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EPN Comments on the Perchloroethylene (PERC) Draft Risk Evaluation

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The Environmental Protection Network (EPN) is an organization of more than 500 U.S. Environmental Protection Agency (EPA) alumni volunteering their time to protect the integrity of EPA, human health, and the environment. We harness the expertise of former EPA career staff and confirmation-level appointees to provide an informed and rigorous defense against current administration efforts to undermine public health and environmental protections.

EPN is submitting these comments to the Science Advisory Committee on Chemicals (SACC) to aid in their review of the perchloroethylene (PERC) draft risk evaluation (RE) during their scheduled May 26-29, 2020, peer review meeting.

PERC, like several of the other chemicals in the First 10 for which risk evaluations have been conducted, is one of a group of organochlorine chemicals classified as Volatile Organic Compounds (VOCs), based on its ability to easily transition from a liquid state to a vapor or gas. It is a high-volume production and use solvent with a wide range of commercial and consumer uses, some of which likely overlap those for other chlorinated VOCs undergoing risk evaluation contemporaneously.

1. **The Timing of Public Comment and Peer Review**

   As EPN has said several times before, and is compelled to say again, the agency is implementing a schedule for review that is inconsistent with best management practices. We continue to be concerned that this process deprives the SACC of scientific and policy input that would be valuable in informing its review of draft risk evaluations and, thus, greatly reduces the value of the public comment process. This recurrence reinforces the view that the current agency approach values a calendar deadline over the integrity of the information going into a decision and represents yet another example of its disdain for the scientific enterprise. Furthermore, the process appears to be a mechanism to discourage comments from the stakeholder community.

   On page 39 of the PERC draft risk evaluation, we, once again, see this disingenuous boilerplate language: "As EPA explained in the Risk Evaluation Rule (82 FR 33726 (July 20, 2017))…. EPA believes peer reviewers will be most effective in this role if they receive the benefit of public comments on draft risk evaluations *prior* (emphasis added) to peer review. For this reason, and consistent with standard agency practice, the public comment period will precede peer review on this draft risk evaluation."

This time, there was no real lead time before the preparatory meeting and only a two week or so lead time granted for public comments to reach the peer review committee before it meets, each of which is clearly inadequate for submitters to prepare meaningful comments on these substantial and consequential assessments. The Federal Register notice (FRN) announcing the availability of the PERC documents and scheduling of the virtual prep meeting and peer review meeting was published May 4, barely 24 hours before the 1:00 pm EDT May 5 prep meeting. The FRN stated that if one wished to submit comments for the prep meeting, or request time to present oral comments, it had to be done **on or before noon, May 1, 2020—THREE DAYS *BEFORE* the FRN WAS PUBLISHED!**

The PERC public comment period runs from May 5 until July 6, 2020, with the peer review committee meeting scheduled for May 26-29, 2020, once again, roughly in the middle of the comment period. However, comments must be submitted to EPA by May 20, 2020, in order for the SACC to receive them before their meeting, leaving the committee less than a week to digest them. Their challenge to prepare for and contribute fully to the PERC review is further complicated by the cancellation of the asbestos peer review meeting originally scheduled for the end of April. The standing members of the committee are going to have to remain poised to participate in a rescheduled asbestos meeting, now set for June 8-11. This only serves to place further pressure on the committee members to maintain a constant state of preparation on important and complex issues.

2. **Conditions of Use to Be Assessed**

EPA proposes to assess 21 categories and 54 subcategories of conditions of use. No categories or subcategories were removed from consideration over the course of the scoping, problem formulation, and risk evaluation development phases of the process.

However, there is no mention in the draft risk evaluation of the court decision in Safer Chemicals Healthy Families v. EPA, Nos. 17-72260 et al. (9th Cir. 2019), that now obligates the agency to consider legacy uses and disposal when conducting assessments in the Existing Chemicals Risk Evaluation program. To that end, the agency must include a discussion of this topic in the final PERC risk evaluation, providing either documentation of the absence of any legacy uses or identifying and then assessing them to the fullest degree for both environmental and human health consequences.

3. **Systematic Review**

EPN is disappointed that the agency continues to employ a flawed approach to identify, sort, select and exclude studies and other information to be used in this risk evaluation and then to grade their quality and acceptability for inclusion in the assessment.

The review by the National Academies of Sciences (NAS) of the draft guidance document entitled "Application of Systematic Review in TSCA Risk Evaluations" will not be completed before the First 10 draft risk evaluations have gone through a round of public comment and peer review. This presents a significant challenge to the integrity of these 10 risk evaluations and, indeed, to the entirety of the Existing Chemicals review program.

EPN believes that no revised risk evaluation for *any* of the First 10 chemicals should be finalized until AFTER the agency receives the report from the NAS committee, revises the guidance in accordance with the recommendations and applies the revised guidance in a re-visit to every step of the process, with particular emphasis on the data evaluation and data integration stages. Furthermore, no draft risk evaluation for the next 22 chemicals should be issued for public comment and peer review until the same milestones are achieved.

4. Aggregate and Cumulative Exposure and Risk Assessment

In the real world, people may be exposed to chemical(s) of concern in a work setting and/or as a user/consumer/bystander of a product as well as through the ambient environment. Similarly, ecological receptors may be exposed to chemical(s) of concern as a consequence of environmental releases related to conditions of use (COUs) as well as through indirect sources in the ambient environment.

For human health impacts, the PERC draft risk evaluation presents risk assessments and risk determinations for acute and chronic inhalation and dermal exposures to workers and inhalation exposure to occupational non-users (ONUs), and for acute inhalation and dermal exposures to consumers and inhalation and, sometimes, dermal exposure to bystanders under a variety of conditions of use. No oral exposure assessments were performed for any COU. For ecological impacts, EPA conducted acute and chronic assessments and provided risk estimations for aquatic species but did not develop quantitative assessments for sediment organisms. Also, it did not analyze other releases to land, including biosolids application to soil or exposure of terrestrial organisms through soil, land-applied biosolids or ambient air.

The agency states that they must describe whether or not they have considered aggregate exposures in their assessments. However, EPA has not conducted such an assessment or made findings of (no) unreasonable risk based upon combined (aggregate) exposures, either to account for multiple routes of exposure known to occur simultaneously during a specific condition of use or with consideration of exposures from non-TSCA-related scenarios.

As in risk evaluations for other existing chemicals, EPA once again is separately evaluating exposures to the chemical of interest by the inhalation and dermal routes, even though they acknowledge that inhalation and dermal exposures can be assumed to occur simultaneously for both workers and consumers. As the agency has stated previously, "For workplace (and

household/consumer) exposures, inhalation and dermal exposures are assumed to occur simultaneously *i.e.*, both occur at the start of the task and continue through the end of the task, shift, or work day."

As before, EPA has provided a feeble excuse for not proceeding with an aggregate assessment by stating "EPA chose not to utilize additivity of exposure pathways at this time within a condition of use because of the uncertainties present in the current exposure estimation procedures…" even while admitting "this may lead to an underestimate of exposure." "Will" would be the more appropriate word than 'may," in this instance. Aggregation can be done under these conditions, and the uncertainties can be accommodated for. One might speculate that this is a ploy to trivialize the existence of risks attendant to COUs.

There is another dimension to the human health and environmental assessments that should be acknowledged and incorporated in the PERC risk evaluation: cumulative risk assessment. The trichloroethylene (TCE) draft risk evaluation included a detailed discussion of the (mammalian) toxicokinetics (ADME) of that substance. The toxicokinetics section in the PERC draft risk evaluation pales by comparison in robustness, referring simply to the toxicokinetics section in the 2012 IRIS Toxicological Review document, which is quite extensive. However, most importantly, the draft risk evaluation fails to acknowledge that, unlike the TCE draft risk evaluation, PERC shares metabolites in common with a number of chlorinated VOCs, most of which are currently subject to the TSCA risk evaluation process. Those listed in Table 3-4 of the TCE risk evaluation (pp 204-205) include [PERC]; 1,1,2,2-tetrachloroethane; trichloroethylene; 1,1,1-trichloroethane; 1,2-dichloroethylene; and 1,2-dichloroethane. [The 2012 IRIS PERC document does discuss similarities and differences between PERC and TCE metabolism, but does not discuss the other four VOCs.]

As EPN argues in its comments on the Scoping documents for the next 20 Risk Evaluation chemicals, we believe that EPA should conduct cumulative assessments of similar chemicals. We identified several criteria that should be applied when determining when a cumulative assessment would be appropriate: 1) concomitant exposure attendant to a category or subcategory of conditions of use; 2) close structural similarities, that is, members of the same chemical class; 3) shared metabolic pathways and byproducts of metabolism; 4) similar toxicity profiles; and 5) similar modes/mechanisms of action of shared toxicity endpoints. The sextet of chemicals listed in Table 3-4 meet most, perhaps all, of the criteria. (Time did not allow for an in-depth documentation of the criteria as they apply to the environmental assessment or of Criterion #5 for the human health assessment.)

The lack of aggregate and cumulative assessment clearly leads to an underestimation of exposure and risk and, potentially, the incorrect declaration of "no unreasonable risk" when one actually exists. As noted above, this situation is compounded by EPA's refusal to consider concomitant

exposures in media/scenarios covered by regulatory measures under other statutes, such as air emissions, drinking water- and waste-related exposures. *Even when an exposure would not be regulated under TSCA, it should be considered when assessing risks that would be regulated under TSCA.* In other cases, the aggregate exposure may best be addressed under another authority, but it would never be identified if it were not assessed under the full life-cycle assessment that TSCA is capable of providing.

EPN has argued repeatedly that assessment of aggregate exposure for COUs, coupled with exposures known or anticipated to exist outside of a COU, should always be implemented as a benchmark of a credible and responsible exposure assessment. While we have previously raised the issue as it relates to human health assessment, the principle applies equally to environmental assessment. For each of the several chlorinated VOCs cited above, including PERC, tailored cumulative assessments also are warranted. To do otherwise is to deny reality and is irresponsible and unethical.

5. Environmental Assessment

a. Exposure Assessment

Fate and transport modeling estimates 88% of PERC in wastewater will be removed by treatment, 82% by volatilization and 6% by adsorption to organic matter in sludge. The overall removal of PERC in sewage treatment plants is expected to range from 88% to 100%. PERC has moderate potential to sorb to sludge and organic matter and, thus, is expected to be present in biosolids, also known as processed sludge. When biosolids are land applied, PERC will volatilize from solid and liquid phases during and after spraying; some PERC may partition from biosolids into soil and groundwater.

PERC has moderate potential to sorb to soil or sediment organic matter and may be transported to groundwater. Anaerobic biodegradation, which is reported to be rapid to very slow depending on local conditions, and microbial populations may be a significant degradation mechanism in soil and groundwater. *However, in anaerobic environments, PERC biodegradation products include potentially hazardous substances including trichloroethylene; cis-1,2-dichloroethylene; and vinyl chloride.* This statement from the risk evaluation [Lines 1748-1749] presents a persuasive argument for incorporating PERC along with reviews of the other relevant chlorinated compounds in the top 10/top 20 priority chemicals.

Modeling based on physical and chemical properties indicates PERC is expected to volatilize from surface water to air and from soil to air. Volatilization half-life from a model river is expected to be 1.4 hours; volatilization half-life from a model lake will be 123 hours. In the atmosphere, PERC vapor is expected to degrade slowly by indirect photolysis (half-life $\geq$ 80 days). Given its slow photodegradation [Line ca. 1757-1759], PERC is expected to undergo long-range atmospheric transport.

Additionally, PERC has been detected in rain from industrial cities in the UK and USA, and in snow in Australia, Italy and Antarctica (Hazardous Substance Data Bank, various). This is a potential problem because PERC and related chlorinated compounds may transition between environmental compartments (air, water, soil), and may adversely affect aquatic and terrestrial food chains because these compounds are toxic both to humans and wildlife.

> Recommendation: Given that global transport of PERC in the atmosphere seems highly relevant to the Clean Air Act (CAA), we need to determine exactly how to integrate such findings and find a way to determine whether EPA is doing what's needed to effectively regulate PERC under the CAA.

The bioaccumulation potential of PERC is low based on measured bioconcentration factors of 312 or lower, and an estimated bioaccumulation factor of 46.

Overall, PERC has moderate potential to accumulate in wastewater biosolids, soil, and sediment; has low potential to accumulate in biota; and is expected to largely volatilize to the atmosphere where it may undergo long range transport and slowly degrade via indirect photolysis.

EPA did not quantitatively analyze exposure to sediment organisms. This is because PERC is expected to be moderately retained in sediment due to its water solubility (206 mg/L) and moderately partition to organic matter (log [K_{OC}]= 2.95). Since PERC has moderate partitioning to organic matter, PERC in sediments is expected to be both adsorbed to the sediment organic matter and to be present in the pore water. However, depending on the microbial populations present and their previous exposure and adaptation to the chemical, PERC may undergo rapid biodegradation in sediment. Thus PERC concentrations in sediment may be lower or somewhat greater than concentrations in overlying water [Lines 8620-8621].

> Recommendation: This observation provides a basis for conducting additional study/monitoring of sediment concentrations of PERC to reduce the levels of uncertainty in assessing risks to organisms exposed to PERC in sediments.

Nevertheless, EPA states that toxicity of PERC to sediment-dwelling invertebrates is expected to be similar to the toxicity to aquatic invertebrates because of the similarities in PERC concentrations.

Although this is a relatively minor point, we disagree with the logic employed where EPA infers sediment-dwelling organisms and organisms living in the water column would exhibit similar toxicities [Line 8620] ". . . because of the similarities in PERC concentrations . . . ," we do not think that logic equates to similarities in sensitivity of different organisms to toxicant concentrations in the environment, i.e., water column versus pore water in sediments.

Recommendation: Conduct testing toxicity of PERC using sediment-dwelling organisms, e.g., *Chironomus dilutus, Hyalella azteca* because it will provide data to resolve this issue.

Similarly, EPA did not analyze PERC for other releases to land during risk evaluation, including biosolids application to soil as indicated in the problem formulation. Neither did EPA assess exposure to terrestrial organisms through soil, land applied biosolids or ambient air. This is because PERC has moderate potential to partition to or accumulate in soil, but it is primarily expected to volatilize to air or migrate through soil into groundwater based on its physical chemical properties. Therefore, physical chemical properties do not support an exposure pathway through water and soil pathways to terrestrial organisms.

EPA also did not include PERC hazard toxicity to terrestrial mammals in their risk evaluation because observed effects in laboratory mammals have been reported mostly at much higher concentrations than have been measured or are predicted to occur in the environment. Additionally, as noted earlier, the bioconcentration factor and bioaccumulation potential of PERC are low. Therefore, it is unlikely that adverse effects will occur in the terrestrial mammalian exposure pathway.

Given the above specific critical comments, we nevertheless agree, in general, with EPA's decision to not conduct risk estimations for sediment pathways, land applied biosolids pathways and terrestrial mammalian exposure pathways.

Environmental releases of PERC to the environment are based on wastewater discharges for COU, as defined by the EPA Administrator, and as understood to be within the life cycle for PERC. EPA estimated daily wastewater discharges and, for each of the 22 occupational exposure scenarios (OES), integrated a summary of release days, number of facilities and daily wastewater discharges. These estimates represent both direct discharges to surface water and indirect discharges to public and non-public wastewater treatment works. EPA did not identify data to estimate wastewater discharges for several OES release sites, e.g., "other spot cleaning/spot removers (including carpet cleaning), laboratory chemicals, and other Department of Defense uses." Overall confidence in almost all of these values was medium.

Surface water concentrations resulting from wastewater releases of PERC from facilities that manufacture, process or use PERC related to TSCA COUs were modeled using EPA's 2014 version of Exposure and Fate Assessment Screening Tool (E-FAST) . Because E-FAST modeling uses upper percentile and/or mean exposure parametric values, it yields typically conservative high-end exposure estimates. Annual releases are converted to daily releases using an estimated days of release per year.

E-FAST modeling assumed the percentage of PERC removed from wastewater during treatment before discharge to a body of water was 80%. However, facilities that directly release effluent to surface water do not treat PERC prior to discharge, therefore EPA did not account for removing any PERC. E-FAST was used to estimate site-specific surface water concentrations for discharges to both free-flowing water bodies and for still water bodies (i.e., bays, lakes, estuaries).

In general, based on their integration of data from modeling, monitoring, and extensive literature review, we agree with the approach EPA used to evaluate environmental exposure.

b. Hazard Assessment

Aquatic hazards were assessed based mostly on high-quality data. Acute, chronic, and algal endpoints that were used in EPA's evaluation are summarized in the following table.

Acute effects (mg/L)	Endpoint*	Value	Geometric mean
Fish	LC50	4.82 –28.1	12
Aquatic invertebrates	LC/EC50	2.49 –18.1 (range)	6.7
Chronic effects (mg/L)	**Endpoint***	**Value**	**Geometric mean**
Fish	ChV	0.5-1.4	0.84
Aquatic invertebrates	ChV	0.37–0.67	0.5
Algae (growth, metabolism)	NOEC/LOEC	0.01-0.02	0.014

[a] LC50 = median lethal concentration; EC50 = median effective concentration; ChV Chronic value; NOEC = no observed effect concentration; LOEC = lowest observed effect concentration

We judge the adequacy of databases from which these hazard values were identified and characterized as adequate for deriving the relevant aquatic concentrations of concern (COC).

We also agree on the appropriateness of the species/populations, durations, and pathways EPA used to assess PERC.

Recommendation: One recommendation that would help improve the hazard component of EPA's aquatic risk evaluation would be to conduct further algal testing using additional species, given that only two named algal species (*Pseudokirchneriella subcapitata, Chlamydomonas reinhardtii*) were incorporated into the risk evaluation of PERC.

c. Risk Determination

EPA's preliminary determinations of unreasonable environmental risks to aquatic organisms for specific COUs of PERC are presented in the following paragraphs.

Using risk quotients (RQ) to compare predicted environmental concentrations against aquatic hazard values, EPA identified a total of 41 unreasonable environmental risks to aquatic organisms (invertebrates, fish, and/or aquatic plants) based on endpoints for immobilization from acute exposure, growth effects from chronic exposure, and mortality or sublethal effects to algae.

Environmental risks

EPA determined that environmental exposures are expected for aquatic organisms for the conditions of use within the scope of the risk evaluation. The drivers for EPA's draft determination of unreasonable risks to aquatic organisms are immobilization from acute exposure, growth effects from chronic exposure and mortality to algae. Algae were assessed separately and not incorporated into acute or chronic COCs because durations normally considered acute for other species (e.g., 48, 72 hours) can encompass several generations of algae. Confidence in acute and chronic COCs for fish and invertebrates is high. Confidence in the algal COC is medium given that the COC for algae is based on a single study and the data were only available for three algal species that may not represent the most sensitive species at a given site. As with many other life forms, algal species tend to vary widely in their sensitivity to chemical pollutants. Because current regulations do not require facilities to report the number of days associated with reported releases, EPA estimated site-specific surface water concentrations for discharges using upper and lower bounds for the range of predicted surface water concentrations. EPA's estimates include consideration of the number of facility operating days per year, partial removal of PERC from industrial wastes or wastewater following treatment and the impacts of any direct releases of wastes to surface waters without treatment. Site-specific surface water concentration estimates for free-flowing water bodies were reported for both the 7Q10 (lowest consecutive 7-day average flow during any 10-year period) and harmonic mean stream flows.

In general, the majority of PERC releases to the aquatic environment do not exceed the aquatic benchmark. However, there are specific facilities for given COUs where estimated or reported releases result in modeled surface water concentrations that exceed aquatic benchmarks.

Nine COUs had RQs >1, indicating risk; no risks were identified for aquatic organisms for the remaining COUs.

Aquatic pathways reported in EPA's Table 4-110 (pages 405-425) give RQs by COU for each of the facilities. Based on data quality, uncertainties and weight of scientific evidence, the overall confidence in nearly all of the aquatic risk estimates is medium.

EPA concludes there is an acute risk to aquatic organisms from indirect releases of PERC to surface water from facilities using PERC from the Incorporation into Formulations COU. That single facility (Lord Corp, Saegertown, PA) had RQs >1 for acute risks, and RQs >1 and 20 days or more of exceedance for chronic and algae risks. Using the scenario of 300 days of indirect release (80% removal) to surface water resulted in a surface water concentration of 136 ppb; algae had an RQ = 97 and 299 days of exceedance; and aquatic invertebrates had a chronic RQ = 2.7 and 127 days of exceedance. Using the scenario of 20 days of indirect release (80% removal) to surface water resulted in a surface water concentration of 2,034 ppb,;algae had an RQ = 1,453 and 20 days of exceedance; and aquatic invertebrates [Line 8511] had an acute RQ = 1.5 and a chronic RQ = 41 with 20 days of exceedance.

EPA identified elevated acute and chronic risk to aquatic organisms from direct release of PERC to surface water from the Incorporation into Formulation COU at a single facility. The facility showing risk has a National Pollutant Discharge Elimination System (NPDES) permit.

However, *[Line 8515-8516]* one of the facilities that was not identified with risk lacked an NPDES permit.

Recommendation: Follow up on any facility that lacks an NPDES permit and is suspected of releasing PERC, or anything else, to surface waters.

Risks from chronic PERC exposures were identified for aquatic organisms based on direct releases from the Processing as a Reactant COU and indirect releases from Incorporation into Formulations COU. Therefore, EPA concludes there is a chronic risk to aquatic organisms based on chronic PERC exposures from release of PERC to surface water from facilities using PERC for the COUs listed above.

Risks from PERC exposures were identified for algae based on **direct releases** from the following COUs:

- Manufacturing
- Processing as a Reactant
- Open Top Vapor Degreasing
- Industrial Processing Aid.

In addition, ***indirect release*** (80% removal) resulted in risks to algae from PERC exposure from the following COUs:

- Manufacturing
- Importing/Repackaging, Industrial Processing Aid
- Incorporation into Formulations
- Waste Handling, Disposal, Treatment, and Recycling.

Again, refer to EPA's Table 4-110 for additional details concerning aquatic risks based on the above COUs.

EPA therefore concludes there is a potential risk to algae from PERC releases to surface water from facilities using PERC for the COUs listed above.

In general, we agree with the risks EPA identified for aquatic organisms.

6. Human Health Assessment

a. Populations Assessed

As noted above, the PERC draft risk evaluation presents risk assessments and risk determinations for acute and chronic inhalation and dermal exposures to workers and inhalation exposure to ONUs, for acute inhalation and dermal exposures to consumers and inhalation and, *only sometimes*, dermal exposure to bystanders under a variety of conditions of use. No oral exposure assessments were performed for any COU.

EPN believes that EPA should re-visit the settings for which dermal exposure to bystanders has not been assessed and reconsider that decision. Unlike the ONUs in the work setting, bystanders in the consumer setting may play a more interactive role in the activity, and like the consumer, have contact with the chemical-containing product or the treated article during/after use. Furthermore, there may be settings in which it would be appropriate to assess oral exposure, particularly to the bystander. Given that bystanders encompass individuals of every age, including toddlers and young children, there may be circumstances in which hand-to-mouth activity contributes to increased exposure following dermal contact.

b. Adequacy of Databases for Hazard ID/Characterization, Benchmark MOEs, and Derivation of PODs

1) Adequacy of the databases for Hazard ID/Characterizations

Beginning with its comments on the draft risk evaluation for Pigment Violet 29 and in comments on other draft risk evaluations (*e.g.,* 1-bromopropane and 1,4-dioxane), EPN has presented what it argues would constitute a database adequate for assessing hazard to the (sub)populations covered in the worker and consumer COU assessments for any chemical of interest, without having to account for deficiencies when conducting hazard and risk characterization.

An adequate database includes the following:

a. Studies that would illuminate the potential for general systemic toxicity over an exposure duration commensurate with that of the actual exposure scenario or that could be extrapolated from shorter-term exposure studies accompanied by the

application of an uncertainty factor representing that extrapolation (e.g., acute short-term or subchronic to chronic);

b. For chronic exposures, studies that would adequately test for carcinogenic potential by the relevant route(s) of exposure or could be extrapolated to those routes of exposure;
c. For acute and chronic exposures, at least one developmental toxicity study;
d. For shorter-term and chronic exposures, a one- or two-generation reproductive toxicity study; and
e. If nervous system effects are observed in exposed humans or animals, a more systematic evaluation of neurotoxicity and developmental neurotoxicity, since the worker population includes women of childbearing age and the consumer/bystander and general population includes infants and young children.

Examination of the hazard database available on PERC reveals a substantial number of studies in both humans and animals that would appear adequate to address the needs for robust assessment without having to account for any key data deficiencies.

However, there does remain one substantial uncertainty. There are indications in both human and animal studies that PERC has the potential to produce adverse effects on the immune system and various hematological components (see Section 3.2.3.1.6. Immune System and Hematological Effects p. 269 of the PERC RE and Section 4.6. Immunotoxicity, Hematologic Toxicity and Cancers of the Immune System p. 4-206 of the 2012 PERC IRIS Toxicological Review). As noted in the PERC risk evaluation, the data on these endpoints were not adequate for dose-response assessment and they were not carried forward for further assessment.

As a result, as EPA notes, "There is uncertainty whether the PODs for other endpoints carried forward are sufficiently protective of any potential immune or hematological effects that were not accounted for in this risk evaluation." The consequences of a potential "insufficiency" are that a conclusion of "no unreasonable risk"'could be made with regard to a condition of use when one actually exists.

2) Benchmark MOEs

a) <u>Immune system and hematological effects</u>

Based upon our assessment of the hazard database and our concurrence with the agency that the information on PERC's potential for causing adverse effects on the immune system and hematological parameters is currently incomplete and inadequate for dose-response assessment and hazard/risk characterization, we recommend the following:

i. Incorporate an additional uncertainty factor of 3X for data deficiencies (UF_D) into each chronic Benchmark MOE relevant for all of the non-cancer

endpoints used in risk estimation and determination (e.g., from 100 to 300 for central nervous system effects, from 30 to 100 for kidney effects, etc.)

ii. Revise chronic inhalation and dermal risk estimations and determinations for all COUs.

iii. If time permits, use enhanced testing authority to solicit additional observations in human cohorts and/or non-human studies to answer the outstanding questions, using standardized or tailored study designs.

iv. If the results of the new studies show the PODs for other endpoints are sufficiently protective of any potential immune or hematological effects, then reduce the Benchmark MOEs accordingly.

b) Susceptible (sub)populations

EPA identified a substantial number of Potentially Exposed and Susceptible Subpopulations in light of PERC's extensive toxicity profile (p 299+):

i. Those with higher body fat composition may be more highly exposed to sustained internal PERC concentrations/doses because of lipophilicity; these include pubescent and adult women (including women of childbearing age) as well as any individual with an elevated body-mass index.

ii. Pregnant women, the developing fetus and newborn infants are all considered highly susceptible subpopulations, and therefore women of childbearing age are susceptible by proxy.

iii. Older men because of effects on male fertility.

iv. Those with pre-existing liver or kidney dysfunction. The partitioning of PERC to fatty tissue is of particular concern for those with fatty liver disease.

v. Those with poor vision or neurocognitive deficiencies may be especially susceptible to these hazards.

vi. Differential impact given variability in CYP metabolic capacity, which is generally believed to vary by approximately 10-fold among all **humans,** perhaps as high as 20-50 fold, which have also been reported in *in vitro* studies.

Co-exposure to other pollutants and drugs may also have either an activating or inhibitory effect on PERC metabolizing enzymes, strengthening the argument for conducting cumulative assessments as argued above.

The identified subpopulations reflect many different health conditions and actually represent large numbers of people. EPA has applied the default uncertainty factor of 10X to account for within-human variability (UF_H) when it established the Benchmark MOEs for each of the non-cancer endpoints of toxicity. One can only speculate whether 10X truly covers the full range of variability in this case. We would assert that, unless EPA can provide empirical evidence that the 10X will be adequate

in this instance, it should increase the UF_H, adjust the Benchmark MOEs and revise the risk determinations accordingly.

c. Cancer Risk Assessment

EPA notes that a majority of the NRC peer review panel for the PERC IRIS draft assessment recommended that the male mouse hepatocellular tumors be used for cancer risk estimation, although some members recommended that the Mononuclear Cell Leukemia (MCL) data (in rats) be used instead (Page 307-308). EPA derived an IUR for both tumor types, but then used only the liver tumor IUR in the subsequent risk estimation and determination steps. *This was an appropriate choice*. While liver tumors observed in mice are often challenged as to their relevance to humans, that relevance is informed by our understanding of the mode(s)/mechanism(s) of action underlying their etiology. In this case, the data do not favor dismissal of relevance. On the other hand, observation of increases in MCL in rats is more clearly of questionable relevance to humans. It is unique to the rat and occurs in untreated, aged F-344 rats at a high and variable rate with a background incidence that has increased significantly over time. It is uncommon in most other rat strains and found in no other mammalian species with no histologically comparable tumor found in humans.

d. Risk Determinations

1) **Personal Protective Equipment (PPE)**

   As EPA notes, "EPA does not know the actual frequency, type, and effectiveness of glove use in specific workplaces with PCE conditions of use"(Page 192), buttressing, once again, our argument that risk determinations should be based solely upon COU scenarios in which workers are NOT using any form of PPE. As we have stated before, risk is underestimated, perhaps significantly so, when assuming workers will use PPE appropriately for the entire duration of the work activity throughout their careers, even when such equipment is not required, provided or used.

2) **Dermal exposure to bystanders should be evaluated for all COUs for which dermal exposure is being assessed for consumers.**
3) **Risk Determinations should be reviewed and revised accordingly, following recalculation of all chronic inhalation and dermal non-cancer Benchmark MOEs as recommended, to account for data deficiencies and human variability.**
4) **Risk determinations should be based upon aggregated and cumulative inhalation and dermal exposures for each COU, not by single chemical or separate routes of exposure.**