95**	**P05**	**P95**
HD_M^I [(e)]	**0.0002 ppm**	0.03 ppm	**0.0002 ppm**	0.01 ppm	**0.001 ppm**	0.05 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b](Composite P95/P50) = $10^{[(\log 3.35)^2 + (\log 1)^2 + (\log 3)^2 + (\log 6.42)^2]^{0.5}} = 11.88$
[c](Composite P95/P50) = $10^{[(\log 1.73)^2 + (\log 1)^2 + (\log 3)^2 + (\log 4.47)^2]^{0.5}} = 6.93$
[d](Composite P95/P50) = $10^{[(\log 1.86)^2 + (\log 1)^2 + (\log 3)^2 + (\log 4.45)^2]^{0.5}} = 7.06$
[e] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

The National Academies and WHO/IPCS have both recommended using the lower confidence limit (LCL) on a probabilistic dose-response distribution for use in decision-making, in place of a traditional reference dose (RfD) or reference concentration (RfC). The National Academies said in *Science and Decisions* that:

> multiple risk-specific doses could be provided…in the various risk characterizations that EPA produces to aid environmental decision-making.[41]

[41] National Research Council. (2009). Science and decisions: Advancing risk assessment, p. 140.

> A Risk-Specific Reference Dose: For quantal effects, the RfD can be defined to be the dose that corresponds to a particular risk specified to be de minimis (for example, 1 in 100,000) at a defined confidence level (for example, 95%) for the toxicity end point of concern.[42]

The WHO/IPCS said:

> the LCL of the HD_M^I can be used as a probabilistic RfD to replace the deterministic RfD. In this case, the probabilistic RfD is the dose that protects the population from a specified magnitude and incidence of effect with a pre-specified per cent coverage (confidence).[43]

Consistent with the guidance from the National Academies and the IPCS, we summarize the above results in the following table of the lower confidence limit (5th percentile or P05) risk-specific doses (HD_M^I) for multiple levels of risk (incidence or I).

Risk-specific dose estimates for non-cancer effects from chronic TCE inhalation exposure: lower confidence limit (P05) of HD_M^I (average daily concentration)

Incidence (I)	Autoimmunity	Decreased thymus weight	Fetal heart malformations	Kidney effects (NTP)	Kidney effects (Maltoni et al.)
5%	0.002 ppm	0.0007 ppm	0.003 ppm	0.005 ppm	0.026 ppm
1%	0.0011 ppm	0.0003 ppm	0.0014 ppm	0.002 ppm	0.009 ppm
0.5%	0.0008 ppm	0.0002 ppm	0.0010 ppm	0.0013 ppm	0.006 ppm
0.1%	0.0004 ppm	0.0001 ppm	0.0005 ppm	0.0006 ppm	0.003 ppm
0.05%	0.0003 ppm	0.0001 ppm	0.0004 ppm	0.0004 ppm	0.002 ppm
0.01%	0.0002 ppm	0.00005 ppm	0.0002 ppm	0.0002 ppm	0.001 ppm

[42] National Research Council. (2009). Science and decisions: Advancing risk assessment, p. 140.
[43] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, p. 12.

For comparison, we also provide the risk-specific doses corresponding to the median (P50) estimates of HD_M^I.

Risk-specific dose estimates for non-cancer effects from chronic TCE inhalation exposure: median (P50) estimate of HD_M^I (average daily concentration)					
Incidence (I)	**Autoimmunity**	**Decreased thymus weight**	**Fetal heart malformations**	**Kidney effects (NTP)**	**Kidney effects (Maltoni et al.)**
5%	0.027 ppm	0.008 ppm	0.020 ppm	0.022 ppm	0.109 ppm
1%	0.014 ppm	0.004 ppm	0.010 ppm	0.009 ppm	0.045 ppm
0.5%	0.011 ppm	0.003 ppm	0.008 ppm	0.007 ppm	0.033 ppm
0.1%	0.006 ppm	0.002 ppm	0.005 ppm	0.003 ppm	0.017 ppm
0.05%	0.005 ppm	0.002 ppm	0.004 ppm	0.003 ppm	0.013 ppm
0.01%	0.003 ppm	0.001 ppm	0.002 ppm	0.0015 ppm	0.007 ppm

Risk characterization of TCE non-cancer risks using the probabilistic dose-response analysis

We reviewed the risk-specific doses provided above and compared them to key exposure values from the EPA TSCA TCE risk evaluation and proposed rule. We found that:

- In this analysis, the immune-related effects have the lowest risk-specific dose estimates, with decreased thymus weight more sensitive than autoimmunity. Risk specific doses for immune-related effects, fetal heart defects and kidney effects (based on NTP study) are within a somewhat narrow range – for example, the risk-specific dose (lower confidence limit of the HD_M^I) for 0.1% (1-in-1000) incidence for these outcomes ranges from 0.0001 ppm to 0.0006 ppm (ADC).
- EPA has proposed a workplace exposure limit, or existing chemical exposure level (ECEL) of 0.0011 ppm for an 8-hour time-weighted average (TWA). For comparison to the risk-specific doses calculated in this appendix, which are based on continuous doses (i.e., average daily concentrations or ADCs), the continuous-dose equivalent of the proposed ECEL is equal to EPA's POD of 0.0037 ppm divided by EPA's benchmark margin of exposure of 10, or 0.00037 ppm.
- At the level of the proposed ECEL, the risk of non-cancer effects can be as high as >1% (1-in-100) for decreased thymus weight, about 0.1% (1-in-1000) for autoimmunity, about 0.05% (1-in-2000) for fetal heart malformation, and about 0.05% (1-in-2000) for kidney effects (based on NTP study).
- To protect workers from risks of 1-in-10,000 for all non-cancer risks would require an ECEL of 0.00005 ppm (ADC; or 0.00015 ppm as an 8-hr TWA), or about 7-fold lower than the ADC-equivalent (0.00037 ppm) of the proposed ECEL. This is based on the lower-

bound (5th percentile) estimated dose for a 0.01% risk of decreased thymus weight – the endpoint designated by EPA as the co-critical effect in the IRIS assessment of TCE. An ECEL protective at the 1-in-10,000 level based on autoimmunity or fetal heart defects would be set at 0.0002 ppm (ADC), or roughly half of EPA's proposed ECEL. To achieve desired protection levels of 1-in-100,000 or 1-in-1,000,000 for all non-cancer effects would require an even lower ECEL.

- EPA's exposure modeling finds that central tendency occupational exposures range from 0.02 ppm to 9.3 ppm (ADC),[44] depending on the condition of use. Central tendency exposure significantly exceed the levels associated with 5% risk of non-cancer effects (with 95% confidence) including immune effects, fetal heart malformations, and kidney effects. Risks are even greater for high-end exposures, which include modeled exposure levels (ADC) of 13.1 ppm (cold cleaning), 88.5 ppm (batch open-top vapor degreasing), and 694.8 ppm (conveyorized vapor degreasing).[45] Comparing the central tendency exposures with median (P50) estimates of the HD_M^I values, risks are approximately 5% (1-in-20) for multiple non-cancer health effects.

[44] US EPA. (2020), Risk Evaluation for Trichloroethylene, Table 2-13.
[45] US EPA. (2020), Risk Evaluation for Trichloroethylene, Table 2-13.

ATTACHMENT: Trichlorethylene intraspecies adjustment calculations [calculation of $GSD_{H\text{-}TK}$, $\log(GSD_{H\text{-}TK})$, and $\log(GSD_H)$ P50 and P95/P50 by endpoint, incorporating TCE-specific toxicokinetic data]

R code for calculation of $GSD_{H\text{-}TK}$ and $\log(GSD_{H\text{-}TK})$ using EPA HEC values[46]

```
formulas:
ln(1st) = mu - sigma(2.32)
ln(50th) = mu
sigma = ln(1st/50th)/-2.32
~~
Median z-zcore = 0
GM = exp(mu)
if have mean: ln(mean) = mu + 0.5*sigma^2

set.seed(385736289)
# make the table with the existing data:
kiel_immune <-c(0.092, 0.033, 2.79)
johnson_malformations <- c(0.012, 0.0037, 3.24)
maltoni_kidney <- c(0.19, 0.025, 7.60)
ntp_kidney <- c(0.042, 0.0056, 7.50)

df <- as.data.frame(rbind(kiel_immune, johnson_malformations, maltoni_kidney,
ntp_kidney))
colnames(df) <- c("HEC50", "HEC01", "ratio")

df <- rownames_to_column(df, var = "study") %>% as_tibble()

#calculate the mu, sigma, and GSD for each outcome
df <- df%>%
      mutate(mu = log(HEC50),
            sigma = log(HEC01/HEC50)/-2.32,
            GSD = exp(sigma),
            mean = mu + 0.5*sigma^2,
            loggsttk_tce = log10(GSD) # fix the value of GSD_TK
            )
```

study	HEC50	HEC01	ratio	mu	sigma	GSD	mean	loggsttk_tce
kiel_immune	0.092	0.0330	2.79	-2.385967	0.4419315	1.555709	-2.288315	0.1919284
johnson_malformations	0.012	0.0037	3.24	-4.422849	0.5071439	1.660542	-4.294251	0.2202498
maltoni_kidney	0.190	0.0250	7.60	-1.660731	0.8742018	2.396961	-1.278617	0.3796610
ntp_kidney	0.042	0.0056	7.50	-3.170086	0.8684927	2.383316	-2.792946	0.3771816

```
kable(df, format="latex", booktabs=TRUE) %>%
      kable_styling(latex_options="scale_down")
```

[46] EPA HEC_{99} values have been relabeled as HEC_{01} values.

R Code for calculating combined TK and TD population variability: log(GSD_H) P50 and P95/P50

Kiel immune

```
## loggsdtk <- exp(rnorm(10^7,m=log(0.167),sd=log(1.718))) ## Original
default for TK

loggsdtd <- exp(rnorm(10^7,m=log(0.221),sd=log(1.891))) ## Original default
for TD

# Kiel immune
loggsdtk <- df$loggsttk_tce[1] ## Replace with TCE value

loggsdtktd<-sqrt(loggsdtk^2+loggsdtd^2) ## Combine TK and TD independently

quantstktd<- quantile(loggsdtktd,prob=c(0.05,0.95)); ## Match 5th and 95th
percentiles to lognormal approximation
gmtktd <- sqrt(quantstktd[2]*quantstktd[1]);
p95p50tktd <- sqrt(quantstktd[2]/quantstktd[1]);
gsdtktd <- (p95p50tktd)^(1/qnorm(0.95))

## GM and GSD for combined TK and TD for
cat("GM", gmtktd," GSD", gsdtktd,"\n");

## GM 0.3693113 GSD 1.421962
#NEW for GM 0.3693113 GSD 1.421962
## P95/P50 and P05, P95 interval
cat("P95/P50", p95p50tktd," P05,P95",quantstktd,"\n")

## P95/P50 1.784344 P05,P95 0.2069731 0.6589784
# P95/P50 1.784344 P05,P95 0.2069731 0.6589784

## Monte Carlo for comparison
prob.vec<-seq(0.01,0.99,0.01);
immune_quantstktd.vec<-quantile(loggsdtktd,prob=prob.vec);
```

Johnson Malformation

```
# Johnson Malformation
loggsdtk <- df$loggsttk_tce[2] ## Replace with TCE value

loggsdtktd<-sqrt(loggsdtk^2+loggsdtd^2) ## Combine TK and TD independently

quantstktd<- quantile(loggsdtktd,prob=c(0.05,0.95)); ## Match 5th and 95th
percentiles to lognormal approximation
gmtktd <- sqrt(quantstktd[2]*quantstktd[1]);
p95p50tktd <- sqrt(quantstktd[2]/quantstktd[1]);
gsdtktd <- (p95p50tktd)^(1/qnorm(0.95))

## GM and GSD for combined TK and TD for
cat("GM", gmtktd," GSD", gsdtktd,"\n");

## GM 0.3948548 GSD 1.37636
#NEW forGM 0.3948548 GSD 1.37636
## P95/P50 and P05, P95 interval
```

```
cat("P95/P50", p95p50tktd," P05,P95",quantstktd,"\n")

## P95/P50 1.691196 P05,P95 0.2334766 0.6677769
# P95/P50 1.691196 P05,P95 0.2334766 0.6677769

## Monte Carlo for comparison
prob.vec<-seq(0.01,0.99,0.01);
malformation_quantstktd.vec<-quantile(loggsdtktd,prob=prob.vec);
```

Maltoni Kidney

```
# Maltoni Kidney
loggsdtk <- df$loggsttk_tce[3] ## Replace with TCE value

loggsdtktd<-sqrt(loggsdtk^2+loggsdtd^2) ## Combine TK and TD independently

quantstktd<- quantile(loggsdtktd,prob=c(0.05,0.95)); ## Match 5th and 95th
percentiles to lognormal approximation
gmtktd <- sqrt(quantstktd[2]*quantstktd[1]);
p95p50tktd <- sqrt(quantstktd[2]/quantstktd[1]);
gsdtktd <- (p95p50tktd)^(1/qnorm(0.95))

## GM and GSD for combined TK and TD for
cat("GM", gmtktd," GSD", gsdtktd,"\n");

## GM 0.5339963 GSD 1.215287
#NEW for GM 0.5339963 GSD 1.215287

## P95/P50 and P05, P95 interval

cat("P95/P50", p95p50tktd," P05,P95",quantstktd,"\n")

## P95/P50 1.378112 P05,P95 0.387484 0.7359066
# P95/P50 1.378112 P05,P95 0.387484 0.7359066

## Monte Carlo for comparison
prob.vec<-seq(0.01,0.99,0.01);
malt_kidney_quantstktd.vec<-quantile(loggsdtktd,prob=prob.vec);
```

NTP Kidney

```
# NTP Kidney
loggsdtk <- df$loggsttk_tce[4] ## Replace with TCE value

loggsdtktd<-sqrt(loggsdtk^2+loggsdtd^2) ## Combine TK and TD independently

quantstktd<- quantile(loggsdtktd,prob=c(0.05,0.95)); ## Match 5th and 95th
percentiles to lognormal approximation
gmtktd <- sqrt(quantstktd[2]*quantstktd[1]);
p95p50tktd <- sqrt(quantstktd[2]/quantstktd[1]);
gsdtktd <- (p95p50tktd)^(1/qnorm(0.95))

## GM and GSD for combined TK and TD for
cat("GM", gmtktd," GSD", gsdtktd,"\n");
```

```
## GM 0.5318582 GSD 1.21697
#NEW GM 0.5318582 GSD 1.21697
## P95/P50 and P05, P95 interval
cat("P95/P50", p95p50tktd," P05,P95",quantstktd,"\n")

## P95/P50 1.381253 P05,P95 0.3850549 0.7346305
# P95/P50 1.381253 P05,P95 0.3850549 0.7346305

## Monte Carlo for comparison
prob.vec<-seq(0.01,0.99,0.01);
NTP_kidney_quantstktd.vec<-quantile(loggsdtktd,prob=prob.vec);
```