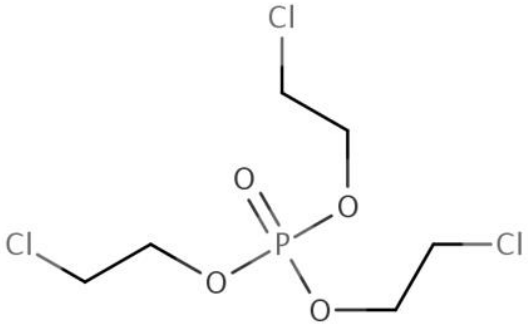
United States
Environmental Protection Agency

EPA-740-R-24-011
September 2024
Office of Chemical Safety and
Pollution Prevention

Tris(2-chloroethyl) Phosphate (TCEP); Regulation under the Toxic Substances Control Act (TSCA)

EPA–HQ–OPPT–2023–0265

Comment Summary and Responses



September 2024

This page intentionally left blank.

Table of Contents

Acronyms and Abbreviations

1-BP	1- bromopropane
AERMOD	American Meteorological Society (AMS)/EPA Regulatory Model
ATSDR	Agency for Toxic Substances and Disease Registry
BCEP	Bis(2-chloroethyl) phosphate
BCHP	Bis(2-chloroethyl) hydrogen phosphate
BCGP	Glucuronide conjugate of bis(2-chloroethyl) 2-hydroxyethyl phosphate
BMD	Benchmark dose
BMDL	Benchmark dose (lower confidence) limit
BMR	Benchmark response
CDR	Chemical Data Reporting
COC	Concentration of concern
CPSC	Consumer Product Safety Commission
CYP	Cytochrome P450 monooxygenases
DRAS	Delisting Risk Assessment Software
EC_{50}	Effect concentration at which 50 percent of test organisms exhibit an effect
ECEL	Existing chemical exposure limit
ECOSAR	Ecological Structure Activity Relationships (model)
EPA	U.S. Environmental Protection Agency
HBCD	Hexabromocyclododecane
HC_{05}	Hazardous concentration for 5% of species
HLC	Henry's Law constant
HERO	Health & Environmental Research Online
IIOAC	Integrated Indoor-Outdoor Air Calculator
IL	Interleukin 6
KOC	Organic carbon-water partition coefficient
KOW	Octanol-water partition coefficient
LC_{50}	Lethal concentration at which 50 percent of test organisms die
LCSA	Lautenberg Chemical Safety Act
MOA	Mode of action
MOE	Margin of exposure
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No-observed-adverse-effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OES	Occupational exposure scenario
OPFR	Organophosphate flame retardants
OPPT	Office of Pollution Prevention and Toxics
OSHA	Occupational Safety and Health Administration
PBPK	Physiologically-based pharmacokinetic
PECO	Population, exposure, comparator, and outcome
PESS	Potentially exposed or susceptible subpopulations
POD	Point of departure
PPE	Personal protective equipment
PV-29	C.I. Pigment Violet 29
RACB	Reproductive assessment by continuous breeding
RQ	Risk quotient

SACC	Science Advisory Committee on Chemicals
SNUR	Significant New Use Rule
SSD	Species sensitivity distribution
TCEP	Tris(2-chloroethyl) phosphate
TCE	Trichloroethylene
TERA	Toxicology Excellence for Risk Assessment
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
UF	Uncertainty factor
U.S.	United States
Web-ICE	Web-based Interspecies Correlation Estimation

Introduction

On December 15, 2023, the U.S. Environmental Protection Agency (EPA) published the *2023 Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP)* and accepted public comment until February 13, 2024. Materials on the draft risk evaluation are available at www.regulations.gov in docket EPA-HQ-OPPT-2023-0265. EPA then conducted a letter peer review to review the approach and methodologies utilized in this document, which began on March 13, 2024, and ended on April 12, 2024. A preparatory virtual public meeting was held on March 5, 2024, for reviewers and the public to comment on and ask questions regarding the scope and clarity of the draft charge questions.

This document summarizes the public and external peer review comments from the letter peer review that the EPA's Office of Pollution Prevention and Toxics (OPPT) received for the risk evaluation of TCEP. It also provides EPA/OPPT's response to the comments received from the public and the peer review. EPA/OPPT appreciates the valuable input provided by the public and peer review. The input resulted in numerous revisions to the risk evaluation document. The peer review and public comments are categorized by the nine themes listed below.

Additionally, within each theme comments that cover similar issues are presented together.

1. Overarching Comments
2. Chemistry, Fate, and Transport of TCEP
3. Releases and Concentrations of TCEP in the Environment
4. Environmental Risk Assessment
5. Human Health Risk Assessment
6. Unreasonable Risk Determination
7. Systematic Review
8. Formatting and Editing
9. Other Comments

Table 1: Index of Comment Submissions Sorted by Submission Number

Submission Number	Commenter Name
EPA-HQ-OPPT-2023-0265-0033	China WTO/TBT National Notification & Enquiry Center
EPA-HQ-OPPT-2023-0265-0035	Environmental Defense Fund (EDF)
EPA-HQ-OPPT-2023-0265-0036	Polyisocyanurate Insulation Manufacturers Association (PIMA)
EPA-HQ-OPPT-2023-0265-0037	Aceto US, LLC
EPA-HQ-OPPT-2023-0265-0038	American Chemistry Council (ACC) North American Flame Retardant Alliance (NAFRA)
EPA-HQ-OPPT-2023-0265-0039	Environmental Protection Network (EPN)
EPA-HQ-OPPT-2023-0265-0040	American Chemistry Council (ACC)
EPA-HQ-OPPT-2023-0265-0041	National Tribal Toxics Council (NTTC)
EPA-HQ-OPPT-2023-0265-0042	University of California, San Francisco Program on Reproductive Health and the Environment
EPA-HQ-OPPT-2023-0265-0043	Alliance for Automotive Innovation
EPA-HQ-OPPT-2023-0265-0044	Earthjustice et al
EPA-HQ-OPPT-2023-0265-0045	Environmental Protection Network (EPN)
EPA-HQ-OPPT-2023-0265-0046	Earthjustice et al
EPA-HQ-OPPT-2023-0265-0047	Earthjustice et al
EPA-HQ-OPPT-2023-0265-0048	Earthjustice et al
EPA-HQ-OPPT-2023-0265-0052	American Chemistry Council (ACC)
EPA-HQ-OPPT-2023-0265-PR	Peer Review Comments

Section 1 – Overarching Comments

General analysis comments

Summary: A public commenter (0044) praised EPA's risk evaluation for taking a whole chemical approach, considering multiple exposure pathways, analyzing fenceline community exposures, and recognizing Tribal communities as a potentially exposed or susceptible subpopulations (PESS). However, the commenter also stated that the risk evaluation resulted in underestimations of exposure and risk. Specific comments are summarized throughout in the following sections.
EPA Response: EPA thanks the commenter for the praise and looks forward to addressing the specific comments.

Summary: A public commenter (0040) stated that EPA made overly conservative estimates in both the hazard and exposure parts of the risk evaluation. The commenter characterized the TCEP risk evaluation as a 'screening-level' evaluation and suggested that according to EPA's own guidance this evaluation should not inform risk management without further refinement. The commenter recommended that EPA incorporate feedback from the Science Advisory Committee on Chemicals (SACC) and ad hoc reviewers.
EPA Response: EPA has reviewed and considered all submitted comments from public and peer reviewers.

Summary: A peer reviewer (OC – R1) stated that the draft risk evaluation is quite comprehensive in its coverage and is an impressive work covering many aspects of the potential risks associated with TCEP.
EPA Response: The EPA thanks the reviewer for their comment.

Section 1.1 – Scope of the draft risk evaluation

Assessing flame retardants as a category

Summary: One public commenter (0044) recommended that instead of considering TCEP as a single chemical, EPA should evaluate organohalogen flame retardants, a class of chemicals which, according to the commenter, includes TCEP, polychlorinated biphenyls, polybrominated biphenyls, and polybrominated biphenyl ethers. The commenter stated that considering TCEP alongside these chemicals with similar properties and uses would prevent a cycle of replacing one hazardous chemical with another. The commenter said that such an approach would not only be consistent with the TSCA statute, but would align with scientific consensus as well as the regulatory approach taken in the European Union. Similarly, a peer reviewer (OC – R5) expressed support for assessing multiple organophosphorus flame retardants and using TCEP as a model to determine the best path forward.
EPA Response: EPA has the authority to prioritize categories of chemicals under TSCA section 6 and would consider comments on whether to assess a chemical individually or as a category during the prioritization stage of the TSCA Risk Evaluation process. Once a single chemical like TCEP is designated high priority, the EPA must assess the risk of that particular chemical rather than a category

to which it might belong. The 90 day comment period for TCEP designation as a high priority substance was from August 22 to November 21 of 2019.

TCEP as an impurity

Summary: A public commenter (0037) suggested that EPA should address products that contain TCEP in small quantities as an impurity and refer to it as an "impurity [condition of use]". The commenter recommended that EPA consider the potential hazard of TCEP as an impurity in other chemicals (such as 2,2-bis(Chloromethyl) trimethylene bis [bis(2- chloroethyl)phosphate] (CASRN 38051-10-4) (V6)) in a case-by-case basis for each chemical which may contain a TCEP impurity. This, according to the commenter, would be consistent with the approach that it took for the trichloroethylene (TCE) risk evaluation as a byproduct of dichloroethane. The commenter requested that EPA make explicit note of such an exclusion in the risk evaluation and similarly exempt the import of products with TCEP impurities from the proposed TCEP significant new use rule (SNUR).

EPA Response: EPA will not be making inapplicability an exemption for or referring to products in the SNUR that may contain TCEP as an impurity as an "impurity [condition of use]" from SNUR notice requirements because EPA has determined that a circumstance where TCEP is an impurity or a byproduct is intended, known, or reasonably foreseen, and therefore falls within existing "conditions of use" for TCEP in the risk evaluation. The conditions of use in this risk evaluation include circumstances where TCEP is a byproduct and as an impurity; therefore, byproducts or impurities and their contribution to the unreasonable risk of TCEP are considered in risk evaluation instead of being considered as significant new uses in the SNUR. ,

Because TCEP is also known to co-occur in formulation with other flame retardants, such as V6, this risk evaluation evaluates TCEP when it co-occurs with other flame retardants in commercial and consumer products (*e.g.,* when it co-occurs with V6). However, it does not evaluate uses of other flame retardants where TCEP may occur as an impurity or as a byproduct.

As explained in the proposed SNURs for certain flame retardants, including TCEP, EPA did not propose to make inapplicable the general exemptions from SNUR notice requirements that are described in 40 CFR 721.45, including exemptions from notification requirements for persons manufacturing or processing the chemical substance only as an impurity or certain byproduct. EPA requested public comment on this proposal and will consider the public comments received before finalizing the SNUR.

Section 1.2 – Conditions of use

General comments

Summary: Two public commenters (0042, 0044) stated that TSCA requires EPA to conduct risk evaluations for all conditions of use. One commenter (0042) wrote that if a condition of use for TCEP was voluntarily discontinued, there exists no reason that users could not resume their activity and therefore EPA must consider this a reasonably foreseen use of TCEP. The commenters also stated that EPA has been authorized to conduct tests and subpoena necessary information to address data gaps in its risk evaluations. According to the commenters, EPA failed to take actions, such as lowering the Chemical Data Reporting (CDR) threshold for TCEP or promptly adding TCEP to the Toxics Release

Inventory (TRI) chemical list, which could have provided data to evaluate the unassessed conditions of use. One commenter (0044) pointed out that EPA denied a 2017 petition to require more TCEP testing.

EPA Response: EPA disagrees that all voluntarily discontinued uses of TCEP should be considered reasonably foreseen conditions of use, since the reasons for discontinuing the use might vary, including technology developments or more cost-effective alternatives, and therefore it is not reasonably foreseen to expect that all of them could resume. Also, certain discontinued uses are not reasonably foreseen because it might not be possible for EPA to identify all conditions of use that were discontinued, since they might not have been reported in previous CDR cycles or there is no reasonably available information about the discontinued uses. However, if EPA fails to identify a future use of TCEP, such possible future uses of TCEP are covered by the SNUR under TSCA. The SNUR under TSCA proposed by EPA on April 8, 2024 includes a reporting requirement before starting a new use of TCEP or resuming discontinued uses of TCEP, and can be found in the Federal Register under 89 FR 24398.

The CDR Rule, under TSCA, requires manufacturers (including importers) to provide EPA with information on the production and use of chemicals in commerce. The information is collected every four years for certain chemicals manufactured and/or imported generally when production volumes for the chemical are 25,000 pounds or more for a specific reporting year. As explained in the draft risk evaluation, the most recent updated 2020 CDR data showed that no company reported the manufacture (including import) of TCEP in the United States from 2016 to 2019, and no company reported processing and use information for the principal reporting year (2019). Under CDR requirements, chemicals are subject to a lower reporting threshold of 2,500 pounds when they are the subject of specific TSCA actions; however, being evaluated within the existing chemical prioritization program is not one of those actions. However, manufacturers (including importers) will be required to report TCEP production volumes of 2,500 lbs or more during the next CDR reporting cycle because of the proposed SNUR for TCEP. In addition, because the CDR collection occurs so infrequently, even if the reporting threshold was lowered for chemicals that enter the prioritization program, it is unlikely that the lower volume information would be available in time for the identification of conditions of use. However, EPA recognizes that the most recent reporting threshold for TCEP in CDR is 25,000 pounds and that some manufacturing could be occurring below that threshold.

EPA issued TSCA Section 4 Test Orders for 2 of the 3 flame retardants (4,4'-(1-methylethylidene)bis[2, 6-dibromophenol] (TBBPA) and triphenyl phosphate (TPP)) on the list of 20 chemicals currently undergoing risk evaluation. Test orders were not issued for TCEP because EPA had not identified any domestic manufacturers or processors (which would be required in order to determine who the recipients of an order would be). As the existing data were evaluated during the systematic review process, it was noted that EPA did not have TCEP site/process specific inhalation monitoring data, site/process specific dermal hand wipe sampling, and in vitro dermal absorption data. EPA determined that modeled data from either our own Generic Scenario documents and other standard EPA models for inhalation and dermal exposure could be used to develop the occupational exposure data for the RE. There is also a 2009 EU Risk Assessment that provides a reasonable worst-case modeling scenarios for inhalation, dermal, and oral exposures (HERO: 3809216).

EPA recently added TCEP to the Toxics Release Inventory (TRI) with the first year of reporting from facilities due July 1, 2024. As of September 2024, there are no TRI entries for TCEP. A facility is required to report to TRI if it meets all three threshold criteria, including that the facility is in a TRI-covered industry, the facility has 10 or more employees, and the facility manufactures (defined to include importing), processes or otherwise uses TCEP in quantities greater than established thresholds during a calendar year. For TCEP these established threshold are 25,000 lbs for manufacturing, 25,000 lbs for processing, or 10,000 lbs for other use. Given the decline in production volume seen in the CDR and Datamyne data in recent years, EPA anticipates receiving few-TRI submissions for TCEP due to the manufacturing, processing, and use reporting thresholds.

Comments on specific conditions of use

Summary: Two public commenters (0036, 0038) stated that the use of TCEP in polyisocyanurate insulation has been phased out in both domestic production and importation. One commenter (0036) further noted that this transition occurred in the mid-1990s to 2000s. According to the commenter, enough time has passed that a majority of TCEP-containing polyisocyanurate insulation has been replaced and any that remains has largely passed its "offgassing period" and therefore no longer contributes to unreasonable human health risk.
EPA Response: EPA considered the off-gassing period in its risk characterization of TCEP containing insulation in Figure 5-22 and accompanying discussion. Figure 5-22 in Section 5.3.5.2 provides a graph of the mean gas phase concentration versus time in days. As seen in the figure, the gas phase concentration has an initial spike followed by a precipitous decline after the first few months.

Section 1.4 – Peer review process

Comments on the letter peer review process

Summary: Multiple public commenters (0039, 0040, 0041, 0042, 0044, 0045, 0052) expressed concern with EPA's decision to employ a letter peer review process. Several of the commenters (0039, 0040, 0045) made comparisons with EPA's approach to the review of the "Asbestos Part 2 White Paper" which commenters claimed was poorly received by reviewers who wished for greater transparency and opportunity for panel discussion. Generally, the commenters highlighted the importance of the TCEP draft risk evaluation review due to the chemical's broad applications, numerous exposure pathways, and high potential for human health impacts. The commenters recommended EPA conduct a SACC panel peer review process in lieu of a letter peer review process to improve transparency in the process and provide opportunity for collaborative interactions between the reviewers and engagement with the public. Commenters also stated that a more robust peer review process would save time in the long run.
EPA Response: Independent, expert peer reviews play an important role in EPA's development of scientifically sound chemical risk evaluations conducted under TSCA. Selecting the right questions to ask reviewers and the right type of peer review is an important part of effectively and efficiently managing EPA's TSCA program. Letter peer review is one means for EPA to obtain independent scientific advice to inform its evaluation of chemical risks. EPA applies the criteria in its own Peer Review Handbook (https://www.epa.gov/osa/peer-review-handbook-4th-edition-2015) to determine on a case-by-case basis which components of each risk evaluation are peer reviewed. Per this handbook and OMB guidance, the EPA determined that a letter peer review was an adequate mechanism for the TCEP Risk Evaluation, "giving due consideration to the novelty and complexity of the science to be reviewed, the relevance of the information to decision making, the extent of prior peer reviews, and the expected benefits and costs of additional review." The Handbook states, "a letter review takes place when EPA seeks individual written peer review comments from independent experts, typically in the form of correspondence to EPA from the peer reviewer… Each reviewer evaluates the draft technical work product independently without consultation with other reviewers. No collaborative or consensus peer review report is developed."

Neither the Agency regulations nor OMB guidance require a specific type of peer review (*e.g.*, committee consensus report or letter peer review) or a particular body to conduct the review.

Comments regarding the peer review charge questions

Summary: A public commenter (0044) questioned the scope of EPA's peer review charge questions. The commenter said that the charge questions are narrow in scope, while ignoring major, overarching concerns such as data gaps. The commenter recommended that EPA seek SACC's advice on addressing data gaps in the risk evaluation.

Similarly, a peer reviewer (OC – R5) said that there are too many detailed charge questions to address effectively without a full SACC dialogue.

EPA Response: The EPA limited the scope of the charge questions to subjects that had not previously been peer reviewed within the TSCA framework. The charge questions focused on novel methods used, and peer reviewers were chosen based on their expertise and ability to answer any one of the subjects covered in the charge questions. However, peer reviewers have the freedom to comment on other aspects of the risk evaluation if they so choose.

As stated previously, per EPA's Peer Review Handbook, the EPA determined that a letter peer review was an adequate mechanism for the TCEP Risk Evaluation, "giving due consideration to the novelty and complexity of the science to be reviewed, the relevance of the information to decision making, the extent of prior peer reviews, and the expected benefits and costs of additional review."

Summary: A public commenter (0043) requested that EPA include the following questions in its peer review charge questions:

- Has EPA taken into consideration the lower exposure potential associated with a chemical that is bound up in an article? For example, has EPA assessed the exposure to TCEP in cured paints versus as a paint additive?
- Has EPA appropriately assessed exposure to articles and replacement parts as directed by TSCA Section 6(2)(D) and (E), specifically for automotive articles and replacement parts. Suggest adding a COU for automotive equipment and replacement parts.
- Is it appropriate for EPA to assume that no personal protective equipment (PPE) or other exposure controls are in place in workplaces where TCEP is present? Does this approach overestimate the risk? At a minimum, should EPA conduct exposure assessments that assess risk both with and without the Occupational Safety and Health Administration (OSHA)-required risk mitigation requirements?

EPA Response: By the time EPA received these comments, charge questions could not be added to our letter peer review process as we were in the middle of the peer review.

Consumer articles were modeled using the various models within CEM 3.0. These models include:

- E6 Emission from article placed in environment
- A_INH1 Inhalation from article placed in environment
- A_ING1 Ingestion after inhalation
- A_ING2 Ingestion of article mouthed
- A_ING3 Incidental ingestion of dust
- A_DER1 Direct transfer from vapor phase to skin

- A_DER2 Dermal dose from article where skin contact occurs
- A_DER3 Dermal dose from skin contact with dust

Each of these models are described in the EPA's CEM Version 3.0 User Guide and Appendices {U.S. EPA, 2022, 11204170}. The TCEP risk evaluation briefly discusses uncertainties related to how TCEP is bound to articles, in its discussion of curing of resins, whether TCEP is entrained in the polymer matrix, and the discussion of blooming potential of TCEP to the surface of treated articles (Sections 4.3.6.2, 5.1.2.2, 5.1.2.4.1, 5.3.2.1.1, 5.3.2.3.2).

EPA evaluated automotive articles and replacement parts in the final risk evaluation of TCEP. The changes made in the final risk evaluation are in the following conditions of use:

- "Processing – incorporation into article – aerospace equipment and products" was edited to "Processing – incorporation into article – aerospace equipment and products and automotive articles and replacement parts containing TCEP;"
- "Industrial use – other use – aerospace equipment and products" was edited to "Industrial use – other use – aerospace equipment and products and automotive articles and replacement parts containing TCEP;"
- "Commercial use – other use – aerospace equipment and products" was edited to "Commercial use – other use – aerospace equipment and products and automotive articles and replacement parts containing TCEP;" and
- "Consumer use – paints and coatings – paints and coatings" was edited to "Consumer use – paints and coatings – paints and coatings, including those found on automotive articles and replacement parts."

In addition to these changes, a new condition of use, "Industrial use – paints and coatings – automotive paints and coatings" was included in the final risk evaluation of TCEP.

Most of these conditions of use were assessed qualitatively and similarly to how aerospace equipment and products and commercial use of paints and coatings were evaluated. An overview of the risk characterization approach for the aerospace equipment and products COUs can be found in Section 5 of the draft risk evaluation of TCEP, Risk Characterization. EPA had previously assumed that workers were provided and always used PPE in a manner that achieves the stated assigned protection factor (APF) for respiratory protection or used impervious gloves for dermal protection. However, EPA believes that the assumed use of PPE in a risk determination could lead to an underestimation of the risk to workers. For example, workers may be highly exposed because they are not covered by OSHA standards, such as self-employed individuals and public sector workers who are not covered by a State Plan; their employers are out of compliance with OSHA standards; the PPE is not sufficient to address the risk from the chemical; or their PPE does not fit or function properly.

Additionally, TSCA risk evaluations are subject to statutory science standards, an explicit requirement to consider risks to potentially exposed or susceptible subpopulations, and a prohibition on considering costs and other non-risk factors when determining whether a chemical presents an unreasonable risk that warrants regulatory actions—all requirements that do not apply to development of OSHA regulations.

Summary: A public commenter (0052) recommended that EPA include as a peer review charge question whether the 2016 study on Japanese medaka constitutes sufficient evidence for a determination of unreasonable risk to the environment. The commenter noted that the study found a

significant effect on body length of medaka embryos but did not find impact on other markers of embryonic development.

EPA Response: By the time EPA received these comments, charge questions could not be added to our letter peer review process as we were in the middle of the peer review.

EPA has identified and reviewed additional studies with TCEP exposure to aquatic invertebrates and invertebrates to improve the Environmental Hazards section of the TCEP Risk Evaluation and is presented within Section 4.2.2 Aquatic Species Hazard. This work improves the representation of species within the Web-ICE application and SSD for deriving an acute Concentration of Concern and increased the number studies representing chronic exposures of TCEP for the identification of a chronic Concentration of Concern for aquatic organisms.

Section 2.2 – Environmental fate and transport (including comments on the approach to estimate degradation in the absence of data)

General comments

Summary: A peer reviewer (1.1.1 – R3) stated that, in the absence of relevant data, relying on anaerobic degradation being 4 to 9 times slower than aerobic degradation is an appropriate assumption and approach to estimate the degradation of TCEP.

EPA Response: The EPA thanks the reviewer for their comment. Additional anaerobic studies were identified and are provided in Appendix F.2.3.2., and additional anaerobic degradation studies were identified and are discussed in Appendix E.2.3.2

Summary: A peer reviewer (1.1.1 – R2) and a public commenter (0040) recommended that EPA characterize TCEP as not biodegradable in aerobic or anaerobic conditions.

- According to the public commenter (0040), the BIOWIN models in EPI Suite may not be suited to analysis of TCEP given the limited data on which they are built. The commenter said that there is not sufficient data to quantify the biodegradable half-life of TCEP and that such a quantification is not material to the risk evaluation.
- In addition, a peer reviewer (1.1.1 – R2) recommended that EPA conclude that TCEP is not biodegradable under anaerobic conditions in sediments. The peer reviewer (1.1.1 - R2) stated that there are large uncertainties regarding the biodegradation of TCEP in water and sediment, and two studies on the biodegradation of TCEP in water found that TCEP is not readily biodegradable, using Organisation for Economic Co-operation and Development (OECD) 301B and OECD 301D methods. The peer reviewer said that it was unclear why it was necessary to default to a water half-life of 10,000 hours and then extrapolate aerobic to anaerobic half-lives.

EPA Response:
For the public commentor (0040) and peer reviewer (1.1.1 – R2):

- The EPA thanks the reviewers for their comment. Additional anaerobic studies were identified and are provided in Appendix F.2.3.2., and additional anaerobic degradation studies were identified and are discussed in Appendix E.2.3.2
  (see below).

  "After systematic review concluded, four studies observing anaerobic biodegradation of TCEP were identified. {Pang, 2018, 10228662@@author-year} studied the fate of TCEP in sewage sludge with four different treatments, two of which were anaerobic digestion studies (Treatments 3 and 4). The results of this study confirm the recalcitrance of TCEP under anaerobic conditions and TCEP concentrations in both treatments were seen to increase over time. The removal rates were –0.41 and –74.8 percent for Treatments 3 and 4, respectively. The authors did not discuss the reasons for the increase in TCEP's final concentrations, but the authors did note that the final concentrations of Tri(n-butyl) phosphate (TnBP) increased during composting due to the "inhomogeneity" of the composts. Because of this uncertainty, {Pang, 2018, 10228662@@author-year} is used qualitatively to support TCEP's persistence in anaerobic environment and will not be used to derive a biodegradation half-life. {Yang, 2021, 8682618@@author-year} carried out biodegradation experiments using activated sludges from aerobic and anerobic ponds of the Nanjing Chendong STP in China mixed with kitchen garbage biomass and agricultural residues. The biodegradation of TCEP under anaerobic conditions was observed to be very slow. The removal of TCEP did not reach 80 percent after 60 days. Because the media and inoculum used in {Yang, 2021, 8682618@@author-year} comprised a rich nutrient profile and high microbial biomass, the direct use of the reported half-lives for estimating persistence in environmental sediments is not appropriate; therefore, this study was excluded from use in this risk evaluation. {Yang, 2023, 11364896@@author-year} studied the degradation of TCEP using an anaerobic enrichment culture from end-of-life vehicles dismantling sites in Guangzhou, China. The study demonstrated that microbes, specifically *Dehalococcoides* sp., was able to anaerobically transform TCEP. However, the microbial community was highly enriched and the system highly controlled. This study will not appropriately represent TCEP's fate under anaerobic conditions and will not be considered in this risk evaluation.

  When considering the results of the {Pang, 2018, 10228662@@author-year} and {Life Sciences Research Ltd, 1990, 6310865@@author-year} studies (Table 2-2), it is highly likely that TCEP will not degrade under anaerobic conditions and be persistent in the sediment compartment."

Summary: A peer reviewer (1.1.1 – R5) wrote that anaerobic degradation tests of a compound of this nature should be simple to complete and should be required for inclusion. The peer reviewer added that, if these data are not provided, the upper limit of persistence should be incorporated into the risk evaluation.

EPA Response: The EPA thanks the reviewer for their comment. The EPA was unable to use test orders since there were no manufacturers to submit them to. The upper limit of persistence that the EPA used is the 30,000–40,000 hours that was extrapolated using the results from an aerobic biodegradation test.

Comments on the references used

Summary: Two peer reviewers (1.1.1 – R1, 1.1.1 – R6) recommended EPA consider additional recent publications. One peer reviewer (1.1.1 – R1) stated that EPA identified one medium quality study in the draft risk evaluation, but the study did not report any degradation of TCEP and was therefore less useful. The peer reviewer stated that they found an article by Yang et al. (2021) that measured the degradation of TCEP in activated sludge under anaerobic conditions, and the peer reviewer recommended that EPA consider if this article could be used to provide a better estimate of the anaerobic degradation of TCEP. Another peer reviewer (1.1.1 – R6) recommended that EPA consider the following recent publications describing anaerobic degradation:

- Yang S, Wu J, Wang H, Yang Q, Zhang H, Yang L, Li D, Deng Y, Zhong Y, Peng P. 2023. New dechlorination products and mechanisms of tris(2-chloroethyl) phosphate by an anaerobic enrichment culture from a vehicle dismantling site. *Environ Pollut* 338:122704. https://doi.org/10.1016/j.envpol.2023.122704.
- Yang X, Fan D, Gu W, Liu J, Shi L, Zhang Z, Zhou L, Ji G. 2021. Aerobic and Anaerobic Biodegradability of Organophosphates in Activated Sludge Derived from Kitchen Garbage Biomass and Agricultural Residues. *Front Bioeng Biotechnol* 9:649049. tps://doi.org/10.3389/fbioe.2021.649049.
- Pang L, Ge L, Yang P, He H, Zhang H. 2018. Degradation of organophosphate esters in sewage sludge: Effects of aerobic/anaerobic treatments and bacterial community compositions. *Bioresour Technol* 255:16-21. https://doi.org/10.1016/j.biortech.2018.01.104.

Both peer reviewers (1.1.1 – R1, 1.1.1 – R6) expressed that, when limited studies are available, the approach taken by EPA is acceptable.

EPA Response:

- Yang, S. et al. (2023) demonstrated that microbes, specifically *Dehalococcoides* sp., was able to anaerobically transform TCEP. However, because the microbial community was highly enriched and the system highly controlled, this study does not appropriately represent the anaerobic degradation of TCEP's fate under standard environmental conditions and will not be considered in this risk evaluation.
- Yang, X. et al. (2021) carried out biodegradation experiments using activated sludges from aerobic and anerobic ponds of the Nanjing Chendong STP in China mixed with kitchen garbage biomass and agricultural residues. Because the media and inoculum comprised a rich nutrient profile and high microbial biomass which does not represent standard environmental conditions, the direct use of the reported half-lives for estimating persistence in environmental sediments is not appropriate.
- Pang et al. (2018) confirms the recalcitrance of TCEP under anaerobic conditions, and TCEP concentrations in both treatments were seen to increase over time. The authors did not discuss the reasons for the increase in final TCEP concentrations, but the authors did note that the final concentrations of Tri(n-butyl) phosphate (TnBP) increased during composting due to the "inhomogeneity" of the composts. Because of this uncertainty, this study will be used qualitatively to support TCEP's persistence in anaerobic environment and will not be used to derive a biodegradation half-life.
- Since the studies will not be used to derive an aerobic biodegradation half-life, the EPA will use the extrapolated half-life derived from 64 FR 60197 and {U.S. EPA, 2000, 10286742@@author-year} as described in the draft risk evaluation.

Summary: A peer reviewer (1.1.1 – R4) stated that they were unable to track down the reference supporting the assumption that anaerobic degradation is 4 to 9 times slower than aerobic degradation.
EPA Response: Guidance on estimating anaerobic degradation rates relative to aerobic degradation rates can be found in Section III.D in 64 FR 60197, and in the documentation (Help files) for the Level III fugacity model of EPI Suite™{U.S. EPA, 2012, 2347246}. Note; anaerobic degradation rates were not used as inputs for the AERMOD or DRAS models. EPA used the 30,000–40,000 hours that was extrapolated using the results from an aerobic biodegradation test.

Summary: A peer reviewer (1.1.1 – R5) stated that the citations for chemical properties in Table 2-1 are deceptive. The peer reviewer expressed that EPA should acknowledge that the values used are based on a single study, and the peer reviewer added that this type of dependence on a single value that cascades into many references is a significant shortcoming of many data mining techniques. The peer reviewer stated that safeguards to prevent such citation inflation should be established.
EPA Response: The EPA thanks the reviewer for their comment. The citations in Table 2-1 were revised, as recommended.

Other specific comments

Summary: A peer reviewer (1.1.1 – R5) commented on line 1312 on page 42 and stated that TCEP accumulation in soil may occur where rainfall is limited. The peer reviewer said that this could be important for threatened or endangered species living in areas where airborne deposition is likely.
EPA Response: The EPA thanks the reviewer for the comment. Precipitation events, such as rain and snow may enhance soil concentrations of TCEP, but accumulation in soil is expected to be unlikely due to its water solubility (7,820 mg/L) and soil log K_{oc} values (2.08–2.52). Dissolved TCEP was observed to be mobile and migrated to groundwater by common soil transport processes such as advection and diffusion.

Section 3.1 – Approach and methodology

Summary: A public commenter (0045) discussed EPA's approach to develop quantitative estimates of exposure and hazards where there is a lack of empirical data. The commenter expressed support for the use of vetted and validated models in evaluating exposure and hazards for risk assessments, stating that they believed it would help fill in critical data gaps.
EPA Response: EPA thanks the reviewer for this comment.

Section 3.2 – Environmental releases

Summary: A public commenter (0044) stated that EPA underestimated the potential environmental releases, occupational exposures, and consumer exposures to TCEP associated with e-waste recycling in the assessment of industrial and commercial sources in the environment. The commenter stated that EPA had not provided adequate information and justification for not considering e-waste recycling

releases in the draft risk evaluation and suggested EPA consider the data from Gravel et al. (2019) and Nguyen (2019).

EPA Response: EPA thanks the reviewer for their comment and reviewed the sources provided in the comment. These sources did not provide new data that could be used to estimate releases that could occur at electronic waste facilities. The rational for why EPA could not quantify e-waste recycling releases is because data regarding releases was not available. Literature that contained data regarding TCEP at e-waste facilities was limited to inhalation monitoring data, which represented very low levels of exposure. Additionally, the total releases are expected to be low for several reasons: The volume of TCEP in e-waste products is low; only a fraction of the products is recycled; and recycling will likely be dispersed over many e-waste sites. Further explanation is located in sections 4.3.6.2 and 5.3.2.3.2.

Section 3.3 – Concentrations of TCEP in the environment

Disposal and groundwater pathways

Summary: In response to Charge Question 3.3, a public commenter (0040) stated that leachate from poorly managed landfills represents a risk to human health regardless of its contents and thus, further analysis into this exposure pathway is unwarranted in the draft risk evaluation.

EPA Response: Spills and natural disasters are generally not considered in the risk evaluations because they are not known or reasonably foreseen. EPA is aware of older, unlined, and poorly managed landfills across the United States which suggest that landfill leachate to groundwater may pose an exposure to the populations living near landfills. Three sites, the Norman Landfill in OK, the Himco dump in IN, and Ft. Devens, MA detected TCEP in groundwater plumes, suggesting landfill leachate as a concern for nearby residents ({Barnes, 2004, 5469339; Buszka, 2009, 4912133; Hutchins, 1984, 1316091}). EPA used a range of leachate concentrations from 1.0×10−4 to 1.0×103 mg/L to account for uncertainties. The top range of the leachate concentration is bounded by solubility.

Summary: Alternatively, other public commenters (0041, 0044) stated that TCEP in wastewater effluent and leachate from landfills and dumps represent additional exposures to aquatic organisms and should be included in risk management efforts. One public commenter (0044) suggested EPA consider data published in studies from Los Angeles and the Washington Department of Ecology, stating that EPA should revise the draft risk evaluation to incorporate accurate loading rates for TCEP-containing waste disposed via landfilling, incineration, and wastewater to avoid substantially understating disposal-related exposures and risks.

EPA Response: EPA appreciates notification of these additional references. The studies from Los Angeles and the Washington Department of Ecology have been incorporated into our revised assessment (section 3.3.3.7). The revised DRAS analysis considers waste volumes up to 817 m^3 (2,500,000 lbs) to account for the uncertainty of TCEP waste volumes associated with past disposals of TCEP. This value is two orders of magnitude higher than the 25,000 lbs CDR threshold.

Masoner et al. 2014 is more comprehensive in describing mass loading and leachate loading. The study describes leachate loading rates for different regions of the U.S., for different ages of waste, for different waste loads, leachate production and precipitation (Table 4).

Section 3.4 – Concentrations of TCEP in the indoor environment

Summary: A public commenter (0044) said that EPA had understated the consumer, worker, and general population exposures to TCEP from polyurethane foam products found in furniture and automobile cushioning, urging EPA to use the higher concentrations found in the Ingerowski study published in 2001.
EPA Response: EPA thanks the commenter for the comment. Although {Ingerowski, 2001, 32734@@author-year} recorded TCEP in polyurethane soft foam at 19,800 mg/kg (1.98 percent), values from {Fang, 2013, 1676728@@author-year} were selected for this furniture foam and auto foam scenarios as they were thought to be more current to the amount of TCEP in polyurethane soft foam in use across the U.S. .

Summary: A public commenter (0038) stated that the dust exposure pathway does not account for product phase out or changes to the composition of products during the 19 years of data that were evaluated and instead suggested EPA review a 2016 study that found decreased concentrations of flame retardants in dust due to a transition in products.
EPA Response: Decreasing trends in the production volume of TCEP are described in Section 5.1.2.4.1. This section describes California TB 117-2013 which may be responsible for the shift in TCEP use in consumer articles. Section 3.4.2 describes the available indoor dust monitoring data without regard to the changing trends in the monitoring data.

Summary: A peer reviewer (OC – R7) suggested that EPA revisit the calculations that derive the indoor/outdoor ratio of 0.65, which was not presented in the draft risk evaluation. The reviewer said that page 61 shows outdoor air measurements between 0.1 and 1ng/m^3 with a maximum across studies of approximately 50 ng/m^3 in a study labelled as "near facility, highly exposed." However, on page 81, EPA lists a range of indoor air concentrations between 10-100 ppm, with several approaching 1,000 ppm. Thus, the reviewer said it is difficult to see how a ratio of 0.65 could be predictive of indoor air. The review said that a statistical summary of the available indoor air data and picking the 95th percentile may be most appropriate.
EPA Response: The IIOAC model is a tool based on EPA's AERMOD that is used for assessing releases to air and exposure potential to chemicals. An indoor-outdoor ratio of 0.65 is used for the mean ratio, whereas a value of 1 is used for the high-end ratio. Figure 19 in Section 10.3 in the IIOAC user guide provides a summary of a range of indoor-outdoor ratios and justifies why 0.65 was used as the default for the screening model. Indoor air concentrations due to use of consumer articles were modeled using the consumer exposure model (CEM), in addition to the modeling of ambient air concentrations using IIOAC/AERMOD.

Section 4 – Environmental Risk Assessment

Comments associated with this issue are summarized in the subsections below.

Section 4.1 – Environmental exposures

Summary: A public commenter (0044) stated that EPA had not adequately assessed the risks to wildlife from TCEP exposure, stating that EPA omitted conditions of use such as releases from

consumer products and disregarded certain exposure pathways such as inhalation because they were seen to present a lower risk than others like dietary exposures. The commenter also suggested that EPA consider the impacts of microplastics and plastics debris ingestion when evaluating ingestion exposure. In the final risk evaluation, the commenter requested that EPA consider aggregate and cumulative risks to wildlife and the bioaccumulation exposure from birds ingesting fish and insects.

EPA Response: Considerations such as: air concentrations of modeled TCEP releases, monitored TCEP within ambient air, and ecologically relevant hazard thresholds for TCEP indicated that inhalation for wildlife is not a significant exposure route. TCEP in the gaseous phase is expected to have a short half-life within the atmosphere (5.8 hours) with particle bound TCEP primarily removed by wet and dry deposition. AERMOD modeling results indicated a maximum ambient air concentration (95th percentile, MetHIGH) of 6.08×10^{-7} μg/m^3 at 1,000 m from a hypothetical facility for the Use of paints and coatings – spray application OES under the 2,500 lb/year production volume using the Suburban forest land category scenario (see Section 3.3.1.2). Comparatively, the hazard threshold derived for terrestrial mammals, represented as a toxicity reference value based on an oral route of exposure, is 44 mg/kg-bw/day. TCEP sampled from ambient air at 13 urban sites in Chicago ranged from 0.032 to 0.34 ng/m^3 with an average 0.75 $\pm$ 0.025 ng/m^3 {Peverly 2015; 2939998}. In addition, the human health portion of the TCEP risk assessment for general population risk estimates found non-cancer MOEs were less than the acute and chronic benchmark MOEs for any COUs at 10 m from stack or fugitive are releases, which are higher exposures than would be expected to wildlife would inhale with farther residence to a TCEP fugitive or stack release.

The role of consumer products and environmental releases within section 3.2.2 detail the following, "Although EPA acknowledges that there may be TCEP releases to the environment via the demolition and disposal of consumer articles and the release of TCEP to wastewater via domestic laundry, the Agency did not quantitatively assess these scenarios due to lack of reasonably available information. EPA instead assessed them qualitatively. EPA uses anecdotal information in the peer-reviewed literature to qualitatively describe potential releases from TCEP d to the environment from consumer articles (Section 5.1.2.2.5)."

The impact of co-exposure with other chemicals is outside of the scope of the risk evaluation for TCEP. The purpose of the risk evaluation under TSCA is to determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, under the conditions of use. Appendix Section F.2.3.1 of the TCEP risk evaluation (RE) recognizes that microplastics can serve as both a source and sink for TCEP and present an uncertainty for the source attribution of TCEP from an original article.

Summary: A public commenter (0045) stated that EPA should include other possible exposure routes from inhalation, deposition from air to surface water, and dermal contact for terrestrial species and consider the impact of an aggregate exposure assessment to fully characterize environmental risks.

EPA Response: Inhalation exposure to wildlife has been addressed within a previous comment. Dermal contact for terrestrial species is addressed within Section 4.3.5 with a section that addresses both dermal contact and inhalation by wildlife. Based on the Guidance for Ecological Soil Screening Levels (US EPA, 2003a, US EPA 2003b) document, for terrestrial wildlife, relative exposures associated with inhalation and dermal exposure pathways are insignificant, even for volatile substances, compared to direct ingestion and ingestion of food (by approximately 1,000- fold). In addition, TCEP is not expected to bioaccumulate in tissues, and the screening level trophic transfer analysis indicated that concentrations will not increase from prey to predator in either aquatic or terrestrial food webs.

Deposition of TCEP from air to surface water was modeled and is detailed within Section 3.3.2.6 of the TCEP risk evaluation. EPA used IIOAC and AERMOD to estimate air deposition from hypothetical facility releases and to calculate pond water concentrations 1,000 m from the hypothetical facility. Pond water concentrations from air deposition were estimated for the COUs with air releases. The annual highest estimated 95th percentile pond water concentration from one year of deposition, across all exposure scenarios, was 0.49 ppb for the commercial use of paints and coatings scenario at an annual production volume of 2,500 lb per year.

Section 4.2 – Environmental hazards (including comments on the calculation of hazardous concentration for 5% of species (HC05) and the calculation of concentration of concern (COC) for aquatic organisms)

General comments

Summary: A public commenter (0040) recommended that EPA identify appropriate hazard endpoints as part of the problem formulation of the risk evaluation in accordance with EPA guidance on ecological risk assessment. The commenter discussed an example where they believed EPA had misapplied the results of the Sun et al. (2016) study to establish chronic fish hazards. The commenter also requested that EPA describe the weight of the scientific evidence for identified ecological hazards and apply it to the determination of a chronic COC. Another commenter (0044) stated that EPA's environmental hazard thresholds were not sufficiently protective of aquatic species and cited a study by Zhao et al. (2021) that documented adverse effects to fish species at lower concentrations of TCEP.

EPA Response: The narrative summary of the Sun et al. 2016 study has been revised to emphasize that the frequency of water changes, nominal concentrations (not analytically verified), and lack of other significant adverse outcomes which are points of uncertainty that the commenter discussed within their review of the study. The environmental hazard section of the TCEP risk evaluation (RE) has been revised to reflect an increased number of acute and chronic exposure studies (Section 4.2.2 and 4.2.5) that have improved the quality of the database, consistency, and biological relevance (Section 4.2.6.1). The revised TCEP RE has additional studies with overall quality determinations of high for the apical assessment endpoints of regulatory interest (*i.e.*, impaired growth, survival, or reproduction).

Responses to Charge Question 2.1 related to data

Summary: In response to Charge Question 2.1, a public commenter (0040) noted that Dyer et al. (2006) developed species sensitivity distributions using EPA's interspecies correlations estimation tool but observed variability in the results based on the surrogate species applied. The commenter recommended that EPA apply its method beyond fish species to include freshwater invertebrates and evaluate the appropriateness of including algal taxa in such an approach. Another commenter (0045) discussed the strengths and uncertainties of using HC05 in the TCEP draft risk evaluation and suggested that EPA provide additional support to conduct testing early in the review process and combining test results with modeling with other in silico, in vitro, and less whole-animal dependent tools to help fill data gaps.

EPA Response: The application of Web-ICE and subsequent SSD in the draft TCEP RE has been revised to include additional vertebrates and invertebrates. EPA calculated an SSD with the SSD Toolbox using acute LC50 hazard data from systematic review and estimated data from the Web-ICE

application (Appendix F.2.1.1) that included 25 fish, 1 amphibian, 12 aquatic invertebrates, and 15 benthic invertebrates. A second SSD was performed for the algae hazard data and was applied with the 5 empirical values and 3 predicted species values detailed in the previous section. The SSD is used to calculate a hazardous concentration for 5 percent of species (HC05). The HC05 estimates the concentration of TCEP that is expected to be protective for 95 percent of species. The SSD plot shows the distribution of invertebrate and vertebrate species sensitivity to TCEP exposure using Burr distribution with the calculated HC05 of 31.6 mg/L with a 95 percent CI of 16.7 mg/L to 57.0 mg/L. For algal species the HC05 for the logistic and normal distributions were 116.2 and 104.2, respectively, with both distributions resulted in the same lower 95% CI of the HC05 at 66 mg/L.

Summary: Several peer reviewers (2.1.1 – R1, 2.1.1 – R5, 2.1.1 – R6) expressed that having TCEP data for more biological species to inform the assessment would be preferable. One peer reviewer (2.1.1 – R6) specifically noted that the Weibull distribution had the best goodness-of-fit and the method was appropriately used, but expressed concern about the species that were used to obtain the lethal concentration at which 50 percent of test organisms die (LC_{50}) toxicity data. The peer reviewer stated that only rainbow trout and zebrafish studies were used to predict LC50 toxicity values for 18 additional aquatic organisms.

Another peer reviewer (2.1.1 – R1) stated that the use of Web-based Interspecies Correlation Estimation (Web-ICE) to estimate the acute toxicity of TCEP for species for which no data is available seems reasonable, but the estimates are based on a small number of fish species which may not accurately reflect the responses of other species. The peer reviewer said that they had found several additional sources in a quick literature search and listed the following:

- A recent article by Zhang et al. (2024) provides TCEP acute toxicity data for 8 marine species ranging from diatoms to fish.
- Acute toxicity values for 6 other freshwater species are presented in the Introduction to the Zhang et al. (2024) article.
- Qiao et al. (2022) presents tables with toxicity values for TCEP in a range of species and at various durations of exposure.
- The European Chemicals Agency database entry for TCEP shows an effect concentration at which 50 percent of test organisms exhibit an effect (EC50) value for immobilization of Daphnia magna of 170 mg/kg, and an algal growth rate inhibition value of 450 mg/L.
- A recent article by Zhang et al. (2022) includes growth curves, which could be used to estimate an EC50 value for the cyanobacteria Microcystic aeruginosa.

The peer reviewer (2.1.1 – R1) recommended that EPA examine these sources and include this information in its estimation of the species sensitivity distribution and HC05, to create a more robust dataset. The peer reviewer expressed concern that they were able to find multiple relevant studies that are missing from the document without difficulty, and the peer reviewer stated that this suggests significant limitations with the current literature review approach.

EPA Response: EPA thanks the commenter for the comment and input to improve this risk evaluation. EPA has been able to add additional studies from systematic review that increase our data landscape for acute and chronic hazard. Revision of the Web-ICE model in the TCEP RE has taken place with the additional acute hazard data. Revisions have been made for the additional empirical and predicted values used in SSD and are documented within Appendix Section F.2.1.1 for Web-ICE and F.2.1.2 for the SSD. Additional acute hazard values from Zhang et al. 2024 were placed through systematic review

and were added to the Environmental Hazard section for vertebrates, invertebrates, green algae, and diatoms.

Additional surrogate species allow for more predicted species from Web-ICE thus increasing our representative species within the SSD. Details of this increases data landscape and incorporation into the TCEP risk evaluation are detailed within Sections 4.2 (Environmental Hazard) and Appendix F.

Responses to Charge Question 2.1 related to the modeling approach

Summary: A peer reviewer (2.1.1 – R2) expressed that this is the first time Web-ICE has been used in a TSCA risk evaluation, and the peer reviewer commented that this is commendable given the effort invested in developing and maintaining this tool. The peer reviewer said that it is important for future revisions to emphasize the scientific soundness of Web-ICE and its associated ICE models. The peer reviewer added that the models have been vetted and validated by EPA scientists and the larger scientific community. The peer reviewer specifically stated that the statement "*Model approaches such as Web-ICE have more uncertainty than empirical data and are not substitutes for empirical data when determining the hazard or risk*" should be revised, as there is a substantial body of literature that indicates that Web-ICE predictions can produce comparable hazard estimates as those derived from empirical data.

EPA Response: The statement on the uncertainty of model approaches such as Web-ICE has been removed from Section 4.2.6.1 Strengths, Limitations, Assumptions, and Key Sources of Uncertainty for the Environmental Hazard Assessment.

Summary: A peer reviewer (2.1.1 – R2) stated that the risk evaluation summarized previously recommended quality criteria for the inclusion of Web-ICE predictions in the assessment, with the addition of narrow 95% confidence intervals. The peer reviewer expressed that this should be revised, because a recent study (Raimondo et al., 2023) indicated that the range between the upper and lower confidence interval is not correlated with the prediction accuracy. The peer reviewer added that an interval range of 2-orders of magnitude has been recommended instead, because it minimizes the Type I and Type II errors. The peer reviewer stated that making this modification would increase the predicted acute toxicity values from 18 aquatic species to 30 aquatic species. In addition, the peer reviewer said that the prediction for 4 fish species would be based on values from both surrogates (rainbow trout) and zebrafish embryo. The peer reviewer included a table with the Web-ICE predicted acute toxicity based on their suggested modifications. The peer reviewer commented that earlier assessments have also suggested that it is preferable to develop species sensitivity distributions from multiple, instead of single, surrogate species. The peer reviewer recommended EPA integrate additional high-quality data into the assessments. Finally, the peer reviewer stated that EPA's approach for calculating the HC05 is scientifically sound, and it follows probabilistic methods used elsewhere for similar purposes.

EPA Response: EPA has reviewed the criteria from Raimondo et al. (2023) and has been in contact with the study's authors. The revision of the Web-ICE and SSD with additional empirical data resulted in 40 species represented in the SSD. The Web-ICE screening for predicted values has been revised to include the reviewer's suggestion and peer-reviewed findings on the role of interval range from one to two orders of magnitude. The number of empirical species represented in the overall SSD and the Web-ICE model have increased from the inclusion of newly reviewed studies.

Summary: A peer reviewer (2.1.1 – R3) stated that, while a formal systematic review criteria was used to identify and categorize data and papers, EPA incorporated a further step to assess the quality of the science. The peer reviewer wrote that papers were not automatically excluded due to lack of meeting the systematic review automatic criteria, but rather assessed for possible quality contribution to the assessment. Finally, the peer reviewer commented that the analysis was not done in isolation, and it included other assessment reports from 2009.

EPA Response: Thank you for your comment and review.

Summary: A peer reviewer (2.1.1 – R4) stated that EPA clearly described the approach for selecting the model that best fits the data distribution. The peer reviewer commented that the Weibull distribution was determined to best fit the distribution of empirical data, but, at the lower end of the distribution, the empirical data lie above the 1:1 line on the Q-Q plot, which indicates that the empirical data points are higher than the predicted values. The peer reviewer stated that EPA could consider modeling the lower end of the distribution separately from the entire distribution. The peer reviewer also acknowledged that the 95% confidence interval includes the empirical data points.

EPA Response: Based on this comment the revised SSD has included the Q-Q plots from more fit distributions to show these data. Revisions also included more narrative on selection criteria within Appendix F.2.1.2 following the guidance detailed within {Etterson, 2020, 5085638}.

Rather than model the lower distribution from the whole, after screening, the predicted acute toxicity values for 46 additional aquatic organisms (22 fish, 1 amphibian, 9 aquatic invertebrates, 14 benthic invertebrate species) were added from the surrogate rainbow trout, zebrafish, and Daphnia magna data (Table_Apx F 1). The toxicity data were then used to calculate the distribution of species sensitivity to TCEP exposure through the SSD toolbox as shown in Figure_Apx F 4 and Table 4 6 {Etterson, 2020, 5085638}. The distribution of acute hazard values from vertebrates and invertebrates was examined to determine if these two groups had similar sensitivity to TCEP. The mean LC50 values for the 26 vertebrates and 27 invertebrates were 399 + 54 mg/L (+ SEM) and 197 + 51 mg/L and were not significantly different ($F = 1.87$, $df = 1,51$, $P = 0.17$). Two predicted values, representing one vertebrate (cape fear shiner) and one invertebrate (tubifex worm), were each four standard deviations from their respective means. When statistical analysis was conducted with these two values omitted as outliers the two groups were not significantly different ($F = 6.24$, $df = 1,49$, $P = 0.015$) with mean LC50 values of 253 + 30 mg/L and 152 + 27 mg/L for vertebrates and invertebrates, respectively. Acute hazard values for invertebrates divided between benthic and water column species were not significantly different ($F = 1.01$, $df = 1,25$, $P = 0.32$) with mean LC50 values of 243 + 90 mg/L and 138 + 27 mg/L, respectively.

Summary: A peer reviewer (2.1.1 – R5) stated that the EPA approach assumes that acute toxicity is the basis upon which aquatic toxicity should be determined, and this is not realistic. The peer reviewer wrote that chronic exposures are much more likely, and HC05s should be based on chronic toxicity values. The peer reviewer stated that if acute toxicity data are used for estimates, adjustment factors are needed. The peer reviewer noted that there are reasonable estimates of acute to chronic aquatic toxicity values and referenced Kienzler et al. (2017). The peer reviewer stated that both acute to chronic adjustments and interspecies extrapolation assessment factors are needed.

EPA Response: Thank you for your submission of Kienzler et al. (2017) and it is of particular interest since the revised TCEP draft now contains acute and chronic hazard data for daphnia from the Japanese Ministry of the Environment (Table 4-3). In contrast to the draft TCEP RE, the revised work also has

five additional chronic exposure studies with fishes (Table 4-2) where the draft TCEP chronic COC was derived from an empirical sub chronic hazard endpoint from a 14 exposure of TCEP to embryo and larvae. The revised Environmental Hazard section of the TCEP risk evaluation now reviews these chronic exposure studies and uses the apical endpoints (*e.g.*, survival, reproduction, growth) in those works to designate a COC based on empirical evidence.

Other comments in response to Charge Question 2.1

Summary: A peer reviewer (2.1.1 – R5) included several line-specific comments:

- The peer reviewer asked if the data labeled 'Chronic' should be labeled 'sub-chronic' in Table 4-2 (page 106).
- The peer reviewer stated that the description of chronic data in line 2563 on page 107 should align with the data in Table 4-2 and with later statements.
- The peer reviewer expressed that lines 2568-70 on page 107 should be written in past or present tense, rather than future tense.
- The peer reviewer stated that, in lines 2709-2717 on page 111, it would be helpful to state what factors contributed to the final assessment factors in the LC50 estimates.

EPA Response: The term "sub-chronic" has been added to the table and the corresponding narrative to better characterize the duration of the Sun et al. 2016 study. The description of chronic aquatic hazard study has been revised within Section 4.2.2 beginning on line 2643 and 2730, for vertebrates and invertebrates, respectively. The use of future tense in this section and others has been revised. The section in the Draft Risk Evaluation in line 2709-2717 was demonstrating possible COCs from ECOSAR values as a comparison to the limited empirical hazard data available. The acute and chronic COCs has the considerations for applied assessment factors in the narrative but the algae COC assessment factors were not described past the application of an AF of 100. Similar to the chronic COC derived from ECOSAR data, the algae COC had an AF of 10 applied for aquatic plants and an additional AF of 10 applied due to uncertainties associated with the use of this ECOSAR hazard value. Ultimately, the presentation of COCs from ECOSAR data had been removed since the revised Risk Evaluation has added empirical hazard data for both acute and chronic data and represents invertebrates, vertebrates, and aquatic plants.

Responses to Charge Question 2.2 related to data

Summary: A peer reviewer (2.2.1 – R1) stated that the use of the SSD toolbox combined with the Web-ICE calculation to calculate the lower confidence limit on the HC05 seems like an acceptable approach. The peer reviewer added that the use of the additional data mentioned in their response to Charge Question 2.1.1 would improve the estimate and result in a narrower confidence interval.

EPA Response: EPA has been able to add additional studies from systematic review that increase our data landscape for acute and chronic hazard. Revision of the Web-ICE model in the TCEP has taken place with the additional acute hazard data. Revisions have been made for the additional empirical and predicted values used in SSD and are documented within Appendix Section F.2.1.1 for Web-ICE and F.2.1.2 for the SSD.

Summary: Several peer reviewers (2.2.1 – R2, 2.2.1 – R3, 2.2.1 – R5) expressed that the data used was insufficient. One peer reviewer (2.2.1 – R2) wrote that, as currently presented, evaluations based on the lower 95% confidence interval introduce unnecessary conservatism. The peer reviewer stated that the incorporation of additional high-quality data could result in a refined HC05 value with a

narrower 95% confidence interval, which would add certainty to the potential use of the HC05 (instead of the lower 95% confidence interval) as the definitive acute COC. The peer reviewer included a graph to depict this. Another peer reviewer (2.2.1 – R3) stated that EPA calculated the COC for aquatic organisms with an assumption that the previously modeled Web-ICE data would be representative of TCEP. The peer reviewer expressed that the absence of multiple species presents major uncertainties and raises concerns about applying standard assumptions. Finally, a peer reviewer (2.2.1 – R5) stated that the species distribution approach is appropriate, but there is insufficient data in all the datasets. The peer reviewer added that the lack of data for amphibians, aquatic invertebrates, and plants is unacceptable for a risk evaluation, risk determination, or risk assessment of compounds known to be present in water. The peer reviewer expressed that if there is a desire to move away from animal testing, in-vitro assessments would provide the best alternative. The peer reviewer additionally wrote that all the data for TCEP toxicity to aquatic species was generated in a Japanese lab, which indicates that the U.S. is providing no leadership in obtaining data that is essential for the processes required by TSCA. The peer reviewer specifically commented that the lack of chronic data for fish presents a problem.

EPA Response: Additional acute hazard data have been reviewed and integrated into the current RE. Specifically, acute hazard data on vertebrates and invertebrates have been added to Table 4-2, and 4-3, respectively, with accompanying narrative on the studies within Section 4.2.2. Chronic hazard data have been added from studies representing several species of fishes with exposure durations ranging from 21 to 120 days (Table 4-2). Chronic aquatic invertebrate hazard data have also been added to the TCEP risk evaluation and is represented within Table 4-3. Aquatic plant hazard data have been added to Table 4-4 also with accompanying narrative. These additional works have increased the data landscape for both acute and chronic exposures and represent expanded taxa which increases confidence in the overall COCs representing within the TCEP risk evaluation for ecologically relevant receptors. It is important to recognize that although there are no empirical hazard endpoints for amphibians, the use of WebICE did result in the inclusion of a predicted acute hazard value for bullfrog, which was included within the SSD.

The EPA has worked with the Japanese Ministry of the Environment to acquire, translate, and review their studies on TCEP. The works were placed through the systematic review process and hazard information has been integrated into the TCEP Risk Evaluation.

The inclusion of additional empirical acute hazard values in WebICE and the resulting SSD did result in decreasing the 95% confidence intervals associated with the HC05. The revised COC from these additional studies did not change much but the representation of additional taxa and the details on the distribution of taxa within the SSD are characterized within Appendix F 2.1.1. In addition to the inclusion of more acute hazard data from Zhang et al. 2024, the SSD presented in that recent work demonstrates strong agreement with the SSD performed within the TCEP Risk Evaluation.

Responses to Charge Question 2.2 related to the calculation of the COC

Summary: In response to Charge Question 2.2, a public commenter (0040) stated that the approach to calculating the COC differs from other EPA offices such as the Pesticide Program and biases the risk quotient (RQ) toward unreasonable risk. Another commenter (0045) discussed the use of a derived COC, stating that the approach to model based on known data and reasonable assumptions seems to be a “best possible solution” to the knowledge gaps.

EPA Response: The TCEP Risk Evaluation derives acute COC from the SSD performed with empirical and Web-ICE modeled hazard information and does not apply any assessment factor. The chronic aquatic COC is represented by a ChV (geometric mean of a NOEC and LOEC for mortality) from a 30-day exposure of TCEP with an assessment factor of 10. There are no RQs $\geq$ 1 for the acute aquatic COC in the draft or revised TCEP RE. The comment from (0040) is specific to the role of Assessment Factors with the ECOSAR data with acute COCs. The revised TCEP RE does not use the ECOSAR data for acute COCs nor did the draft TCEP which calculated an acute COC based on the lower 95th percentile of the HC05 for an aquatic SSD.

Summary: In response to Charge Question 2.2, a peer reviewer (2.2.1 – R6) expressed that it is unclear why a secondary acute COC was derived. The peer reviewer stated that the scenarios to use acute COC or secondary acute COC are not provided in Section 4.2, and the peer reviewer expressed that the 10-fold difference between the acute COC and secondary acute COC could be better explained.

EPA Response: This revision has been accepted as recommended. The secondary COCs were not carried through to the Environmental Risk Characterization and were not used for the formation of Risk Quotients. This review and comments have identified a critical gap in information on chronic duration exposure studies with TCEP on aquatic organisms. The EPA has identified and evaluated several chronic duration studies conducted on aquatic vertebrates and has updated the chronic hazard assessment portions of the TCEP RE to reflect these newly identified studies.

Summary: A peer reviewer (2.2.1 – R2) expressed that the use of a data-driven acute COC for aquatic organisms is an improvement over the application of traditional assessment factors. The peer reviewer stated, however, that EPA did not provide a scientific justification for the lower 95% confidence interval. The peer reviewer recommended that future updates to the risk evaluation clearly explain the rationale behind the selection of the lower 95% confidence interval, even if the justification is based on a policy decision. Additionally, the peer reviewer stated that revisions regarding the lower 95% confidence interval should include appropriate citations. The peer reviewer noted that the complete citation for U.S. EPA, 2022c is missing in the draft risk evaluation.

EPA Response: The justification for using the lower 95th percent confidence interval as the acute Concentration of Concern over other options such as the HC05 or application of assessment factor has been added to Section 4.2.4. A manuscript is currently under review within Integrated Environmental Assessment and Management titled "Evaluation of Interspecies Correlation Estimation (ICE) models for chemicals evaluated under the Toxic Substances Control Act". This submission evaluates the use of the WebICE model in TSCA chemical evaluations and includes TCEP along with other chemicals within the TSCA program.

Summary: A peer reviewer (2.2.1 – R2) recommended EPA re-evaluate the chronic COC used in the risk evaluation. The peer reviewer noted that the value was based on a single endpoint for a single species (Sun et al., 2016), and the peer reviewer stated that there are two issues with this study that were not flagged in the risk evaluation. First, the peer reviewer commented that the study did not provide any details on the methodology used for quantifying the body length of the larval medaka. Second, the peer reviewer stated that the study did not include chemical analyses of the exposure media, so the concentrations used in the toxicity tests were not confirmed. The peer reviewer also said that TCEP did not cause other adverse effects on any of the additional developmental endpoints in the study. The peer reviewer stated that too much weight was given to a study that may not meet all the

quality criteria needed for the risk evaluation, and the peer reviewer expressed that the conclusion of unreasonable risk in Section 6.2.2 is not fully supported.

EPA Response: The review and critique of the Sun et al. (2016) is welcome and resulted in better representation of chronic aquatic hazard for TCEP after this comment and others. As a result, more chronic duration studies were identified and placed through the systematic review process. Ultimately, six studies of fishes (including Sun et al. 2016) were available and represent TCEP exposure with subchronic and chronic durations ranging from 14 to 120 days. Apical assessment endpoints of regulatory interest (*i.e.*, impaired growth, survival, or reproduction) in addition to organ level and above endpoints are detailed within the narrative in 4.2.2 and summarized within table 4-2.

Summary: A peer reviewer (2.2.1 – R4) stated that EPA considered two approaches for calculating the acute COC for aquatic organisms, and EPA chose the SSD approach because it relies on multiple data points rather than the single daphnid study used in the Ecological Structure Activity Relationships (model) (ECOSAR) approach. The peer reviewer said that EPA should provide further justification for the selection, because the values are 20x different and the selected value is less protective.

EPA Response: Within the draft TCEP risk evaluation the ECOSAR COC would have been 3.4 mg/L compared to the draft COC from the SSD of 85 mg/L. The potential use of an ECOSAR COC was dervied from an estimated 48 hour LC50 (170 mg/L) from daphnia with an Assessment Factor (AF) of 50. This AF for the acute COC was represented with the application of an AF of 5 for acute invertebrate hazard value and an additional AF of 10 for uncertainties associated with the use of an ECOSAR hazard value for a water column invertebrate. Although more protective, the use of an ECOSAR value for the acute COC would represent a more speculative approach as the AFs account for wide gaps in information on a variety of unrepresented taxa when using a single ECOSAR value for daphnia.

The presentation of ECOSAR modeling demonstrated potential TCEP hazard values for green algae and daphnia that were not represented with empirical data in the DRAFT TCEP risk evaluation. Since submission of the draft TCEP risk evaluation, EPA has acquired the acute and chronic daphnia studies from the Japanese Ministry of the Environment (Table 4-3) in addition to algae hazard data (Table 4-4) and additional hazard data both recommended from peer review and newly published works (Table 4-2). The revised acute COC continues to use the SSD approach and now is represented with more empirical hazard values from a greater variety of taxa. The revised acute COC of 16,700 ppb represents empirical data as compared to the single ECOSAR value from a 48-hour daphnia of 170,000 ppb with assessment factors (50) applied.

Other comments in response to Charge Question 2.2

Summary: A peer reviewer (2.2.1 – R5) recommended that EPA define the two hazard values in the 4th column of Tables 4.2 and 4.3.

EPA Response: These tables have been revised with a footnote in the fourth column (hazard value) to indicate that the third column (endpoint) details the type of hazard endpoint value represented (*e.g.*, LC50, EC50, NOEC, LOEC, etc).

Summary: A peer reviewer (2.2.1 – R5) specifically commented on lines 12395-12408. The peer reviewer stated that the text describes a process in which measures of TCEP toxicity to fish were

compared to the Web-ICE results, and the data were excluded from the dataset if the measured data did not fit the Web-ICE model. The peer reviewer asked what dataset the data was excluded from. The peer reviewer expressed that, if there are chemicals that do not fit the model, the solution is not to exclude the chemicals. Additionally, the peer reviewer stated that TCEP falls into the category of very polar general narcosis toxicants, and models like Web-ICE are likely to underestimate the toxicities of very polar general narcosis toxicants.

EPA Response: WebICE predicts toxicity values for species based on empirical hazard values and there are model fit statistics associated with surrogate (empirical) and predicted pairs (R^2, MSE, Slope). This section (Page 460 within Appendix F.2.1.2) has been revised to be clearer about the model selection criteria from Willming 2016 as it applies to the predicted hazard values from the WebICE model results. Predicted species and their corresponding hazard values that met these criteria are presented within Table Apx F-1. The statistics and parameters of the WebICE model information for each WebICE module are located here: https://www3.epa.gov/webice/iceDownloads.html .

The WebICE v4.0 database has a total of 1517 species-chemical combinations, with narcosis representing by 306 species-chemical combinations with an average inter-test range of acute toxicity tests of 9.1 with 80th and 90th percentiles of 5.8 and 12.6, respectively. The model also includes other MOAs such as neurotoxicity (N = 172) and AChE inhibition (N = 255) with additional documentation on the aquatic MOA models is available here: https://www3.epa.gov/webice/iceDownloads.html
The increased number of empirical hazard endpoints increases confidence that the resulting SSD does not underestimate TCEP acute toxicity. The reviewer's comment on the role of very polar general narcosis toxicants is noted and resonates with the inclusion of recent chronic duration studies on fishes with hazard values presented in Table 4-2.

Section 4.3 – Environmental risk characterization

Summary: A public commenter (0040) suggested that EPA employ a tiered approach to risk evaluation using a screening-level deterministic RQ approach first and following up with more refined approaches if the RQ is greater than 1.0, similar to the approach used by the EPA Office of Pesticide Programs. The commenter stated that the aquatic risk characterization was based on "flawed and implausible assumptions", including the volume of estimated releases from a single facility to surface water.

EPA Response: TCEP is not listed on the National Emissions Inventory (NEI) and was only recently added to TRI, with the first year of reporting from facilities due July 1, 2024. As of September 2024, there are currently no TRI entries for TCEP. The 2016 CDR data {U.S. EPA, 2019, 6277143} included a single reporting site, Aceto Corporation in Port Washington, New York, importing TCEP, with no downstream industry sectors identified. TCEP was not reported in the 2020 CDR {U.S. EPA, 2020, 6277143}. EPA modeled environmental releases and occupational exposures for these hypothetical scenarios. For each OES, where monitoring data were not available, daily releases were estimated per media of release based on EPA Standard Models, Generic Scenarios (GSs), and/or Emission Scenario Documents (ESDs) to generate annual releases and for the estimation of associated release days.

Chronic RQ values for COUs with releases to water are presented with several scenarios for flow and production volume with revisions presented within Section 4.3.6.1 and additional Tables within Appendix G-1. For example, 7Q10 flow values have been calculated to represent the 50th and 90th percentile of the distribution of SIC codes of the industry sectors. Results from both central tendency and high-end estimate scenarios at each flow regime are now represented to demonstrate the importance of receiving waters flow in TCEP concentrations and days of exceedance reported within

the PSC model. For the Environmental Risk Characterization for TCEP EPA did employ a screening level trophic transfer analysis as a tiered approach for determining potential risk with terrestrial and aquatic pathways to relevant terrestrial biota.

Revisions to the chronic COC include a value dervied from 30-day TCEP exposure, resulting in a longer duration above the COC concentrations to demonstrate days of exceedance. Please note that this COC is not limited to embryo/larval development as the previous COC was derived from a 14-day exposure in embryo/larvae.

Summary: A public commenter (0044) stated that EPA had not evaluated sufficient diversity of bird species and life stages and did not consider risks to wildlife species that are listed as threatened or endangered under the Endangered Species Act such as salmon, marine mammals, and loggerhead sea turtles, contrary to EPA's own guidance on risk assessments.

EPA Response: The environmental risk characterization was performed with the landscape of reasonably available hazard data from TCEP toxicity studies to evaluate risk to environmental receptors. The use of the WebICE model for acute TCEP toxicity to aquatic organisms has allowed for the inclusion of several salmonid species and numerous freshwater mussels, both taxa representing species of conservation concern (Appendix F.2.1.1).

Summary: Another commenter (0045) suggested that EPA has understated the hazard and risk to aquatic invertebrates from chronic exposure to TCEP because no actual empirical exposure duration data for fish were available and suggested that EPA use a cold freshwater fish species and a testing procedure that incorporates a longer exposure duration, which the commenter described as more appropriate to address chronic exposure for aquatic vertebrates.

EPA Response: Additional chronic hazard studies on TCEP have been identified and reviewed within our Systematic Review Process. These studies were integrated into the Environmental Hazard section of the RE and are summarized in the narrative of Section 4.2.2 and Table 4-2. Rainbow trout are represented with empirical acute hazard data within our SSD for the formation of an acute COC for the TCEP risk evaluation. Although the species represented are not characterized as cold-water fishes, sub chronic exposures from one study and chronic exposure effects from 5 studies within aquatic vertebrates represent a variety of exposure durations, life history stages, and fish species (Table 4-2). Sub chronic and chronic duration exposures of TCEP to aquatic vertebrates produced effects including: mortality {Hu, 2022, 11365033; Wang, 2022, 11365040}; growth/development {Sun, 2016, 4292102; Hu, 2022, 11365033; Hu, 2023, 11365083; Wang, 2022, 11365040}; organ level effects within liver {Sutha, 2020, 6772951; Hu, 2022, 11365033; Hu, 2023, 11365083}, gills {Sutha, 2020, 6772951}, kidney {Sutha, 2020, 6772951}, and heart rate {Wang, 2022, 11365040}.

Section 5 – Human Health Risk Assessment

Comments associated with this issue are summarized in the subsections below.

Section 5.1 – Human exposures (including comments on milk concentrations (Verner), dry and wet air deposition, and disposal and groundwater pathway, aggregate exposure, exposure to certain PESS)

Exposure scenarios for Tribal populations

Summary: Several public commenters (0035, 0041, 0044) expressed support for EPA's inclusion of Tribal populations in PESS and the Agency's efforts to quantify their greater exposures via higher fish consumption, but said EPA failed to comprehensively assess the factors that increase Tribal population's exposures to and susceptibility to harm from TCEP. One of the public commenters (0035) stated that though EPA claimed that quantifying unique exposure scenarios for Tribal populations was not possible, Harper et al. (2012) published extensive guidance on conducting risk assessments in Tribes and developed specific exposure factors for Tribal lifeways. The commenter suggested that EPA draw on these data. Another commenter (0041) stated that EPA needs to aggregate these exposures across pathways and conditions of use by including background exposures from non-TSCA uses, accounting for increased Tribal susceptibility, and considering cumulative impacts on Tribal people from TCEP exposure. The commenter, along with another public commenter (0044), also said that the exposures of Tribal people via fish ingestion are underestimated in the risk evaluation by:

- using a mean current fish consumption rate vs. a 95th percentile rate for Tribal populations, when both 50th and 95th percentile exposure values are used in determining occupational and general population exposures, and when 95th percentile values are available for many different Tribes and they are much higher than 216 g/day;
- using a fish consumption rate from only one Tribe, when much higher rates and for many different Tribes are available in peer-reviewed literature;
- disregarding the higher mean current fish consumption rate of 770 g/day for Alaskan communities published in Chapter 10 of the EPA Exposure Factors Handbook with no explanation;
- using the lower fish bioaccumulation factor in determining risk; and
- using the 33-year value for residential mobility which does not apply to Tribal members who typically spent most, if not all, of their lives living on their Tribal lands.

EPA Response: The mean current ingestion rate was used to quantify a central tendency scenario that may represent current use patterns for tribal populations. However, EPA also integrated the heritage fish consumption rate, which is much higher than any of the available 95th percentile current ingestion rates in the suggested literature. The 770 g/day for the Alaskan communities is a maximum rather than a mean ingestion rate and still lower than the heritage consumption rate of 1646 g/day.

For the bioaccumulation factors, risk determination was based on the lower value because of the considerable uncertainties with the higher value, as explained in Section 5.1.3.7.1 and 5.3.5. The study that reported the higher BAF value for walleye collected surface water and fish tissue at different years, thus it is difficult to hypothesize if TCEP surface water conditions at the time of collection influenced BAF values. Both BAF values resulted in fish tissue concentrations that were several magnitudes higher than both the monitored data and the calculations based on the bioconcentration factor that the environmental assessment conducted (Table 5-31). Lastly, Tables 5-61, 5-63, and 5-65 present acute noncancer, chronic noncancer, and cancer risk estimates, respectively, for the different BAFs and fish ingestion rates. For Tribal populations, the risk estimates vary by 1-2 magnitudes based on the BAF value. These different estimates do not result in significantly different risk conclusions.

EPA thanks the commenter for highlighting the 33-year value for residential mobility. EPA has changed the 33-exposure duration to 78 years (the full lifetime) for lifetime drinking water and lifetime ambient air inhalation risk estimates. For the fish ingestion pathway, the fish ingestion rates used in this RE were specific to adult tribal members aged 16-78 years. EPA did not factor in residential mobility and used 62 years, rather not 33, as the exposure duration.

Summary: Conversely, a public commenter, in two submissions to the docket (0040, 0052), said that it is unclear why EPA selected the highest estimated fish ingestion rate for the Kootenai Tribe when it was acknowledged that this may overestimate fish consumption.

EPA Response: EPA acknowledged this uncertainty. However, the fish ingestion rate for the Kootenai Tribe was selected as the most appropriate fish ingestion rate from the reasonably available data to characterize a sentinel exposure scenario. Other rates were not considered primarily because it is unclear if they represented fish ingestion only or fish used for trade and other purposes.

Summary: A public commenter (0044) said that EPA must account for the impact of solid waste disposal practices on Tribal communities, which is increased due to substandard landfill infrastructure, open dumps, and open burning of solid waste. Additionally, the commenter said that EPA overlooked TCEP concentrations in the Arctic environment due to contaminated air and other environmental media, as well as organophosphate flame retardants, brominated flame retardants, and other persistent organic pollutants. The commenter suggested EPA look at a recent study, Moran et al. (2023), which reported vapor phase TCEP concentrations in ambient air in the Yupik community of Sivuqaq that are significantly higher than the levels reported in literature cited in the draft risk evaluation.

EPA Response: EPA appreciates the commenter sharing the Moran et al. 2023 reference. This study has now been incorporated into the ambient air and deposition sections (3.3.1 and 3.3.2.6), as well as the discussion regarding disposals for TCEP (5.1.2.2.5).

The air concentrations and deposition values reported in Moran et al. 2023 are lower than the maximum concentrations and deposition values evaluated in the TCEP risk evaluation. EPA has identified Tribal populations as a PESS in the TCEP risk evaluation and has done an analysis on Tribal fish ingestion exposure (Section 5.13.4.4). While EPA has not done a specific Tribal analysis related to substandard landfill infrastructure, open dumps or the open burning of solid waste, the TCEP risk evaluation does evaluate the potential for TCEP to leach from TCEP containing landfills (Section 3.3.3.7), and does calculate inhalation risks from breathing ambient air (Section 5.1.3.2) and dermal and ingestion risk for children playing in soils of nearby facilities emitting TCEP (Sections 5.1.3.3.2, and 5.1.3.4.5).

Without a full characterization of open burning of solid wastes containing TCEP, and lack of monitoring data describing open burning of TCEP containing solid wastes, the data needed to produce quantitative risk estimates from open burning is not reasonably available.

Aggregate exposure to TCEP

Summary: A public commenter (0035) expressed support for EPA's decision to aggregate exposures for each consumer condition of use across dermal, ingestion, and inhalation routes of exposure. However, the commenter said that EPA considered each condition of use and scenario in isolation, which does not provide an accurate picture of humans' real-world exposure to TCEP. The commenter recommended that EPA aggregate exposures across occupational and consumer conditions of use and stated that EPA did not justify its decision to forego an aggregate exposure assessment. Additionally, the commenter, along with another commenter (0044), suggested that EPA should aggregate exposure across routes and pathways in the general population, even though EPA claimed that the individual exposure estimates were based on release estimates assuming a product volume of 2,500 pounds and an aggregation would double count the production volume. Aggregating soil ingestion and drinking water

exposures would total an estimated 5,000 lbs, which is still well below the CDR threshold and within the range of estimated exposures included by EPA in the draft risk evaluation, according to the commenter. The commenters (0035, 0044) said that failing to aggregate exposures is in violation of TSCA.

One of the commenters (0044) further stated that under TSCA, EPA must evaluate those reasonably foreseen combinations of exposures and EPA cannot claim to lack reasonably availably data indicating co-exposures. By failing to address aggregate exposures to lactating individuals, the commenter claimed that EPA underestimated infants' and children's exposure to TCEP. The commenter also wrote that EPA underestimated this exposure by assuming

- that infants breastfeed for a maximum of one year despite contrary evidence; and
- that infants mouth toys and products containing TCEP for seven to ten minutes per hour, significantly less than the duration that EPA's Exposure Factors Handbook recommends for use in risk assessment.

Finally, the commenter questioned EPA's claim that when a single exposure pathway or condition of use is sufficient to establish unreasonable risk, the consideration of additional, aggregate exposures is unnecessary, which misunderstands the purpose of a risk evaluation. If EPA has not considered aggregate exposures to determine the full extent of a chemical's unreasonable risks, then it will not have sufficient information to properly manage the chemical and ensure that such risks are eliminated. Another commenter (0045) similarly expressed disappointment that the Agency has not incorporated aggregate exposure into its risk characterization, and stated that even if there appears to be a predominate source of exposure, all routes should still be assessed and combined when determining if a condition of use poses an unreasonable risk or not. The commenter recommended that EPA develop aggregate exposure assessments and risk estimates for each condition of use. A peer reviewer (OC – R6) said that EPA stated several times that they did not aggregate exposures, thereby missing opportunities to specifically quantify exposure estimates among sensitive or highly exposed sub-groups including infants and workers. The commenter said that EPA's comment on Line 5125 that background levels of TCEP in indoor air and indoor dust are not considered or aggregated in this assessment does not reflect real world exposure scenarios and EPA should update their methodology.

EPA Response: A full discussion of EPA's consideration of aggregate exposure is provided in Section 5.1.4 of the risk evaluation and details the conditions of aggregating exposure across routes within the consumer assessment. Because the health outcomes are systemic and EPA did not identify evidence of differences in toxicokinetics across exposure routes, considers it is possible to aggregate risks across exposure routes for all exposure durations and endpoints for the selected PODs identified in Sections 5.2.6.1 and 5.2.6.2 but only if exposure scenarios indicate that aggregation is reasonable. For the milk pathway (from page 583 of RE): EPA combined exposures for the milk pathway across all routes for each COUs/OESs within workers and consumers. However, for the general population, EPA only assessed the oral route when assessing the milk pathway because exposure estimates showed that oral doses were several magnitudes higher than dermal or inhalation doses.

Because data were not reasonably available to indicate that co-exposures of multiple TCEP-containing activities or products in the occupational and indoor environment, EPA did not assess aggregate exposure across consumer, commercial, or industrial COUs, see section 5.1.4.

TSCA Section 6(b)(4)(F)(ii) directs EPA to "describe whether aggregate or sentinel exposures to a chemical substance under the conditions of use were considered, and the basis for that consideration" in risk evaluations. Therefore, EPA may, but is not required to, consider aggregate exposure in the risk

evaluations. 40 CFR 702.33 defines aggregate exposure as "the combined exposures to an individual from a single chemical substance across multiple routes *(i.e.,* dermal, inhalation, or oral) and across multiple pathways (*i.e.,* exposure from different sources)". Therefore, aggregate exposure includes combined exposures from a single chemical across multiple routes and multiple pathways. 40 CFR 702.33 defines sentinel exposure as "the exposure from a single chemical substance that represents the plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures."

Susceptible subpopulations

Summary: A public commenter (0044) said that EPA failed to evaluate as PESS people who experience "greater susceptibility" to harm from TCEP exposures because of their cumulative exposures to multiple chemicals and non-chemical stressors, which the commenter described as a violation of TSCA. The National Academies have repeatedly called for the consideration of cumulative exposures in chemical risk evaluations, according to the commenter, and asked agencies to "move beyond source-by-source and pollutant-by-pollutant…risk assessment". Yet, EPA did not evaluate co-exposures to TCEP and microplastics, benzo-a-pyrene, or other flame retardants, according to the commenter.

The commenter also stated that EPA failed to calculate TCEP's increased risks to truck drivers, students residing in dormitories, and firefighters. First, TCEP is used in automotive foam, posing increased risks to long-haul truck drivers who spend long periods of time in their vehicles, according to the commenter, but this was never considered in the risk evaluation. Second, the commenter stated that though EPA claims that it conducted a qualitative assessment for firefighters, it never determined whether firefighters are exposed to unreasonable risk or the extent of those risks. Finally, the commenter said that high levels of TCEP have been detected in dust in student dorms and common areas, and EPA needs to consider this in the risk evaluation.

EPA Response: EPA thanks the commenter for highlighting the concern about co-exposures, non-chemical stressors and cumulative exposures. The impact of co-exposure with other chemicals is outside of the scope of the risk evaluation for TCEP. At present, the purpose of the risk evaluation under TSCA is to determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, under the conditions of use. EPA accounted for the following PESS groups: 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, fence line communities who live near facilities that emit TCEP, and firefighters.

While EPA did not provide quantitative estimates for all of these groups, where data and assessments approaches were readily available, EPA quantified exposures for the various COUs.

A summary of the information found on firefighters is presented in Section 5.3.3. EPA has incorporated additional information of TCEP found in automobiles with the revision of the paints and coatings COU, and the incorporation of additional literature discussing TCEP in automobiles (Hoehn et al. 2024 in Section 5.1.2.2). The consumer assessment included an analysis of exposure from auto foam containing TCEP (Section 5.1.2).

Dermal exposure assessment

Summary: A public commenter (0040) stated that the Abdallah et al. (2016) study selected by EPA may over-predict dermal absorption for both workers and the general populations because it used acetone and 20% Tween-BO (aka Polysorbate 80) as vehicles, which may function as penetration enhancers. Additionally, the commenter said that EPA relied upon individual deterministic modeling point estimates for its dermal exposure assessments, which led to a substantial degree of uncertainty in the Agency's risk conclusions, and did not apply a tiered approach to its inhalation, dermal, or ingestion exposure assessments for any consumer exposure assessments.

The commenter also stated that in several instances, EPA used the OPPT Dermal Exposures to Volatile Liquid Model with default central tendency and upper bound loading rates for the dermal exposure estimation. The commenter said that these loading rates are not specific to any scenario assessed in the risk evaluation, nor are they specific to TCEP and chemicals similar to TCEP, but rather are default values used in the absence of any other scenario-specific information. Per EPA's Draft Protocol, using a generic default value should result in the weighing of "slight" in the weight of evidence assessment, not "moderate" and the commenter stated that the reason for this discrepancy is unclear.

EPA Response: Thank you for the comment. EPA used values from a technical report, A Laboratory Method to Determine the Retention of Liquids on the Surface of the Hands (U.S. EPA, 1992b) to estimate dermal loading values. These are based on the activity/scenario that is most likely involved for each process (*i.e.*, routine/incidental contact and immersion). Dermal loading is covered in Appendix D.2.2. in the Engineering Supplemental File.

Recycling of e-waste (processing)

Summary: A public commenter (0040) stated that for the OES regarding recycling of e-waste, EPA directly used monitoring data for TCEP but employed a data summary approach that appears to have overestimated inhalation exposures by 1,000-fold or greater. To correct this, the commenter said that AIHA recommends using the 95th percentile of a dataset relevant to a similar exposure groups as a decision metric, and using the 95% upper confidence limit to determine a certainty level.

EPA Response: The available monitoring data only provided summary statistics (minimum, maximum, median) rather than discrete samples. Therefore, EPA could not create a full distribution of monitoring results across the sources to use in estimating central tendency and high-end exposures (From Supplemental file Section 3.7.4.3)

Verner physiologically based pharmacokinetic (PBPK) model

Summary: A public commenter (0040) questioned the use of the Verner et al. model due to the differences in tissue distribution and half-lives of elimination. The commenter suggested that studies by Toxicology Excellence for Risk Assessment (TERA) and Minegishi et al. further inform this issue. For example, a report by TERA (2016) prepared for the Consumer Product Safety Commission (CPSC) described the elimination of TCEP as biphasic with a half-life of elimination in adipose tissue of 87 hours. The TERA report also referenced a study by Minegishi et al. (1987) which provides a detailed toxicokinetic study of radiolabeled flame retardants. The commenter expressed concern that EPA did not identify this highly informative study even though it's located in the health & environmental research online (HERO) database.

EPA Response: EPA added a summary of {Minegishi, 1988, 656593@@author-year} to Section 5.2.2 and Appendix J.1, which is consistent with other studies' findings that most of TCEP (>75%) is eliminated within the first 24 hours. No changes were made in how EPA modeled TCEP concentrations in human milk. A challenge with using radiolabeled compounds for ADME studies, such as the one by {Minegishi, 1988, 656593@@author-year}, is that half-lives of the parent compound can be overestimated. After administration, whether the ^{14}C is still tagged to the parent compound or a metabolite cannot be determined. It is also possible that the functional group containing the radiolabeled carbon could have reattached to another substance that is no longer TCEP. Despite limitations in applying the Verner model to TCEP, it is the best approach based on reasonably available information for estimating infant exposure through human milk ingestion.

Summary: Several peer reviewers (3.1.1 – R1, 3.1.1 – R2, 3.1.1 – R3, 3.1.1 – R4, 3.1.1 – R6) expressed support for the use of the Verner model and said that it is clearly and transparently described. However, one of the reviewers (3.1.1 – R1) said that one may raise caution with regards to assumptions of milk intake rates used and thus the actual dose that a child may receive across different ages of development, composition of breast milk, and the social constraints that limit use of breastfeeding. Therefore, it is anticipated that the estimated exposure will be relatively higher than what will occur. Another reviewer (3.1.1 – R4) stated that in addition to the sensitivity analysis for the input parameters half-life, KOW, age at pregnancy, and lipid fraction, EPA should describe the uncertainties associated with the maternal oral doses used. Further, the reviewer suggested that EPA justify the exposure duration of one year, as some infants breastfeed for much longer. Finally, one of the reviewers (3.1.1 – R6) mentioned two other studies that described TCEP concentrations in breast milk in the US: Ma et al. (2019) and Yao et al. (2023).

EPA Response: This risk evaluation used the milk intake rates from the Exposure Factors Handbook (EFH), which stratified the rates for different age groups from birth up to the first year of life. EPA did not consider exposure beyond one year as a result (Section 5.1.3.4.7). Social and physiological or biological components that may affect the estimated infant dose were only considered to the extent that the EFH factored those elements into the milk intake rates. Regarding the uncertainties associated with the maternal oral doses, Section 5.1.3.7.2 describes that route-to-route extrapolation to an oral-equivalent dose can potentially underestimate exposure because of the first-pass effect. However, TCEP's relatively slow clearance rate of approximately 18 hours gives it time to partition out of the liver and mitigate the effect of TCEP concentrations in milk.

EPA thanks the reviewer for identifying those two studies. Ma et al. (2019) has been added to the summary of biomonitoring data in Section 5.1.3.4.7 and Appendix H.5.3. Yao et al. (2023) only measured TCEP concentrations in dairy milk and was not included for further consideration.

Summary: A peer reviewer (3.1.1 – R5) provided line by line suggestions regarding the Verner model:

- Line 13216 – The reviewer stated that that the term "milk concentration" is incorrect as these are TCEP concentrations in milk. The reviewer cautioned EPA against using this type of wording and said it should be carefully attended throughout the draft risk evaluation and all agency documents.
- Line 13220 – The reviewer said that the listed pKa of -9.1 seems unlikely as it does not make sense that TCEP is an acid, but perhaps a base. Additionally, NR, N/R, and N/A are not defined in the table.
- Lines 13229-13232 – The reviewer said that the Verner model only addresses persistent organic pollutants exposures for Inuit Peoples, and that there are no data for compounds as polar as TCEP. The commenter said that modeling of compounds with different functionality can be problematic. The commenter recommended that validation with an organophosphorus compound is needed for this model to be useful.
- Lines 13330-13335 – the reviewer questions the detection or quantification limits for the different studies, and asked if the means from data sets with non-detects include those data in calculation of means or not.
- Lines 13337-13338 – the reviewer said that the magnitude of confidence bands clearly indicates that more measured data are needed to ground truth and better parameterize the model for use in estimating TCEP partitioning.

EPA Response: The following revisions have been made: milk concentrations corrected to "TCEP concentrations in milk" throughout the document, acronyms defined at the bottom of Table H-11, removed the pKa with an explanation in Table H-17 (*i.e.,* no pKa value was identified), and addition of how non-detects were handled in Section H.5.3. While the range of modeled TCEP concentrations in milk are several magnitudes lower and higher than the minimum and maximum of measured concentrations, respectively, the infant's dose is consistently below the mother's. Although the model was originally built for persistent organic pollutants that are less polar than TCEP, membrane permeability of TCEP is still possible because its topological polar surface area (PSA) is below 140 Å. Monitoring data that measured TCEP in human milk also supports the conclusion that TCEP can accumulate in human milk despite its polarity.

Furthermore, a new study identified by another peer reviewer was added to compare modeled and measured TCEP concentrations in human milk {Ma, 2019, 7268788}. That study collected 100 samples from mothers across the U.S., and TCEP was detected in 37% of the samples. The maximum measured concentration is lower than the upper bound of the modeled TCEP concentrations in human milk. Although the sample size is small, it adds confidence that protecting the mother from exposure to TCEP will also protect the nursing infant. Lastly, the large spread in modeled concentrations can be attributed to the wide range of maternal doses and not necessarily the model itself.

Summary: A peer reviewer (3.1.1 – R7) also discussed the lack of calibration or validation data for TCEP within this modeling framework and said it is a substantial barrier to placing confidence in the modeling results. In order to build confidence in the Verner model, the reviewer recommended that EPA evaluate whether a clearance rate can be established in rats and mice based upon the cited studies and then scale that metabolic rate to humans. Additionally, the reviewer said that the nursing exposure predictions appear to be highly uncertain, as they are several orders of magnitude lower than the maternal doses.

EPA Response: EPA is unable to find clearance rates in rodent studies except for a value from a completed assessment. {TERA, 2013, 5155526@@author-year} cited a 1994 study that measured a

clearance rate after intravenous administration; however, the primary study could not be located for further evaluation on data quality and applicability.

The nursing exposure predictions are 1-2 orders of magnitude lower than the maternal doses. EPA revised the tables in Section H 5.4 to make the units consistent and improve clarity.

Extrapolating from the inhalation to oral routes of exposure

Summary: A peer reviewer (3.1.2 – R1) stated that the approach seems reasonable.

EPA Response: EPA thanks for the reviewer for this comment.

Summary: Several peer reviewers (3.1.2 – R2, 3.1.2 – R3, 3.1.2 – R4, 3.1.2 – R5, 3.1.2 – R6, 3.1.2 – R8) expressed concern with extrapolating from the inhalation to oral route of exposure.. One reviewer (3.1.2 – R2) stated that while estimating based on a young adult physiology provides information for extrapolating, transferring that estimate to the young, elderly, or health compromised may not be accurate, and these age and health related differences were not incorporated into the estimate. Similarly, another reviewer (3.1.2 – R3) stated that EPA does not provide any evidence that route-to-route extrapolation is appropriate, and several limitations were not addressed such as differences in metabolism via inhalation exposure vs oral exposure, and differences in absorption from lungs compared to gastrointestinal tract. Two reviewers (3.1.2 – R4, 3.1.2 – R8) stated that assuming inhalation exposure would result in the same absorbed dose as would oral exposure is incorrect, while another peer reviewer (3.1.2 – R6) stated that significant errors can occur due to this assumption. The reviewer also stated that when exposure is via inhalation, the blood may move directly from the lung to major organs so the toxicant may encounter sensitive nervous system tissue or the liver before moving to digestive organs and kidneys. Thus, the reviewer said that simple dosimetry is inappropriate without understanding the toxicokinetics and toxicodynamics of the compound in specific organisms. Finally, the reviewer said that it is important to understand the membrane partitioning/transition of TCEP relative to other toxicants, especially polar ones. Another reviewer (3.1.2 – R7) said that the exposure frequency and working years fixed in Equation 5-23 may not be relevant if the target population is women of reproductive age.

EPA Response: EPA acknowledges that route-to-route extrapolation introduces uncertainties to the modeled TCEP concentrations in human milk. However, the exposure estimates for the nursing infant are consistently lower than the mother's by at least one order of magnitude. EPA does not expect the conclusion that the mother is more sensitive than the infant to change despite the assumption that inhalation exposure would result in the same absorbed oral dose. Furthermore, all the toxicity values to estimate risks from TCEP exposure were derived from oral studies, and EPA assumed absorption via the oral route to be 100 percent.

The exposure frequency is considered the maximum number of days a worker is exposed for the dose metric of interest and assumes 5 days/week, 50 weeks/year. Those values are relevant to all workers. The 40 working years may be too high for women of reproductive age, but 40 years is also averaging time for exposure years of 40. This cancel the inputs such that the working years becomes irrelevant.

Intrinsic hepatic clearance

Summary: A peer reviewer (3.1.3 – R1) recommended against assuming that intrinsic hepatic clearance would remain constant throughout all life stages. The reviewer stated that while few studies have been conducted on the metabolism of TCEP and its possible bioactivation, there is evidence that metabolism by the cytochrome P450 monooxygenases (CYPs) play an important role, as reported in Burka et al. (1990). It is also known that aggregate cytochrome P450 levels are much lower at birth and increase fairly quickly with age (Hart and Timbrell, 1979). The reviewer suggested that EPA assume that the CYP metabolism of infants at birth are approximately 30% of their adult level (Ginsberg et al., 2004) and suggested that the percent metabolism be modeled to increase in a linear or stepwise fashion until an adult level was reached at approximately 12 months of age (Alcorn and McNamara, 2003; Ginsberg et al., 2004), after which it would remain constant through the remainder of life (Klotz, 2009). Another reviewer (3.1.3 – R4) also recommended that EPA look into the literature that addresses enzyme ontogeny and development in humans, such as Cytochrome P450 isozymes.

Another peer reviewer (3.1.3 – R2) stated that the documented age-related changes in hepatic clearance clearly support the need to scale any estimate of compound half-life and clearance based on relevant physiological factors as identified in the literature. Such factors include organ weight, blood flow, age (immature or elderly). Similarly, another peer reviewer (3.1.3 – R4) said that scaling according to body weight is a good alternative. On the other hand, another reviewer (3.1.3 – R5) suggested scaling by age since body weight can have a large variation in the same age.

EPA Response: EPA added a discussion of CYP levels and metabolic rate to Appendix H.5.6. In brief, it described how EPA increased the half-life of TCEP as a proxy for an infant's reduced CYP levels and thus longer clearance rate. The higher half-life value was used throughout the first year of life, and assuming an infant's metabolism remains at 30% of an adult for the entire simulation period is hence protective. Only the half-life as a proxy for metabolism rather than other physiological parameters was explored because it did not require changing any of the model inputs determined by the model's original authors. Varying the half-life still did not change EPA's conclusion that the nursing infant is exposed to lower levels of TCEP through human milk ingestion than the mother.

Summary: A peer reviewer (3.1.3 – R3) said it was reasonable to assume constant clearance. Another peer reviewer (3.1.3 – R6) stated that while scaling metabolic clearance across species based upon body size is a useful tool, it is well known that this does not work well in humans. Thus, the reviewer said that it would be speculative and highly uncertain to add to the modeling complexity by simulating anything but a uniform intrinsic clearance.

EPA Response: EPA thanks the reviewers for their comments.

Gaseous phase vs. particle phase

Summary: A peer reviewer (3.2.1 – R1) stated that Wolschke et al. (2016) is a well-designed study and the use of 82%/18% proportion is appropriate for this risk evaluation.

EPA Response: EPA thanks the reviewer for their comments.

Summary: A peer reviewer (3.2.1 – R2) provided line-by-line comments regarding TCEP partitioning between the gaseous phase and particulate phase:

- Lines 1665-1670 – the reviewer said that there is a need for more data to be generated to inform these types of evaluations, and that sampling artifacts could contribute significantly to uncertainties in vapor/particle ratios.
- Lines 1942-1956 – the reviewer said the explanation that snowmelt controls the upper end of TCEP concentrations in soil may hold an approach for evaluating the airborne contributions and possibly forms of TCEP.
- Lines 1681-1682 – the reviewer stated that the process of selecting the 82%/18% ratio is not described in Appendix H.3.3 and there is no mention of Wolschke et al. (2016) in any text within the Appendices. The reviewer stated that a brief description is needed along with why data from this study was chosen to the exclusion of others.

EPA Response: EPA agrees with the commenters that the uncertainty in the vapor/particle ratio and sampling artifacts could significantly contribute to uncertainties in the assessment. EPA summarized the available literature on particle size fractions, and gas versus vapor partitioning as described in section 3.3.1.2.1. EPA has further clarified in section 3.3.1.2.1 that the suggestion from {Okeme, 2018, 5165658@@author-year} was considered when adopting the gaseous phase and particulate phase proportion from {Wolschke, 2016, 3374439@@author-year}.

EPA thanks the reviewer for the suggestion that snowmelt example may hold an approach for evaluating the airborne concentrations and forms of TCEP. {Mihajlović, 2012, 2662833@@author-year} indicates that the meltwater generated at the snow surface percolated downwards due to gravity picking up chemicals present at the snow grain edge, and that for this reason amplified concentrations of TCEP were detected in soil samples.

Summary: A peer reviewer (3.2.1 – R3) suggested that EPA look to relevant US papers if they are available, like Liu et al. (2023).

EPA Response: EPA has reviewed Liu et al 2023, which observed the gas-particle phase portioning of TCEP in indoor and outdoor air environments in an urban environment in China. Liu et al 2023 utilizes quartz fiber filter (QFF) rather than the glass fiber filters (GFF)suggested by Okeme et al., 2018 and the vales reported may be vulnerable to sampling artifacts.

Leaf cuticular resistance

Summary: A peer reviewer (3.2.2 – R1) stated that there is no indication of what measure of vapor pressure is being modeled in Figure Apx_H.5. According to the reviewer, high variances in the function for the leaf cuticular resistance uptake to lipids (rcl) values are problematic for the use of these data for modeling. The reviewer said it would be helpful to determine if compounds with these higher rcl have any structural similarities or experimental anomalies. If there is no way to improve this estimation method, the reviewer suggested the mean and worst case 95% CL should be used in modeling TCEP partitioning. Additionally, the reviewer suggested that it would be helpful to depict the range of TCEP vapor pressures on graph Apx. H-5 by shading or defining the range on the graph. The reviewer said there are no unit designations for either vapor pressure or resistance on the axes of this figure.

EPA Response: Figure Apx_H.5 has been labeled to include the unit of measure for vapor pressure (Pascals). The chemical dataset utilized to calculate the relationship for rcl did not include values for TCEP. EPA utilized this approach as it was the best approach reasonably available.

EPA appreciates the suggestion to use a 95% CL when modeling TCEP portioning. EPA has not included a central tendency and high-end estimate for the rcl parameter as it is only one parameter, among a number of parameters that have been used to estimate gaseous deposition (Table_Apx H-8). However, EPA has included 10th, 50th and 95th percentiles estimates for air concentrations and deposition at various distances to account for uncertainties in the ambient air modeling.

Particle size deposition parameters

Summary: A peer reviewer (3.2.3 – R1) stated that the mass fraction 2.5 microns or smaller has units of length, which seems incorrect, and said that the value should be reported as a fraction. The fraction of 0.4 is consistent with what is presented in Lee and Patterson (1969) according to the reviewer. Another reviewer (3.2.3 – R2) commented that there is no mention of mass fractions 2.5 microns or smaller in Appendix H3.3 and there is no reasonable description of particle sizes in Section 3.3.1.

EPA Response: EPA thanks the commenter for the comment. Table_Apx H-9 has been updated to remove the µm from the mass fraction value. MMAD refers to the median mass aerodynamic diameters which is typically reported in micrometers (µm), a measure of length. Many studies report mass fractions of TCEP that is found among various dust sample or particulate matter sizes ({He, 2018, 4728480} and {Schreder, 2016, 3222316}).

A brief discussion on the mass fractions and particles sizes of TCEP is available in Section 3.3.1.2.1. EPA used the defaults for phosphates suggested in AERMOD for mass fraction 2.5 µm or smaller (0.4) which cites {Delumyea, 1979, 774505@@author-year} and {Lee, 1969, 33980@@author-year}, and the default MMAD for phosphates which was listed as 2.2 µm.

Exposure controls and PPE use

Summary: A public commenter (0040) stated that EPA did not assess other types of exposure controls throughout all exposure assessments for TCEP, including the use of fume hoods, general dilution ventilation and chemical safety cabinets. The commenter said that the assumption of a lack of these exposure controls is not realistic.

Similarly, a public commenter (0043) stated that by adopting an assumption during the risk assessment phase that no PPE is used, there is a greater potential to overestimate risk. The commenter said that this approach does not appear to fix a perceived problem, but rather replaces it with a potentially greater problem creating a false and misleading perception of worker risk. The commenter recommended that EPA ensure that OSHA workplace standards and requirements of the OSHA general duty clause be taken into consideration when assessing the potential exposures associated with any industrial use of TCEP.

EPA Response: EPA had previously assumed that workers were provided and always used PPE in a manner that achieves the stated assigned protection factor (APF) for respiratory protection or used impervious gloves for dermal protection. However, EPA believes that the assumed use of PPE in a risk determination could lead to an underestimation of the risk to workers. For example, workers may be highly exposed because they are not covered by OSHA standards, such as self-employed individuals

and public sector workers who are not covered by a State Plan; their employers are out of compliance with OSHA standards; the PPE is not sufficient to address the risk from the chemical; or their PPE does not fit or function properly.

Additionally, TSCA risk evaluations are subject to statutory science standards, an explicit requirement to consider risks to potentially exposed or susceptible subpopulations, and a prohibition on considering costs and other non-risk factors when determining whether a chemical presents an unreasonable risk that warrants regulatory actions—all requirements that do not apply to development of OSHA regulations.

Production volume estimate

Summary: Two public commenters (0035, 0044) stated that EPA's risk evaluation of TCEP relied on assumptions that they claim may underestimate exposure and risk for both occupational and general populations. Both commenters said that EPA's TCEP production volume estimate lacks adequate conservatism and noted the significance of this figure which informs subsequent risk calculations. Citing historical production volumes much higher than the EPA's estimate of 2,500 lb as well as the 25,000 lb CDR threshold, the commenters stated that EPA does not adequately justify its estimate and suggested that the actual production volume may significantly exceed it. One of the commenters (0044) listed several possible sources of error in the Datamyne shipping data used by EPA, namely the mislabeling of TCEP and the exclusion of TCEP containing articles. Both commenters recommended that, in its risk evaluation, EPA use the upper bound estimate of 25,000 lb in place of the 2,500 lb central estimate. They suggested that this would provide necessary conservatism for PESSs and better account for high historic production levels which may have resulted in lingering effects.

EPA Response: The results from both the 2,500 lb and 25,000 lb PVs are included in the Supplemental Files.

Duration of residence

Summary: A public commenter (0044) stated that EPA should use a longer duration of residence than 33 years to assess the exposure resulting from living near air and water contamination and suggested EPA expand this duration to exposures over a lifetime.

EPA Response: EPA thanks the commenter for the comment. EPA has revised its exposure durations to 78 years for inhalation estimates from ambient air, and drinking water estimates.

Disposal

Summary: A public commenter (0044) stated that in the draft risk evaluation EPA has not adequately assessed the risks to health and environment posed by TCEP disposal. The commenter stated that according to EPA's findings, the disposal of TCEP-containing products would continue to be a significant source of TCEP releases over a long time horizon. They stated that EPA's approach of considering waste disposal within each condition of use is flawed because it will not fully account for the exposures for people working in or living near disposal facilities.

EPA Response: Uncertainties for disposal are described in Section 4.3.6.2 that include:

- Without a full characterization of non-hazardous landfill (*e.g.,* Norman Landfill) conditions and historical wastes (*e.g.,* Himco Dump and Fort Devens) around the country, the data needed

to produce quantitative risk estimates for disposal is not reasonably available. EPA does not have data representing municipal and managed landfills and is uncertain how often contaminant migration occurs given modern practices of non-hazardous landfill and historical site management. Source attribution of the consumer uses to the leaching concentration exhibited within Sections 3.3.3.7 and 3.3.3.8 are not reasonably available; therefore, it is unknown if these concentrations are the result of consumer and/or commercial disposal.

- For the commercial uses that have been phased out, any currently used products that contain TCEP are expected to be disposed of in landfills but will represent just a fraction of previous amounts from when TCEP was used more widely. Further data are lacking with which to estimate exposure and risk from disposal or waste treatment activities for these COUs and EPA has not quantified such risks. EPA's confidence in these exposures is indeterminate and cannot quantify risk for the disposal or waste treatment activities for these COUs. EPA acknowledges that while some releases and exposures could occur during the disposal of the wide variety of items that TCEP has found its way into, based on a review of the limited information on TCEP within groundwater at landfills and wastewater runoff presented in the section above, these are expected to be minimal and dispersed, and exposures are expected to be negligible.

TSCA Section 6(b)(4)(F)(ii) directs EPA to "describe whether aggregate or sentinel exposures to a chemical substance under the conditions of use were considered, and the basis for that consideration" in risk evaluations. Therefore, EPA may, but is not required to, consider aggregate exposure in the risk evaluations. 40 CFR 702.33 defines aggregate exposure as "the combined exposures to an individual from a single chemical substance across multiple routes (*i.e.*, dermal, inhalation, or oral) and across multiple pathways (*i.e.*, exposure from different sources)". Therefore, aggregate exposure includes combined exposures from a single chemical across multiple routes and multiple pathways.

A full discussion of EPA's consideration of aggregate exposure is provided in Section 5.1.4 of the risk evaluation and details the conditions of aggregating exposure across routes. Included are discussions of the limitations for aggregating across COUs, and across exposures scenarios. For example, Section 5.1.4 describes the different ways in which exposures can be aggregated (*e.g.*, across COUs, across Exposure Scenarios) Without any information indicating co-exposures to multiple COUs, or exposure across multiple exposure scenarios, EPA is unable to conduct an aggregate exposure assessment. Furthermore, as described in section 5.1.4, it would be misleading for EPA to aggregate exposures across exposure scenarios when the individual scenarios were based on the total production volume of 2,500 lbs per OES, and aggregating would double count the production volume.

DRAS model

Summary: A peer reviewer (3.3.1 – R1) discussed EPA's use of the Hazardous Waste DRAS to assess groundwater concentrations of TCEP after TCEP-containing consumer products have been disposed of into a non-hazardous landfill. The reviewer remarked that there are less than two pages of text to describe the new approach, which is inadequate, and Appendix H.5 offers a paragraph to introduce the DRAS model before sending readers to old technical support for the DRAS software. The reviewer concluded that there is insufficient information in the draft risk evaluation for anyone other than an experienced DRAS user. Additionally, regarding Line 2112, the reviewer commented that regulatory decisions that influence public and environmental health should not be made using a "back of the envelope computation".

Another peer reviewer (3.3.1 – R2) discussed the landfill modeling and said that a more scientific approach would be to consider typical TCEP levels in cushions, fabrics, construction, and demolition

waste streams and then estimate the total TCEP loaded into a municipal landfill based upon a population disposal model. The reviewer also said that Table 3-7 is difficult to interpret and is not related to actual landfill leachate data, so it doesn't appear that EPA tried to calibrate the DRAS model against actual data. Finally, the commenter suggested 0.25 miles as the default distance to the nearest private well.

EPA Response: EPA thanks the reviewer for the comment. The language in sections 3.3.3.8 has been revised to help clarify the selection of leachate concentrations and loading rates for the DRAS analysis. EPA has added additional language in Section 3.3.3.8 that calibrate the DRAS model the reported groundwater monitoring concentrations in the monitoring literature and water quality portal. In addition, EPA has increased the range of the DRAS analysis, bounding the leachate concentration by TCEP's solubility, and increasing the loading rate to account for past disposal practices. To account for the uncertainties in estimating current loading rates, EPA varied loading rates over four orders of magnitude. While current production volumes are anticipated to be lower (2,500 lb), usage of TCEP was higher in the past and the leaching occurring from landfills may be a result of past disposal practices.

While EPA appreciates the comment regarding estimating the total TCEP loaded to a municipal landfill based on a population disposal model, there is limited information available on municipal disposal of TCEP making it difficult to estimate TCEP loading. Rather EPA, conducts a bounding exercise using an EPA peer reviewed model (DRAS) to estimate TCEP groundwater concentrations from landfill leachate.

Note, no default distance was 'selected' for the DRAS analysis. The DRAS analysis is a simulation of more than 700 different landfills, and the estimates are "within" 1 mile of a poorly managed landfill. The 3-4 RCRA Delisting Technical Support Document Chapter 3: Exposure Scenario Selection Revised October 2008 survey data are entered in the EPACMTP model as an empirical distribution: minimum = 0 m, median = 427 m, and maximum = 1,610 m (approximately 1 mile) (U.S. EPA 1997e).

Summary: A peer reviewer (3.3.2 – R1) stated that given the paucity of information in the draft risk evaluation, it is difficult to ascertain a domain of applicability of the DRAS model. The reviewer suggested that if sufficient data are available for monitored sites, the domain of applicability could be chemicals of similar structure and function as those measured near waste disposal sites that are present in aquifers with properties similar to those in the monitored group. Estimates for chemicals in such aquifers could be sorption, degradation, and movement, according to the reviewer. The reviewer said that the bounds of these domain need to be *clearly* stated in the draft risk evaluation.

EPA Response: EPA has revised the DRAS analysis to reflect the paucity of information surrounding TCEP loading, and leachate concentrations. EPA has increased the range of the DRAS analysis, bounding the leachate concentration by TCEP's solubility, and increasing the loading rate to account for past disposal practices. To account for the uncertainties in estimating current loading rates, EPA varied loading rates over four orders of magnitude. While current production volumes are anticipated to be lower (2,500 lbs), usage of TCEP was higher in the past and the leaching occurring from landfills may be a result of past disposal practices.

Exposure values for cancer assessment

Summary: A peer reviewer (OC – R1) stated that the use of TCEP has dropped considerably in recent years and most exposures will likely follow this trend. The peer reviewer expressed that the cancer dose calculations (*e.g.*, Lifetime Average Daily Dose) need to account for these changes in exposure.
EPA Response: EPA thanks the reviewer for the comment. Lifetime Average Daily Dose equations are calculated by substituting the value of an individual's lifetime for the AT (averaging time) variable in the dose equation. It is true that the phasing out of a chemical would mean that an individual would have greater exposures earlier in life and lower exposures later in life. In such cases the 'ED' (exposure duration) variable would be less than the AT term. In the TCEP risk evaluation, EPA estimated exposures to TCEP from current and ongoing conditions of use that are expected to occur currently. It is difficult to predict whether these exposures would continue to decrease as they have done in the past decade or whether they would increase in the future. Therefore, since information is unavailable EPA assumed 78 years for ED and 78 years for AT for the environmental analysis (*e.g.*, drinking water exposures, ambient air inhalation exposures) and consumer analysis. The *Supplemental TCEP Consumer Modeling Results* includes a table of Lifetime Cancer Risk estimates by a range of exposure durations. For articles that are used over a shorter exposure duration, the lifetime cancer risk estimate can be adjusted by ED/AT. For example, if a carpet is used in a household for 20 years, the lifetime cancer risk estimate can be adjusted by 20/78. CEM 3.2 assumes that the consumer article containing TCEP would be replaced with a similar article containing TCEP. Organophosphate esters such as TCEP have begun phasing out from consumer articles. Thus the 78/78 assumption for ED/AT is conservative. Hence, this table provides the risk calculations with a range of exposure durations (1, 5, 20, 33, 57 years).

General comments on the exposure assessment

Summary: A public commenter (0040) suggested that EPA conduct a sensitivity analysis for key parameters used in its exposure models and mitigate the potential for unrealistic results that may occur when multiple upper-bound default values are used simultaneously. To start, the commenter suggested that EPA should apply a similar Monte Carlo analysis for the key inputs to its dermal model, including the TCEP concentration, skin loading, fraction of skin exposed, exposure duration and exposure frequency inputs. Additionally, the commenter recommended that EPA use probabilistic methods for determining inputs for parameters that also account for the use of engineering controls, administrative controls, and PPE.
EPA Response: EPA follows a hierarchy of using relevant data, if available, or modelling when data are not available. Additionally, EPA is always interested in improving our models and appreciates the commentor's suggested improvements; as improved models and/or methods become available, they will be incorporated into future Risk Evaluations.

Summary: A public commenter (0040) suggested that EPA should mitigate uncertainty in exposure estimates for OESs by performing targeted analyses to develop similar exposure groups within an OES when the OESs consist of multiple exposure groups.
EPA Response: For occupational exposures, EPA analyzes workers and occupational non-users (ONUs) as separate exposure groups. Where reasonably available data allows, EPA provides separate

estimates of exposures that each group could be subjected to during the activities that are reasonably expected to occur during a given OES.

Summary: A peer reviewer (OC – R1) stated that it seems unreasonable to assume that sentinel exposures (*e.g.*, subsistence fishers) may not be exposed to TCEP via other exposures scenarios. The result, according to the commenter, may be an underestimation of risk for some PESS.

EPA Response: In the risk evaluation procedural rule, EPA defines sentinel exposure as "the exposure to a single chemical substance that represents the plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures" (40 CFR 702.33).

As described in Section 5.1.5, the sentinel exposure for these general population exposure scenarios was fish ingestion for subsistence fisherman and fishers who are members of Tribes. The sentinel exposure for the consumer assessments by route were inhalation from building and construction materials (roofing insulation) for consumers, oral ingestion of TCEP from children's mouthing of foam seating and bedding products (foam toy blocks), and children's dermal absorption of TCEP from wood resin products (wood flooring).

Section 5.1.4 describes the different ways in which exposures can be aggregated (*e.g.*, across COUs, across Exposure Scenarios) Without any information indicating co-exposures to multiple COUs, or exposure across multiple exposure scenarios, EPA is unable to conduct an aggregate exposure assessment. Furthermore, as described in section 5.1.4, it would be misleading for EPA to aggregate exposures across exposure scenarios when the individual scenarios were based on the total production volume of 2,500 lbs per OES, and aggregating would double count the production volume.

While it is plausible that co-exposures across scenarios could occur, EPA did not quantitively assess aggregate exposure across exposure scenarios because no data was available indicating the co-exposure of TCEP from multiple exposure scenarios.

Section 5.2 – Human health hazard (including comments on confidence levels, male reproductive effects from Chen et al. (2015), and benchmark response (BMR) of 5 percent for the benchmark dose (BMD) modeling)

Confidence levels

Summary: A public commenter (0040) said they applied the proposed Judgement Levels for Evidence Integration of the SACC and obtained results no stronger than "evidence suggests" for all cancer and non-cancer endpoints for TCEP which differs from EPA's "likely" conclusions.

EPA Response: EPA uses the framework in the 2021 Draft Systematic Review Protocol {U.S. EPA, 2021, 10415760}. As an example, EPA determined that the reproductive endpoint has an indeterminate judgement for human data, moderate judgement for animal data, and slight mechanistic evidence. Using the 2021 Draft Protocol, these evidence-stream judgements lead to the overall judgment that "TCEP likely causes reproductive toxicity in humans under relevant exposure circumstances." The *ORD Staff Handbook for Developing IRIS Assessments* {U.S. EPA, 2022, 10367891} also states that this combination of evidence-stream judgements can also indicate an overall judgement that TCEP *likely causes* reproductive toxicity in humans *given sufficient exposure circumstances*.

Summary: A peer reviewer (2.3.1 – R4) stated that, based on the confidence summary for each field, the overall hazard confidence values seemed reasonable.
EPA Response: EPA thanks the commenter for the comment.

Summary: A peer reviewer (2.3.1 – R7) stated that "consistency/concordance" should be considered in assigning confidence ratings for a given endpoint. For example, Bradford Hill evidence criteria were mentioned as evidence criteria, but ultimately did not make it onto the list of considerations. The reviewer stated that the overall rating of "moderate" undervalues the level of evidence that TCEP causes these various effects. The reviewer suggested adding a new column to provide a level of confidence in the outcome and Table 5-53 would reflect the level of confidence in the endpoint itself. Finally, the reviewer said that given that there are always uncertainties in modeling dose response information or evaluating PESS variabilities, "it's hard to imagine anything higher than moderate".
EPA Response: EPA did consider the Bradford Hill considerations when integrating the evidence for human health hazard, as stated in Section 5.2.1: **"**The Agency integrated data from these evidence streams to arrive at an overall evidence integration conclusion for each health outcome category (*e.g.*, reproductive toxicity). When weighing and integrating evidence to estimate the potential that TCEP may cause a given human health hazard outcome, EPA uses several factors adapted from Sir Bradford Hill {Hill, 1965, 71664}. These elements include consistency, dose-response relationship, strength of the association, temporal relationship, biological plausibility, and coherence, among other considerations." Table 7-13 in the 2021 Draft Systematic Review Protocol {U.S. EPA, 2021, 10415760} describes the use of Bradford Hill criteria more completely when determining evidence integration judgments. Also, the specific Bradford Hill considerations are listed, as relevant to an evidence stream and hazard endpoint for TCEP, in the evidence integration tables in Appendix K of the risk evaluation as factors that increase or decrease the strength of the evidence. Table 5-53 in the RE includes a column called "Evidence Integration Conclusion," which is the sum of all the Bradford Hill considerations. In the introduction to Section 5.2.7, EPA added reference to Section 5.2.1 where the use of Bradford Hill criteria is described.

Uncertainty factors

Summary: A public commenter (0044) stated that, when calculating TCEP's hazards, EPA disregarded the best available science, as well as EPA's own risk assessment guidance, concerning the use of uncertainty factors (UFs). The commenter said that EPA failed to apply two critical UFs and misapplied another. First, the commenter (0044), along with other commenters (0042, 0045), stated that EPA omitted critical UFs when characterizing non-cancer risk in the draft risk evaluation. The commenter said that the risk evaluation 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. One of the commenters (0042) said that the subchronic UF would increase the benchmark margin of exposure (MOE) and in turn lower EPA's threshold for identifying risks of concern by a factor of 3 to 10, which results in a significant underestimation of risk, according to the commenter. One of the commenters (0045) said a UF of 100 should serve as the benchmark MOE for chronic exposure scenario risk characterizations.

Second, the commenter (0044) said that EPA failed to apply the recommended UFs for database deficiencies, despite acknowledging significant gaps in EPA's understanding of TCEP's exposures and hazards. And finally, the commenter (0044) said that EPA misapplies the intraspecies UF which is intended to account for "variations in susceptibility" within the general population. The commenter said that this UF is designed to cover the myriad sources of variations within the general population, and not the increased risks faced by discrete PESS, which is how EPA applied it.

EPA Response:{NTP, 1991, 5469669@@author-year} evaluated histopathology of male reproductive organs after two years. The continuous breeding study {NTP, 1991, 10603716 @@author-year} that used a chronic exposure duration also evaluated sperm effects at the highest dose. Although it is possible that an additional chronic study would result in more sensitive effects on seminiferous tubules, EPA considers that the existing chronic studies adequately evaluated male reproductive effects and a subchronic to chronic duration uncertainty factor is not needed.

Database UF is applied for deficiencies in the toxicological database that might lead to a lower POD. Under TSCA, there is no universal list of hazard data that is required to consider a database sufficient to conduct risk evaluation, nor is there a minimum set of data required to conduct a risk evaluation. The decision to incorporate UF database in TSCA risk evaluations is determined on a case-by-case basis, and for TCEP, EPA determined that the database of studies did not identify deficiencies. Multiple studies evaluated short-term, subchronic, and chronic effects and covered major organ systems. In addition, studies evaluated various aspects of neurotoxicity or neurotoxicity-related endpoints in both rats and mice (clinical signs, histopathology, neurobehavioral changes, cholinesterase, and other biochemical changes). In particular, {Yang, 2018, 5469245@@author-year} conducted the Morris water maze in rats after 60 days of exposure; the Morris water maze measures spatial learning and memory, and was an important assessment given that lesions were found in the hippocampus. In addition, newly identified epidemiological studies examined neurobehavior and IQ in children and depression and stress in mothers. Multiple reproductive outcomes are well covered. The reproductive assessment and continuous breeding study {NTP, 1991, 10603716} includes endpoints recommended for evaluation in OECD Test Guideline 416 (2-Generation Reproduction Toxicity Study). {NTP, 1991, 10603716@@author-year} examined F0 and F1 adults (changes in reproductive organs, sperm parameters, and estrous cyclicity) as well as reproductive performance of both generations (fertility, viability of F1 and F2 offspring, sex of offspring, birthweight). Reproductive endpoints were also evaluated in subchronic and chronic studies. {Chen, 2015, 4199395@@author-year} examined reproductive endpoints in adolescent male mice and males appear to be more sensitive than females.

Regarding the intraspecies UF, EPA has used all chemical-specific information that is available. For example, male reproductive effects are the basis of one of the PODs, and they represent a susceptible subpopulation. When chemical-specific information is not available, EPA relies on using the intraspecies UF value of 10. EPA recognizes that the intra-species UF is not specific, and Section 5.3.3, Table 5-79: Summary of PESS Considerations Incorporated into the Risk Evaluation acknowledges that it is not known whether the UF of 10 would cover various subpopulations (such as individuals with Klinefelter's, which is one of the examples identified by the commenter). EPA has added the following statement to Appendix E for more clarity: "In addition, given that EPA is using a default UF_H in the absence of data regarding whether adverse effects from TCEP exposure differ for certain subpopulations (such as those with genetic polymorphisms or underlying diseases), it is also not known whether the chosen default UF_H would fully cover pre-existing diseases or disorders {U.S. EPA, 2002, 88824@@author-year}."

Male reproductive effects (Chen et al.)

Summary: A public commenter, in two submissions to the docket (0040, 0052), said they applied SACC's recommendations for evidence integration judgment which resulted in an Evidence Integration Judgment of "suggestive" for male reproductive effects, therefore, the mail reproductive effects identified by EPA are likely insufficient to support causality for risk evaluation.
EPA Response: EPA uses the framework in the 2021 Draft Systematic Review Protocol {U.S. EPA, 2021, 10415760} to arrive at evidence integration judgments. As an example, EPA determined that the reproductive endpoint has an indeterminate judgement for human data, moderate judgement for animal data, and that there is slight mechanistic evidence. Using the 2021 Protocol, these evidence-stream judgements lead to the overall judgment that "TCEP likely causes reproductive toxicity in humans under relevant exposure circumstances." The *ORD Staff Handbook for Developing IRIS Assessments* {U.S. EPA, 2022, 10367891} also states that this combination of evidence-stream judgements can also indicate an overall judgement that TCEP *likely causes* reproductive toxicity in humans *given sufficient exposure circumstances*.

Summary: A public commenter (0042) stated that EPA continues to rely on scientifically deficient methods for non-cancer dose-response analysis and risk characterization. For example, EPA used the MOE approach which is a scientifically inappropriate approach for characterizing risk and is inconsistent with amended TSCA's requirements to use the "best available science", according to the commenter. The commenter went on to state that the MOE does not estimate the proportion of the exposed population projected to experience a specified health endpoint or the number of individuals affected. The commenter stated that the National Academies and the World Health Organization have outlined more robust methods for risk estimation that more accurately account for variability and vulnerability across the human population. The commenter applied the World Health Organization methodology to estimate risks of male reproductive effects and found that the risk level is 25,000 times higher than the target range that EPA typically applies for protection of carcinogenic risks. The commenter recommended that EPA include this approach to non-cancer dose-response and risk characterization in the final TCEP risk evaluation.
EPA Response: EPA thanks the commenter for the comment. EPA does not want to a priori preclude the use of any methods or data types, in order to allow its risk evaluations to change as science advances. EPA will utilize current policies, models, and screening methods, but is committed to being consistent with the best available science and weight of the scientific evidence approaches to guide the Agency in using this information. EPA recognizes the advancing science to inform risk evaluation and will not discourage the use of new methods as long as they are consistent with the standards in section 26 of TSCA. EPA also recognizes that different approaches require different types and amounts of data and will select and employ methods that are fit for purpose within the context of a particular risk evaluation. In some cases, it may be necessary to utilize default parameters in modeling and risk calculations, and to utilize conservative assumptions, whereas in other cases assumptions may be replaced with specific or specialized data. It should also be noted, in addition, their use will be peer reviewed, and the public will have the opportunity to comment on them during the public comment periods. EPA has utilized the MOE approach in previous risk assessments, citing its utility. However, EPA does agree with comments that there are numerous ways to characterize risk, of which MOE is just one. There will be risk scenarios where one approach may be better than another and, as commenters correctly pointed out, the science of risk characterization is still evolving, particularly for non-cancer hazards. Hence, OPPT will use risk characterization approach(es) suitable for the purpose

of the risk evaluation and that the best available science and data support. EPA does not agree with the commenter to use another approach for the TCEP risk evaluation.

Summary: A public commenter (0045) stated that EPA used as a point of departure the BMDL5 instead of the frequently defaulted BMDL10 to accommodate for the nature and severity of the effects observed in the Chen et al. study. The commenter stated that this requires an additional 3X UF to account for subchronic extrapolation.

EPA Response:
Use of 5% BMR to set a BMDL5: In consultation with a reproductive/developmental toxicologist and another EPA office that routinely conducts dose-response modeling, EPA concluded that a BMR of 5 percent to be appropriate for the severity of effects that can result in significant reproductive effects, including decreased fertility and viability observed in {NTP, 1991, 1060371@@author-year}. EPA acknowledges that the modeling is not ideal because the BMD is low on the dose-response curve compared with the doses tested in the study. However, BMD modelers identified the importance of choosing a BMR a priori. EPA has already cited publications supporting the use of this BMR {Blessinger, 2020, 6966510; Lanning, 2002, 2850042}.

In the risk evaluation, EPA expanded the justification for the severity of effects that warrants a BMR of 5 percent. Even if the effects are not life-threatening to the parents, the possibility of decreased viability in offspring is of concern. Furthermore, EPA expects that humans may be more sensitive to male reproductive toxicants than rodents.

Most peer reviewers supported EPA's use of the 5 percent BMR because of the severity of the effect.

Subchronic to chronic UF: {NTP, 1991, 5469669@@author-year} evaluated histopathology of male reproductive organs after two years. The continuous breeding study {NTP, 1991, 10603716 @@author-year} that used a chronic exposure duration also evaluated sperm effects at the highest dose. Although it is possible that an additional chronic study would result in more sensitive effects on seminiferous tubules, EPA considers that the existing chronic studies adequately evaluated male reproductive effects and a subchronic to chronic duration uncertainty factor is not needed.

Summary: Two peer reviewers (2.3.2 – R1, 2.3.2 – R3) stated that they agree with the choice to use Chen et al. for both short-term and chronic exposures scenarios. One reviewer (2.3.2 – R1) said that it looks to be a reliable study which was conducted during a potentially sensitive life stage which results in a health-protective POD for the risk evaluation. Therefore, this reviewer asserted that this POD will likely be protective of the other adverse effects identified in the TCEP toxicity studies of other non-cancer endpoints. The second reviewer (2.3.2 – R3) commented that one limitation of this study is that the feed consumption was not reported, therefore, the dose is uncertain. This reviewer stated that EPA may want to consider using an additional uncertainty factor to address the dose uncertainty.

EPA Response: Because the feed consumption was not reported, it is not clear whether the intake of TCEP could be higher or lower than the reported doses. Therefore, EPA is not planning to add an uncertainty factor to this study.

Summary: A peer reviewer (2.3.2 – R2) stated that the data obtained from the National Toxicology Program (NTP) studies and Chen et al. clearly demonstrated the potential for species and strain

differences (and possibly age differences) in the manifestation of effects on the male reproductive system. The reviewer said that there were points of comparative concern with the absence of exposure related differences in testes weights or pathology of male reproductive organs at dose levels in the reproductive assessment by continuous breeding (RACB) F0 adult CD-1 mice that were seen in the Chen et al. study. However, the reviewer stated that the use of male reproductive effects reported in Chen et al. were in line with the available findings and appropriate for use in this assessment.

EPA Response: EPA thanks the commenter for the comment. EPA has described these uncertainties related to differences in results among studies within the risk evaluation.

Summary: A peer reviewer (2.3.2 – R4) stated that they are hesitant to endorse the use of the Chen et al. study and would not use it as a part of the quantitative risk assessment. The reviewer said that the limitations described by EPA in Table 5-48 are serious and the use of nominal doses in the absence of food consumption and bodyweight data are questionable.

EPA Response: EPA agrees that there are important limitations to {Chen, 2015, 4199395@@author-year}, as identified by the peer reviewer. However, EPA has chosen to use this study because: 1) TCEP has a limited data set and this study has an adequate overall quality determination; 2) other studies also have limitations; 3) human males are sensitive to reproductive effects and this study identified significant degeneration of seminiferous tubules; and 4) it is possible that if additional toxicological studies were to be conducted on male reproductive effects of TCEP, similar effects might be observed.

Summary: A peer reviewer (2.3.2 – R5) stated that the Chen et al. study is considered high-quality and that the reproductive toxicity observed in male rats is considered to be a sensitive endpoint relevant to humans. The reviewer stated that the Chen et al. study was also used for the chronic exposure scenario and the calculated Human Equivalent Dose (HED) is within an order of magnitude of the HEDs calculated for short-term exposure for neurotoxicity and developmental toxicity. The reviewer stated that the use of the same study for subchronic and chronic exposures seems appropriate. However, the reviewer asserted that EPA failed to apply an uncertainty factor for the chronic exposure scenario, which typically relies on a lower value than the subchronic exposure scenario. As such, EPA should justify the lack of an uncertainty factor adjustment.

EPA Response: {NTP, 1991, 5469669@@author-year} evaluated histopathology of male reproductive organs after two years. The continuous breeding study {NTP, 1991, 10603716 @@author-year} that used a chronic exposure duration also evaluated sperm effects at the highest dose. Although it is possible that an additional chronic study would result in more sensitive effects on seminiferous tubules, EPA considers that the existing chronic studies adequately evaluated male reproductive effects and a subchronic to chronic duration uncertainty factor is not needed.

Summary: A peer reviewer (2.3.2 – R6) stated that the use of Chen et al. is generally supported by the strengths of the study which also has the lowest HED among the other studies considered by EPA. The reviewer stated that the limited dose groups used in the Chen et al. study, only at 100 and 300 mg/kg-day, were a weakness to derive BMDL5 as the reduction in the numbers of seminiferous tubules was 22% and 41%, respectively, in these dose groups. The reviewer said that, for the chronic exposure scenario, the Chen et al. study had a much shorter exposure duration of 35 days, giving it a disadvantage in its use in providing the HED. However, the reviewer stated that the advantage of the Chen et al. study is that it identified histopathological changes in the seminiferous tubules which was

not seen in the NTP (1991a) study even though the NTP study had a much longer exposure duration. The reviewer suggested that EPA should provide additional details on the potential explanation of differences between these study findings in order to better understand this comparison.

EPA Response: EPA does not have additional details to explain the differences. In the absence of these details, EPA is using a sensitive study (more sensitive than chronic studies) to evaluate risks from TCEP. This is recommended by the EPA guidelines for reproductive toxicity risk assessment {U.S. EPA, 1996, 30019}, which suggests using the most sensitive species.

Summary: A peer reviewer (2.3.2 – R7) stated that the use of the Chen et al. dose response to define both short-term and chronic PODS is reasonable. The reviewer commented that TCEP is clearly a male reproductive toxicant and supported by the RACB crossover studies by NTP. The reviewer said that the NTP 1991 RACB protocol should have detected the anti-male effect at 175 mg/kg/day given that it covered critical windows of development, but only found male reproductive effects at higher doses. The reviewer reasoned that there is less likelihood or concern that the Chen et al. study missed a critical window of vulnerability and that the calculated BMDL HED from Chen et al. is in line with other reproductive endpoints. The reviewer agreed with EPA's decision to use this endpoint (histopathologic evidence of decrease seminiferous tubules) as the most sensitive indicator of TCEP non-cancer effect for the purposes of POD development across endpoints and exposure timeframe,

EPA Response: EPA thanks the commenter for the comment.

Cancer risks

Summary: A public commenter (0044) stated that EPA understated TCEP's cancer risks. When calculating TCEP's cancer risks, EPA relied exclusively on kidney tumor data even though TCEP exposures have been associated with other cancer sites as well. The commenter stated that EPA must consider all known cancer sites in its dose-response analysis and its determination of whether TCEP presents unreasonable risk and recommended that EPA add non-kidney cancers associated with TCEP exposure to its analysis of cancer risk.

EPA Response: EPA considered information supporting evidence of other tumor types (mononuclear cell leukemia, thyroid, Harderian gland, and liver) in rodents {NTP, 1991, 5469669} and two studies of thyroid cancer in humans {Hoffman, 2017, 4161719;Liu, 2022, 11364830} to be slight. Mononuclear cell leukemia is a common spontaneous cancer in F344 rats and most incidence (other than females at the highest dose) were within historical controls. Statistically significant increased thyroid cancer was seen in female rats but not male rats or mice; humans showed inconsistent results in two studies. Increased Harderian tumor incidence was only seen in female B6C3F1 mice but not in male mice or in either sex of rats. Dose-related trend in liver tumor incidence was seen only in one sex of one species (male B6C3F1 mice), with only borderline statistical significance when comparing the high dose to controls. Due to the slight evidence associated with these tumors, EPA did not add them to the incidence of kidney cancer.

Summary: A public commenter (0042) also stated that though EPA has appropriately modeled cancer dose-response as a linear relationship with no threshold, EPA incorrectly states that because TCEP does not act through a known mutagenic mode of action (MOA), there is a threshold below which there is no cancer risk. The commenter stated that EPA provides no evidence to support its speculation that there is a threshold for TCEP's cancer risk, and the absence of a mutagenic MOA is not sufficient

evidence. The commenter recommended that EPA remove the statements regarding a cancer threshold for TCEP from the draft risk evaluation before it is finalized.

EPA Response: EPA has revised certain language in sections 5.2.5.3; 5.2.6.2; and 5.2.7.1.3 to indicate that the dose-response is not clear based on lack of adequate data to determine the mechanisms.

Summary: A peer reviewer (2.3.1 – R1) agreed with EPA's conclusions concerning each identified tumor type, that the available data indicate that TCEP has little genotoxic potential, and that it is unlikely that TCEP acts through a mutagenic MOA. The reviewer stated that EPA should note that the dataset used is incomplete and lacks an *in vivo* genotoxicity study of acceptable quality. The reviewer recommended that the statement indicating that TCEP has little genotoxic potential should be qualified.

EPA Response: In the evidence integration section (5.2.5.4), EPA added language to note that *in vivo* studies are limited**: "**The mechanistic evidence for carcinogenesis is *slight.* Available data indicates that TCEP has little if any genotoxic potential, but data are limited to assess *in vivo* genotoxicity."

Benchmark dose

Summary: A public commenter (0040) said that though EPA attempted to justify a 5% BMR, the modeled response is not predictive, as indicated by empirical data, and the BMR and/or selected model must be re-examined. Additionally, the commenter said that for the cancer endpoint, EPA's BMD modeling does not comport with EPA's BMD Guidance and is possibly biased toward a more precautionary approach due to EPA's a priori exclusion of animals expiring prior to the study conclusion.

Similarly, a peer reviewer (2.3.3 – R4) stated that the doses and response data used for the modeling presented in Table 1-1 are concerning and that they are uncomfortable basing the BMDL on a BMR of 5%. The reviewer reasoned that the biological data from the Chen et al. study showed the BMR associated with decreases of 22.2 and 40.7 percent at 100 and 300 mg/kg-day, which are lower than the actual study results. The reviewer stated that they do not understand the scientific basis for choosing 5% given these data and refers the reader to their previous comment for Charge Question 2.3.2.

EPA Response: ***Five percent BMR:*** In consultation with a reproductive/developmental toxicologist and another EPA office that routinely conducts dose-response modeling, EPA determined a BMR of 5 percent to be appropriate for the severity of effects that can result in significant reproductive effects, including decreased fertility and viability observed in {NTP, 1991, 10603716 @@author-year}. EPA acknowledges that the modeling is not ideal because BMD is low on the dose-response curve compared with the doses tested in the study. However, BMD modelers identified the importance of choosing a BMR a priori. EPA has already cited publications supporting the use of this BMR {Blessinger, 2020, 6966510; Lanning, 2002, 2850042}.

In the final risk evaluation, EPA expanded the justification for the severity of effects that warrants a BMR of 5 percent. Even if the effects are not life-threatening to the parents, the possibility of decreased viability in offspring is of concern. Furthermore, EPA expects that humans are likely to be more sensitive to male reproductive toxicants than rodents.

Most peer reviewers supported our use of the 5 percent BMR because of the severity of the effect.

Cancer – exclusion of animals expiring: The commenter's concern appears to be that EPA adjusted the cancer data for mortality *a priori* without justification. This is not the case. Survival was reduced in high-dose male and female rats in the NTP study. It was noted that female rats dying early frequently showed brain lesions (associated with TCEP exposure), suggesting a cause of early death unrelated to the observed kidney tumors. The adjustment was made to try to account for the observed difference in mortality across treatment groups in the study. This practice conforms with EPA BMD and cancer guidelines, as well as the FDA guidance quoted by the commenter.

Summary: Two peer reviewers (2.3.3 – R1, 2.3.3 – R5) stated that the use of a BMDL05 seems appropriately justified. One of the reviewers (2.3.3 – R1) said this is due to the severity of the testicular effects, the potential for high sensitivity of humans, and the indication from the description of an unavailable study (Shepel'skaia and Dyshginevich (1981)) that TCEP may exhibit reproductive toxicity at low doses. However, one of the peer reviewers (2.3.3 – R3) expressed concern that the BMD and BMDL fall quite close to the control group and are lower than the biologically and statistically adverse response, increasing uncertainty about the values. The reviewer stated that, while not ideal, the other studies had limitations as well. Another peer reviewer (2.3.3 – R2) stated that the use of Chen et al. for male reproductive effects (decreased numbers of seminiferous tubules) was an appropriate endpoint for BMD modeling. The reviewer expressed concern as to whether this reflects the functional outcomes observed in the NTP studies given that similar pathology was not reported.

EPA Response: EPA thanks the commenter for the comment. EPA has consulted with reproductive and dose-response modeling experts to choose the BMR of 5 percent based on severity. EPA also discusses the uncertainties, including that the BMD and BMDL are below the doses used in the study. Given the limited database and concern that changes in sperm measures are expected to have greater impacts in humans than rodents, EPA considers the BMR of 5 percent to be appropriate for the risk evaluation of TCEP even though it does fall below the responses within the study at 100 and 300 mg/kg-day; no NOAEL was identified in the study so if the study had included lower doses, one of them may have shown a response similar to 5 percent.

EPA acknowledges the differences in outcomes among studies. EPA chose the more sensitive endpoint in the absence of information to definitively identify the more appropriate study.

Summary: A peer reviewer (2.3.3 – R3) stated that the BMR of 5 % seems appropriate based on the severity of the effect accompanied by disintegration of tubules, decreased testosterone levels, and testes weights at the highest dose. The reviewer expressed concern that the BMD and BMDL fall quite closely to the control group and are lower than the biologically and statistically adverse response, increasing uncertainty about the values. The reviewer stated that, while not ideal, the other studies had limitations as well. Another peer reviewer (2.3.3 – R6) stated that a BMR of 5% is protective of public health, given the severity of the impact on fertility (reduction in the number of seminiferous tubules), that infertility is increasingly of concern in US, and the lack of strong human study data. A peer reviewer (2.3.3 – R7) stated that a BMR of 5% is supportable in general for reproductive and developmental endpoints given their severity, as long as the data and model fit are supportive of predicting a reliable 5% response. The reviewer noted that the data were "well behaved" within the experimental and extrapolated range, and this was shown in the Benchmark Dose Modeling Supplemental File, in which "acceptable data fits were obtained for several models with predictions of

the selected model fit for BMDL5 within a reasonable range (some estimates lower, some higher) across model fits."
EPA Response: EPA thanks the commenter for the comment.

Neurotoxicity risks

Summary: A public commenter (0044) said that EPA failed to use the most sensitive study, Tilson et al. (1990), when calculating TCEP's neurotoxic effects. The commenter said that none of EPA's arguments against using the study justifies the decision to understate TCEP's neurotoxicity risks, and stated that the study has been favorably cited in an analysis conducted for the CPSC, by Environment Canada and Health Canada, and previously by EPA itself.
EPA Response: {Moser, 2015, 3008543@@author-year} remains the best (but not ideal) study given that the effects were seen beyond the technical definition of acute (≤ 24 hr). As stated on line 7750 of the RE, EPA identified a NOAEL from Moser et al. 2015 with effects seen only at the highest dose. The other acute studies identified only a NOAEL or LOAEL with effects observed only at the highest dose or the only dose in the study. {Moser, 2015, 3008543@@author-year} resulted in the most sensitive endpoint with an identified NOAEL, and EPA considers this to be appropriate for the acute endpoint.

Summary: A peer reviewer (2.3.1 – R1) agreed with EPA's summary statement on the confidence level for neurotoxicity and stated that neurotoxic effects were seen in multiple quality studies in both mice and rats. Another peer reviewer (2.3.1 – R2) stated that neurotoxicity was clearly demonstrated across the various studies and the apical endpoints were suggestive of excitotoxicity. A third reviewer (2.3.1 – R3) stated that the evidence for neurotoxicity in animals is robust with several studies showing consistent neurotoxic clinical and behavioral findings. However, this reviewer (2.3.1 – R3) added that the inference across evidence streams for an overall judgement of "likely causes neurological/behavioral effects in humans under relevant exposure circumstances" is unclear because of the limited mechanistic and human data. The reviewer also said that it is unlikely humans would be exposed to a similar exposure scenario as a bolus gavage dose in rodents. In the discussion of the strengths, limitations, etc. for acute non-cancer endpoints, the reviewer said there was no discussion beyond the Moser and Hazleton Laboratories study which are reproductive/development neurotoxicity studies. According to the reviewer, the Yang (2018) study was not discussed, though it was considered for endpoint selection. This reviewer remarked that it was unclear why short-term and chronic exposure scenarios were assessed together.
EPA Response: EPA thanks the commenter for the comment. EPA uses the framework in the draft systematic review protocol published in December 2021 for inferencing across evidence streams. Table 7-14. Classification for Weight of the Scientific Evidence for Causal Determinations for Characterizing Potential Human Health Hazards provides guidance and example scenario for overall evidence integration judgement in narrative. Yang et al was discussed in section 5.2.3.1.1 in both the "Laboratory Animals" and in the "Mechanistic information" sections.

Summary: A peer reviewer (OC – R2) expressed that there are several statements related to neurotoxicity in the draft risk evaluation that should be edited for accuracy:

- The peer reviewer stated that the statement regarding tremors in line 6448 of the RE is misleading.
- The peer reviewer wrote that the document states incorrectly in line 6385 of the RE that 13 rats showed tremors. The peer reviewer said that only two rats showed tremors and were terminated, and the rest were decreased to 90 mg/kg.
- The peer reviewer commented on line 6392 and requested that EPA check how many animals showed ataxia, salivation, gasping, convulsions, and occasional hyperactivity. The peer reviewer stated that it was not the full cohort.

EPA Response: Although {Moser, 2015, 3008543@@author-year} state that they euthanized two dams due to tremors and decreased the dose from 125 to 90 mg/kg-day, the study does not specifically state how many dams showed tremors. The authors provided an excel spreadsheet to EPA that showed 13 dams with tremors ranging from very slight to greater than moderate. The two dams with greater than moderate tremors were sacrificed on day 3.

EPA summarized the information on female rats that showed ataxia, salivation, gasping as {NTP, 1991, 5469669@@author-year} presented the information (line 6392); the number of female rats with these signs was not identified. Therefore, there is no revision necessary.

Reproductive toxicity

Summary: A peer reviewer (2.3.1 – R1) agreed with EPA's summary statement on the confidence level for reproductive toxicity and stated that almost all of the evidence comes from one species (mouse).

EPA Response: EPA thanks the commenter for the comment.

Developmental toxicity

Summary: A peer reviewer (2.3.1 – R1) agreed with EPA's summary statement on the confidence level for developmental toxicity and stated that several studies in one NTP report provide evidence for developmental toxicity and that the evidence primarily comes from one species (mouse).

EPA Response: Thank you for your comments. However, based on comments from other reviewers, EPA has decided that the evidence is suggestive but not sufficient to indicate that TCEP causes developmental toxicity. Section 5.2.3.1.3 of the risk evaluation has been updated.

Summary: A peer reviewer (2.3.1 – R2) stated that it was not clear which studies were used as the basis to make a determination of "moderate." For example, the reviewer said that the Moser et al (2015) study did not interpret the data to represent developmental toxicity, the Hazleton Laboratories 1983 study did not demonstrate altered viability or growth of mouse offspring, and the effects observed from the NTP RACB study did not suggest developmental toxicity. If EPA assigned a ranking of "moderate" to developmental toxicity, the reviewer recommended additional supporting data. A second peer reviewer (2.3.1 – R3) stated that the evidence suggested in Appendix K is not consistent with a moderate developmental toxicity health hazard. This reviewer noted that most of the evidence of toxicity from the Moser and Hazleton Laboratories indicate reproductive toxicity.

EPA Response: Although EPA believes that differences in study protocols between the RACB and prenatal studies may explain differences in outcomes, EPA agrees with the commenter given lack of

evidence in several prenatal/postnatal studies and in an additional study recently translated to English {Kawashima, 1983, 4992702}. Therefore, EPA has changed the evidence for animal studies to *slight.* EPA has also recently identified human epidemiology studies that resulted in *slight* evidence. Overall, the evidence integration conclusion in Section 5.2.3.1.3 has been changed to "suggestive but not sufficient to indicate that TCEP causes developmental toxicity." Given this change in the evidence integration conclusion, the information for developmental toxicity was not considered for dose response modeling (Section 5.2.6) or summarized in the weight of scientific evidence section (5.2.7).

Nephrotoxicity

Summary: Two peer reviewers (2.3.1 – R1, 2.3.1 – R3) agreed with EPA's summary statement on the confidence level for kidney effects and stated that neurotoxic effects were seen in quality studies in both mice and rats. One reviewer (2.3.1 – R3) stated that it was unclear if kidney weight was a relative or absolute value, and that the distinction should be made.
EPA Response: There was a statistically significant 12% and 10% increase in absolute kidney weight and an 8% and 10% increase in relative to body kidney weights at 175 and 350 mg/kg/day, respectively in male rats during the 16-day study. Absolute kidney weights were significantly increased 21.9% in males at 350 mg/kg/day. Relative-to-body kidney weights were increased 24.9% and absolute kidney weights were significantly increased 7%, 7%, 16.9%, and 46.5% and relative-to-body kidney weights were significantly increased 9.2%, 11.1%, 13.3%, and 22.2% in females given 44, 88, 175, and 350 mg/kg/day, respectively. During the 16 weeks study, male mice receiving 700 mg/kg/day had significantly reduced absolute kidney weights, decreased 19.4% compared to the controls. Relative-to-body kidney weights were decreased at 175, 350, and 700 mg/kg/day by 13.3%, 16.0%, and 14.1% compared to controls during the 16 weeks study.

Summary: A peer reviewer (2.3.1 – R2) agreed that the data support a determination of "moderate" for kidney toxicity and kidney adenomas and carcinomas but stated that it is not clear whether that represents an independent call of "moderate" for kidney toxicity and one for cancer. The reviewer suggested that ranking cancer as "moderate" requires additional supporting information.
EPA Response: EPA thanks the commenter for the comment. The confidence levels of moderate were chosen separately for non-cancer kidney toxicity and for kidney cancers (see section 5.2.3.1.4. for kidney toxicity and section 5.2.5.4 for cancer, as well as separate evidence integration tables in Appendix K in the risk evaluation), although some consideration was given across endpoints when assigning the individual evidence integration conclusions and confidence levels.

Liver toxicity

Summary: Two peer reviewers (2.3.1 – R1, 2.3.1 – R3) agreed with EPA's summary statement on the confidence level for liver effects. One reviewer (2.3.1 – R3) noted that it was unclear if liver weight was a relative or absolute value, and that the distinction should be made.
EPA Response: EPA thanks the commenter for the comment. In section 5.2.3.2, EPA revised the evidence integration section to identify whether liver weight changes were absolute or relative to body weight.

General comments on hazard identification

Summary: A public commenter (0045) stated that no adequate human data were identified for use in the assessment of potential noncancer or cancer risk of TCEP exposure to humans, and none of the available evidence demonstrated that TCEP causes the effects of concern in humans. However, the commenter agreed that the available data do identify neurotoxicity, reproductive toxicity, developmental toxicity, and kidney toxicity including cancer as the most likely and sensitive potential adverse human health hazard outcomes associated with TCEP exposure.
EPA Response: EPA thanks the commenter for the comment. EPA has since identified additional human data and has added this information to the TCEP RE. In Section 5.2.3.1, EPA added studies on neurological, kidney, immune/hematological, thyroid, lung, and developmental effects, and in Section 5.2.5.1, EPA added additional cancer studies.

Summary: A public commenter (0045) also stated that they agree with the approaches taken to derive the oral and dermal human equivalent doses, inhalation Human Equivalent Concentrations and Cancer Slope Factors Inhalation Unit Risks. Finally, the commenter said that they disagree with the weight-of-evidence assessment and stated that there was not clear evidence of renal tubule cells carcinomas in rats.
EPA Response: EPA agrees with the commenter that the evidence is based on adenomas and has revised section 5.2.5.4. **Evidence Integration Summary** from "clear evidence of renal adenomas and carcinomas in rats" to the following: "clear evidence of carcinogenic activity in rats based on renal tubule adenomas," which matches the conclusion from {NTP, 1991, 5469669@@author-year}. The commenter still agrees that the tumors can be used for dose response, and EPA also agrees with this conclusion. Furthermore, most peer reviewers agree with the weight of the scientific evidence for cancer and EPA will keep the overall weight of scientific evidence the same.

Summary: A peer reviewer (2.3.1 – R7) stated that they agree with EPA's separation of likely TCEP outcomes (kidney cancer, neurotoxicity, reproductive toxicity, developmental toxicity, kidney toxicity) from endpoints with only suggestive or indeterminate evidence (*e.g.*, liver, thyroid). This reviewer stated that it is unclear how EPA judges "Endpoint/POD" sensitivity and such sensitivity determinations should be clarified.
EPA Response: EPA thanks the commenter for the comment. If the endpoint is relevant as an apical endpoint for use in the RE document, considerations regarding sensitivity are focused primarily on the dose at which the effect occurs, with the lower the dose associated with greater sensitivity, without explicit consideration of the magnitude of uncertainty factors/margins of exposure.

Summary: A peer reviewer (OC – R6) suggested that EPA conduct a non-cancer risk quantification in the draft risk evaluation.
EPA Response: EPA did quantify risks from non-cancer endpoints as presented in Section 5.3. EPA did not provide a probabilistic assessment of non-cancer effects.

Section 5.3 – Human health risk characterization (including comments on types of PESS)

PESS

Summary: A public commenter (0042) stated that to date, EPA has not employed a consistent or structured approach to identifying PESS in TSCA risk evaluations, including scope documents. One inconsistency was a difference in whether health conditions related to a chemical's hazards were considered and whether fenceline communities were included. For example, fenceline communities were identified as PESS in hexabromocyclododecane (HBCD), but not for 1,4-dioxane, 1-bromopropane (1-BP), or C.I. Pigment Violet 29 (PV-29). The commenter stated that Rayasam et al. (2022) recommended that EPA prepare a comprehensive methodology to identify PESS and quantify their risks consistently within risk evaluations. To do this, the commenter recommended that first, EPA focus on identifying susceptible subpopulations based on either chemical-specific evidence or the broader literature on intrinsic and extrinsic susceptibility factors. Once appropriate subgroups are identified, EPA can then consider the availability of chemical-specific data. The commenter also suggested EPA focus on lifestage, pre-existing disease, individual activities, occupational exposures, geographic factors, socio-demographic factors, nutrition, genetic, aggregate exposure, and other chemical and non-chemical stressors to properly identify PESS.

A peer reviewer (OC – R6) similarly stated that EPA did not 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.

EPA Response: EPA conducted a comprehensive literature search to identify any chemical-specific human health hazard and exposure data and evaluated these data for data quality and described the available TCEP-specific PESS information in Appendix D, with a summary in Section 5.3.3. For human health hazards, EPA also identified mechanistic and toxicokinetic data and summarized any PESS information in the TCEP risk evaluation. EPA similarly identified and summarized chemical-specific PESS information resulting from the comprehensive exposure literature search.

For non-cancer effects, EPA applied an intraspecies uncertainty factor of 10 to account for more sensitive populations (*e.g.*, pre-existing disease, etc). EPA also considered exposure to other chemical and non-chemical stressors in Appendix D and section 5.3.3.

Risk characterization

Summary: A public commenter (0045) stated that upon examination of Table 5-57 in the draft risk evaluation, which presents the risk estimates for each condition of use, the Agency failed to implement aggregate exposure approaches but provided estimates separately by route of exposure. The commenter stated that this practice assures an underestimation of the real world risk in which actual exposure is occurring.

The commenter also discussed Tables 5-58 "Acute and Chronic Non-cancer Consumer Risk Summary" and Table 5-59 "Lifetime Cancer Consumer Risk Summary" and said that they present risk characterization on a route-by-route basis rather than in the aggregate. The commenter said that these tables are incomplete and contrary to the Agency's stated goal of increased transparency. Further, the commenter discussed multiple tables in Section 5 of the draft risk evaluation and again expressed disappointment that these tables do not present aggregate MOEs or cancer risk estimates for scenarios

reflecting multi route exposures, and all the tables also include findings only for conditions of use that exceed an acceptable threshold.

EPA Response: EPA thanks the commenter for the comment. A full discussion of EPA's consideration of aggregate exposure is provided in Section 5.1.4 of the risk evaluation and details the conditions of aggregating exposure across routes within the consumer assessment.

Because data were not reasonably available data to indicate co-exposures of multiple TCEP containing activities or products in the occupational and indoor environment, EPA did not assess aggregate exposure across consumer, commercial, or industrial COUs.

Section 6 – Unreasonable Risk Determination

Comments associated with this issue are summarized in the subsections below.

Section 6.1 – Unreasonable risk to human health

Summary: A public commenter (0044) stated that EPA's unreasonable risk thresholds are unsupported and under-protective. First, the commenter stated that EPA has historically supported the use of a 1-in-1,000,000 cancer risk threshold under TSCA but in this draft risk evaluation, EPA replaced the benchmark with a range of extra cancer risk from 1-in-10,000 to 1-in-1,000,000. EPA set this threshold for unreasonable occupational cancer risks at the less protective end of that range, claiming it is consistent with The National Institute for Occupational Safety and Health (NIOSH) guidance. However, the commenter stated that EPA misinterpreted NIOSH guidelines, which described 1-in-10,000 not as a target cancer risk level but rather a "starting point for continually reducing exposures in order to reduce the remaining risk". For consumers, the general public, and fenceline communities, EPA also claims that it typically considers the benchmark for cancer risk to be within the range of 1-in-10,000 to 1-in-1,000,000, which, according to the commenter, is a departure from the approach set forth in EPA's Draft TSCA Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities. The commenter claimed that this "range" of risk levels is up to 100 times less protective than EPA's prior approach and far less transparent.

However, citing the draft risk evaluation's findings for cancer and non-cancer risk from both occupational and general public exposures, the commenter expressed support for EPA's determination that TCEP presents unreasonable risk to human health.

EPA Response: EPA appreciates the comment and clarified the unreasonable risk determination to make clear what cancer benchmarks EPA considers in the unreasonable risk determination. As explained in Section 5.3.1 of the risk evaluation of TCEP, "EPA considers a range of extra cancer risk from 1×10^{-4} to 1×10^{-6} to be relevant benchmarks for risk assessment (U.S. EPA, 2017a). Consistent with NIOSH guidance (Whittaker et al., 2016), under TSCA, EPA typically applies a 1×10^{-4} benchmark for occupational scenarios in industrial and commercial work environments subject to OSHA requirements. EPA typically considers the general population and consumer benchmark for cancer risk to be within the range of 1×10^{-4} and 1×10^{-6}. Again, it is important to note that these benchmarks are not bright lines and EPA has discretion to find unreasonable risks based on other risk-related considerations based on analysis. Exposure-related considerations (*e.g.*, duration, magnitude, population exposed) can affect EPA's estimates of the excess lifetime cancer risk."
The following paragraph in Section 6.1.2 of the draft risk evaluation of TCEP has been edited:

"The health risk estimates for workers, ONUs, consumers, the general population, and infants through the milk pathway are presented in Section 5.3.2. For consumer and general population exposures, risk estimates are provided in Sections 5.3.2.2 and 5.3.2.3 of this draft risk evaluation only when margins of exposure (MOEs) were smaller than benchmark MOEs for non-cancer effects or when cancer risks exceeded benchmark risk levels of 1 in 1,000,000 (1×10^{-6}). A complete list of health risk estimates for consumers and the general population is in the following supplemental files of the draft risk evaluation (see also Appendix C): *Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP) – Supplemental Information File: E-FAST Modeling Results, Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP) – Supplemental Information File: Exposure Air Concentration Risk Calculations*, and *Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP) – Supplemental Information File: TCEP Consumer Modeling Results, Risk Calculations and Sensitivity Analysis"*

The revised paragraph reads:

"The health risk estimates for workers, ONUs, consumers, the general population, and infants through the milk pathway are presented in Section 5.3.2. For occupational, consumer, and general population exposures, risk estimates are provided in Sections 5.3.2.1, 5.3.2.2, and 5.3.2.3 of this draft risk evaluation only when margins of exposure (MOEs) were smaller than benchmark MOEs for non-cancer effects or when cancer risks exceeded benchmark risk levels. Standard cancer benchmarks used by EPA and other regulatory agencies are an increased cancer risk above benchmarks ranging from 1 in 1,000,000 to 1 in 10,000 (*i.e.,* 1×10^{-6} to 1×10^{-4}) depending on the subpopulation exposed. In this draft risk evaluation, EPA used 1×10^{-4} as the benchmark for the cancer risk to individuals in industrial and commercial workplaces, and for consumer and general population exposures EPA used a benchmark of 1 in 1,000,000 (1×10^{-6}) for cancer risk. A complete list of health risk estimates for workers, consumers, and the general population is in the following supplemental files of the draft risk evaluation (see also Appendix C): *Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP) – Supplemental Information File: E-FAST Modeling Results, Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP) – Supplemental Information File: Exposure Air Concentration Risk Calculations*, and *Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP) – Supplemental Information File: TCEP Consumer Modeling Results, Risk Calculations and Sensitivity Analysis*."

The fenceline analysis mentioned by the commenter, Draft TSCA Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities, was designed to serve as a screening level analysis to identify the highest possible risk, and therefore a 1 in 1,000,000 range was used. However, the draft analysis was not designed to determine unreasonable risk. In this risk evaluation of TCEP, EPA is considering the range of 1×10^{-4} and 1×10^{-6} for consumers and the general population and brings other risk-related considerations that can affect the excess lifetime cancer risk for consumers and general population. Based on such risk characterizations, EPA is determining how the COUs contribute to the unreasonable risk of TCEP.

Section 6.2 - Unreasonable risk to the environment

Summary: A public commenter (0040) opined that EPA did not use the best available science in determining whether TCEP poses unreasonable risk to the environment. They stated that EPA's use of a risk quotient is more appropriate for a screening-level risk assessment but is overly conservative for a complete risk determination.

EPA Response: For each occupational exposure scenario, where monitoring data were not available, daily releases were estimated per media of release based on EPA Standard Models, Generic Scenarios (GSs), and/or Emission Scenario Documents (ESDs) to generate annual releases and for the estimation of associated release days. The representation of these releases were coupled with flow conditions comprising TCEP SIC codes with 50th percentile and 90th percentile 7Q10 flows detailed within Appendix H2.

Concentrations of TCEP in surface water and pore water were modeled based on environmental releases to determine TCEP concentrations for these relevant aquatic media. Like the first 10 chemicals to undergo risk evaluation under the amended Toxic Substances Control Act, RQs were presented in addition to the metric of the number of days of exceedance denoting the duration of the chemical exceeding the COC within flowing receiving water. The role of days of exceedance accompanies each aquatic based RQ value. The days of exceedance must also be greater than the experimental exposure duration associated within the hazard, in this case 30 days.

Understanding the concern from the public commenter, within the draft TCEP RE, the Environmental Risk Characterization section has included tables that represent RQs and days of exceedance for surface water and pore water at both production volume (2,500 lbs/year and 25,000 lbs/year) under high-end and central tendency scenarios. Additionally, the Environmental Risk Characterization within the final TCEP RE provides combinations of production inputs coupled with 7Q10 flow values to represent both the 50th percentile and 90th percentile of TCEP SIC codes. The representation of different production values, releases, and flows provides perspective on modeled concentrations compared to aquatic COCs and the duration of those concentrations.

EPA characterized the environmental risk of TCEP using RQs. As described in EPA's Guidelines for Ecological Assessment, risk quotients are commonly used for chemical stressors, where reference or benchmark toxicity values are widely available. Also, as explained in Section 6.2.3 Basis for EPA's Determination of Unreasonable Risk of Injury to the Environment, the RQ is not treated as a bright-line, and other risk-based factors may be considered, including confidence in the hazard and exposure characterization, duration, magnitude and uncertainty, for purposes of making an unreasonable risk determination.

EPA has moderate confidence in the chronic aquatic hazards and aquatic exposures contributing to unreasonable risk. Additionally, the Agency has moderate to robust confidence in the terrestrial exposures and hazards, which do not contribute to unreasonable risk. Because exposure via soil and the terrestrial food web was determined to be the driver of exposure, EPA does not expect exposure to TCEP via air or surface water to contribute to unreasonable risk to terrestrial organisms. Similarly, EPA does not expect exposure to TCEP via biosolids to contribute to unreasonable risk to the environment. The Agency's overall environmental risk characterization confidence levels were varied and are summarized in Table 4-23.

Section 6.3 – Other comments

Summary: A public commenter (0043) stated that the Lautenberg Chemical Safety Act (LCSA) specifically prescribes assessment requirements for "articles and replacement parts", which, according to the commenter, requires that EPA consider these conditions of use separately from the consideration of the chemical as a whole. The commenter stated that the LCSA includes this provision for articles and replacement parts to account for the lower exposure risk presented by these items compared to direct chemical exposure. The commenter stated that members of the automotive industry are waiting

on EPA to clarify how it will approach these assessment requirements. Once the determination is made, the industry can begin an effort to address conditions of use of concern.

Referencing the discussion in the draft risk evaluation regarding aircraft and aerospace articles, the commenter stated that automotive articles share similar limited exposure profile. The commenter recommended that EPA include manufacture of automobiles and automobile replacement parts in the no unreasonable risk determination.

EPA Response: EPA evaluated automotive articles and replacement parts in the final risk evaluation of TCEP. The changes in the final risk evaluation are in the following conditions of use:

- "Processing – incorporation into article – aerospace equipment and products" was edited to "Processing – incorporation into article – aerospace equipment and products and automotive articles and replacement parts containing TCEP;"
- "Industrial use – other use – aerospace equipment and products" was edited to "Industrial use – other use – aerospace equipment and products and automotive articles and replacement parts containing TCEP;"
- "Commercial use – other use – aerospace equipment and products" was edited to "Commercial use – other use – aerospace equipment and products and automotive articles and replacement parts containing TCEP;" and
- "Consumer use – paints and coatings – paints and coatings" was edited to "Consumer use – paints and coatings – paints and coatings, including those found on automotive articles and replacement parts."

In addition to these changes, a new condition of use, "Industrial use – paints and coatings – automotive paints and coatings" was assessed in the final risk evaluation of TCEP. These conditions of use were assessed qualitatively and similarly to how aerospace equipment and products and commercial use of paints and coatings were evaluated. An overview of the risk characterization approach for the aerospace equipment and products COUs can be found in Section 5 of the draft risk evaluation, Risk Characterization.

The risk determination of the final risk evaluation indicates how these COUs contribute (or not) to the unreasonable risk of TCEP.

Summary: Citing the draft risk evaluation's findings for cancer and non-cancer risk from both occupational and general public exposures, a public commenter (0044) expressed support for EPA's determination that TCEP presents unreasonable risk to human health and the environment. The commenter also stated that the draft risk evaluation contains several important improvements from EPA's prior TSCA risk evaluations:

- EPA made a risk determination for TCEP as a whole chemical;
- EPA calculated the aggregate risks to consumers who are exposed to TCEP from multiple exposure routes;
- EPA evaluated TCEP's risk to fenceline communities;
- And EPA correctly identified Tribal populations as PESS.

EPA Response: EPA appreciates the supporting comment.

Section 7 – Systematic Review

Summary: In response to Charge Question 2.3.1, public commenters (0040, 0045) requested that EPA address how the SACC's recommendations on evidence integration will be adopted, as it impacts the derived toxicity values for risk evaluations, and suggested these recommendations be incorporated via finalizing the Draft Systematic Review Protocol.
EPA Response: EPA relied on the Draft 2021 Systematic Review Protocol {U.S. EPA, 2021, 10415760} for guidance and will continue to review and update the TSCA systematic review processes for future chemicals.

Summary: Two public commenters (0042, 0045) suggested that EPA fully incorporate recommendations provided by organizations such as the National Academies of Sciences, Engineering, and Medicine and the SACC, including disregarding numeric quality scores and changes to the study quality evaluation metrics, on the 2021 Draft Systematic Review Protocol to reflect TSCA's "best available science" requirement.
EPA Response: During development of the systematic review process overall, EPA consulted many existing systematic review frameworks and experts and has relied on best available science throughout the process. One primary goal was to develop data quality criteria that were consistent across disciplines as much as possible. For example, among the hazard disciplines (animal toxicity, ecotoxicity, epidemiology) EPA updated criteria in the *2021 Draft Systematic Review Protocol* {U.S. EPA, 2021, 10415760} to increase consistency, which is of primary importance because some studies are used for both disciplines. Thus, EPA necessarily drew from frameworks for both disciplines rather than relying only on frameworks (*e.g.*, IRIS) for the human health hazard discipline. EPA implemented several recommendations from NASEM when preparing the *2021 Draft Systematic Review Protocol* {U.S. EPA, 2021, 10415760}. For future chemicals, EPA is implementing a domain-based set of criteria for human health animal toxicity studies for TSCA risk evaluations that further responds to peer-review comments. Thus, EPA under TSCA continues to use best available science in updates to the systematic review process. Until there is an update to the *2021 Draft Systematic Review Protocol* {U.S. EPA, 2021, 10415760} under TSCA, EPA will present any updates to the systematic review processes in the individual chemical protocol documents that accompany the risk evaluations.

Summary: A public commenter (0042) stated that EPA references inconsistent population, exposure, comparator, and outcome (PECO) statements to identify relevant health effects studies that may inappropriately exclude no-apical effects such as cellular-level outcomes and recommended revising the PECO statement used in the TCEP risk evaluation and include that PECO statement in the chemical-specific systematic review protocol. The commenter further requested that EPA release a new TSCA systematic review methodology document that states how consistent practices will be applied to all TSCA rulemakings and for EPA to prepare a chemical-specific review protocol for each TSCA risk evaluation it conducts that does not reference the 2021 Draft Protocol for critical elements such as PECO statements.
EPA Response: EPA has considered all relevant health effects from studies identified as supplemental (including cellular level effects) when conducting evidence integration for TCEP.

For future chemicals, EPA's PECO statements will identify all *in vivo* animal toxicity studies as meeting PECO so that studies with less than organ level responses can be immediately identified and evaluated if they are relevant for further consideration in the risk evaluation.

Section 8 – Formatting and Editing

Summary: A public commenter (0037) stated that EPA misattributed TCEP activity to Aceto US, L.L.C. According to the commenter, Aceto Corporation produced TCEP but declared bankruptcy and ceased operations in 2019. Aceto US, L.L.C is a separate legal entity, but EPA incorrectly attributed activity by Aceto Corporation to Aceto US, L.L.C. in three instances on page 24 and once on page 87 of the draft risk evaluation. The commenter requested that EPA correct these misattributions.

EPA Response: EPA has edited the draft risk evaluation of TCEP to correctly attribute activity to Aceto Corporation rather than Aceto US LLC. The following edits have been made to Section 1.1.1, Life Cycle and Production Volume, of the final risk evaluation:

- "The production volumes for TCEP reported to CDR for years 2012 to 2015 were all from one company, Aceto US LLC, a chemical manufacturer and supplier importing TCEP in chemical form. Aceto US LLC indicated to EPA that TCEP was imported and used as a flame retardant for unsaturated polyester resins and for aircraft furniture {U.S. EPA, 2020, 10617335}" was edited to "The production volumes for TCEP reported to CDR for years 2012 to 2015 were all from one company, Aceto Corporation, a chemical manufacturer and supplier importing TCEP in chemical form. Aceto Corporation indicated to EPA that TCEP was imported and used as a flame retardant for unsaturated polyester resins and for aircraft furniture {U.S. EPA, 2020, 10617335};"
- "Note that for 2014, the Aceto US LLC data is included in the total production volume for CDR and Datamyne" was edited to "Note that for 2014, the Aceto Corporation data is included in the total production volume for CDR and Datamyne;" and
- "For 2014, Aceto US LLC's production volume is included in both the CDR data and the Datamyne data" was edited to "For 2014, Aceto Corporation's production volume is included in both the CDR data and the Datamyne data."

EPA found no other instances of misattributing activity to Aceto US LLC throughout the draft risk evaluation for TCEP.

Summary: A peer reviewer (OC – R1) wrote that, based on its structure in the Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profile and in Burka et al. (1991), the abbreviation BCGP should refer to the glucuronide conjugate of bis(2-chloroethyl) 2-hydroxyethyl phosphate rather than bis(2-chloroethyl) 2-hydroxyethyl phosphate itself, as indicated on pages 249, 402, and 525. The peer reviewer stated that the text should be corrected.

EPA Response: EPA revised the names in these three sections of the RE.

Summary: A peer reviewer (OC – R1) stated that the statement "were identified as hydrogen phosphate (BCHP)" in line 13697 on page 524 should read "were identified as bis(2-chloroethyl) hydrogen phosphate (BCHP)." In addition, the peer reviewer recommended adding "and alcohol dehydrogenase pathways" after "glucuronidation" in line 13694 on page 524.

EPA Response: EPA has made this revision.

Summary: A peer reviewer (OC – R1) wrote that the HERO link for "Chen, G; Jin, Y; Wu, Y; Liu, L; Fu, Z. (2015a). Exposure of male mice to two kinds of organophosphate flame retardants (OPFRs) induced oxidative stress and endocrine disruption. *Environ Toxicol. Pharmacol.* 40: 310-318" in the document leads to a different citation.
EPA Response: EPA thanks the commenter for the comment. The hyper link has been corrected.

Summary: A peer reviewer (OC – R1) commented that the metabolite bis(2-chloroethyl) phosphate (BCEP) should be included in the list of abbreviations. The peer reviewer added that it should be prominently noted in both the metabolism section and elsewhere that BCEP and BCHP are names for the same metabolite.
EPA Response: EPA added BCEP to the list of abbreviations in Appendix A. Section 5.2.2 and Appendix J.1.3. now state that BCHP and BCEP are synonyms of each other.

Summary: A peer reviewer (OC – R1) stated that Table 560 should have a footnote explaining what Drinking Water (Diluted) means.
EPA Response: EPA thanks the commenter for the comment. A footnote describing the diluted estimates has been added to Table 5-40 and Table 5-41 of the final TCEP Risk Evaluation: **"**A method was derived to incorporate a dilution factor to estimate TCEP concentrations at drinking water locations downstream from surface water release points. Since no location information was available for facilities releasing TCEP, a dilution factor and distances to drinking water intake was estimated for each relevant SIC code. Table 5-26 provides the 50th quantile distances and 50th quantile dilution factors for the relevant SIC codes."

Summary: A peer reviewer (OC – R1) expressed that it would be helpful to the reader if the MOEs that were less than the target MOE were shown in bold so that they can be easily identified. In addition, the peer reviewer stated that it would be helpful if cancer risks that exceed the targeted risk value were bolded or marked in another easily identifiable manner.
EPA Response: EPA does not bold these low MOEs or high cancer risk values because they may not be considered unreasonable risks. The reader should focus on risks included in Chapter 6, where the unreasonable risk determinations are presented.

Section 9 – Other Comments on the Draft Risk Evaluation

Existing chemical exposure limit (ECEL)

Summary: Two public commenters (0038, 0040) expressed concern regarding the ECEL proposed for TCEP and stated that an inhalation exposure limit is unnecessary for TCEP as dermal exposures are the predominant exposure risk. Another public commenter (0044) stated that establishing an ECEL during the risk evaluation phase is premature and could be viewed as "prejudging" risk management regulations. The commenter suggested that the proposed ECEL is not protective enough, failed to consider multiple exposure routes

for workers, and is inconsistent with TSCA's mandate to regulate to the extent necessary to eliminate unreasonable risk.

EPA Response: EPA routinely establishes occupational exposure values to accompany the TSCA risk evaluations as recommended in comments on previous TSCA risk evaluations. These values identify levels EPA considers to be without appreciable risk and are useful when EPA considers options for managing risks from TCEP. Although the commenter is correct that dermal exposures are predominant, EPA must consider risk via all relevant exposure routes. The establishment of inhalation values is standard practice and has been implemented by many United States agencies and organizations for use in managing and/or communicating inhalation risks.

EPA realizes that the draft appendix was confusing and has changed the title of Appendix N to **Occupational Exposure Value Derivation and Analytical Methods Used to Detect TCEP.** The value in this appendix is calculated based on the POD from the risk evaluation and exposure assumptions for workers and is *not* meant to be a regulatory limit. As described in the updated appendix: "Any existing chemical exposure limit (ECEL) used for occupational safety risk management purposes could differ from the occupational exposure value presented in this appendix based on additional consideration of exposures and non-risk factors consistent with TSCA section 6(c)."

The calculated occupational exposure value for TCEP represents the inhalation exposure concentration below which workers and occupational non-users are not expected to exhibit any appreciable risk of adverse toxicological outcomes, accounting for PESS. Although dermal exposures contribute to the majority of risk to workers, including occupational non users, EPA determined worker inhalation exposure from one COU (commercial use of paints and coatings) contributes to the unreasonable risk to TCEP, and so EPA derived an occupational exposure value for TCEP. It is derived based on the most sensitive human health effect (*i.e.*, cancer) relative to benchmarks and standard occupational scenario assumptions of 8 hours per day, 5 days per week exposures for a total of 250 days exposure per year, and a 40-year working life. EPA expects that at the occupational exposure value of 0.008 ppm (0.09 mg/m3), a worker or occupational non-user also would be protected against neurotoxicity from acute occupational exposure as well as male reproductive effects from short-term and chronic occupational exposures if ambient exposures are kept below this draft occupational exposure value. EPA has not separately calculated a draft short-term (*i.e.*, 15-minute) occupational exposure value because EPA did not identify hazards for TCEP associated with this very short duration.

If EPA chooses to set an ECEL to manage risks from TCEP, the feasibility of compliance will be considered when setting the final ECEL during risk management. Any ECEL used for occupational safety risk management purposes could differ from the occupational exposure value presented in the risk evaluation based on additional consideration of exposures and non-risk factors, consistent with TSCA section 6(c).

De minimis

Summary: A public commenter (0043) recommended that EPA identify and establish a de minimis level for TCEP and other TSCA chemicals below which EPA has no reasonable basis to conclude that the chemicals pose a risk. The commenter also requested that EPA issue a TSCA Section 6(i)(1) order for conditions of use that have been determined to pose no unreasonable risk once the final risk evaluation is released.

EPA Response: As explained in the Procedures for Chemical Risk Evaluation Under the TSCA final rule (89 FR 37028, May 3, 2024), EPA will make a single determination as to whether the chemical substance presents an unreasonable risk of injury to health or the environment under the conditions of use. In the final risk evaluation for TCEP, EPA is concluding that TCEP presents unreasonable risk as a chemical substance. Pursuant to 15 U.S.C. 2605(a) EPA will propose risk management actions to address the unreasonable risk of TCEP. Since EPA is not concluding that TCEP presents no unreasonable risk, EPA will not be issuing a section 6(i)(1) order. However, in the final determination of unreasonable risk, EPA has identified conditions of use that do not significantly contribute to the unreasonable risk of TCEP.

EPA has included additional narrative based on weight fractions in Sections 5.3.5.1 and 5.3.5.2.

Public access

Summary: A public commenter (0044) requested that EPA prepare a non-technical summary document of the draft risk evaluation in multiple languages that follows Interstate Technology and Regulatory Council risk communication principles to provide for meaningful outreach, public access, and process transparency.

EPA Response: EPA publishes a non-technical summary with the final TCEP Risk Evaluation with information about what TCEP is, how it is used, how you might be exposed to it, etc. in plain language. EPA will consider translating this document as the need arises.

Registration evaluation

Summary: A public commenter (0033) suggested that EPA list the other countries that have completed a registration evaluation under the principle of equivalence under the Technical Barriers to Trade Agreement to avoid repeated evaluations.

EPA Response: EPA used reasonably available information, defined in 40 CFR 702.33, in a fit-for-purpose approach, to develop a risk evaluation that relies on the best available science and is based on the weight of the scientific evidence in accordance with TSCA sections 6 and 26. EPA reviewed reasonably available information and evaluated the quality of the methods and reporting of results of the individual studies using the evaluation strategies described in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021) and the TCEP Systematic Review Protocol (U.S. EPA, 2023n).

EPA also identified key assessments conducted by other EPA programs and other U.S. and international organizations. Depending on the source, these assessments may include information on COUs (or the equivalent), hazards, exposures, and potentially exposed or susceptible subpopulations. Some of the most pertinent assessments that were consulted for TCEP include the following:

- U.S. EPA's 2009 *Provisional Peer-Reviewed Toxicity Values (PPRTV) for Tris(2-chloroethyl)phosphate (TCEP) (CASRN 115-96-8)*;
- 2009 *European Union Risk Assessment Report: CAS: 115-96-8: Tris (2-chloroethyl) phosphate, TCEP*;
- Environment Canada and Health Canada's 2009 *Screening Assessment for the Challenge Ethanol, 2-chloro-, phosphate (3:1) (Tris(2-chlrorethyl) phosphate [TCEP])*;
- Australia's 2016 *Ethanol, 2-chloro-, phosphate (3:1): Human health tier II assessment*;
- Australia's 2017 *Ethanol, 2-chloro-, phosphate (3:1): Human health tier III assessment*;
- ATSDR's 2012 *Toxicological Profile for Phosphate Ester Flame Retardants*;

• NTP's 1991 Technical Report on *Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CASRN 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies)*; and

• IARC's 1999 Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 71.

Literature review

Summary: A peer reviewer (OC – R1) noted that the literature review on TCEP related to human health effects took place in 2019, and the peer reviewer was unsure when the literature review occurred for other topics. The peer reviewer stated that updates should be performed to ensure that important new studies have not been missed. A list of post-2019 literature was provided by the reviewer, organized into three categories: neurotoxicity, developmental toxicity, and kidney toxicity.

EPA Response: EPA updated the literature search from 2019 to target animal toxicity studies conducted via the inhalation route as well as epidemiological studies of any human health effects (inclusive of inhalation, dermal, and oral routes). No animal toxicity studies were found. EPA did identify several epidemiological studies that were screened and then evaluated for data quality along with additional studies identified by peer reviewers. EPA then incorporated the epidemiological studies into the TCEP RE. In Section 5.2.3.1, EPA added epidemiology studies on neurological, kidney, immune/hematological, thyroid, lung, and developmental effects, and in Section 5.2.5.1, EPA added epidemiological studies on cancer.