Environmental Protection Network

(202) 656-6229
environmentalprotectionnetwork.org
info@environmentalprotectionnetwork.org

EPN Comments on EPA's Draft Risk Evaluation for Tris(2-Chloroethyl) Phosphate (TCEP)
Docket No: EPA-HQ-OPPT-2023-0265
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The Environmental Protection Network (EPN) harnesses the expertise of more than 600 former Environmental Protection Agency (EPA) career staff and confirmation-level appointees from Democratic and Republican administrations to provide the unique perspective of former regulators and scientists with decades of historical knowledge and subject matter expertise.

Background

On December 13, 2023, EPA released the draft risk evaluation for tris(2-chloroethyl) phosphate (TCEP) for public comment and (letter) peer review. TCEP was designated a High Priority substance for Toxic Substances Control Act (TSCA) evaluation in 2019 during the second round of prioritization. This is the first chemical on that list of 20 for which a draft risk evaluation has been issued.

EPA is proposing to determine that TCEP, *as a whole chemical substance*, presents unreasonable risk to human health and the environment.

EPA preliminarily identified unreasonable risks of both cancer and noncancer health effects related to some, but not all, of the TCEP conditions of use (COUs). Affected are: (1) breastfed infants, (2) people who handle TCEP or products formulated with TCEP at work, (3) people who breathe or ingest dust containing TCEP that comes off of consumer products, and (4) people who eat large amounts of fish contaminated with TCEP. The agency also preliminarily identified unreasonable risks following chronic exposure to fish from TCEP's use as a laboratory chemical and to sediment-dwelling organisms for all uses that were quantitatively evaluated.

EPN Review and Comments

Comment Highlights

- Risk evaluations for high-profile, high-priority substances, with high risk potential and complex data sets and questions, such as Tris(2-chloroethyl) Phosphate (TCEP), should always be subjected to publicly-staged, collaborative peer reviews to ensure transparency and enhanced public engagement.
- A final generic systematic review protocol that is applicable to all TSCA chemicals should be finalized and issued with all deliberate speed.
- Increased use of models to estimate hazard and exposure in both the human health and environmental assessments filled in critical data gaps, resulting in a more robust risk evaluation. EPN supports the use of such approaches but only if these tools have been appropriately vetted and validated.
- EPN generally concurs with the overall findings of EPA's draft risk evaluation of environmental hazards and risks posed by TCEP, but suggests that the chronic hazard posed by TCEP to aquatic vertebrates may well be more effectively and accurately characterized by using a cold freshwater fish species and a testing procedure that incorporates a longer exposure duration more appropriate for

assessing chronic toxicity to aquatic vertebrates.

- EPN generally agrees with the approaches taken to derive the oral and derma Human Equivalent Doses (HEDs), inhalation Human Equivalent Concentrations (HEC) and Cancer Slope Factors (CSF) Inhalation Unit Risks (IUR) and subsequent risk characterizations, with the exception of that for chronic non-cancer effects. The benchmark Margin of Exposure (MOE) should be increased from 30 to 100 to account for the extrapolation of duration of exposure (35 days to chronic).
- Aggregate exposure assessments and risk estimates should be developed for every chemical's occupational and consumer COU, included in all COU risk characterizations and, rather than route-specific risk estimates, serve as the basis for determining whether or not a COU constitutes an unreasonable risk.
- Tables which summarize the dermal, inhalation, and ingestion non-cancer and lifetime cancer risk estimates for each occupational and consumer COU/Occupational Exposure Scenario (OES) should include the results for *all* scenarios quantified, not just those which are below the non-cancer risk benchmarks or above the lifetime cancer benchmarks. This is essential to assure transparency and credibility and allows the reader to be explicitly aware of the full, comprehensive assessment.

Specific comments

1. Peer Review

In the December 13, 2023 Federal Register Notice, EPA stated that it will employ a letter peer review process to gather feedback from the selected scientific experts. The primary focus of that letter peer review will be on the analysis of physical chemical properties, the fate of TCEP in the environment, releases of TCEP to the environment, environmental hazard and risk characterization for terrestrial and aquatic species, and human health hazard and risk characterization for workers, consumers, and the general population. Draft charge questions for the peer reviewers are available in the chemical's docket.

On January 24, 2024, EPN submitted a letter to Deputy Administrator Janet McCabe and Office of Chemical Safety and Pollution Prevention Assistant Administrator Michal Freedhof expressing our concerns about EPA's plans to conduct only a letter peer review of the draft TCEP risk evaluation.
As we noted in that letter:

"TCEP is the first of the high-priority chemicals selected for risk evaluation during the second round of prioritization in 2019 to have a draft risk evaluation released for peer review and public comment. It is a data-rich chemical possessing a toxicity profile of many endpoints of serious concern (e.g. scenarios that impact every life stage). Many of the approaches being used in the hazard and exposure assessments for TCEP are new to the TSCA program. For all of these reasons, the peer review for TCEP should be carried out in a public, collaborative setting.

The EPA Peer Review Handbook and OMB Peer Review Bulletin provide robust frameworks for conducting peer review, including how it is to be conducted. Serious thought must be given to selecting the appropriate type of peer review to be carried out for a particular scientific product. These frameworks recognize that complex and novel assessments with far-reaching impacts on regulation and policy must receive the highest level of peer review—a transparent panel review process with collaboration among the reviewers, interaction with the public, and a consensus report synthesizing the reviewers' range of perspectives. External peer review by independent experts under this approach helps to assure that agency assessments and management decisions are based on the best available science and reflect the highest level

of robust scientific integrity

Questionable peer reviews will negatively impact EPA, as seen with the recent letter peer review of the Asbestos Part 2 White Paper. The reviewers were divided on a fundamental issue — the choice of cancer potency factors for the six asbestos fibers — that might have been resolved through a collaborative panel review process. Several of the reviewers criticized the lack of transparency and prohibition of interaction between them. They emphasized that a letter review was inadequate for a substance as important and complex as legacy asbestos.

Risk evaluations for high-profile, high-priority substances, with high risk potential and complex data sets and questions, should always be subjected to publicly-staged, collaborative peer reviews. One might have made a valid argument to conduct a letter review on the Asbestos Part 2 White Paper as an initial step in a more comprehensive process for the entire draft evaluation that includes a publicly-staged collaborative peer review. But it appears that no peer review at all is planned for the draft Part 2 evaluation. This will deprive EPA and the public of further independent scientific input not only on the choice of cancer potency factors but on numerous other major issues as well. The same adverse consequences will also impact the TCEP risk evaluation.

Draft risk evaluations that introduce the use of new approaches for the first time should also be subjected to a publicly-staged collaborative peer review, like a SACC review, so that the integrity, relevance, and application of the new approaches can be robustly discussed. EPA's current choice of doing only a letter peer review of the TCEP draft risk evaluation is, therefore, insufficient.

Until the Existing Chemical Review program matures to the point where a standard operating procedure has been defined and all stakeholders know what to expect, EPA has an obligation to subject its products to a robust collaborative public peer review. In the end, this will save time and resources, because the agency won't have to "do it again," as happened with the first 10 risk evaluations, and it will provide a sounder foundation for the follow-up risk management rulemakings necessary under TSCA.

In closing, we recommend that EPA reexamine its peer review mechanisms for Asbestos Part 2 and TCEP and convene full SACC peer review processes for both evaluations."

A copy of this letter is being submitted separately to the TCEP docket.

a. Systematic Review

In the introductory paragraph to Charge Question 2.3 EPA mentions "process improvements regarding systematic review." In 2021, the National Academy of Sciences, Engineering and Medicine (NASEM) reviewed[1] the first draft of EPA OPPT's Systematic Review Protocol[2]. Later that year, EPA released an update, the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances*[3], which addressed comments and recommendations received from NASEM. In 2022, the TSCA Scientific Advisory Committee on Chemicals (SACC) and the public provided comments on the 2021 document.

The NASEM report had included a recommendation that "the agency should create a handbook for TSCA review and evidence integration methodology that details the steps in the process. The effort to develop and publicly vet a handbook could help make the process more straightforward, transparent, and easier to follow."

[1] NASEM, 2021. Consensus Study Report on The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations. National Academies Press. Washington, DC.

[2] U.S. EPA, 2018. Application of Systematic Review in TSCA Risk Evaluations.

[3] U.S. EPA, 2021. Draft systematic review protocol supporting TSCA risk evaluations for chemical substances, Version 1.0: A generic TSCA systematic review protocol with chemical-specific methodologies.

No such document has been issued to date. Instead of an update to the 2021 Draft Systematic Review Protocol, the systematic review protocol for the Draft Risk Evaluation for TCEP describes, in minimal detail, some clarifications and approaches that differ from those presented in the 2021 Draft Systematic Review Protocol. They are said to be responsive to (1) the 2022 SACC comments, (2) the 2022 public comments, or (3) to reflect chemical-specific risk evaluation needs.

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This is not an appropriate solution to the need for development and use of a generic systematic review protocol that is applicable to all TSCA chemicals. We strongly urge the NASEM recommendation for creation of a (generic) handbook to be published, presumably as a stand-alone document, be followed with all deliberate speed. It should include a section/appendix, as does the 2021 draft, that highlights the changes made to the 2021 protocol in response to the 2022 SACC and public comments and recommendations. In addition, justification for not implementing a particular recommendation needs to be included in this section/appendix. Some of this material can be found in the TCEP systematic review protocol, but it should be extracted from the TCEP document and inserted into the generic handbook/guidance. This is necessary to assure consistency in application of the protocol across chemicals and to provide the reader of an application of the protocol to a specific chemical the ability to judge if the process is credible, thorough, straightforward, transparent, and easy to follow.

2. Environmental Risk Assessment

Reviews of the first series of Risk Evaluations prepared under the Existing Chemicals Review Program, as mandated in the 2016 amended TSCA, revealed the relative paucity of empirical data available for the assessment of risk to non-human species when compared to those available for the assessment of risk to humans. The situation with TCEP is consistent with this observation. However, we did notice an increase in the number of modeling tools the agency has used to develop quantitative estimates of exposure and hazard, employing some of these tools for the first time in a TSCA Risk Evaluation. The TCEP exposure and hazard assessments have been informed by both modeling as well as monitoring and other empirical data.

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EPN supports the use of modeling approaches to fill in critical data gaps but only if these tools have been appropriately vetted and validated.

a. Exposure Assessment

Exposure to aquatic species is expected to occur through surface water and sediment. This was modeled to estimate concentrations in each source near industrial and commercial use sites.

While TCEP is not expected to bioaccumulate upward through the food chain, there are data in the published literature that show residues in tissues of several aquatic species including fish. EPA also estimated fish tissue concentrations for each COU, using the modeled water releases from the industrial and commercial use sites. This information is important not only for characterizing exposure and risk to certain aquatic and non-human terrestrial species but also to certain human populations who consume fish from near these sites.

Terrestrial species are expected to be exposed to TCEP through contact with soil, air, and surface water. This results in oral exposures via food and drinking water, inhalation from air, and dermal contact with soil

and surface water.

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The exposures of terrestrial species includes deposition from air to soil and surface water ("indirect" contamination). EPA did account for the transfer of chemical from air to soil but not to surface water, asserting that its presence in surface water is too short-lived to make a difference. In the end, EPA evaluated risk to a variety of terrestrial species only via air (as transferred to soil, but not surface water) and soil leading to dietary exposure (the oral route). Each pathway was evaluated separately; that is, no aggregate exposure assessment was done. Further, EPA did not conduct an assessment of dermal exposure via any pathway — soil, surface water or air. In fact, the likelihood of dermal exposure was never mentioned in any of the sections on exposure, hazard, or risk characterization related to any non-human species in the ecosystem.

Dismissing or ignoring these possible routes of exposure (inhalation directly from air, deposition to water, and dermal contact) results in an unknown (perhaps significant) degree of underestimation of real world aggregate exposure or risk. Whether or not this makes any difference in the total number and nature of COUs that should be determined as posing an unreasonable risk also remains unknown, but there is a possibility that some may have been mislabeled.

b. Aquatic Species Hazard

Aquatic hazard data were available for TCEP only for three species of fish: Japanese medaka (*Oryzias latipes*), rainbow trout (*Oncorhynchus mykiss*), and zebrafish (*Danio rerio*). Unfortunately, no high quality studies were available to assess the effects of TCEP on other aquatic vertebrates or aquatic invertebrates and plants.

Mortality was the endpoint used to estimate aquatic hazards from acute exposures. The empirical data from two 96-hour exposure duration fish studies were supplemented with hazard predictions modeled using Web-based Interspecies Correlation Estimation (Web-ICE). LC50/LD50s were generated for additional species for which no empirical data were available. The outputs were used with the empirical fish data to create a species sensitivity distribution (SSD) and calculate a TCEP concentration of concern (COC) for acute exposures to fish and additional aquatic species (85,000 ppb) representing the lower 95th percentile of the HC05.

A COC for chronic exposure to aquatic species (55.9 ppb) was derived, based upon empirical fish data (assessment endpoint = growth and development of the Japanese medaka).

During risk characterization, the acute and chronic COCs were compared with known or modeled TCEP concentrations in surface water and/or sediments associated with the industrial and commercial sites to determine if any of the site-specific exposure scenarios exceeded an acceptable risk threshold.

c. Terrestrial Species Hazard

Terrestrial hazard data for TCEP were available for soil invertebrates, mammals, and avian species. No assessment of hazard or risk was conducted for any plant species.

Using empirical toxicity data for nematodes and earthworms, EPA derived a chronic hazard value for terrestrial invertebrates of 612 mg/kg soil. Empirical toxicity data for mice and rats were used to estimate a chronic toxicity reference value (TRV) for terrestrial mammals of 44 mg/kg-bw/day. Empirical toxicity data

from one bird study were used to estimate a chronic TRV for avian species of 0.0025 mg/kg-bw/day.

EPN Comments on the Hazard Assessment

The paucity of empirical data available to assess hazard to aquatic species prompted the agency to make use of several modeling tools to develop broadly representative numerical values in order to derive quantitative estimates of risk.

One of these benchmarks was the HC05. The HC05 estimates the concentration of TCEP that is expected to be protective for 95 percent of species. This HC05 can then be used to derive a COC, and the lower bound of the 95 percent confidence interval (CI) of the HC05 can be used to account for uncertainty instead of dividing by an Adjustment Factor (AF).

There are both strengths and uncertainties to using a calculated HC05 in the TCEP Risk Evaluation. The following discussion of Strengths and Uncertainties addresses, in part, the EPN perspective on Charge Question 2.1.1: Please comment on how EPA/OPPT calculated the HC05 and its associated strengths and uncertainties in the TCEP Risk Evaluation in Section 4.2.

Strengths

EPA's draft evaluation of environmental hazard and risk posed by TCEP appears to have incorporated thorough quality control methods to assess the rigor of the available test data. The draft assessment of environmental hazard posed by TCEP appears to be well reasoned and balanced. The clear characterization of quality of data used to assess environmental risk, i.e., Slight, Moderate, or Robust (Table 4 23) supports this view.

Also, the modeling used in setting hazard levels, e.g., Web-ICE, was peer reviewed and the website was beta tested. Given the lack of some important (empirical) data at key points in the review process, the agency made what we think is an informed and sound decision about how best to proceed with the hazard and risk evaluation, i.e., using a calculated HC05 in the absence of valid empirical data resulting from properly conducted toxicity testing and/or research studies.

Uncertainties

The use of modeling as an aid to assessing hazard and risk of chemicals has historically been viewed as a weakness because of the uncertainties then inherent in the use of statistical processes; but the paucity of relevant and reliable empirical data over the years has motivated scientists to make better use of whatever data are available to bridge the gaps in empirical data from toxicity testing and research.

In order to improve the rigor of this and future hazard and risk characterizations, we recommend that EPA encourage and provide additional support for conducting needed testing early in the review process as well as modeling coupled with other *in silico*, *in vitro*, and less whole animal-dependent tools to help fill data gaps. Such support will help bolster this and other environmental hazard and risk evaluations by reducing those uncertainties which handicap more rigorous analyses.

A second benchmark is the COC. EPA defines the COC as the concentration of a given chemical in a stream. Harm to the aquatic environment is more likely to occur if the COC is exceeded.

There are both strengths and uncertainties to using a derived COC in the TCEP Risk Evaluation**.** The following discussion of Strengths and Uncertainties addresses, in part, the EPN perspective on Charge Question 2.2.1: Please comment on how EPA/OPPT calculated the COC for aquatic organisms and its associated strengths and uncertainties in Section 4.2 of the TCEP Risk Evaluation.

Strengths

Using a calculated COC for aquatic organisms permits the agency to assess risk to aquatic species. Clearly this is a strength because it permits a clear and direct comparison of toxic effects experienced by aquatic organisms with the projected concentrations to which they are expected to be exposed.

Uncertainties

It is to be expected that uncertainties will result when on-site empirical data are not available and risk assessors will nevertheless still need to make decisions about issues where levels of uncertainty surround environmental risk. A useful approach in such circumstances is to project from what is known and model the situation, making appropriate assumptions, and then making the best possible decisions using the best available information that is at hand. We think that what EPA has done in assessing environmental risks as posed by TCEP is reasonable.

d. Risk Characterization

Aquatic. Based upon the draft proposed scope of the exposure and hazard assessments supported by modeled estimates, there are no acute risk quotients (RQs) greater than 1, but there are chronic RQs above 1 which have corresponding days of exceedance greater than 14 days within the sediment compartment (sediment and benthic pore water) for five of the 20 remaining COUs. Because of TCEP's affinity to bind to sediment and its persistence in the aquatic compartment, there could be a lasting effect on benthic biota which would potentially impact communities following chronic TCEP exposure. EPA has moderate confidence in these RQ inputs for the acute and chronic aquatic assessments. Only the laboratory chemicals COU resulted in a chronic RQ greater than 1 with over 14 days of exceedance within surface water. Table 4-20 gives a succinct analysis of exposure scenarios and corresponding environmental risk for aquatic receptors with TCEP in surface water, sediment, and pore water.

Monitoring data show that the RQs from TCEP concentrations in surface water and sediment within the Water Quality Portal database or published literature were below 1, i.e., representing no unreasonable risk. However, differences in magnitude between modeled and measured concentrations may be due to measured concentrations not being geographically or temporally close to releases of TCEP from a facility.

General Comments Regarding Environmental Assessment

Aside from some specific observations and criticisms presented above and below, EPN generally concurs with the overall findings of EPA's draft risk evaluation of environmental hazards and risks posed by TCEP.

Nonetheless, we also offer the following comments below which might help strengthen the evaluation.

We suspect that the actual hazard and risk to aquatic invertebrates from chronic exposure to TCEP may be understated because no actual empirical chronic exposure duration data for fish were available and no adjustments were made to account for the extrapolation of less-than-lifetime to lifetime exposure conditions. The Japanese medaka (*Oryzias latipes*) was tested for a 14-day endpoint (LOEC/NOEC) for

development and growth at 0, 0.25 or 1.25 mg/L; that information was then used to generate a chronic hazard value of 0.559 mg/L.

Furthermore, the medaka is a warm water fish, typically doing its best in rice paddies, marshes, ponds, and slow moving streams in 15–28° C water. The medaka also is considerably less sensitive to toxic substances than other species of fish that prefer colder water, e.g, the rainbow trout (*Oncorhynchus mykiss*), which is typically tested at 10-12° C. One recent study bolstering our concern about this difference found that cold freshwater fish were the most sensitive species tested in 57% of the analysis groups where the most sensitive species could be determined, and that species was always the Rainbow Trout [4]. Arguably, the chronic hazard posed by TCEP to aquatic vertebrates may well be more effectively and accurately characterized by using a cold freshwater fish species and a testing procedure that incorporates a longer exposure duration more appropriate for assessing chronic toxicity to aquatic vertebrates. Fish early life stage toxicity test guidelines available from EPA[5] and OECD[6] both provide for a considerably longer duration of exposure for the Japanese medaka, i.e., 30 days post hatch, than was used in the studies cited and used EPA's draft risk evaluation. Given the cushion for dealing with uncertainties in assessing this risk, e.g., by using SSD methods, assessment factors, and related techniques, our suggestion may or may not be warranted. Nevertheless, we think it is worth addressing.

Another weakness in the draft risk evaluation is that no amphibian, aquatic invertebrate, or aquatic plant studies were reasonably available for use in a quantitative assessment, and this absence of data from relevant and reliable testing or research is why the agency needed to use modeling approaches. We think this modeling approach is a sound one. When no reliable test data are available, the next best strategy is to develop and utilize models that reasonably approximate reality, and that is what has been done.

Table 4-6.TCEP Evidence Table Summarizing the Overall Confidence Derived from Hazard Thresholds integrates multiple factors, e.g., database quality, consistency, strength and precision, to document EPA's level of confidence in the hazard thresholds which have been generated for aquatic and terrestrial species. We think this approach is admirable because it demonstrates the overall effort by the agency to exercise and maintain rigor in its analyses in the draft risk evaluation. Not surprisingly, the evidence for the chronic mammalian assessment was the only category that was rated with robust hazard confidence, given the relatively rich database, e.g., rodent testing, from which to draw.

3. Human Health Assessment

a. Hazard Identification

No adequate human data were identified for use in the assessment of potential noncancer or cancer risk of TCEP exposure to humans. However, data were available in several animal species and strains which were useful in identifying endpoints of concern, some of which could be used for quantitative assessment of potential risk. None of the available evidence demonstrated that TCEP causes the effects of concern in humans, but it was accorded a likely judgment.

EPN agrees that the available data do identify neurotoxicity, reproductive toxicity, developmental toxicity,

[4] Ceger P, Allen D, Blankinship A, Choksi N, Daniel A, Eckel WP, Hamm J, Harwood DE, Johnson T, Kleinstreuer N, Sprankle CS, Truax J, Lowit M. Evaluation of the fish acute toxicity test for pesticide registration. *Reg. Toxicol. Pharmacol.* 139 (Mar), 105340.
[5] https://www.epa.gov/sites/default/files/2015-07/documents/850-1400.pdf
[6] https://www.oecd-ilibrary.org/environment/test-no-210-fish-early-life-stage-toxicity-test_9789264203785-en

and kidney toxicity including cancer as the most likely and sensitive potential adverse human health hazard outcomes associated with TCEP exposure (hazard identification). Data from some of the studies on each of these endpoints also are useful for quantification of these hazards (hazard characterization).

EPN also agrees that the information associated with skin and eye irritation, mortality, hepatic, immune/hematological, thyroid, lung/respiratory, and endocrine toxicity ("other effects") and body weight is not sufficient to be considered critical to the risk evaluation.

b. Dose Response Assessment

The spectrum of exposure scenarios associated with the TCEP COUs reflect a multiplicity of durations of exposure (e.g., acute, short-term, chronic). The agency determined that hazard characterizations reflecting this variety of exposure durations warranted development. This effort resulted in a series of Points of Departure (PODs) to be used in acute and/or short-term/chronic settings, as appropriate for the nature of the COU and its affected (sub)populations (occupational/occupational non-user (ONU), consumer/bystander, general population, binned by lifestage).

c. Route-to-Route Extrapolation

Data adequate for the dose-response assessments were available only from oral toxicity studies in animals. Given the absence of TCEP-specific physiologically-based pharmacokinetic models, EPA extrapolated the Human Equivalent Doses (HED) and Cancer Slope Factors (CSF) derived for the oral route to the inhalation and dermal routes, the latter with the additional accommodation for percentage of dermal absorption. Based upon the Herr et al. 1991 data[7], EPA determined that oral absorption may be greater than 95 percent. And since there were no empirical data available on percentage of exposure by the inhalation route, EPA assumed that absorption by both routes was 100%.

EPN agrees with the approaches taken to derive the oral and dermal HEDs, inhalation Human Equivalent Concentrations (HEC) and Cancer Slope Factors (CSF) Inhalation Unit Risks (IUR).

d. Non-cancer Points of Departure and Benchmark Margins of Exposure

i. Acute Exposure

EPA selected a Point of Departure (POD) from the animal NOAEL of 40 mg/kg/day, extrapolated to a daily (oral and dermal) HED of 9.46 mg/kg and daily (inhalation) HEC of 51.5 mg/m^3 (4.41 ppm) from the prenatal/postnatal neurodevelopmental toxicity study[8] with a total Uncertainty Factor (UF) of 30 chosen to serve as the benchmark Margin of Exposure (MOE) to be used during risk characterization. EPN agrees with these choices.

The following discussion on short-term and chronic exposure represents EPN's comments in response to Charge Questions 2.3.2 and 2.3.3.

ii. Short-term Exposure

EPA derived a POD ($BDML_5$ = 21 mg/kg/day), a daily HED of 2.73 mg/kg and a daily HEC of 14.9

[7] Herr, DW; Sanders, JM; Matthews, HB. (1991). Brain distribution and fate of tris(2-chloroethyl) phosphate in Fischer 344 rats. *Drug Metab Dispos* 19: 436-442.

[8] Moser, VC; Phillips, PM; Hedge, JM; McDaniel, KL. (2015). Neurotoxicological and thyroid evaluations of rats developmentally exposed to tris(1,3-dichloro-2-propyl)phosphate (TDCIPP) and tris(2-chloro-2-ethyl)phosphate (TCEP). *Neurotoxicol Teratol* 52: 236-247.

mg/m^3 (1.27ppm) from a 35-day repeated dose study[9], supported by Johnson et al. (2003)[10], with a total UF of 30 chosen as the benchmark MOE to be used during risk characterization. EPN agrees with these choices.

iii. Chronic exposure

EPA derived the same POD ($BDML_5$ = 21 mg/kg/day), a daily HED of 2.73 mg/kg, and daily HEC of 14.9 mg/m3 (1.2ppm) from the same study by Chen et al. (2015a), supported by Johnson et al. (2003), with a total UF of 30 chosen as the benchmark MOE to be used during risk characterization**.**

EPN does NOT agree with all of these choices. Given that the Chen et al. study is of short-term, not chronic, exposure duration (35 days), an additional uncertainty factor must be employed to accommodate for the difference in exposure durations. EPA's traditional default choice for this extrapolation is 3, which we consider adequate in this case. Thus, a total UF of 100 should serve as the benchmark MOE for chronic exposure scenario risk characterizations.

EPA has stated that they derived and used as a POD the $BMDL_5$ (which is lower than the more frequently-employed default $BMD(L)_{10}$) to accommodate for the nature and severity of the effects observed in the Chen et al study. That is appropriate but it does not also accommodate for the duration disparities. Thus, the necessity for the additional 3X UF to account for the subchronic to chronic extrapolation.

e. Cancer hazard identification and dose response assessment

One high-quality case-control study was identified[11] which examined the association between TCEP/other flame-retardant exposure and papillary thyroid cancer in adults. The authors concluded that papillary thyroid cancer was positively associated with exposure to TCEP (and potentially other flame retardants) in dust above the median concentration (odds ratio of 2.42 (CI 1.10 to 5.33) ($p < 0.05$)). EPN agrees with the agency that this study has limitations that preclude it from being a candidate for use in dose response assessment.

On the other hand, the 1991 NTP bioassay[12] is a high quality chronic study designed to evaluate the carcinogenic potential of TCEP in rats and mice. It is the best candidate for use in dose response assessment. Groups of 50 males and 50 females of each species were administered TCEP in corn oil via oral gavage 5 days per week for 104 weeks. Rats received 0, 44, or 88 mg/kg and mice received 0, 175, or 350 mg/kg per day.

NTP findings: Results revealed treatment-related increased incidences of renal tubule cell and thyroid follicular cell adenomas in both male and female rats. None of the neoplastic lesions identified in mice could unequivocally be attributed to treatment with TCEP. Overall, NTP concluded that there is *clear* evidence of

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[9] 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.

[10] Johnson, PD; Goldberg, SJ; Mays, MZ; Dawson, BV. (2003). Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. *Environ Health Perspect* 111: 289-292.

[11] Hoffman, K; Lorenzo, A; Butt, CM; Hammel, SC; Henderson, BB; Roman, SA; Scheri, RP; Stapleton, HM; Sosa, JA. (2017). Exposure to flame retardant chemicals and occurrence and severity of papillary thyroid cancer: A case-control study. *Environ Int* 107: 235-242.

[12] Herr, DW; Sanders, JM; Matthews, HB. (1991). Brain distribution and fate of tris(2-chloroethyl) phosphate in Fischer 344 rats. *Drug Metab Dispos* 19: 436-442.

renal tubule adenomas in male and female rats and that the thyroid follicular cell neoplasms and mononuclear cell leukemia observed in rats *may* have been related to TCEP administration but acknowledged uncertainty related to this association. There was *equivocal* evidence in mice based on marginally increased incidence of renal tubule cell neoplasms in males and marginally increased incidence of harderian gland adenomas in females. EPN agrees with the agency that this study is best suited for evaluation of cancer hazard and dose response assessment.

A number of acceptable genotoxicity studies have been conducted, some of which evaluated TCEP's potential for direct interaction with cellular DNA, others for indirect effects. The overall weight-of-evidence (WOE) for mutagenicity is *negative*. EPA concluded that direct mutagenicity is not expected to be a predominant mode of action. EPN agrees with EPA on the overall WOE that the evidence for mutagenicity is negative, but would submit that mutagenicity is not likely to be involved in any mode of action.

EPA has concluded that TCEP is "*likely to be carcinogenic to humans*." The agency's conclusion is based on their interpretation that there is clear evidence of renal tubule adenomas and carcinomas in rats, equivocal evidence of kidney tumors in mice, the rarity of the kidney tumors in rodents, and equivocal evidence for several other tumors in rats or mice**.**

EPN does not fully agree with this WOE assessment. In our view, there was not clear evidence of renal tubule cell carcinomas in rats. No carcinomas were seen at either dose in females, and there was just one in a high dose male. However, a carcinoma was seen in one control male, which negates any statistical significance.

This difference of opinion notwithstanding, the NTP results can be used for dose response assessment. As EPA points out, the existing mechanistic evidence for carcinogenesis is *slight*. Those data that do exist (primarily on genotoxicity) indicate that TCEP has little, if any, mutagenic potential. Limited additional data indicate that TCEP may influence cell cycle dysregulation, cell proliferation, apoptosis, ion transport, induction of oxidative stress, and altered cellular energetics in kidney tissues and cells and in other cell types. These phenomena, along with non-mutagenicity, when evaluated as potential/likely key events in a mode of action (MOA)/adverse outcome pathway (AOP), generally exhibit non-linear dose responses. If any of these phenomena were shown to be elements of the MOA/AOP for the renal tubule tumors, application of a non-linear dose response model would be warranted. However, no MOA/AOP analyses have been carried out for TCEP. Thus, the agency is obligated, as a matter of policy, to assume that the dose responses for carcinogenicity are linear in nature, and as a consequence has applied linear low-dose extrapolation models for dose response assessment consistent with that assumption. While necessary to employ this approach, as per policy, it has likely led to a significant overestimation of cancer risk.

4. Aggregate Exposure

In Section 5.1.4, EPA defines aggregate exposure as "the combined exposures to an individual from a single chemical substance across multiple routes and across multiple pathways" (40 CFR 702.33).

Aggregate exposure assessments can be constructed in a number of different ways. The key qualifying factor supporting aggregation is the demonstration that exposure is co-occurring, that is, overlapping either in full or in part, over some finite time period. Aggregation could be implemented in cases where simultaneous exposure is occurring by at least two routes within a single specific exposure scenario (e.g., manufacture of a chemical) or across two or more separate exposure scenarios (e.g., manufacture of a chemical and disposal

of that chemical).

Examples of a single source scenario that would warrant the combining of fully overlapping inhalation and dermal exposures would be in the case of a worker in her/his occupational setting or the combining of co-occurring inhalation, dermal and oral exposures of a consumer during the use of a product containing the agent of concern. These scenarios represent/reflect every COU associated with every chemical undergoing evaluation in the Existing Chemicals Review program. EPN has repeatedly recommended that aggregate exposure assessments be conducted for every chemical's occupational and consumer COU, be included in all COU risk characterizations, and serve as the basis for determining whether or not a COU constitutes an unreasonable risk. To not do this results in the underestimation of the risk and potential mistakes in the unreasonable risk determination. This example of aggregate exposure and risk assessment is relatively simple to do. Validated tools are available. The agency has experience.

More challenging is the development of aggregate exposure assessments when two or more separate exposure scenarios are the focus of the assessment. A relatively simple circumstance to deal with would be the case of a worker exposed in the occupational setting who then goes home and uses a product containing the same chemical of concern while retaining residues from exposure received during the workday.

Assessing most of the multiple exposure scenarios is far more complicated than that simplistic example. There are uncertainties for each population group associated with which pathways co-occur and for how long, whether or not the same routes apply to each individual or the sources of exposure are the same or different. There is also variability within a given exposure pathway. And most challenging is the paucity of empirical or modeled exposure data available for use in such an assessment. EPN encourages the agency to expeditiously continue to expand its efforts to develop, validate, and integrate aggregate (and cumulative) assessment tools such as the fenceline methodology (Draft Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities Version 1.0).

EPN Comments

EPN remains dismayed and disappointed that the agency has not incorporated aggregate exposure into its risk characterizations. We had held out hope that this time would be different when we read the following two paragraphs in the document.

In the introductory paragraph of Section 5 Human Health Risk Assessment, EPA states that it assessed human health risks of TCEP exposure to workers and ONUs, consumers, and the general population with Section 5.1 describing exposures to workers and ONUs via the inhalation and oral routes; workers via the dermal route; consumers via the inhalation, dermal, and oral routes; and the general population also via the oral, dermal, and inhalation routes.

In Section 5.2.9, Hazard Considerations for Aggregate Exposure, EPA states that "it conducted route-to-route extrapolation of the toxicity values from the oral studies for use in the dermal and inhalation exposure routes and scenarios. *Because the health outcomes are systemic and are based on the oral studies, EPA 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*" (emphasis added).

EPA presents acute and chronic exposure estimates in the consumer assessment in Section 5.1.2.3 and Appendix I.1.1. As they note, exposure estimates to consumer articles are often dominated by a single route

but there are also exceptions where aggregate exposures across routes are necessary to consider. The Supplemental TCEP Consumer Modeling Results includes a figure that aggregates the consumer exposure estimates by route (inhalation, dermal, ingestion) for each COU and life stage combination. In all cases, even if there appears to be a predominant source of exposure, all routes should still be assessed and combined when determining if a COU poses an unreasonable risk or not. Otherwise, the potential risk will be understated, perhaps significantly, and it could be possible that combining risk from all relevant routes would shift a chemical's unreasonable risk determination from Reasonable to Unreasonable.

EPA intended to develop exposure estimates for every COU/OES. Lack of adequate empirical data and/or relevant models precluded the agency from doing so for all COUs. If monitoring data were available, EPA characterized central tendency and high-end inhalation exposures. Where no inhalation monitoring data were identified, but inhalation exposure models were available, EPA also estimated central tendency and high-end exposures. If both inhalation monitoring data and exposure models were available, where applicable, EPA presented central tendency and high-end exposures using both approaches. EPA identified measured dermal exposure estimates only for dust generated at e-waste facilities. Monitoring data were not available for any other COUs, so any other dermal estimates derived were modeled. For many cases, there were no monitoring data to estimate inhalation exposure for ONUs. In some cases, this was addressed with the use of exposure models. However, most OESs do not contain inhalation exposure estimates for ONUs. Dermal assessments were not conducted for the ONUs, as is the standard practice.

No adequate empirical data were available for exposure assessment so models were employed to estimate exposure from each of the five consumer COUs. Exposures via the inhalation, oral, and dermal routes to TCEP-containing consumer products were estimated using EPA's Consumer Exposure Model (CEM).

Given that route-specific exposure estimates were developed for those COUs possessing adequate empirical data and/or modeling outputs, there was ample opportunity to integrate these aggregate exposure estimates into the risk characterizations for each individual COU and use them to inform the determination of (un)reasonable risk, as we have recommended repeatedly in the past.

6. Risk Characterization

a. Occupational Risk Characterization

Table 5-57 summarizes cancer and non-cancer risk estimates for the inhalation and dermal exposures for all OESs assessed. These risk estimates are based on exposures estimated for workers who do not use personal protective equipment (PPE) such as gloves or respirators. When both monitoring and modeling data were available for inhalation exposures, EPA only presented the risk estimates for the most reliable data source in the summary table. Estimates for inhalation and dermal exposures that have PPE factored in are contained in the Draft Risk Evaluation for TCEP – Supplemental Information File: Risk Calculator for Occupational 7986 Exposures[13].

Regrettably, upon examination of Table 5-57, which presents the risk estimates for each COU, one can see that, once again, the agency fails to implement aggregate exposure approaches, but continues to provide estimates separately by route of exposure. As EPN and others have said before, this practice assures an

[13] U.S. EPA. (2023k). Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP) – Supplemental Information File: Risk Calculator for Occupational Exposures. Washington, DC: Office of Pollution Prevention and Toxics, Office of Chemical Safety and Pollution Prevention.

underestimation of the real world risk in which actual exposure is occurring simultaneously by two or more routes.

b. Consumer Risk Characterization

Table 5-58 Acute and Chronic Non-cancer Consumer Risk Summary summarizes the dermal, inhalation, and ingestion MOEs used to characterize non-cancer risk for acute, short term, and chronic exposure and presents these values for all life stages for each COU. Once again, risk characterizations are presented on a route-by-route basis rather than in the aggregate. Furthermore, if one were to accept that the composite uncertainty factor or benchmark MOE for chronic exposure should be 100 rather than 30 (see EPN argument for the change above in the section on Non-cancer Points of Departure and Benchmark Margins of Exposure), ALL of the COU- specific exposure scenarios would be more unacceptable because total aggregated exposure doses would be higher.

Table 5-59 Lifetime Cancer Consumer Risk Summary summarizes the dermal, inhalation, and ingestion lifetime cancer risk estimates for each consumer COU. The same observation holds for non-cancer effects: ALL of the COU- specific exposure scenarios would be more unacceptable because total aggregated exposure doses would be higher.

Risk estimates in Table 5-58 and Table 5-59 are only presented for COUs, routes, and age groups that are determined to be below the non-cancer risk benchmarks or above the lifetime cancer benchmarks. For cancer, EPA uses a range of cancer benchmarks from 1 in 10,000 to 1 in 1,000,000 to consider and characterize lifetime cancer risks from consumer exposure. Table 5-59 presents the risk estimates that were above the lifetime cancer benchmark of 1 in 1,000,000.

EPN sees these two tables as incomplete and contrary to the agency's stated goal of increased transparency As the agency notes, the draft risk evaluation presents only COU exposure scenarios (uncombined) which exceed acceptable thresholds (i.e., below the non-cancer risk benchmarks and/or above the lifetime cancer benchmarks). This lack of transparency is unacceptable. **The risk characterization results for *all* COUs should be presented so the reader can be explicitly aware of the full, comprehensive assessment.** And, it is possible if the agency were to appropriately combine routes relevant to these left-out COUs and/or adjust the composite UF for chronic exposures, the risk determinations of some of those currently not listed in the tables may also shift from Acceptable to Unreasonable.

c. General Population Risk Characterization

EPA quantitatively assessed human exposures to TCEP concentrations via oral ingestion of drinking water, soil, and fish, dermal exposures to soil and surface water, and inhalation of ambient air. EPA assessed risk associated with each of these exposure scenarios by comparing doses to acute, short-term, and chronic human equivalent concentrations and doses. Furthermore, EPA assessed the lifetime cancer risk from TCEP exposure via these routes. As noted previously, EPA uses a range of cancer benchmarks from 1 in 10,000 to 1 in 1,000,000 to characterize lifetime cancer risks for the general population.

Table 5-60 and Table 5-61 summarize the MOEs used to characterize acute non-cancer risks for oral exposures for the applicable COUs. Table 5-62 and Table 5-63 summarizes the chronic non-cancer MOE estimates for the applicable COUs. Table 5-64 summarizes the lifetime cancer oral risk for the applicable COUs. Oral ingestion non-cancer MOEs and cancer risks are presented for drinking water, diluted drinking water, landfill leachate to groundwater and subsequent migration to drinking water, 8245 incidental ingestion

during swimming, fish ingestion, and soil ingestion for children playing with soil. Table 5-65 summarizes the acute and chronic non-cancer dermal MOEs for incidental dermal exposures during swimming and dermal ingestion of soils for children playing with soil associated with applicable COUs. Table 5-66 presents the general population chronic inhalation MOEs used to characterize risk for the applicable COUs. Table 5-67 presents the general population lifetime cancer inhalation risk estimates for the applicable COUs. Inhalation MOEs and risk estimates are provided for various distances from a hypothetical facility for two meteorology conditions (one for central tendency meteorology; and one for higher-end meteorology). Unfortunately, as before, there are no tables presenting aggregate MOEs or cancer risk estimates for scenarios reflecting multi-route exposures. And, all but one of the tables include findings only for COUs, that exceed an acceptable threshold (i.e., less than the benchmark MOE or greater than 1 in a million cancer risk). Thus, these tables suffer from the same inadequacies as those for the other categories described above.