February 13, 2024

Comments from Scientists, Academics, and Clinicians on the Tris(2-chloroethyl) Phosphate (TCEP) Draft Risk Evaluation Under TSCA

Submitted online via Regulations.gov to docket EPA-HQ-OPPT-2023-0265-0005

These comments are submitted on behalf of the undersigned scientists, academics, and clinicians. We declare that we have no direct or indirect financial or fiduciary interests in the subjects of these comments. The co-signers' institutional affiliations are included for identification purposes only and do imply institutional endorsement or support. We appreciate the opportunity to provide written comments on EPA's *Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP)* (hereafter referred to as the *TCEP Draft Risk Evaluation*) conducted under the Toxic Substances Control Act (TSCA),[1] which requires EPA to evaluate chemical risks based on the "best available science."[2] TCEP is a flame retardant chemical that is also used as a plasticizer and in paints and coatings.

EPA appropriately determined that TCEP as a whole chemical presents unreasonable risk to human health and the environment based on high risks of cancer (including some exposures exceeding 1-in-1,000 cancer risk) and non-cancer effects to workers, consumers and the general population from multiple TCEP conditions of use. However, the TCEP Draft Risk Evaluation also failed to evaluate risks for several conditions of use and relied on scientific methods and assessments that are not consistent with the "best available science,"[3] which can lead to underestimating risk to human and environmental health.

EPA continued to rely on a systematic review methodology that is not consistent with best practices, violating TSCA's "best available science" requirement. The National Academies of Sciences, Engineering, and Medicine ("NASEM") recommended the use of existing systematic review methods and improved approaches for TSCA risk evaluations in 2021, and EPA has still not implemented most of these recommendations.[4] EPA's Science Advisory Committee on Chemicals ("SACC") has also recommended best practices in systematic review to the Agency in multiple reports.[5] EPA should prepare a new TSCA systematic review methodology that is aligned with the best available scientific methods and issue updated draft systematic review protocols for all risk evaluations currently in development, including TCEP.

The TCEP Draft Risk Evaluation also relied on a hazard assessment that violates TSCA's "best available science" requirement. While EPA found that neurotoxicity, reproductive toxicity, developmental toxicity, kidney toxicity and cancer are all likely hazards of TCEP, it failed to

[1] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP).
[2] 15 USC §2625 (h).
[3] *Id.*
[4] National Academies of Sciences, Engineering, and Medicine (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations.
[5] U.S. EPA (2022). Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2022-2, p. 71. https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0414-0044.

provide quantitative estimates of non-cancer risk. We applied methods developed by the World Health Organization ("WHO") to quantify the non-cancer risk of male reproductive harm from chronic oral TCEP exposure, and found that EPA's current approach results in acceptance of exposures producing an upper bound risk of 1-in-40, a risk level 25,000 times higher than the target range that EPA typically applies for protection of carcinogenic risks (1-in-1,000,000). EPA also inappropriately stated that a threshold exists for cancer risk, and did not appropriately use science-based adjustment factors.

EPA also failed to adequately identify and calculate risks posed to potentially exposed or susceptible subpopulations ("PESS"), as required under TSCA.[6] Among the populations exposed to high risks from TCEP are breast-fed infants and people who consume fish (fishers in the general population, subsistence fishers and tribal populations), but EPA failed to consider individuals with pre-existing disease, genetic factors, lifestyle factors, or exposures to other chemical and non-chemical stressors that may increase susceptibility to harm from TCEP exposure. A failure to evaluate risk to these groups violates TSCA and results in risk characterization that is not representative of the human population.

EPA also failed to estimate risks for some TCEP conditions of use (for example, cushions in commercial furniture, consumer paints), claiming that it lacked sufficient data and that most of these uses have been discontinued EPA is obligated under TSCA to estimate risks for all conditions of use that are "reasonably foreseen."[7] Since any use that is voluntarily discontinued could resume, they should be considered "reasonably foreseen" and EPA should include risk estimates for these uses in the final TCEP risk evaluation. TSCA also requires EPA to consider "reasonably available information" when conducting risk evaluations,[8] which includes data and information that EPA "can reasonably generate, obtain, and synthesize for use in risk evaluations."[9] EPA failed to use its authority under TSCA to fill critical data gaps that could result in a more complete assessment of conditions of use. EPA also failed to use its authority to list TCEP to the Toxics Release Inventory ("TRI") in time to generate chemical release data to inform exposure assessments in the TCEP Draft Risk Evaluation, which precluded its ability to adequately assess fenceline community exposures and risks.

Finally, the TCEP Draft Risk Evaluation is the first EPA has released since it completed the initial 10 risk evaluations conducted under the amended TSCA in January 2021, and the first to not undergo panel peer review by EPA's SACC. EPA relied on the SACC to conduct panel peer reviews of the first 10 risk evaluations as well as EPA's proposed methods for fenceline assessment and systematic review to be used in the forthcoming risk evaluations, and provided EPA with numerous critical recommendations for improvement. For the TCEP Draft Risk Evaluation, EPA has chosen to conduct a letter peer review, which precludes collaboration and consensus among reviewers and transparency and public participation in the review process, all of which are critical to maintaining scientific integrity and addressing potential financial conflicts of interest among reviewers. SACC panel peer review would also enable the examination of cross-cutting issues that arise in multiple evaluations and the extent to which EPA has addressed previous SACC recommendations, including those made to improve the fenceline

[6] 15 U.S.C. §§ 2602(12).
[7] 15 USC §2602 (4).
[8] 15 U.S.C. § 2625(k).
[9] 40 C.F.R. § 702.33 (defining "reasonably available information").

screening methodology. We therefore urge EPA to conduct a SACC panel peer review for the TCEP Draft Risk Evaluation and all TSCA risk evaluations that are currently in development

Our detailed comments on the TCEP Draft Risk Evaluation address the following issues:

1. **EPA has made some improvements in its approach to systematic review in the TCEP Draft Risk Evaluation, but additional critical improvements are required.**
   a. **EPA has taken an important step by not using quantitative scoring for study quality evaluation. This should be made explicit in future systematic reviews and in an updated TSCA systematic review handbook.**
   b. **EPA has retained other problematic aspects of its approach to study quality evaluation that are inconsistent with best practices in systematic review.**
   c. **Publication of a chemical-specific systematic review protocol is a critical improvement, but further steps are required for consistency with best practices.**
      i. **A chemical-specific protocol has been prepared, but it was not released in advance of the risk evaluation.**
      ii. **The TCEP systematic review protocol is incomplete.**
      iii. **EPA references inconsistent PECO statements to identify relevant health effects studies that may inappropriately exclude non-apical effects such as cellular-level outcomes.**
      iv. **The TCEP protocol continues to use unclear terminology regarding evidence synthesis and integration.**
      v. **EPA should prepare a new TSCA systematic review methodology that is aligned with the best available scientific methods and issue updated draft systematic review protocols for all risk evaluations currently in development, including TCEP.**

2. **EPA should apply best available scientific methods to improve the TCEP hazard and risk assessment.**
   a. **EPA should apply existing methods to generate quantitative estimates of non-cancer risks from TCEP exposures.**
   b. **EPA's statements regarding a threshold for cancer are not scientifically supported and must be removed.**
   c. **EPA failed to apply an adjustment factor for the subchronic duration of the animal study used for estimating risk of male reproductive effects. This along with other appropriate factors needs to be added into the assessment.**

3. **EPA has not appropriately identified potentially exposed or susceptible subpopulations (PESS), as required by TSCA.**

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

Sincerely,

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Detailed comments:

1. **EPA has made some improvements in its approach to systematic review in the TCEP Draft Risk Evaluation, but additional critical improvements are required.**

    a. **EPA has taken an important step by not using quantitative scoring for study quality evaluation. This should be made explicit in future systematic reviews and in an updated TSCA systematic review handbook.**

We support EPA's decision to discard the quantitative scoring method, which was previously used in TSCA systematic reviews and methodology documents to assess study quality and exclude some studies from consideration based on their quantitative scores, despite repeated criticism from peer reviewers and public commenters. EPA originally put forward its approach to systematic review under TSCA in 2018.[10] In its review of the 2018 TSCA systematic review method, the National Academies of Sciences, Engineering, and Medicine ("NASEM") said:

> The reliance on numeric quality scores is problematic because scores do not distinguish between high- and low-quality studies, and the relationship between quality scores and an association or effect is inconsistent and unpredictable…More generally, the use of numerical scoring in critical appraisal does not follow standards for the conduct of systematic reviews.[11]
>
> Do not use numeric scores to evaluate studies.[12]

In 2021, EPA released its *Draft Toxic Substances Control Act (TSCA) Systematic Review Protocol* (hereafter referred to as the *2021 Draft TSCA Method*), asserting that this document addressed the NASEM recommendations. However, the 2021 draft retained a quantitative study scoring method. The review of the 2021 Draft TSCA Method by EPA's Science Advisory Committee on Chemicals ("SACC") reiterated the earlier NASEM recommendation:

> EPA should follow NASEM recommendations and best practices of systematic review by removing its approach to determine an overall quality score based on the combination of quantitative ratings of each individual data quality evaluation metric, which is essentially a quantitative scoring approach.[13]

Since completion of the SACC review of the 2021 method, EPA has not issued an updated systematic review methodology. The TCEP Draft Risk Evaluation and its systematic review protocol provide the first indication of how EPA will proceed in conducting TSCA systematic review. According to the risk evaluation and the protocol, EPA has now taken an important step by discarding the previous quantitative study scoring approach:

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[10] U.S. EPA (2018). Application of systematic review in TSCA risk evaluations.
[11] National Academies of Sciences, Engineering, and Medicine (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, p. 39.
[12] National Academies of Sciences, Engineering, and Medicine (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, p. 40.
[13] U.S. EPA (2022). Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2022-2, p. 71. https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0414-0044.

> EPA has updated the data quality evaluation process and will not implement quantitative methodologies to determine both metric and overall data or information source data quality determinations.[14]
>
> To respond to both SACC and public comments regarding the inappropriate use of quantitative methodologies to calculate both "Metric Rankings" and "Overall Study Rankings," *EPA decided to not implement quantitative methodologies to attain either metric and overall data/information source quality determinations.*[15] (emphasis in original)

EPA has instead rated each study quality evaluation metric using only the qualitative terms "high," "medium," "low," and "critically deficient." This is an important improvement to EPA's TSCA systematic review methodology and should be incorporated into an updated TSCA systematic review methodology handbook and applied in all future TSCA risk evaluations.

b. EPA has retained other problematic aspects of its approach to study quality evaluation that are inconsistent with best practices in systematic review.

The TCEP Draft Risk Evaluation retains certain study quality evaluation metrics that are not consistent with best practices, violating TSCA's requirement for EPA to rely on the "best available science"[16] when conducting risk evaluations and make decisions based on the "weight of the scientific evidence."[17] EPA's approach to study quality evaluation typically applies a set of metrics that assessors must evaluate for each relevant study during systematic review. The TCEP systematic review protocol states that the study quality metrics in the *2021 Draft TSCA Method* were retained for the TCEP risk evaluation without revision (with the exception of minor edits to one toxicology metric).[18] In applying the 2021 metrics, EPA inappropriately applied metrics to evaluate study quality based on statistical power and statistical significance, disregarding recommendations by the NASEM. In *The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations,* the NASEM stated that:

> Many markers of a high-quality study (e.g., whether a study's investigator has performed a sample size calculation and whether the study is reported adequately or has received appropriate ethical approvals) are unlikely to have any direct implication for the potential for a study to be affected by bias.[19]
>
> **Statistical power and statistical significance are not markers of risk of bias or quality**. **Statistical significance is not a measure of association or strength of association and should not be used to evaluate studies**. In fact, combining multiple

[14] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 34.
[15] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP) Supplemental File: Systematic Review Protocol for the Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 6.
[16] 15 U.S.C §2625 (h).
[17] 15 U.S.C §2625(i),
[18] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP) Supplemental File: Systematic Review Protocol for the Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 51. There are 22 metrics for evaluating epidemiology studies and 24 metrics for evaluation toxicology studies.
[19] National Academies of Sciences, Engineering, and Medicine (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, p. 35.

small, low-powered but similar studies in a synthesis is one of the potential benefits of systematic review.[20] (emphasis added)

Despite these very explicit NASEM statements about the inappropriateness of these metrics being included in the study quality evaluations; EPA continues to use "Statistical power (sensitivity)" as a study quality metric.[21] EPA must discontinue the use of these metrics in the TCEP Draft Risk Evaluation systematic review and for all risk evaluations that are currently in development.

c. Publication of a chemical-specific systematic review protocol is a critical improvement, but further steps are required for consistency with best practices.

i. A chemical-specific protocol has been prepared, but it was not released in advance of the TCEP Draft Risk Evaluation.

Along with TCEP Draft Risk Evaluation, EPA released a *Systematic Review Protocol for the Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP)* as a supplemental file. This is the first time EPA has released a chemical-specific systematic review protocol for a TSCA systematic review, which is consistent with best available scientific methods in systematic review and responds to recommendation of the NASEM and the SACC.

However, for future TSCA risk evaluations, EPA must publish a chemical-specific systematic review protocol for public comment first in the process of conducting each risk evaluation (well in advance of completing the draft risk evaluation), which is also consistent with best practices for systematic review.[22,23] EPA's TSCA program should follow the established procedures of EPA's IRIS program, which makes a draft protocol for each assessment publicly available in advance of its release for public comment. Following the public comment process, the IRIS program then publishes an updated protocol, as needed. For example, for the IRIS assessments of five per- and polyfluoroalkyl substances ("PFAS"), a draft protocol was made available for public comment for 45 days. The IRIS program then followed up with a revised protocol to address public comments, with documentation of the changes, that was published before the release of the PFAS draft assessments.[24] EPA should be following this same approach for all TSCA risk evaluations.

ii. The TCEP systematic review protocol is incomplete.

The application of systematic review in the TCEP Draft Risk Evaluation includes elements that are not included in the TCEP systematic review protocol. For example, EPA's TCEP systematic review protocol continues to require an overall study quality rating. EPA says that it is no longer

[20] National Academies of Sciences, Engineering, and Medicine (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, p. 39.
[21] U.S. EPA (2021). Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances Version 1.0, Table_Apx R-7. Evaluation Criteria for Epidemiological Studies, Metric 13.
[22] Institute of Medicine (2011). Finding what works in health care: Standards for systematic reviews.
[23] National Research Council (2014). Review of EPA's Integrated Risk Information System (IRIS) process.
[24] U.S. EPA (2021). Systematic Review Protocol for the PFAS IRIS Assessments. https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345065 (accessed 1 February 2024).

applying a quantitative scoring method to the overall study quality determination, but it does not discuss a new approach to determining overall study quality in either the TCEP systematic review protocol or in the draft risk evaluation. The draft risk evaluation's description of the approach to human health hazard assessment includes:

> EPA considered studies that received **low, medium, or high overall quality determinations** for hazard identification, evidence integration, and dose-response analysis…Information from studies of **uninformative** quality were only discussed on a case-by-case basis for hazard identification and evidence integration and were not considered for dose-response analysis. For example, if an uninformative study identified a significantly different outcome compared with high- or medium-quality studies and the uninformative rating was not expected to influence the specific results being discussed, EPA considered the uninformative study for the hazard outcome being considered.[25] (emphasis added)

The systematic review protocol, however, does not state that the overall quality ratings that may be selected for a study are high, medium, low, or uninformative, nor does it state how ratings of the many individual study metrics are combined to determine an overall rating. The study quality term "uninformative" does not appear anywhere in the protocol. This indicates that the TSCA Draft Risk Evaluation is inappropriately applying methods that are not stated in the systematic review protocol.

To adhere to best practices in systematic review, EPA should not derive an overall study rating, and instead implement the domain-based approach of the Navigation Guide.[26] However, if EPA continues to develop overall study ratings, the method for doing so must be stated in systematic review protocols prior to their application.

In addition, the TCEP Draft Risk Evaluation acknowledges that studies rated as uninformative may provide useful information (for example, in the quotation above); therefore, EPA should not use the term "uninformative" to describe relevant studies.

The TCEP systematic review protocol also fails to present a PECO statement for identifying relevant health hazard studies. A PECO (Population, Exposure, Comparator, Outcome) statement provides criteria used to decide which studies are relevant to include in a systematic review and is a critical element of any systematic review protocol.[27,28] EPA instead references the previous draft PECO statement for TCEP included in the 2021 Draft TSCA Method. Other elements of the hazard evidence identification process similarly reference the 2021 document, which is cited repeatedly in Section 5.5 "Environmental and Human Health Hazard" of the TCEP protocol. Similarly, as discussed above, the 2021 Draft TSCA Method is referenced for the approach to study quality evaluation. Each chemical-specific protocol should be a stand-alone document that

[25] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 247.
[26] Lam J, Koustas E, Sutton P, Padula AM, Cabana MD, Vesterinen H, Griffiths C, Dickie M, Daniels N, Whitaker E, Woodruff TJ. Exposure to formaldehyde and asthma outcomes: A systematic review, meta-analysis, and economic assessment. PLoS One. 2021 Mar 31;16(3):e0248258. doi: 10.1371/journal.pone.0248258.
[27] Institute of Medicine (2011). Finding what works in health care: Standards for systematic reviews.
[28] National Toxicology Program (2019). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration.

incorporates all systematic review methods to be applied in conducting the assessment, and should not simply reference previous protocols. Dividing the methods across multiple documents increases the risk of mistakes and confusion in conducting the risk evaluation, and makes review of the risk evaluation challenging for peer reviewers and the public. As recommended by the SACC,[29] EPA should develop a TSCA systematic review handbook that can be cited in future protocols for specific elements that do not vary across risk evaluations, but only a final handbook should be cited in protocols and not the *2021 Draft TSCA Method*.

iii. EPA references inconsistent PECO statements to identify relevant health effects studies that may inappropriately exclude non-apical effects such as cellular-level outcomes.

As noted above, the TCEP-specific systematic review protocol issued in 2023 references the *2021 Draft TSCA Method* concerning the PECO statement used for identification of evidence relevant to assessing TCEP's human health hazards. The protocol states:

> During data screening, EPA followed the process described in Appendix H.5.7 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021), to conduct TIAB and full-text screening for TCEP literature search results, as guided by the PECO statement. **The same PECO statement was used during TIAB and full-text screening** for references considered for the evaluation of environmental and human health hazard resulting from exposure to TCEP.[30] (emphasis added)

This statement is unclear because Appendix H.5.7 of the *2021 Draft TSCA Method* presents two different PECO statements: one to be used for title-abstract screening (Table_Apx H-31) and a different PECO to be used for full text screening Table_Apx H-33). The 2023 TCEP systematic review protocol does not indicate which PECO statement has been used in conducting the TCEP risk evaluation. One important difference between the two versions of the PECO statement is in specifying the outcomes considered relevant. In Table_Apx H-31, outcomes are:

> **Human**: All health outcomes (both cancer and non-cancer)
> **Animal and Plants**: All biological effects (including bioaccumulation from laboratory studies with concurrently measured water and tissue concentrations).
>
> **<u>Screener note:</u>**
> - **Measurable biological effects relevant for humans, animals and plants may include but are not limited to:** mortality, behavioral, population, cellular, physiological, growth, reproduction, systemic, point of contact effects.[31]

In Table_Apx H-33, important changes are made to the outcomes (additions are <u>underlined</u>, deletion shown in ~~strikethough~~):

[29] U.S. EPA (2022). Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2022-2, p. 33.
[30] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP) Supplemental File: Systematic Review Protocol for the Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), pp. 19-20.
[31] U.S. EPA (2021). Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances Version 1.0, Table_Apx H-31.

Human: All health outcomes (cancer and non-cancer) at the organ level or higher.
Animal and Plants: All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth.

Screener note:

- Measurable biological effects relevant for humans, animals and plants may include but are not limited to: mortality, behavioral, population, ~~cellular,~~ physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects.
- Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.[32]

The PECO statement in Table_Apx H-33 incorporates several limitations on health effects studies that are considered by EPA to be relevant for hazard identification. For human studies, this second PECO statement specifies that only studies "at the organ level or higher" are to be included. For animal studies, the second PECO statement specifies that only "apical" effects "measured at the organ level or higher" are to be included. The "screener note" for this PECO deletes "cellular" from the list of relevant measurable biological effects and indicates that "Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic."[33]

EPA says in the TCEP Draft Risk Evaluation that the same PECO was used for title-abstract and full-text screening, but it never states which version of the PECO was used. If EPA used the second version of the PECO (Table_Apx H-33) in conducting the risk evaluation, this would be contrary to the clear advice of the SACC, which said:

> EPA should not limit PECO/RESO statements to apical endpoints but consider expanding outcomes to include known upstream markers of effect such as biochemical markers of effect or other outcomes at the cellular level.[34]

Public comments on the 2021 Draft TSCA Method also detail the many problems with restricting the included studies to only those with apical outcomes or effects at the organ level or higher.[35] Inclusion of the PECO in the TCEP systematic review protocol would have avoided any confusion regarding which version of the PECO was applied. To adhere to best practices in systematic review, EPA should specify which PECO statement was used in the TCEP Draft Risk Evaluation, and include that PECO statement in the chemical-specific systematic review protocol.

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[32] U.S. EPA (2021). Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances Version 1.0, Table_Apx H-33.

[33] *Id.*

[34] U.S. EPA (2022). Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2022-2, p 29. https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0414-0044.

[35] Comment submitted by University of California, San Francisco Program on Reproductive Health and the Environment (UCSF PRHE): Comments on the Draft Toxic Substances Control Act (TSCA) Systematic Review Protocol. February 18, 2022. EPA-HQ-OPPT-2021-0414-0015. https://www.regulations.gov/comment/EPA-HQ-OPPT-2021-0414-0015.

iv. The TCEP protocol continues to use unclear terminology regarding evidence synthesis and integration.

EPA's use of unclear terminology for evidence synthesis and integration is an additional shortcoming of the TCEP systematic review protocol. The NASEM has recommended the use of the term "evidence synthesis" for assembling the evidence and drawing conclusions from a single evidence stream (e.g. toxicology, epidemiology), and "evidence integration" for the subsequent process of drawing conclusions considering all evidence streams. The SACC review of EPA's 2021 Draft TSCA Method document reiterated this recommendation:

> The EPA did not follow the recommendation of NASEM to separate evidence synthesis from evidence integration. To quote NASEM: "Evidence synthesis deals with more homogeneous data within a single stream, and evidence integration deals with more heterogeneous data from multiple streams."[36]
>
> The EPA could improve the clarify, transparency, and efficiency of its process by adopting the NASEM recommendation to use "synthesis" for drawing conclusions separately for each evidence stream (i.e., human, animal, and mechanistic evidence) and use 'integration' for drawing conclusions considering all evidence streams in combination – in context of the risk evaluation process/needs.[37]

In the TCEP systematic review protocol, however, EPA disregards the advice of both the NASEM and the SACC by continuing to use the term "evidence integration" for both steps.[38] This is one more area in which EPA's approach differs from best practices in systematic review, violating TSCA. In addition, failing to adopt consistent and vetted terminology decreases the clarity of the risk evaluation and creates confusion for peer reviewers and the public regarding the procedures applied to drawing conclusions from a single stream of evidence.

v. EPA should prepare a new TSCA systematic review methodology that is aligned with the best available scientific methods and issue updated draft systematic review protocols for all risk evaluations currently in development, including TCEP.

EPA has made some improvements in its approach to systematic review under TSCA, particularly regarding the discontinuation of its quantitative approach to study quality evaluation. However, EPA has not indicated if these improvements, including changes to study quality evaluation, will be applied in all future TSCA risk evaluations. EPA has instead stated that systematic review methods may vary across TSCA assessments. In doing so, EPA has failed to

[36] U.S. EPA (2022). Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2022-2, p 83. https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0414-0044.
[37] U.S. EPA (2022). Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2022-2, p 88. https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0414-0044.
[38] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP) Supplemental File: Systematic Review Protocol for the Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), pp. 73-75.

implement the more than 200 recommendations issued by the SACC in its review of the *2021 Draft TSCA Method*.

To adhere to best practices in systematic review, including those recommended by the NASEM and SACC, EPA should issue a new TSCA systematic review methodology document that states methods to be applied consistently to all TSCA rulemakings, which must include applying only qualitative methods for study quality evaluation. EPA should also prepare a chemical-specific systematic review protocol for each TSCA risk evaluation it conducts, and these protocols should be complete, stand-alone documents that do not refer to the *2021 Draft TSCA Method* for critical elements, such as PECO statements and methods for study quality evaluation. The chemical-specific protocols for ongoing and future risk evaluations should also be released for public comment well before the draft risk evaluations are completed to allow for public input, scrutiny, and opportunities for improvement. We urge EPA to consistently adopt the practices of the IRIS program for systematic review protocol development and publication across all EPA programs and offices.

2. EPA should apply best available scientific methods to improve the TCEP hazard assessment.

a. EPA should apply existing methods to generate quantitative estimates of non-cancer risks from TCEP exposures.

The TCEP Draft Risk Evaluation continues to rely on the scientifically-deficient methods for non-cancer dose-response analysis and risk characterization employed in previous TSCA risk evaluations. EPA's methods for non-cancer risk evaluation do not provide a quantitative estimate of risk. Instead, they rely on calculation of a margin of exposure ("MOE"), defined as:

> Margin of Exposure = Non-cancer point of departure / Human exposure.[39]

The MOE approach is a scientifically inappropriate approach for characterizing risk and is inconsistent with amended TSCA's requirements to use the "best available science" and to ensure protection of "potentially exposed and susceptible subpopulations" ("PESS").[40] Use of the MOE, which relies on a point of departure ("POD") with no extrapolation to lower doses, is a simplistic approach that only examines the ratio of the POD to the exposure level and determines whether this ratio "is interpreted as a human health risk of concern" or if "the risk is not considered to be of concern."[41] The MOE does not estimate the proportion of the exposed population projected to experience a specified health endpoint or the number of individuals affected, and it perpetuates the scientifically flawed notion that a "safe" or "no risk" level of

[39] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 296.
[40] 15 USC §2625 (h) and 15 USC §2602 (12).
[41] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 296.

chemical exposure can be identified for a diverse exposed population.[42,43] The National Academies[44] and the World Health Organization ("WHO")[45] have outlined more robust methods for risk estimation that more accurately account for variability and vulnerability across the human population and have been demonstrated in published case studies.[46,47,48,49]

We applied the WHO methodology to estimate risks of adverse effects from chronic inhalation and oral exposure to TCEP using EPA's identification of hazards and estimation of points of departure (PODs). Specifically, we estimated risks of male reproductive effects (decreased numbers of seminiferous tubules), using EPA's POD of 2.73 mg/kg-d for oral exposure and 14.9 mg/m^3 for inhalation exposure.[50] The PODs are drawn from a 35-day study in mice. EPA's approach to risk characterization (i.e. selection of a "benchmark MOE") included an interspecies adjustment factor and a human variability adjustment factor, but inappropriately omitted an adjustment factor accounting for the subchronic duration of the mouse study. Our application of the WHO methodology includes an adjustment for study duration along with the interspecies and human variability adjustments.

In applying the WHO methodology (see Technical Appendix for details) to risks of adverse male reproductive effects from oral exposure to TCEP, we found that:

- 0.06 mg/kg-d is the lower bound (95% confidence) chronic human oral dose at which male reproductive effects are expected in 1% of the population,
- 0.02 mg/kg-d is the lower bound (95% confidence) chronic human oral dose at which male reproductive effects are expected in 0.1% of the population,
- 0.008 mg/kg-d is the lower bound (95% confidence) chronic human oral dose at which male reproductive effects are expected in 0.01% (1-in-10,000) of the population.
- EPA's non-cancer risk characterization for oral exposure to TCEP uses 2.73 mg/kg-d as the point of departure, and a benchmark MOE of 30.[51] This means that EPA concludes "the risk is not considered to be of concern"[52] for any chronic exposure less than 2.73 mg/kg-d / 30 = 0.09 mg/kg-d. By applying the WHO methodology, we found that the upper bound risk at an exposure of 0.09 mg/kg-d is 2.5%, or 1-in-40. This risk level is

[42] Woodruff, T. J., Rayasam, S. D. G., Axelrad, D. A., Koman, P. D., Chartres, N., Bennett, D. H., Birnbaum, L. S., Brown, P., Carignan, C. C., Cooper, C., Cranor, C. F., Diamond, M. L., Franjevic, S., Gartner, E. C., Hattis, D., Hauser, R., Heiger-Bernays, W., Joglekar, R., Lam, J., . . . Zeise, L. (2023). A science-based agenda for health-protective chemical assessments and decisions: overview and consensus statement. Environ Health, 21(Suppl 1), 132. https://doi.org/10.1186/s12940-022-00930-3.

[43] McGartland, A., Revesz, R., Axelrad, D. A., Dockins, C., Sutton, P., Woodruff, T. J. (2017). Estimating the health benefits of environmental regulations. Science, 357(6350), 457-458. https://doi.org/10.1126/science.aam8204.

[44] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, Chapter 5.

[45] WHO. (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11, 2nd edition. https://www.who.int/publications/i/item/9789241513548.

[46] 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.

[47] Nielsen, G. H., Heiger-Bernays, W. J., Levy, J. I., White, R. F., Axelrad, D. A., Lam, J., Chartres, N., Abrahamsson, D. P., Rayasam, S. D. G., Shaffer, R. M., Zeise, L., Woodruff, T. J., Ginsberg, G. L. (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.

[48] Blessinger, T., Davis, A., Chiu, W. A., Stanek, J., Woodall, G. M., Gift, J., Thayer, K. A., Bussard, D. (2020). Application of a unified probabilistic framework to the dose-response assessment of acrolein. Environ Int, 143, 105953. https://doi.org/10.1016/j.envint.2020.105953.

[49] Ginsberg, G. L. (2012). Cadmium risk assessment in relation to background risk of chronic kidney disease. J Toxicol Environ Health A, 75(7), 374-390. https://doi.org/10.1080/15287394.2012.670895.

[50] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), Table 5-56.

[51] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), Table 5-56.

[52] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 296.

25,000 times higher than the target range that EPA typically applies for protection of carcinogenic risks (see below).

Following EPA's approach for extrapolating from oral exposures to inhalation exposures, the above values can be expressed as inhalation exposures in mg/m^3 by multiplying by 5.44.[53] For example, the lower bound (95% confidence) chronic human inhalation dose at which male reproductive effects are expected in 0.01% (1-in-10,000) of the population is 0.008 x 5.44 = 0.04 mg/m^3.

EPA must incorporate this approach to non-cancer dose-response and risk characterization in the final TCEP risk evaluation. Our analysis demonstrated that EPA's current approach results in acceptance of any exposures less than those producing an upper bound risk of 1-in-40, a risk level that is unacceptably high, even by EPA's own standards; EPA typically applies a target range of protection for carcinogenic risks of 1-in-10,000 (10^{-4}) to 1-in-1,000,000 (10^{-6}).[54] To offer the strongest public health protections, EPA should target any upper bound risks of non-cancer effects from TCEP exposure to be no more than 1-in-1,000,000 risk level.

b. EPA's statements regarding a threshold for cancer are not scientifically supported and must be removed.

EPA has appropriately modeled cancer dose-response as a linear relationship with no threshold, consistent with EPA's *Guidelines for Carcinogen Risk Assessment* for a carcinogen without an identified mode of action (MOA). However, EPA incorrectly states that because TCEP does not act through a known mutagenic MOA, there is a threshold below which there is no cancer risk:

> Because direct mutagenicity is not likely to be the predominant MOA, using linear low dose extrapolation is a health conservative analysis that would overpredict risks **assuming that TCEP acts via a threshold MOA**.[55] (emphasis added)

> Assuming all TCEP exposure is associated with some risk is likely to be health conservative because EPA does not believe that a mutagenic MOA is likely for TCEP and **a threshold below which cancer does not occur is expected to exist**. However, information is lacking with which to determine an appropriate threshold.[56] (emphasis added)

EPA provides no evidence to support its speculation that there is a threshold for TCEP's cancer risk. The absence of a known mutagenic MOA is not sufficient evidence to support these statements, as carcinogens acting by other MOAs can operate with no threshold. Further, the NASEM states that human variability, exposure to other chemicals, and background disease processes alone can result in linear dose-response relationships at low doses, regardless of whether mutagenic MOAs are known:

[53] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 530, Equation_Apx J-3.
[54] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 296.
[55] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 291.
[56] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 334 (repeated on page 418).

> Background exposures and underlying disease processes contribute to population background risk and can lead to linearity at the population doses of concern.[57]
>
> The current EPA practice of determining "nonlinear" MOAs does not account for mechanistic factors that can create linearity at low dose. The dose-response relationship can be linear at a low dose when an exposure contributes to an existing disease process…Effects of exposures that add to background processes and background endogenous and exogenous exposures can lack a threshold if a baseline level of dysfunction occurs without the toxicant and the toxicant adds to or augments the background process. Thus, even small doses may have a relevant biologic effect. That may be difficult to measure because of background noise in the system but may be addressed through dose-response modeling procedures. Human variability with respect to the individual thresholds for a nongenotoxic cancer mechanism can result in linear dose-response relationships in the population…In the laboratory, nonlinear dose-response processes—for example, cytotoxicity, impaired immune function and tumor surveillance, DNA methylation, endocrine disruption, and modulation of cell cycles—may be found to cause cancer in test animals. However, given the high prevalence of those background processes, given cancer as an end point, and given the multitude of chemical exposures and high variability in human susceptibility, the results may still be manifested as low-dose linear dose-response relationships in the human population.[58]

To adhere to best practices in risk characterization, EPA must remove the statements quoted above regarding a cancer threshold for TCEP from the TCEP Draft Risk Evaluation before it is finalized.

c. EPA incorrectly failed to apply an adjustment factor for the subchronic duration of the animal study used for estimating risk of male reproductive effects.

EPA omitted critical uncertainty factors (UFs) when characterizing non-cancer risk in the TCEP Draft Risk Evaluation, violating TSCA's "best available science" requirement. To estimate the non-cancer risks of TCEP, EPA used data from a 35-day mouse study (Chen et al. 2015)[59] to derive a POD for male reproductive effects (decreased number of and degeneration of seminiferous tubules), and employed the "benchmark MOE" bright-line approach to determine whether a chronic exposure is sufficiently below the POD. To calculate the benchmark MOE for risk characterization using the Chen et al. POD, EPA applied an interspecies uncertainty factor (UF) of 3 to account for uncertainties related to any animal-to-human differences remaining after calculation of a human equivalent concentration, and an intraspecies UF of 10 to account for uncertainties around human variability, for an overall UF of 30 (10 x 3). Thus, according to EPA, any exposure less than 30-fold lower than the POD "is interpreted as a human health risk of concern" and for exposures more than 30-fold lower "the risk is not considered to be of concern."[60]

[57] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 8.
[58] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, pp. 129-130.
[59] Chen, G; Jin, Y; Wu, Y; Liu, L; Fu, Z. (2015). Exposure of male mice to two kinds of organophosphate flame retardants (OPFRs) induced oxidative stress and endocrine disruption. Environ Toxicol Pharmacol 40: 310-318.
[60] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 296.

The section of the TCEP Draft Risk Evaluation on determination of the benchmark MOE makes no mention of the subchronic-to-chronic study duration UF that is usually applied to account for the lower dose that may produce the same effect if a chronic study were conducted. Inclusion of a subchronic UF would increase the benchmark MOE and in turn lower EPA's bright line for identifying risks of concern by a factor of 3 to 10. Failure to increase the benchmark MOE applied to the POD for male reproductive effects from Chen et al. with a subchronic UF therefore results in significant underestimation of risk, potentially by up to an order of magnitude. The risk evaluation acknowledges the uncertainty in using a POD from a subchronic study:

> it is uncertain whether the POD would be lower if Chen et al. (2015a) extended the exposure duration.[61]

> Using Chen et al. (2015a) to represent chronic exposure durations adds uncertainty to the risk evaluation. If the specific effect identified by Chen et al. (2015a) were measured in a chronic study in the same species starting in adolescence, the POD could be more sensitive. Therefore, it is possible that risks might be under-predicted.[62]

However, the risk evaluation lacks any discussion of the possible use of a subchronic UF to address that uncertainty. As discussed above, EPA must use probabilistic methods, including adjustment for the subchronic study duration, for dose-response assessment and risk characterization of non-cancer effects.

3. EPA has not appropriately identified potentially exposed or susceptible subpopulations (PESS), as required by TSCA.

In the TCEP Draft Risk Evaluation, EPA identifies the following groups as PESS:

> infants exposed through human milk from exposed individuals, children and male adolescents who use consumer articles or are among the exposed general population, subsistence fishers, tribal populations, pregnant women, workers and consumers who experience aggregated or sentinel exposures, fenceline communities who live near facilities that emit TCEP, and firefighters.[63]

Identification of PESS for each chemical assessed is a critical aspect of conducting risk evaluation under TSCA, and TSCA requires EPA to

> determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other nonrisk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation.[64]

[61] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 283.
[62] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 290.
[63] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 329.
[64] 15 USC §2605(b)(4)(A).

In the final 2017 TSCA Risk Evaluation Framework Rule, EPA defined PESS (using the statutory definition) as:

> a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly.[65]

To date, EPA has not employed a consistent or structured approach to identifying PESS in its TSCA risk evaluations, including scope documents for ongoing risk evaluations. EPA's approach and terminology for identifying PESS varied considerably in the first 10 risk evaluations. Among the inconsistencies were differences in whether health conditions related to a chemical's hazards were considered and whether fenceline communities were included.[66,67] For example, fenceline communities were identified as PESS for hexabromocyclododecane (HBCD), but not for 1,4-dioxane, 1-bromopropane (1-BP), or C.I. Pigment Violet 29 (PV-29); children were identified as PESS for 1-BP and HBCD, but not for 1,4-dioxane or PV-29.[68] To remedy the problem of inconsistent and incomplete identification of PESS, Rayasam et al. recommended that:

> EPA should prepare a comprehensive methodology to identify PESS and quantify their risks consistently within and across the TSCA risk evaluations.[69]

EPA has not yet proposed such a methodology. The consideration of PESS in Table 5-69 and Appendix D of the TCEP Draft Risk Evaluation is a useful initial step towards developing a consistent, structured approach to identifying PESS in TSCA risk evaluations. The table gives explicit consideration to each of the following factors that may lead to increased chemical exposures or susceptibility to harm from chemical exposures: lifestage, pre-existing disease, lifestyle activities, occupational and consumer exposures, socio-demographic factors, nutrition, genetics/epigenetics, unique activities, aggregate exposures, and other chemical and non-chemical stressors.

EPA, however, has violated TSCA's mandate to consider each of the relevant factors in identifying populations groups that "due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects."[70] The TCEP Draft Risk Evaluation says:

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[65] U.S. EPA (2017). Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act (Final) 40 CFR 702.

[66] Rayasam, S. D. G., Koman, P. D., Axelrad, D. A., Woodruff, T. J., Chartres, N. (2022). Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States. Environmental science & technology, 56(17), 11969–11982. https://doi.org/10.1021/acs.est.2c02079.

[67] McPartland, J., Shaffer, R. M., Fox, M. A., Nachman, K. E., Burke, T. A., Denison, R. A. (2022). Charting a Path Forward: Assessing the Science of Chemical Risk Evaluations under the Toxic Substances Control Act in the Context of Recent National Academies Recommendations. Environmental health perspectives, 130(2), 25003. https://doi.org/10.1289/EHP9649.

[68] Rayasam, S. D. G., Koman, P. D., Axelrad, D. A., Woodruff, T. J., Chartres, N. (2022). Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States. Table-S3 Environmental science & technology, 56(17), 11969–11982. https://doi.org/10.1021/acs.est.2c02079.

[69] Rayasam, S. D. G., Koman, P. D., Axelrad, D. A., Woodruff, T. J., Chartres, N. (2022). Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States. Environmental science & technology, 56(17), 11969–11982. https://doi.org/10.1021/acs.est.2c02079.

[70] 15 U.S.C. § 2605(b)(4)(A); *id*. § 2602(12).

> susceptibility factors that are generally considered to increase susceptibility of individuals to chemical hazards…include pre-existing diseases, alcohol use, diet, stress, among others. The effect of these factors on susceptibility to health effects of TCEP is not known; therefore, EPA is uncertain about the magnitude of any possible increased risk from effects associated with TCEP exposure.[71]

EPA's default approach seems to be that a susceptible subgroup will not be identified as PESS when there are not chemical-specific quantitative data on the magnitude of increased susceptibility for a given susceptibility factor. TSCA does not require chemical-specific quantitative data to identify or evaluate risk to PESS; TSCA simply requires EPA to rely on the "best available science" when evaluating risk to PESS. The best available science demonstrates that both *intrinsic* factors, which include biological traits like age, genetic makeup, and pre-existing health conditions, and *extrinsic* factors, which include psychosocial stress from experiencing income inequality, violence, racism, healthcare inequity, or food insecurity, can individually or collectively increase susceptibility to harm from chemical exposures.[72] EPA should therefore focus first on identifying susceptible subpopulations based on either chemical-specific evidence or the broader literature on intrinsic and extrinsic susceptibility factors, and then, as a separate step, consider how to account for the elevated risks for each group. The initial identification of PESS, however, should not be contingent on chemical-specific data to quantify risk for a susceptible subgroup. Once the appropriate groups are identified as PESS, EPA should then consider the availability of chemical -specific data. When such data are absent, the application of generic adjustment factors (beyond the customary 10x factor for human variability) should be applied to ensure that risks to PESS are not underestimated.[73]

Lifestage. EPA has appropriately identified infants (exposed from human breast milk), children, male adolescents and pregnant women as PESS. However, infants as PESS should not be restricted to human breast milk exposure, as infants are also likely to be exposed to TCEP via ingestion of household dust (e.g. hand to mouth behaviors). In addition, EPA's risk evaluation understates the magnitude of human breast milk exposures for some infants by assuming a maximum breastfeeding duration of one year. Data from the Centers for Disease Control and Prevention ("CDC") indicate that 37.6 percent of infants born in 2020 were breastfeeding at age 12 months, and 17.3 percent were breastfeeding at age 18 months.[74]

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[71] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 418.

[72] Woodruff, T. J., Rayasam, S. D. G., Axelrad, D. A., Koman, P. D., Chartres, N., Bennett, D. H., Birnbaum, L. S., Brown, P., Carignan, C. C., Cooper, C., Cranor, C. F., Diamond, M. L., Franjevic, S., Gartner, E. C., Hattis, D., Hauser, R., Heiger-Bernays, W., Joglekar, R., Lam, J., … Zeise, L. (2023). A science-based agenda for health- protective chemical assessments and decisions: Overview and consensus statement. Environmental Health,21(1), 132. https://doi.org/10.1186/s12940-022-00930-3; Rachel Morello-Frosch et al., *Understanding the Cumulative Impacts of Inequalities in Environmental Health: Implications for Policy*, 30 Health Affs. 879 (2011), https://www.healthaffairs.org/doi/pdf/10.1377/hlthaff.2011.0153; Cliona M. McHale et al., *Assessing Health Risks from Multiple Environmental Stressors: Moving from G×E to I×E*, 775 Mutational Rsch. 11 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5863617/; Devon C. Payne-Sturges et al*., Methods for Evaluating the Combined Effects of Chemical and Nonchemical Exposures for Cumulative Environmental Health Risk Assessment*, 15 Int'l. J. Env't Rsch. & Pub. Health 2797 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6313653/; Gilbert C. Gee et al., *Environmental Health Disparities: A Framework Integrating Psychosocial and Environmental Concepts*, 112 Env't Health Persps. 1645 (2004), https://doi.org/10.1289/ehp.7074; Gina M. Solomon et al., *Cumulative Environmental Impacts: Science and Policy to Protect Communities* 37 Ann. Rev. Pub. Health 83, 87–88 (2016), https://www.annualreviews.org/doi/pdf/10.1146/annurev-publhealth-032315-021807; Patricia D. Koman et al., *Population Susceptibility: A Vital Consideration in Chemical Risk Evaluation Under the Lautenberg Toxic Substances Control Act*, 17 PLoS Biology 1, 4 (2019), https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3000372.

[73] Julia R. Varshavsky et al., Current Practice and Recommendations for Advancing How Human Variability and Susceptibility Are Considered in Chemical Risk Assessment, 21(Suppl 1) Env't Health Article No. 133, at 3 (2023), https://doi.org/10.1186/s12940-022-00940-1.

[74] Centers for Disease Control and Prevention (2024). Results: Breastfeeding Rates. National Immunization Survey - Child (NIS-Child). https://www.cdc.gov/breastfeeding/data/nis_data/results.html (accessed 30 January 2024).

EPA's approach to identifying susceptible lifestages is too narrow. Enhanced susceptibility of infants, children, women of reproductive age and people of age 65 years or older is well-established, and these groups should be identified as PESS for each TSCA risk evaluation, regardless of whether there are chemical-specific data to quantify those differences. Further, EPA makes no adjustments to quantify the enhanced risks to the susceptible lifestages. Instead, EPA applies the customary 10x human variability factor, which is routinely applied in EPA risk assessments and is not sufficient to address human variability in response to chemical exposures.[75] EPA acknowledges that "The magnitude of differences in toxicokinetics and toxicodynamics for some individuals may be greater than accounted for by the UF_H of 10,"[76] but it then continues to apply this insufficient value. The WHO's International Programme on Chemical Safety ("IPCS") found that an adjustment factor of approximately 42X is needed to account for the range in human variability in response to chemical exposure when estimating a risk-specific dose intended for a risk of 1% (1-in-100), with larger factors necessary for protection of the population at lower risk levels.[77]

Pre-existing disease. EPA did not identify any groups as PESS based on pre-existing disease or health conditions. EPA identified neurotoxicity, reproductive toxicity, developmental toxicity, and kidney toxicity as likely hazards of TCEP, but it disregarded the prevalence in the U.S. population of vulnerabilities to these hazards. For example, the CDC estimates that 14% of U.S. adults have chronic kidney disease; this affects not just older adults, but also 6% of adults ages 18-44 years.[78] Given that kidney toxicity is a hazard of TCEP, people with chronic kidney disease should be considered a susceptible subpopulation in the TCEP Draft Risk Evaluation. Risk estimation for this group should also incorporate an adjustment factor (in addition to the customary human variability factor) representing the enhanced risk of kidney effects from TCEP exposure. Similarly, population groups with biological susceptibility to the neurotoxic, reproductive and/or developmental effects of TCEP should also be considered PESS, and appropriate adjustments to the estimation of risks of each outcome for these groups should be made.

Individual activities. Subsistence fishers (including tribal populations) are identified as PESS in the TCEP Draft Risk Evaluation based on elevated TCEP exposures. However, no "lifestyle" or "individual" activities are identified for enhanced susceptibility. EPA mentions smoking as a lifestyle factor that could influence susceptibility to chemical exposures, but it failed to identify smokers as PESS because it found no chemical-specific information. Smoking tobacco has numerous biological effects that could enhance susceptibility to the hazards of TCEP, such as adverse effects on the kidney. Smokers should be considered PESS even if there is not direct TCEP-specific evidence. In addition, we recommend using the term "individual activities" instead of "lifestyle activities."

[75] Julia R. Varshavsky et al., Current Practice and Recommendations for Advancing How Human Variability and Susceptibility Are Considered in Chemical Risk Assessment, 21(Suppl 1) Env't Health Article No. 133, at 3 (2023), https://doi.org/10.1186/s12940-022-00940-1.
[76] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), Table 5-69.
[77] WHO (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11, 2nd edition, Table 4.5. https://www.who.int/publications/i/item/9789241513548.
[78] Centers for Disease Control and Prevention (2023). Chronic Kidney Disease in the United States, 2023. https://www.cdc.gov/kidneydisease/publications-resources/CKD-national-facts.html.

Occupational exposures. EPA appropriately identified firefighters as an occupational group with elevated TCEP exposures. However, in discussing the relevant evidence, EPA omitted the important 2022 study by Trowbridge *et al*.[79] EPA also failed to consider firefighter exposures in its unreasonable risk determination for TCEP. According to Appendix D of the TCEP Draft Risk Evaluation, firefighter exposures are classified as "background" and "EPA did not identify sources of increased COU or pathway specific exposure for firefighters."[80] However, it is highly likely that elevated firefighter exposures arise from the presence of consumer and commercial products containing TCEP in burning structures, and firefighter exposures should be a consideration in EPA's unreasonable risk determinations for those products. In addition, EPA failed to consider that workers may be occupationally exposed to other chemicals sharing common adverse outcomes with TCEP (e.g. neurological, reproductive and kidney effects). People who experience occupational exposures to other toxic chemicals that are linked to similar adverse health outcomes as TCEP can have enhanced susceptibility to the adverse effects of TCEP and should be identified and evaluated as PESS in the TCEP Draft Risk Evaluation.

Geographic factors. Geographic factors were not included in Table 5-69 of the TCEP Draft Risk Evaluation. However, EPA has considered geographic factors as contributors to PESS in previous assessments and appropriately identified fenceline communities near facilities that emit TCEP as PESS in the TCEP Draft Risk Evaluation, so it is unclear why an entry for this factor is omitted from Table 5-69. Although EPA has estimated exposures to fenceline communities, it has not considered the many characteristics that can enhance susceptibility to the effects of TCEP and are common in fenceline communities. In general, people living in fenceline communities are more likely to be people of color and are more likely to experience increased exposures to multiple chemical and non-chemical stressors that make them more susceptible to harm, including a broad range of non-chemical stressors like pre-existing disease, racism, and poverty.[81] EPA is therefore required under TSCA to account for these enhanced susceptibilities when evaluating risks to fenceline communities.

Socio-demographic factors. The TCEP Draft Risk Evaluation says "EPA did not evaluate exposure differences between racial groups."[82] At a minimum, EPA should assess the demographic profile of populations living in locations likely to experience elevated exposures (e.g. sites with TCEP in groundwater, sites near facilities producing, using, or disposing of TCEP). EPA conducted such an analysis for the proposed TSCA risk management rule for trichloroethylene,[83] and this approach should be incorporated in all TSCA risk evaluations. If EPA does not have the data necessary to conduct a robust, accurate, and scientifically-sound environmental justice analysis of chemicals subject to TSCA risk evaluation, it should develop and execute a strategy for obtaining the data and analyzing it. For example, EPA could use its TSCA authorities to gather information from industry on TCEP manufacturing/processing sites and products containing TCEP. EPA failed to use its authority to list TCEP to the Toxics Release

[79] Trowbridge J, Gerona R, McMaster M, Ona K, Clarity C, Bessonneau V, Rudel R, Buren H, Morello-Frosch R (2022). Organophosphate and Organohalogen Flame-Retardant Exposure and Thyroid Hormone Disruption in a Cross-Sectional Study of Female Firefighters and Office Workers from San Francisco. Environ Sci Technol. 56(1):440-450. Doi: 10.1021/acs.est.1c05140.

[80] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), Table_Apx D-1.

[81] Ronald White et al., Env't Just. Health All. For Chem. Pol'y Reform et al., Life at the Fence line: Understanding Cumulative Health Hazards in Environmental Justice Communities (2018), https://ej4all.org/assets/media/documents/Life%20at%20the%20Fenceline%20-%20English%20-%20Public.pdf.

[82] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), Table 5.69.

[83] U.S. EPA (2023). Economic Analysis of the Proposed Regulation of Trichloroethylene Under TSCA Section 6(a), Section 10.6.

Inventory ("TRI") in time to generate chemical release data to inform exposure assessments in the TCEP Draft Risk Evaluation, which precluded its ability to adequately assess fenceline community exposures and risks.

The TCEP Draft Risk Evaluation says:

> EPA did not identify specific evidence that sociodemographic factors influence susceptibility to TCEP although it is known that they can affect susceptibility to disease.[84]

TSCA requires EPA to account for enhanced susceptibility to chemical exposures in chemical risk evaluations. EPA must account for socio-demographic factors associated with enhanced susceptibility in its identification of PESS and in analyzing risks to those groups. For example, people experiencing poverty or racial discrimination may experience psychosocial stress[85,86,87,88,89] that can enhance susceptibility to the adverse effects of toxic chemicals including TCEP, and should be identified as PESS even if there is not direct chemical-specific evidence.

Nutrition. EPA correctly states that "Nutrition can affect susceptibility to disease generally," but it did not identify any PESS because it "did not identify specific evidence that nutritional factors influence susceptibility to TCEP."[90] People with food insecurity or lack of access to nutritious food can experience enhanced susceptibility to the adverse effects of toxic chemicals, including TCEP, and should be identified as PESS even if there is not direct chemical-specific evidence.

Genetics. EPA states that "genetic disorders may increase susceptibility to male reproductive effects; this was addressed through a 10× UF for human variability."[91] EPA assumes that a 10-fold factor is sufficient to account for human variability in response to chemical exposures, including the impacts of genetics and all the other susceptibility factors in the table, even though the National Academies[92] and the WHO[93] have both compiled evidence that a larger factor is necessary to ensure public health protection. EPA must accordingly increase the uncertainty factor it uses to account for enhanced susceptibility to TCEP based on genetic disorders.

Aggregate exposures. EPA has only partially accounted for aggregate exposure in the TCEP Draft Risk Evaluation. EPA aggregated across exposure pathways for consumers and separately for workers, but it did not aggregate exposures for workers who also experience consumer and general population exposures, and did not aggregate exposures for consumers who have

[84] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), Table 5-69.
[85] Clougherty J. and C. Rider (2020). Integration of psychosocial and chemical stressors in risk assessment. *Current Opinion in Toxicology* 22: 25-29.
[86] Couch, S. R., and C.J. Coles (2011). Community Stress, Psychosocial Hazards, and EPA Decision-Making in Communities Impacted by Chronic Technological Disasters. *American Journal of Public Health,* 101(S1), S140-S148.
[87] Gee, G.C., and D.C. Payne-Sturges (2004). Environmental Health Disparities: A Framework Integrating Psychosocial and Environmental Concepts. *Environmental Health Perspectives,* 112(17), 1645-1653.
[88] McEwen, B.S., and P. Tucker (2011). Critical Biological Pathways for Chronic Psychosocial Stress and Research Opportunities to Advance the Consideration of Stress in Chemical Risk Assessment. *American Journal of Public Health,* 101(S1), S131-S139.
[89] Padula, A.M., Z. Rivera-Núñez, and E.S. Barrett (2020). Combined Impacts of Prenatal Environmental Exposures and Psychosocial Stress on Offspring Health: Air Pollution and Metals. *Current Environmental Health Report* 7: 89–100.
[90] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), Table 5-69.
[91] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), Table 5-69.
[92] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, Table 4-1.
[93] WHO (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11, 2nd edition, Table 4.5. https://www.who.int/publications/i/item/9789241513548.

exposure to multiple consumer products or who experience general population exposures. EPA says that these exposures were not aggregated because it did not have data indicating such co-exposures. EPA should not require chemical-specific evidence to conduct aggregate exposure evidence. It can reasonably model scenarios in which exposures are combined across products and across worker, consumer and general population exposures. For example, some individuals with occupational exposure to TCEP are likely to live close to where they work and would therefore also be exposed as members of the general population.

Other chemical and non-chemical stressors. EPA's approach to consideration of other stressors in identifying PESS and accounting for risks to PESS is too narrow. EPA mentions experimental findings of benzo-a-pyrene interactions with TCEP, but does not specifically identify persons with exposure to benzo-a-pyrene as PESS and makes no effort to account for the elevated risks arising from those exposures. Further, EPA does not give any consideration to other chemical stressors that share common adverse outcomes with TCEP. For example, the draft risk evaluation identifies "differences in numbers and degeneration of seminiferous tubules" as the "Most Critical Endpoint" among TCEP non-cancer effects.[94] EPA's 2023 draft document on application of cumulative risk assessment to phthalates under TSCA discusses the extensive experimental evidence of seminiferous tubule atrophy/degeneration from phthalate exposure and finds that it is "a sensitive, adverse effect frequently reported by board certified pathologists."[95]

EPA should consider males who experienced prenatal exposure to phthalates as a PESS for the TCEP Draft Risk Evaluation to recognize that pre-existing damage to the seminiferous tubules that may have occurred from phthalate exposure would make males more vulnerable to further harm from TCEP exposure. The consequence of early-life phthalate exposure would be that the risks of male reproductive harm would occur at lower TCEP doses than EPA has estimated in the TCEP Draft Risk Evaluation, and an adjustment factor should be incorporated to account for that increased vulnerability to damage of the seminiferous tubules. In addition, TCEP and phthalates can be used together in polyvinyl chloride,[96] further supporting the joint consideration of TCEP and phthalates under TSCA. Direct experimental evidence of joint action of phthalates and TCEP is not necessary; the joint action can be inferred from the evidence of a common adverse outcome. Populations exposed to other chemicals sharing common adverse effects with TCEP should similarly be identified as PESS.

EPA should expand its identification of PESS based on the factors described above and should expand on the approach of Table 5-69 and Appendix D to develop a comprehensive, consistent, and structured methodology for identifying PESS in all TSCA risk evaluations.

[94] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 289.
[95] U.S. EPA (2023). Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act, p. 69.
[96] European Union Risk Assessment Report: Tris(2-chloroethyl) Phosphate, TCEP. July 2009. https://echa.europa.eu/documents/10162/2663989d-1795-44a1-8f50-153a81133258

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

In the *TCEP Draft Risk Evaluation*, EPA selected male reproductive effects (decreased numbers of seminiferous tubules) for estimation of risks from chronic oral and inhalation exposures. 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. For the TCEP male reproductive effects, the *TCEP Draft Risk Evaluation* concludes that an MOE of 30 or more indicates that "the risk is not considered to be of concern."[97] EPA's approach to risk characterization does not actually estimate risks of adverse effects in the population with chronic exposure to TCEP, but instead simply applies a "bright line" judgment of whether or not the MOE is adequate. 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),[98] 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.[99,100,101,102,103]

We applied the IPCS approach for "quantal-deterministic" endpoints and the "approximate probabilistic" calculation (see IPCS report Fig 3.5, panel C)[104] to estimate risks of reduced numbers of seminiferous tubules from chronic oral and inhalation exposure to TCEP. The analysis involved the following steps:

1. Derivation of IPCS POD and corresponding uncertainty adjustments
2. Application of study duration adjustments
3. Application of interspecies adjustments
4. Application of intraspecies adjustments
5. Calculation of HD_M^I - the human dose (HD) of TCEP 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 50th percentile value (P50) as a central estimate and the ratio of 95th percentile to 50th percentile (P95/P50) as a measure of uncertainty. All POD and HD_M^I values presented in this analysis are for continuous exposures.

We demonstrate each of these steps starting with the EPA oral exposure POD to derive a set of oral HD_M^I values for different levels of population incidence, then discuss derivation of a corresponding set of inhalation exposure HD_M^I values.

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[97] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 296.

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

[99] 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.

[100] Nielsen, G. H., Heiger-Bernays, W. J., Levy, J. I., White, R. F., Axelrad, D. A., Lam, J., Chartres, N., Abrahamsson, D. P., Rayasam, S. D. G., Shaffer, R. M., Zeise, L., Woodruff, T. J., Ginsberg, G. L. (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.

[101] 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.

[102] 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

[103] 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.

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

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 benchmark dose, lower confidence limit (BMDL) and applied adjustments provided by the IPCS methodology. At the same time, we incorporated quantitative uncertainties for each of these adjustments.

EPA used a benchmark response (BMR) of 5% to derive the BMDL for decreased numbers of seminiferous tubules from TCEP exposure. The chronic oral non-cancer $BMDL_{05}$ value expressed as a human equivalent dose (HED) is 2.73 mg/kg-d.[105]

The first POD adjustment in the IPCS methodology is to convert the $BMDL_{05}$ to a BMD_{05} as follows:

$$BMD_{05}(HED) = BMDL_{05}(HED) \times (BMD_{05} / BMDL_{05})$$

This adjustment is used because the *Draft TCEP Risk Evaluation* does not report the BMD_{05} as an HED. However, both the BMD_{05} and $BMDL_{05}$ are available in terms of the animal dosage, before derivation of the HED, and can be used for computation of the BMD_{05} / $BMDL_{05}$ ratio. The necessary values for this ratio were obtained from EPA's supplemental file of BMD modeling results,[106] and the ratio calculated as follows:

$$BMD_{05} / BMDL_{05} = 28.8 / 20.8 = 1.38$$

The $BMD_{05}(HED)$ is then:

$$BMD_{05}(HED) = 2.73 \text{ mg/kg-d} \times 1.38 = 3.77 \text{ mg/kg-d}$$

In the IPCS methodology, uncertainty in the BMD is represented by the P95/P50 ratio, which is equal to the same ratio of BMD / BMDL, or 1.38.

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 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 $(P95/P50)^2$."[107]

The median (P50) estimate of the ED_{50} is then derived by multiplying the $BMDL_{05}(HED)$ 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:

[105] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), Table 5-49.
[106] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP) Supplemental File: Benchmark Dose Modeling Results for TCEP, Table 1-2.
[107] 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.

Determination of point of departure (POD) and its uncertainty[a] for probabilistic dose-response analysis of oral chronic TCEP exposure		
Aspect	**P50**	**P95/P50**
$BMDL_{05}$(HED)[b]	2.73 mg/kg-d	1
BMD/BMDL ratio[c]	1.38	1.38
BMD-to-ED_{50} adjustment[d]	3.0	1.5
IPCS POD = ED_{50}(HED)	**11.3 mg/kg-d**[e]	**1.68**[f]

[a] Uncertainty is expressed as the ratio of the 95th percentile (P95) to the 50th percentile (P50)
[b] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), Table 5-49.
[c] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP) Supplemental File: Benchmark Dose Modeling Results for TCEP, Table 1-2.
[d] 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.
[e] ED_{50}(HED) = $BMDL_{05}$(HED) x BMD/BMDL ratio x BMD-to-ED_{50} adjustment
[f] (Composite P95/P50) = $10^{[(\log 1)^2 + (\log 1.38)^2 + (\log 1.5)^2]^{0.5}} = 1.68$

Step 2: Application of study duration (subchronic-to-chronic) adjustments

In the study by Chen et al. that provides the finding of male reproductive effects and the $BMDL_{05}$ used by EPA for estimating risks, mice were exposed for a subchronic duration of 35 days rather than a chronic duration.[108] The section of the *TCEP Draft Risk Evaluation* on determination of the benchmark MOE[109] makes no mention of the subchronic-to-chronic study duration uncertainty factor that is usually applied to account for the lower dose that may produce the same effect if a chronic study were conducted, even though this is a standard element of EPA's methodology for non-cancer dose-response assessment.[110] We applied the IPCS adjustments for subchronic-to-chronic study duration: a central estimate (P50) of 2, and representing uncertainty with a P95/P50 factor of 4.[111]

In the IPCS approximate probabilistic calculation template, those values are entered as follows:

Duration adjustments ($AF_{Subchronic}$) for probabilistic dose-response analysis of chronic TCEP exposure		
Aspect	**P50**	**P95/P50**

[108] Chen, G; Jin, Y; Wu, Y; Liu, L; Fu, Z. (2015). Exposure of male mice to two kinds of organophosphate flame retardants (OPFRs) induced oxidative stress and endocrine disruption. Environ Toxicol Pharmacol 40: 310-318.
[109] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 286, "Uncertainty Factors Used for Non-cancer Endpoints."
[110] U.S. EPA (2002). A Review of the Reference Dose and Reference Concentration Processes, p. 4-45. EPA/630/P-02/002F.
[111] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.2.

$AF_{Subchronic}$	2	4

Step 3: Application of interspecies (animal-to-human) 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 $BMDL_{05}$ values incorporate 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).

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.[112] We incorporated these IPCS recommendations, which are entered In the IPCS approximate probabilistic calculation template as follows:

Interspecies adjustments ($AF_{Interspecies}$) for probabilistic dose-response analysis of chronic TCEP exposure		
Aspect	**P50**	**P95/P50**
$AF_{Interspecies-BS}$	1	1
$AF_{Interspecies-TK/TD}$	1	3

Step 4: Application of intraspecies (human variability) adjustments

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 from the POD to lower levels of incidence. The IPCS report provides $AF_{intraspecies}$ for several incidence (I) values. The P50 and P95/P50 values for $AF_{intraspecies}$ provided by IPCS for several values of I, along with additional values of I of interest for this analysis, are provided in the following table:

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

Lognormal approximation of uncertainty distributions for intraspecies variability ($AF_{Intraspecies}$) for varying levels of population incidence (I)		
Incidence (I)	**$AF_{Intraspecies}$**	
	P50	**P95/P50**
5%[a]	4.98	2.82
2.5%[b]	6.77	3.43
1%[a]	9.69	4.32
0.1% (1-in-1,000)[a]	20.42	6.99
0.01% (1-in-10,000)[a]	37.71	10.39
0.001% (1-in-100,000)[b]	64.25	14.65

[a] IPCS Table 4.5
[b] Calculated for this analysis using the same methods that were used to derive IPCS Table 4.5

Step 5: 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 this analysis, the "M" represents the male reproductive effect of reduced numbers of seminiferous tubules. The following tables present the HD_M^I results for I = 5%, 2.5%, 1%, 0.1%, 0.01%, and 0.001% using the POD, $AF_{Subchronic}$, $AF_{Interspecies}$, 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 in the tables 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.

Calculation of HD_M^I for chronic oral exposure to TCEP: reduced numbers of seminiferous tubules (Incidence = 5%)		
Aspect	**P50**	**P95/P50**
$BMDL_{05}$(HED)	2.73 mg/kg-d	1
BMD/BMDL ratio	1.38	1.38
BMD-to-ED_{50} adjustment	3.0	1.5
IPCS POD = ED_{50}(HED)	**11.3 mg/kg-d**	**1.68**
$AF_{Subchronic}$	2	4
$AF_{Interspecies\text{-}BS}$	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intraspecies\ (I=5\%)}$	4.98	2.82
HD_M^I	1.14 mg/kg-d[a]	8.29[b]
	P05	**P95**
$HD_M^{I\ (c)}$	**0.14 mg/kg-d**	9.4 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Subchronic}$ x $AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 1.68)^2 + (\log 4)^2 + (\log 1)^2 + (\log 3)^2 + (\log 2.82)^2]^{0.5}} = 8.29$
[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 for chronic oral exposure to TCEP: reduced numbers of seminiferous tubules (Incidence = 2.5%)		
Aspect	**P50**	**P95/P50**
$BMDL_{05}$(HED)	2.73 mg/kg-d	1
BMD/BMDL ratio	1.38	1.38
BMD-to-ED_{50} adjustment	3.0	1.5
IPCS POD = ED_{50}(HED)	**11.3 mg/kg-d**	**1.68**
$AF_{Subchronic}$	2	4
$AF_{Interspecies-BS}$	1	1
$AF_{Interspecies-TK/TD}$	1	3
$AF_{Intraspecies\ (I=2.5\%)}$	6.77	3.43
HD_M^I	0.84 mg/kg-d[a]	9.19[b]
	P05	**P95**
$HD_M^{I\ (c)}$	**0.09 mg/kg-d**	7.7 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Subchronic}$ x $AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 1.68)^2 + (\log 4)^2 + (\log 1)^2 + (\log 3)^2 + (\log 3.43)^2]^{0.5}} = 9.19$
[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 for chronic oral exposure to TCEP: reduced numbers of seminiferous tubules (Incidence = 1%)		
Aspect	**P50**	**P95/P50**
$BMDL_{05}$(HED)	2.73 mg/kg-d	1
BMD/BMDL ratio	1.38	1.38
BMD-to-ED_{50} adjustment	3.0	1.5
IPCS POD = ED_{50}(HED)	**11.3 mg/kg-d**	**1.68**
$AF_{Subchronic}$	2	4
$AF_{Interspecies\text{-}BS}$	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intraspecies\ (I=1\%)}$	9.69	4.32
HD_M^I	0.59 mg/kg-d[a]	10.53[b]
	P05	**P95**
$HD_M^{I\ (c)}$	**0.06 mg/kg-d**	6.2 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Subchronic}$ x $AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 1.68)^2 + (\log 4)^2 + (\log 1)^2 + (\log 3)^2 + (\log 4.32)^2]^{0.5}} = 10.53$
[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 for chronic oral exposure to TCEP: reduced numbers of seminiferous tubules (Incidence = 0.1%)		
Aspect	**P50**	**P95/P50**
$BMDL_{05}$(HED)	2.73 mg/kg-d	1
BMD/BMDL ratio	1.38	1.38
BMD-to-ED_{50} adjustment	3.0	1.5
IPCS POD = ED_{50}(HED)	**11.3 mg/kg-d**	**1.68**
$AF_{Subchronic}$	2	4
$AF_{Interspecies\text{-}BS}$	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intraspecies\ (I=0.1\%)}$	20.42	6.99
HD_M^I	0.28 mg/kg-d[a]	14.58[b]
	P05	**P95**
$HD_M^{I\ (c)}$	**0.02 mg/kg-d**	4.0 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Subchronic}$ x $AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 1.68)^2 + (\log 4)^2 + (\log 1)^2 + (\log 3)^2 + (\log 6.99)^2]^{0.5}} = 14.58$
[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 for chronic oral exposure to TCEP: reduced numbers of seminiferous tubules (Incidence = 0.01%)		
Aspect	**P50**	**P95/P50**
$BMDL_{05}$(HED)	2.73 mg/kg-d	1
BMD/BMDL ratio	1.38	1.38
BMD-to-ED_{50} adjustment	3.0	1.5
IPCS POD = ED_{50}(HED)	**11.3 mg/kg-d**	**1.68**
$AF_{Subchronic}$	2	4
$AF_{Interspecies\text{-}BS}$	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intraspecies\ (I=0.01\%)}$	37.71	10.39
HD_M^I	0.15 mg/kg-d[a]	19.68[b]
	P05	**P95**
$HD_M^{I\ (c)}$	**0.008 mg/kg-d**	3.0 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Subchronic}$ x $AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 1.68)^2 + (\log 4)^2 + (\log 1)^2 + (\log 3)^2 + (\log 10.39)^2]^{0.5}} = 19.68$
[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 for chronic oral exposure to TCEP: reduced numbers of seminiferous tubules (Incidence = 0.001%)		
Aspect	**P50**	**P95/P50**
$BMDL_{05}$(HED)	2.73 mg/kg-d	1
BMD/BMDL ratio	1.38	1.38
BMD-to-ED_{50} adjustment	3.0	1.5
IPCS POD = ED_{50}(HED)	**11.3 mg/kg-d**	**1.68**
$AF_{Subchronic}$	2	4
$AF_{Interspecies\text{-}BS}$	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intraspecies\ (I=0.001\%)}$	64.25	14.65
HD_M^I	0.09 mg/kg-d[a]	25.96[b]
	P05	**P95**
$HD_M^{I\ (c)}$	**0.003 mg/kg-d**	2.3 mg/kg-d

[a] HD_M^I (P50) = IPCS POD / ($AF_{Subchronic}$ x $AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 1.68)^2 + (\log 4)^2 + (\log 1)^2 + (\log 3)^2 + (\log 14.65)^2]^{0.5}} = 25.96$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

The above tables present HD_M^I values for oral exposure to TCEP. The corresponding values for inhalation exposure can be derived in two ways, which each provide the same results:

1. Multiply oral HD_M^I values by a factor of 5.44 mg/m^3 per mg/kg-d. This factor is obtained from information provided in the *TCEP Draft Risk Evaluation*.[113]
2. Replace EPA's oral $BMDL_{05}$ (2.73 mg/kg-d) in the above tables with EPA's inhalation $BMDL_{05}$ (14.9 mg/m^3) and recalculate the ED_{50} and the HD_M^I values using the same adjustments.

The National Academies and the 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.[114]

[113] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 530, Equation_Apx J-3.
[114] 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.[115]

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).[116]

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), for both oral and inhalation exposures.

Risk-specific dose estimates for chronic exposure to TCEP: reduced numbers of seminiferous tubules		
Incidence (I)	HD_M^I lower -confidence limit (P05)	
	Oral	Inhalation
5%	0.14 mg/kg-d	0.75 mg/m^3
2.5%	0.09 mg/kg-d	0.50 mg/m^3
1%	0.06 mg/kg-d	0.30 mg/m^3
0.1% (1-in-1,000)	0.02 mg/kg-d	0.10 mg/m^3
0.01% (1-in-10,000)	0.008 mg/kg-d	0.04 mg/m^3
0.001% (1-in-100,000)	0.003 mg/kg-d	0.02 mg/m^3

Interpretation of results

Based on application of the WHO/IPCS methodology to TCEP chronic exposures, we find that:

- 0.06 mg/kg-d is the lower bound (95% confidence) chronic human oral dose and 0.30 mg/m^3 is the lower bound (95% confidence) chronic human inhalation dose at which male reproductive effects are expected in 1% of the population.

[115] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 140.
[116] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, p. 12.

- 0.02 mg/kg-d is the lower bound (95% confidence) chronic human oral dose and 0.10 mg/m^3 is the lower bound (95% confidence) chronic human inhalation dose at which male reproductive effects are expected in 0.1% of the population.
- 0.008 mg/kg-d is the lower bound (95% confidence) chronic human oral dose and 0.04 mg/m^3 is the lower bound (95% confidence) chronic human inhalation dose at which male reproductive effects are expected in 0.01% (1-in-10,000) of the population.
- EPA's non-cancer risk characterization for oral exposure to TCEP uses 2.73 mg/kg-d as the point of departure, and a benchmark MOE of 30.[117] This means that EPA concludes "the risk is not considered to be of concern"[118] for any chronic oral exposure less than 2.73 mg/kg-d / 30 = 0.09 mg/kg-d. Our analysis finds that the upper bound risk at an oral exposure of 0.09 mg/kg-d is 2.5%, or 1-in-40.
- EPA's non-cancer risk characterization for inhalation exposure to TCEP uses 14.9 mg/m^3 as the point of departure, and a benchmark MOE of 30.[119] This means that EPA concludes "the risk is not considered to be of concern"[120] for any chronic inhalation exposure less than 14.9 mg/m^3 / 30 = 0.50 mg/m^3. Our analysis finds that the upper bound risk at an inhalation exposure of 0.50 mg/m^3 is 2.5%, or 1-in-40.

The estimates of HD_M^I presented here were based entirely on input values and equations available from the WHO/IPCS methodology document and from EPA's *TCEP Draft Risk Evaluation*. An important caveat to these calculations is that the values used to represent human variability may be understated. The IPCS default human variability distribution is based on 37 data sets for human toxicokinetic variability and 34 data sets for human toxicodynamic variability. Most of these data sets were obtained from controlled human exposure studies of pharmaceuticals conducted in small samples of healthy adults, representing considerably less variability than found in the general population.[121,122,123] If human variability is underestimated, then the actual dose associated with each incidence level (e.g. I =1%, I = 0.1%) will be lower than the values obtained from this analysis – or in other words, risk at each dose will be underestimated.

[117] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), Table 5-56.
[118] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 296.
[119] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), Table 5-56.
[120] U.S. EPA (2023). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP), p. 296.
[121] WHO. (2017). *Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11, 2nd edition.* https://www.who.int/publications/i/item/9789241513548.
[122] Hattis, D., Lynch, M.K. (2007). Empirically observed distributions of pharmacokinetic and pharmacodynamic variability in humans—Implications for the derivation of single-point component uncertainty factors providing equivalent protection as existing reference doses. In Lipscomb, J.C. & Ohanian, E.V. (Eds.), *Toxicokinetics in risk assessment* (pp. 69-93). Taylor & Francis Group. https://doi.org/10.1201/b14275.
[123] Axelrad, D. A., Setzer, R. W., Bateson, T. F., DeVito, M., Dzubow, R. C., Fitzpatrick, J. W., Frame, A. M., Hogan, K. A., Houck, K., Stewart, M. (2019). Methods for evaluating variability in human health dose-response characterization. Hum Ecol Risk Assess, 25, 1-24. https://doi.org/10.1080/10807039.2019.1615828.